2021-1876

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT LLC, CILAG GMBH INTERNATIONAL,
Plaintiffs-Appellees,

v.

ZYDUS PHARMACEUTICALS (USA) INC.,
Defendant-Appellant.

On appeal from the United States District Court for the District of New Jersey, Case No. 3:17-cv-05319-FLW-DEA, Hon. Freda L. Wolfson

OPENING BRIEF FOR DEFENDANT-APPELLANT

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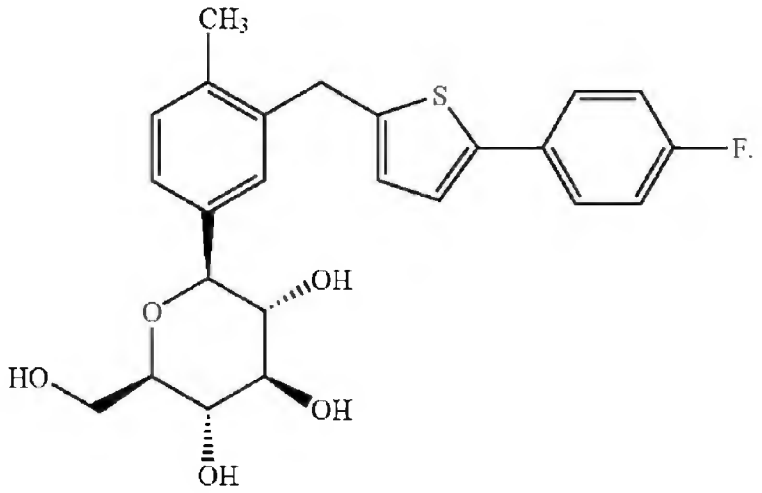
July 6, 2021

Claims 12 and 20 of U.S. Patent No. 7,943,788

12. 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

20. A compound having the following structure:



(Appx298)

CERTIFICATE OF INTEREST

Case Number: 2021-1876

Short Case Caption: Mitsubishi Tanabe Pharma Corporation v. Zydus Pharmaceuticals (USA) Inc.

Filing Party/Entity: Defendant-Appellant Zydus Pharmaceuticals (USA) Inc.

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box.** Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: July 6, 2021 Signature: /s/ Jay Deshmukh

Name: Jay Deshmukh

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.
Zydus Pharmaceuticals (USA) Inc.	None/Not Applicable	Cadila Healthcare Limited

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).		
Saiber LLC: Sean R. Kelly, Geri L. Albin, and Katherine Ann Escanlar		
Kasowitz Benson Torres LLP: Trevor Welch (no longer with the firm) and Shelley Ivan.		
Arent Fox LLP: Bradford C. Frese, Gary A. Coad, Janine A. Carlan, and Richard J. Berman		

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).		
Mitsubishi Tanabe Pharma Corporation et al. v. Dr. Reddy's Laboratories, Inc. et al., Civil Action No. 3:19-cv-18764 (D.N.J.)		

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).		
None/Not Applicable		

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

STATEMENT OF RELATED CASES

Pursuant to Fed. Cir. R. 47.5, Appellant states that no appeal from this same civil action was previously before this or any other appellate court.

Appellant further states that it is aware of the following other pending case that may directly affect or be directly affected by this court's decision in the pending appeal: *Mitsubishi Tanabe Pharma Corporation et al. v. Dr. Reddy's Laboratories, Inc. et al.*, Civil Action No. 3:19-cv-18764 (D.N.J.). That case concerns U.S. Patent No. 7,943,788, which is also the subject of the pending appeal.

The parties to this appeal are also engaged in a separate district court litigation concerning Appellant's same proposed generic pharmaceutical products that are at issue in this appeal, but different patents: *Mitsubishi Tanabe Pharma Corporation et al. v. Sandoz Inc. et al.*, Civil Action No. 1:17-cv-5005 (consolidated) (D.N.J.).

STATEMENT OF JURISDICTION

Defendant/Appellant Zydus Pharmaceuticals (USA) Inc. ("Zydus") timely appeals from a final judgment of the United States District Court for the District of New Jersey in a patent infringement action. The district court had jurisdiction over the parties' claims and counterclaims under 28 U.S.C. §§ 1331, 1338(a), and 2201 and 21 U.S.C. § 355(c)(3)(D). This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

STATEMENT OF ISSUES PRESENTED

Whether the district court erred in rejecting Appellant's obviousness-type double patenting invalidity defense against the '788 patent by holding that the earlier-expiring '219 patent does not qualify as a double patenting reference against the later-expiring, commonly owned '788 patent, where the '788 patent expires later on account of having received a patent term adjustment pursuant to 35 U.S.C. § 154(b).

INTRODUCTION

The rule against obviousness-type double patenting ("OTDP") is a longstanding common-law doctrine that prevents a patent owner from obtaining two separate patents covering substantially similar, or "patentably indistinct," subject matter. Under this doctrine, if an asserted claim is patentably indistinct from a claim in an earlier, commonly-owned patent (*i.e.*, a "reference patent"), the asserted claim is invalid. In *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014), this Court held that "the determining factor" for assessing which patent qualifies as an "earlier" OTDP reference against the other is the patents' expiration dates, establishing the general rule that "an earlier-expiring patent can qualify as an obviousness-type double patenting reference for a later-expiring patent[.]" *Id.* at 1215-17. This rule serves the "bedrock principle of our patent system that when a patent expires, the public is free to use not only the same invention claimed in the expired patent but also obvious or patentably indistinct modifications of that invention." *Id.* at 1214.

The undisputed facts of this case establish that (a) U.S. Patent Nos. 7,943,788 ("the '788 patent") and 8,222,219 ("the '219 patent") are commonly-owned, (b) the '788 patent is set to expire more than two years after the '219 patent, and (c) the asserted claims of the '788 patent are patentably indistinct from claim 22 of the '219 patent. Thus, under this Court's precedent, the '219 patent

qualifies as an invalidating OTDP reference against the '788 patent, unless one of this Court's exceptions applies. But no such exception applies here.

That the '788 patent expires later only on account of having been granted a patent term adjustment ("PTA") pursuant to 35 U.S.C. § 154(b)[1] is of no moment. Under § 154(b), the United States Patent and Trademark Office ("PTO") may grant a patent a period of additional patent life due to PTO delays during the patent prosecution process, but § 154 does not at all exempt a patent from still complying with the rule against OTDP. To the contrary, as this Court noted in reaffirming *Gilead*, in situations where "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO[,] … the doctrine of obviousness-type double patenting ensures that a particular invention (and obvious variants thereof) does not receive an undue patent term extension." *AbbVie, Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1372 (Fed. Cir. 2014) (citing, *inter alia*, 35 U.S.C. § 154(b)).

Moreover, § 154(b) specifically contemplates the applicability of OTDP by barring terminally disclaimed patents from benefiting from PTAs. *See* 35 U.S.C. § 154(b)(2)(B) ("No patent the term of which has been disclaimed beyond a

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[1] Unless otherwise indicated, citations to statutes and regulations herein are to their current versions.

specified date may be adjusted under this section beyond the expiration date specified in the disclaimer."). A terminal disclaimer is a statutory mechanism that causes the later-expiring patent to expire at the same time as the earlier-expiring OTDP reference patent, thereby "supplant[ing] a finding of invalidity for double patenting" by fulfilling one of the doctrine's main goals of "prevent[ing] an inventor from securing a second, later expiring patent for the same invention." 35 U.S.C. § 253(b); *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1373 (Fed. Cir. 2005); *AbbVie*, 764 F.3d at 1373; *Gilead*, 753 F.3d at 1213-14. The terminal disclaimer bar to PTAs in § 154(b), thus, reflects clear congressional intent that the roughly two century-old rule against OTDP should remain in full effect regardless of any PTO delays or eligibility for a PTA. Thus, when the '219 patent expires, the public should be free to use the '219 patent's claimed invention and the patentably indistinct modifications claimed in the '788 patent. *See Gilead*, 753 F.3d at 1214.

In rejecting Zydus's OTDP defense, the district court turned precedent on its head, erroneously concluding that the '219 patent cannot legally qualify as an OTDP reference against the '788 patent solely because the '788 patent expires later due to having received a § 154(b) PTA. Appx64-66. To reach that conclusion, the district court unduly expanded the narrow exception to OTDP that this Court carved out specifically for patent term extensions ("PTEs") under 35 U.S.C. § 156.

See Novartis AG v. Ezra Ventures LLC, 909 F.3d 1367, 1374-75 (Fed. Cir. 2018) (holding that a § 156 PTE cannot create an OTDP problem). As this Court has held, § 156 is a substantively different statute than § 154(b). See *Merck & Co. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317, 1322 (Fed. Cir. 2007) ("§ 154(b)(2)(B) expressly excludes patents in which a terminal disclaimer was filed from the benefit of a term adjustment for PTO delays. There is no similar provision that excludes patents in which a terminal disclaimer was filed from the benefits of Hatch-Waxman extensions [under § 156]."). To expand *Ezra*'s narrow exception for § 156 PTEs to apply to § 154(b) PTAs, as the district court did below, defies the very logic for creating the PTE exception in the first place and permits the narrow exception to swallow the rule.

The district court further erred as a matter of law by requiring a showing of "gamesmanship." The invalidity defense of OTDP does not require a showing of gamesmanship, deceptive intent, or any other impropriety or *mens rea*. In any event, the district court's ruling clearly creates a potential for gamesmanship by significantly amplifying the value of avoiding OTDP rejections, and the resulting need to file terminal disclaimers, during prosecution. By treating OTDP disparately during prosecution and in post-prosecution litigation, the district court's ruling creates an exploitable loophole that incentivizes patent applicants to orchestrate prosecution in a manner that strategically avoids OTDP rejections

during prosecution, to obtain a § 154(b) PTA that would otherwise be unavailable if a terminal disclaimer was filed during prosecution and at the same time is immune from OTDP in post-prosecution litigation. Congress could not have possibly intended such an incongruous result that would discourage full and open disclosure to the PTO and permit circumvention of § 154(b)(2)(B).

The OTDP issue on appeal is an important question of law that will impact numerous other pending and future cases,[2] has been decided differently by at least one other district court,[3] and thus requires this Court's clarification of the law.

STATEMENT OF THE CASE

A. The Nature of the Case

This is an appeal from a district court judgment in a patent infringement litigation under the Hatch-Waxman Act. Appx2245. The case arises under 35 U.S.C. § 271(e)(2) from Zydus's submission of Abbreviated New Drug Applications ("ANDAs") seeking U.S. Food and Drug Administration ("FDA") approval of

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[2] For example, the parties in this appeal are engaged in a separate pending action concerning a different canagliflozin patent that presents this very same legal question. *See Mitsubishi Tanabe Pharma Corp. v. Aurobindo Pharma USA, Inc.*, No. 17-cv-5005 (D.N.J.). Other cases involve the very same issue. *See, e.g., Kove IO, Inc. v. Amazon Web Services, Inc.*, No. 18-cv-8175 (N.D. Ill.), D.I. 304.

[3] *See Magna Elecs., Inc. v. TRW Auto. Holdings Corp.*, No. 12-654, 2015 WL 11430786 (W.D. Mich. (Dec. 10, 2015)).

generic canagliflozin drug products before the expiry of certain patents that purportedly cover the reference branded products. Appx4-5; Appx2244-2245.

B. The Parties and Their Products

Zydus is a New Jersey corporation that is engaged in the development, manufacture, and sale of generic drug products in the United States. Appx6; Appx2142; Appx2245. In 2017, Zydus filed ANDA Nos. 210541 and 210542, seeking FDA-approval to market generic versions of INVOKANA® and INVOKAMET®, respectively, prior to the expiration of the '788 and '219 patents and U.S. Patent No. 8,785,403 ("the '403 patent"), which are listed in the FDA's Orange Book with respect to the branded products. Appx4-6; Appx2244-2245.

Appellees collaborate in the patenting and marketing of INVOKANA® and INVOKAMET® in the United States. *Id.*

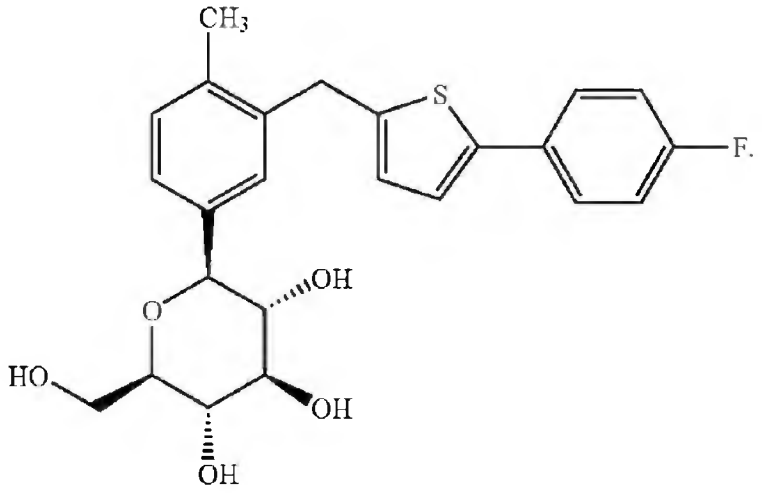
C. The Patent-at-Issue

The '788, '219, and '403 patents are part of the same patent family and concern canagliflozin and related compounds. Appx4-7; Appx2246-2248. This appeal concerns the validity of just claims 12 and 20 of the '788 patent, which Zydus contends are invalid for OTDP based on claim 22 of the '219 patent. Appx298; Appx414.

Claims 12 and 20 of the '788 patent, reproduced below, are directed to the same compound, canagliflozin:

> 12. 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

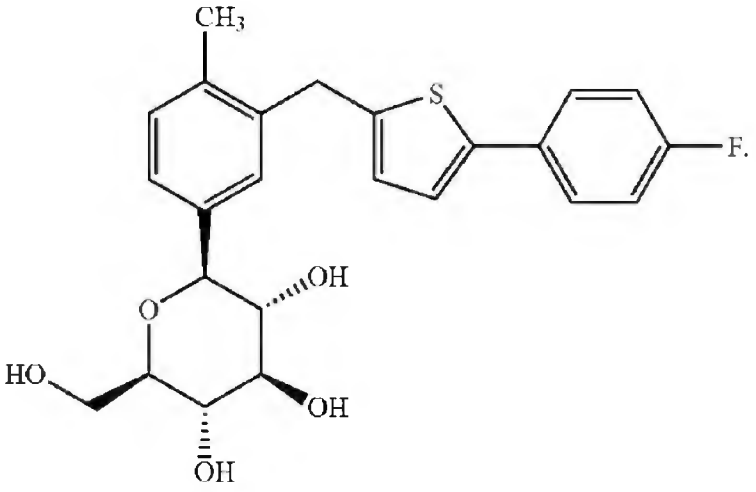
> 20. A compound having the following structure:



Appx6-7; Appx298.

Claim 22 of the '219 patent, reproduced below together with claims 20 and 21 from which it depends, covers a method of using canagliflozin to treat type 2 diabetes mellitus:

> 20. A method for treating or delaying the progression or onset of a disease selected from diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, and hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound having the following structure:



21. The method according to claim 20, wherein the disease is diabetes mellitus.

22. The method according to claim 21, wherein the disease is type 2 diabetes mellitus.

Appx7-8; Appx414.

1. The Relevant Patent Family

The '788 patent-at-issue and the '219 reference patent stem from the same international application. Appx6-8. Four applications in this patent family are relevant to this appeal:

First, on July 30, 2004, the applicants filed International Application No. PCT/JP2004/011312 ("the international application"). Appx6; Appx2246.

Second, on January 31, 2005, the applicants filed U.S. Application No. 11/045,446 ("the '446 application") as a continuation-in-part of the international application. *Id.* On May 17, 2011, the '446 application issued as the '788 patent.

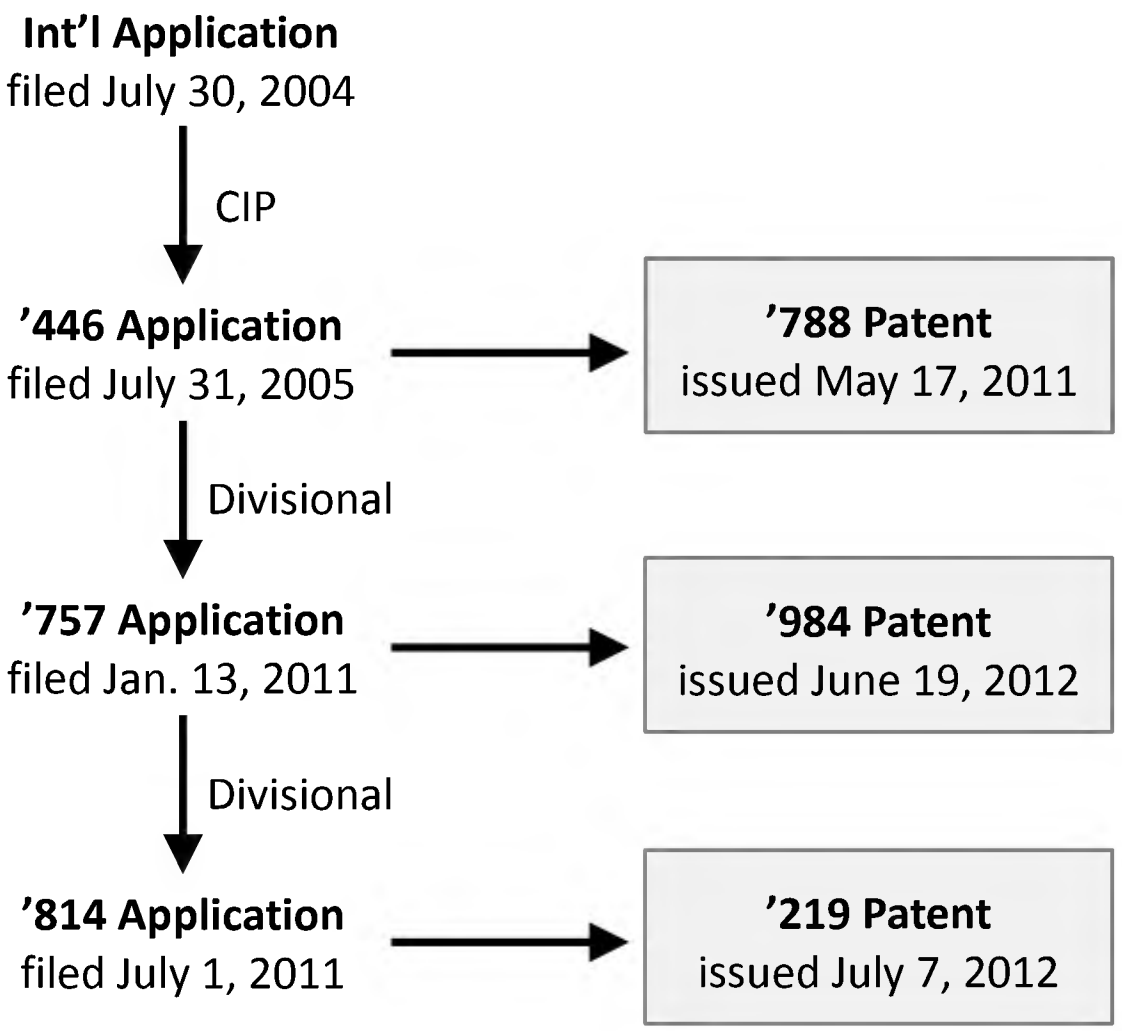
Id.; Appx182. The '788 patent is the patent-in-suit that Zydus contends is invalid for OTDP.

Third, on January 13, 2011, the applicants filed Application No. 13/005,757 ("the '757 application") as a purported divisional of the '446 application. Appx7; Appx2247. The patent that ultimately issued from the '757 application, U.S. Patent No. 8,202,984 ("the '984 patent"), was not asserted in this litigation. *See* Appx416 ("a division of application No. 13/005,757, filed on Jan. 13, 2011, now Pat. No. 8,202,984").

Fourth, on July 1, 2011, the applicants filed Application No. 13/174,814 ("the '814 application") as a purported divisional of the '757 application. Appx7; Appx2247. On July 17, 2012, the '814 application issued as the '219 patent.[4] *Id.*; Appx300. Zydus contends that the '219 patent qualifies as an OTDP reference against the '788 patent.

The relationships between these applications are illustrated below:

[4] The '403 patent, a continuation of the '219 patent, has no bearing on this appeal. Appx416.



2. Patent Expiration Dates

The '788 and '219 patents' statutory 20-year terms are measured from the international application's July 30, 2004 filing date. Accordingly, absent any extensions or adjustments, both patents would have been set to expire on July 30, 2024. Appx60-61.

Upon issuance, however, the '788 patent was granted a PTA pursuant to 35 U.S.C. § 154(b), extending the 20-year term of the patent by 1,079 days (*i.e.*,

nearly 3 years). Appx61. As a result, the '788 patent is currently set to expire on July 14, 2027, instead of July 30, 2024. *Id.*

The '219 patent, in contrast, did not receive a §154(b) PTA, but was granted a PTE pursuant to 35 U.S.C. § 156 that extends its term by 254 days beyond July 30, 2024. *Id.* As a result, the '219 patent will expire on April 11, 2025. *Id.* The '219 patent's PTE is not in dispute.

No terminal disclaimer has been filed against the '788 patent. Without any disclaimer, the '788 patent's expiry is more than two years after that of the later-filed '219 patent.

D. The Proceedings Below

On July 20, 2017, Plaintiffs filed a Complaint alleging that Zydus infringes the '788, '219, and '403 patents by virtue of having filed its ANDAs. Appx2140-2142, Appx2245. Prior to trial, Zydus stipulated to infringement, but maintained its invalidity defenses. Appx2213-2217.

The district court conducted a six-day remote bench trial over Zoom commencing on September 24, 2020, regarding the validity of the asserted claims of the three patents-in-suit. Appx5; Appx176-178. The first five trial days were primarily devoted to the issue of obviousness under 35 U.S.C. § 103, and the last day, November 5, 2020, was devoted to OTDP. *Id.* On that last day, the district court heard opening statements regarding OTDP, followed by testimony from each

sides' patent prosecution experts on issues relating to the applicability of the 35 U.S.C. § 121 safe-harbor. Appx1866-1870.

After the parties submitted proposed post-trial findings of fact and conclusions of law, Plaintiffs moved to strike three OTDP-related arguments in Zydus's papers that Plaintiffs contended were not previously raised. Appx178-179. On December 8, 2020, the district court issued an order denying two of the three parts of Plaintiffs' motion, but granting the third. Appx132-134. The district court found it "appropriate for Zydus to respond to" Plaintiffs' gamesmanship arguments and also permitted Zydus to argue that "the safe harbor cannot protect the '788 patent because the '219 was filed after the issuance of the '788 patent." Appx132-133. The district court, however, struck "Zydus's argument that a restriction requirement in the '984 patent prosecution prevents application of the safe harbor" because "the prosecution history of the '984 patent was not made part of the trial record nor does it appear that the patent was mentioned in any way during trial" and declined Zydus's request for the district court to take judicial notice of the prosecution history of the '984 patent. Appx134. The district court accepted Plaintiffs' request for oral argument on the two unstricken arguments, which the court heard on December 22, 2020. Appx2097-2100.

On March 22, 2021, the district court issued an Order (Appx67-68) and Opinion (Appx69-131), upholding the validity of all asserted claims of the patents-

in-suit. The district court subsequently corrected minor errors in the original Opinion and, on April 7, 2021, issued a Redacted & Corrected Opinion (hereinafter, "Opinion"). Appx4-66.

In its Opinion, the district court rejected Zydus's OTDP defense because the court concluded that the '219 patent did not qualify as an OTDP reference against the '788 patent, despite the commonly-owned '219 patent being the earlier-expiring patent. Appx60-66. The district court noted that "the Federal Circuit has not . . . had occasion to consider the instant situation[,]" but found that "in light of the Federal Circuit's decisions in *Ezra* and *Breckenridge*, ... the '219 Patent is not a proper reference to invalidate the '788 Patent under the principles of obviousness-type double patenting." Appx64. The district court found that "as in *Ezra* this case does not raise the traditional concern with obviousness-type double patenting of a patent owner extending his exclusive rights to an invention through claims in a later-filed patent that are not patentably distinct from claims in the earlier filed patent.'" Appx64-65 (citing *Ezra*, 909 F.3d at 1374; internal quotation marks omitted). The district court stated that, "[u]nlike in *Gilead*, the granting of a PTA does not present the potential for gamesmanship by inventors to secure a second, later expiring patent for the same invention." Appx65. The district court further stated: "Perhaps more importantly, however, the district Court is swayed by the Federal Circuit's observation that 'a judge-made doctrine' should not be used to

'cut off a statutorily-authorized time extension.' Appx66. Agreeing with Zydus's position would mean just that." *Id.* (citing *Ezra*, 909 F.3d at 1375). The district court expressly declined to consider the parties' arguments on the safe-harbor issue. Appx66.

On April 5, 2021, the district court entered Final Judgment in favor of Plaintiffs. Appx1-3. Zydus timely appealed. Appx4282-4285.

SUMMARY OF THE ARGUMENT

The district court committed reversible error by rejecting Zydus's defense that asserted claims 12 and 20 of the '788 patent are invalid for OTDP in view of claim 22 of the '219 patent.

1. The undisputed record establishes that (a) the '788 and '219 patents are commonly owned, (b) the '788 patent is set to expire more than two years after the '219 patent's expiry, and (c) the asserted claims of the '788 patent are not patentably distinct from claim 22 of the '219 patent. Under these undisputed facts and this Court's precedent in *Gilead* and *AbbVie*, the earlier-expiring '219 patent qualifies as an OTDP reference against the later-expiring '788 patent, and the patentably indistinct asserted claims of the '788 patent are invalid. *See Gilead*, 753 F.3d at 1214-17; *AbbVie*, 764 F.3d at 1373-74.

2. That the '788 patent expires later only on account of having received a § 154(b) PTA does not change this conclusion. Indeed, this Court has

acknowledged that § 154(b) PTAs can cause related patents to expire at different times, which is the type of "problem" that the doctrine of OTDP was designed to correct to "ensure[] that a particular invention (and obvious variants thereof) does not receive an undue patent term extension." *AbbVie*, 764 F.3d at 1373. Furthermore, § 154(b)(2)(B) expressly bars terminally disclaimed patents (*i.e.*, patents whose terms the patentee voluntarily shortened to overcome an OTDP problem) from benefiting from PTAs. Thus, Congress clearly intended OTDP to apply in full force to patents that are otherwise eligible for § 154(b) PTAs.

3. The district court erred as a matter of law in concluding that the '219 patent does not qualify as an OTDP reference against the '788 patent. Appx61-66. In so concluding, the district court failed to appreciate the significance of § 154(b)'s express bar for terminally disclaimed patents, and the intertwined nature of terminal disclaimers and OTDP. Appx65. Instead, the district court wrongly expanded *Ezra*'s narrow OTDP exception, which this Court had carved out specifically for § 156 PTEs, to cover § 154(b) PTAs too. Appx64-66.

a. Unlike § 154(b), § 156 is silent as to the impact of terminal disclaimers. Based on this very textual distinction, this Court has held that Congress must have intended § 156 PTEs to be immune from the effects of terminal disclaimers. *Merck*, 482 F.3d at 1322. *Ezra*, in turn, was merely a "logical extension" of this Court's holding in *Merck*, and similarly concluded that

§ 156 PTEs cannot create OTDP problems. *Ezra*, 909 F.3d at 1373-74. *Ezra*'s narrow exception for § 156 PTE therefore stemmed from § 156's silence regarding terminal disclaimers, in contrast to § 154(b)'s express bar of PTAs for terminally disclaimed patents. The district court's expansion of *Ezra* to shield § 154(b) PTAs from OTDP therefore causes the exception to swallow the rule.

b. The district court was wrongly "swayed by the Federal Circuit's observation [in *Ezra*] that 'a judge-made doctrine' should not be used to 'cut off a statutorily-authorized time extension.'" Appx66 (citing *Ezra*, 909 F.3d at 1375). While that "observation" may have made sense in the specific context of § 156, which does not reference terminal disclaimers or OTDP, it is inapplicable to § 154(b), which specifically contemplates the applicability of OTDP. Under Supreme Court precedent, "where a common-law principle is well established, the courts may take it as given that Congress has legislated with an expectation that the principle will apply except when a statutory purpose to the contrary is evident." *See Arista Networks, Inc. v. Cisco Sys., Inc.*, 908 F.3d 792, 802 (Fed. Cir. 2018) (citations and quotation marks omitted). Given that OTDP is a "well-established," "longstanding doctrine of patent law" that the "Federal courts for over a century have applied" (*Gilead*, 753 F.3d at 1212-13), § 154(b) should be interpreted with understanding that OTDP is applicable to patents that are otherwise eligible for PTAs, particularly given that the statute specifically contemplates its applicability.

The district court therefore erred in expanding *Ezra*'s "observation" regarding § 156 to § 154(b).

c. The district court's opinion was also flawed because it required a showing of "gamesmanship" and found no "potential for gamesmanship" in the context of § 154(b) PTAs. Appx65-66. The invalidity defense of OTDP does not require a showing of gamesmanship, deceptive intent, or any other impropriety or *mens rea*. In any event, the district court's ruling creates significant potential for gamesmanship. Patent applicants are readily capable of tracking which and to what extent applications have faced PTO delays and are therefore eligible for § 154(b) PTAs. Applicants can use that information strategically to orchestrate the timing and applications in which to prosecute their claims to obtain the longest PTAs and avoid OTDP rejections for their most valuable claims. Under the district court's ruling, if an applicant can avoid an OTDP problem during prosecution and thereby avoid the need to file a terminal disclaimer during prosecution, the applicant can then receive the full benefit of a § 154(b) PTA in the resulting patent. If, however, the applicant discloses the OTDP problem during prosecution and files a terminal disclaimer, § 154(b)(2)(B) would then bar the resulting patent from benefiting from any PTA. Such an incongruous result is be contrary to congressional intent in enacting the terminal disclaimer bar to PTAs in

§ 154(b)(2)(B) and contrary to good patent policy that aims to encourage full and open disclosure during prosecution.

4. The district court expressly declined to decide Appellees' rebuttal argument below that a finding of OTDP is foreclosed by the safe-harbor of § 121. Appx66. Because Appellees failed to go forward with evidence sufficient to trigger the safe-harbor's potential application, this Court should reverse the district court's OTDP ruling and need not remand for the district court to make a safe-harbor determination.

ARGUMENT

I. LEGAL STANDARD

A. Legal Framework of Obviousness-Type Double Patenting

"A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for [OTDP]." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). Invalidity based on OTDP "must be proven by clear and convincing evidence." *AbbVie*, 764 F.3d at 1372.

"The prohibition against double patenting is a longstanding doctrine of patent law … based on the core principle that, in exchange for a patent, an inventor must fully disclose his invention and promise to permit free use of it at the end of his patent term." *Gilead*, 753 F.3d at 1212 (discussing basis and history of OTDP, dating back to the 19th century). "Federal courts for over a century have applied

the principles of the doctrine as a means to preserve the public's right to use not only the exact invention claimed by an inventor when his patent expires, but also obvious modifications of that invention that are not patentably distinct improvements." *Id.* at 1212-13.

"While often described as a court-created doctrine, obviousness-type double patenting is grounded in the text of the Patent Act." *AbbVie*, 764 F.3d at 1372. The doctrine was created to "prevent claims in separate applications or patents that do not recite the 'same' invention, but nonetheless claim inventions so alike that granting both exclusive rights would effectively extend the life of patent protection." *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013) (quoting *Perricone*, 432 F.3d at 1373).

"There are two justifications for obviousness-type double patenting." *Id.* "The first is 'to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about.'" *Id.* (quoting *In re Van Ornum*, 686 F.2d 937, 943-44 (C.C.P.A. 1982)); *see also Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1346 (Fed. Cir. 2010) ("[OTDP] prevent[s] the extension of the term of a patent ... by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." (quoting *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985))). "The

second rationale is to prevent multiple infringement suits by different assignees asserting essentially the same patented invention." *Hubbell*, 709 F.3d at 1145.

"Generally, an obviousness-type double patenting analysis entails two steps." *Eli Lilly*, 251 F.3d at 968. "First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences." *Id.* Second, the district court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Id.* "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.*

"[A]n earlier-expiring patent can qualify as an obviousness-type double patenting reference for a later-expiring patent[.]" *Gilead*, 753 F.3d at 1217. The patents' expiration dates—not their issuance dates—are "the determining factor for double patenting inquiries." *Id.* at 1215-16. "Permitting any earlier expiring patent to serve as a double patenting reference for a patent subject to the URAA [*i.e.*, The Uruguay Round Agreements Act of 1994] guarantees a stable benchmark that preserves the public's right to use the invention (and its obvious variants) that are claimed in a patent when that patent expires." *Id.* at 1216. "[U]sing the expiration date as a benchmark in post-URAA cases of obviousness-type double patenting preserves the ability of inventors to use a terminal disclaimer of later-expiring patents to create one expiration date for their term of exclusivity over their

inventions and obvious variants[.]" *Id.* The concepts of OTDP and terminal disclaimers are thus highly intertwined.

"While the ultimate conclusion that a patent is invalid under the doctrine of obviousness-type double patenting is reviewed *de novo*, the underlying factual determinations . . . are reviewed for clear error." *AbbVie*, 764 F.3d at 1372.

1. Effect of Terminal Disclaimers on Double Patenting

A terminal disclaimer is a voluntary and intentional relinquishment by the patentee of "the entire term, or any terminal part of the term, of the patent granted or to be granted." 35 U.S.C. § 253(b). "In cases where … obviousness-type double patenting is present, a terminal disclaimer can preserve the validity of the later-expiring patent by aligning its expiration date with that of the earlier-expiring patent." *Gilead*, 753 F.3d at 1217; *see also Perricone*, 432 F.3d at 1375 ("A terminal disclaimer can indeed supplant a finding of invalidity for double patenting."). "[A] terminal disclaimer 'causes such ... patents to expire together, a situation ... which is tantamount for all practical purposes to having all the claims in one patent.'" *Gilead*, 753 F.3d at 1213-14 (quoting *Application of Braithwaite*, 379 F.2d 594, 601 (C.C.P.A. 1967)). Indeed, terminal disclaimers "'had been provided for in section 253 of the 1952 patent act for that very purpose.'" *Id.* at 1213-14 (quoting *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1280 (Fed. Cir. 1992)).

2. Patent Term Adjustments under § 154(b)

Under the current statute, the term of a U.S. patent normally expires 20 years from the patent's earliest claimed U.S. application filing date, 35 U.S.C. § 154(a)(2); but that was not always the case. "The Uruguay Round Agreements Act of 1994, which became effective on June 8, 1995, changed the term for a U.S. patent from seventeen years from the patent issue date to twenty years from the earliest effective filing date." *See Gilead*, 753 F.3d at 1211; *see also* URAA, Pub. L. No. 103-465, 108 Stat 4809 (1994) (revising 35 U.S.C. § 154 to provide a "term beginning on the date on which the patent issues and ending 20 years from the date on which the application for the patent was filed in the United States"). "Because time spent in the PTO could now eat up part of the patent term, Congress also provided a list of specific situations in which the patent owner could seek an adjustment of the patent's term to offset delays in the PTO." *Chudik v. Hirshfeld*, 987 F.3d 1033, 1035 (Fed. Cir. 2021).

Under the URAA's then-new patent term regime, expiration dates would be calculated from the date of filing, but could be extended by a PTA for up to five years if prosecution was delayed by interference proceedings, secrecy orders, or appellate review of the application. 35 U.S.C. § 154(b) (1994). The new law, however, expressly foreclosed such an extension based on appellate review where the patent was "subject to a terminal disclaimer." *Id.* § 154(b)(2) ("A patent shall

not be eligible for extension under this paragraph if it is subject to a terminal disclaimer due to the issue of another patent claiming subject matter that is not patentably distinct from that under appellate review").

In 1999, Congress partially rewrote § 154 to expand the availability of PTAs to broader categories of PTO delays. *See Mayo Found. for Med. Educ. & Research v. Iancu*, 938 F.3d 1343, 1345 (Fed. Cir. 2019). As part of that amendment, Congress deleted the "subject to a terminal disclaimer" exception language in § 154(b)(2) and rewrote it more broadly as new subparagraph (2)(B), which states as follows:

> No patent the term of which has been disclaimed beyond a specified date may be adjusted under this section beyond the expiration date specified in the disclaimer.

Consolidated Appropriations Act, 2000, Pub. L. No. 106-113, § 4402, 113 Stat 1501, 1501A-559 (1999). Thus, in its current form, "§ 154(b)(2)(B) expressly excludes patents in which a terminal disclaimer was filed from the benefit of a term adjustment for PTO delays." *Merck*, 482 F.3d at 1322.

In 2014, the Federal Circuit upheld the continued viability of applying the doctrine of OTDP to post-URAA patents, despite the URAA's change from a 17-years-from-issuance patent term regime to a 20-years-from-earliest-filing regime. *See AbbVie*, 764 F.3d at 1372-74. In maintaining the longstanding doctrine of OTDP, the Court recognized OTDP's "crucial purpose of … prevent[ing] an

inventor from securing a second, later expiring patent for the same invention"—a "problem [that] still exists" under the URAA. *Id.* As one of just two examples of the persistence of this problem under the URAA, the Court cited § 154(b) PTAs, under which "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO." *Id.* (citing, *inter alia*, 35 U.S.C. § 154(b)). The Court concluded that "[w]hen such situations arise, the doctrine of obviousness-type double patenting ensures that a particular invention (and obvious variants thereof) does not receive an undue patent term extension." *Id.*

3. Patent Term Extensions under § 156

For patents covering FDA-approved drugs, 35 U.S.C. § 156 permits a patentee in certain situations to select a single patent covering the drug to receive a patent term extension (PTE) of up to five years. 35 U.S.C. § 156; *see Merck*, 482 F.3d at 1320-21. Section 156 was codified as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (*i.e.*, the Hatch-Waxman Act) to "restore the value of the patent term that a patent owner loses during the early years of the patent because the product cannot be commercially marketed without approval from a regulatory agency (*e.g.*, Food and Drug Administration approval)." *Ezra*, 909 F.3d at 1369. As such, "[t]he Hatch-Waxman Act provided for patent term extensions in § 156 to partially compensate NDA applicants" for the loss of patent

life during regulatory review. *Biogen Int'l GmbH v. Banner Life Scis. LLC*, 956 F.3d 1351, 1355 (Fed. Cir. 2020).

Unlike § 154(b), however, § 156 does not mention terminal disclaimers. *Merck*, 482 F.3d at 1322. Thus, unlike with a § 154(b) PTA, a terminal disclaimer cannot negate a § 156 PTE, which can operate to extend a patent's term even beyond a terminally disclaimed expiration date. *Id.* at 1322 ("The express prohibition [in § 154(b)] against a term adjustment regarding PTO delays, the absence of any such prohibition [in § 156] regarding Hatch-Waxman extensions, and the mandate in § 156 that the patent term shall be extended if the requirements enumerated in that section are met, support the conclusion that a patent term extension under § 156 is not foreclosed by a terminal disclaimer.").

Correspondingly, in *Ezra*, this Court found "as a logical extension of this court's holding in *Merck*" that the grant of § 156 PTE cannot in-and-of-itself create an OTDP problem, holding that an earlier-expiring patent may not be used as an OTDP reference against a patent that expired later only on account of having received a § 156 PTE. *Ezra*, 909 F.3d at 1375. The Court in *Ezra*, however, did not rule on the impact of a § 154(b) PTA on OTDP.

B. The § 121 Safe-Harbor

35 U.S.C. § 121 contains a safe-harbor provision that can protect a patent from otherwise being invalidated as a result of OTDP if certain requirements are met. Section 121 states as follows:

> If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions. If the other invention is made the subject of a divisional application which complies with the requirements of section 120 it shall be entitled to the benefit of the filing date of the original application. **A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.** The validity of a patent shall not be questioned for failure of the Director to require the application to be restricted to one invention.

35 U.S.C. § 121 (bolding added). The safe-harbor provision, the third sentence of § 121 (in bold, above), "in certain circumstances protects a patent that issues on a divisional application from invalidation based on a related patent that issued on an application as to which a restriction requirement was made, or on an application filed as a result of such a requirement." *G.D. Searle LLC v. Lupin Pharm., Inc.*, 790 F.3d 1349, 1352 (Fed. Cir. 2015).

The Federal Circuit "appl[ies] 'a strict test' for application of section 121, 'given the potential windfall a patent term extension could provide to a patentee.'" *Id.* at 1354 (quoting *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1382 (Fed. Cir. 2003)); *see also Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1353 (Fed. Cir. 2009) (requiring "a strict application of the plain language of § 121"). Among other stringent requirements, a party invoking the § 121 safe-harbor must show that both the challenged patent and the reference patent were filed "as a result of" a restriction requirement. *Boehringer*, 592 F.3d at 1352; *G.D. Searle*, 790 F.3d at 1354.

"Whether the requirements of [35 U.S.C.] § 121 have been satisfied is a question of law that [this Court] address[es] *de novo*." *In re Janssen Biotech, Inc.*, 880 F.3d 1315, 1321 (Fed. Cir. 2018).

II. The Earlier-Expiring '219 Patent Qualifies as a Double Patenting Reference Against the Later-Expiring '788 Patent

The Federal Circuit should reverse the district court's erroneous ruling that claims 12 and 20 of the '788 patent are not invalid for OTDP. The undisputed facts of this case establish:

(a) the '788 and '219 patents are commonly-owned (Appx2244);

(b) the '219 patent is set to expire more than two years before the '788 patent (Appx61); and

(c) claims 12 and 20 of the '788 patent claim the same compound (canagliflozin) as that recited in claim 22 of the '219 patent, and are therefore not patentably distinct, Appx2246-2247, Appx830-832.[5]

Based on these undisputed facts, the district court should have found under this Court's precedent that the earlier-expiring '219 patent qualifies as an OTDP reference against the commonly-owned '788 patent and that claims 12 and 20 of the '788 patent are therefore invalid for OTDP in view of patently indistinct claim 22 of the '219 patent. *See Eli Lilly*, 251 F.3d at 968 ("A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting."); *Gilead*, 753 F.3d at 1215-17 (" [A]n earlier-expiring patent can qualify as an obviousness-type double patenting reference for a later-expiring patent[.]"); *AbbVie*, 764 F.3d at 1374 ("We now make explicit what was implicit in *Gilead*: the doctrine of obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates.").

That the '788 patent expires later only on account of having received a § 154(b) PTA is of no moment. After all, "it is a bedrock principle of our patent system that when a patent expires, the public is free to use not only the same invention claimed in the expired patent but also obvious or patentably indistinct

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[5] "A claim cannot be patentably distinct over anticipatory subject matter." *Geneva*, 349 F.3d at 1383.

modifications of that invention … [a]nd that principle is violated when a patent expires and the public is nevertheless barred from practicing obvious modifications of the invention claimed in that patent because the inventor holds another later-expiring patent with claims for obvious modifications of the invention." *Gilead*, 753 F.3d at 1214. Indeed, in *AbbVie*, this Court sustained the continued viability of applying the OTDP doctrine to post-URAA patents, recognizing that even in the post-URAA context "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO." *AbbVie*, 764 F.3d at 1373 (citing, *inter alia*, 35 U.S.C. § 154(b)). The Court concluded that "[w]hen such situations arise, the doctrine of obviousness-type double patenting ensures that a particular invention (and obvious variants thereof) does not receive an undue patent term extension." *Id.* Thus, *AbbVie* confirmed OTDP's applicability to post-URAA patents due, in part, to its applicability to § 154(b) PTAs.

Contrary to the district court's ruling, § 154(b) does not exempt a patent with a PTA from complying with the rule against OTDP, but rather its statutory text compels compliance. The statute expressly prohibits patent from receiving the benefits of PTAs if they are subject to terminal disclaimers, which exist for the purpose of remedying OTDP problems. 35 U.S.C. § 154(b)(2)(B) ("No patent the term of which has been disclaimed beyond a specified date may be adjusted under

this section beyond the expiration date specified in the disclaimer."); *Gilead*, 753 F.3d at 1213-14 ("[O]bviousness-type double patenting could be overcome by filing a terminal disclaimer, which had been provided for in section 253 of the 1952 patent act for that very purpose." (quoting *Gen. Foods*, 972 F.2d at 1280)).

By enacting the terminal disclaimer bar to PTAs in § 154(b), Congress was clearly more concerned about guaranteeing the public the right to use a claimed invention and its obvious variants upon patent expiration than it was about guaranteeing a patentee additional patent term due to PTO delay. *See Gilead*, 753 F.3d at 1214-15 ("[T]he primary ill avoided by enforcement of the double patenting doctrine is restriction on the public's freedom to use the invention claimed in a patent and all obvious modifications of it after that patent *expired*." (emphasis in original)); *Longi*, 759 F.2d at 894 ("Since the second patent would expire simultaneously with the first, this use of a terminal disclaimer is consistent with the policy that the public should be free to use the invention as well as any obvious modifications at the end of the patent's term.")

The '219 patent's qualification as an OTDP reference against the '788 patent is entirely consistent with the statutory text of § 154(b) and clear congressional intent for OTDP to remain broadly applicable notwithstanding any PTO delays that might otherwise qualify a patent for a PTA. The district court should be reversed.

A. The District Court Failed to Appreciate the Significance of § 154(b)'s Express Bar to Terminally Disclaimed Patents Receiving the Benefit of Patent Term Adjustments

In ruling that the '219 patent did not qualify as an OTDP reference against the '788 patent, the district court relied principally on this Court's holding in *Ezra*, which carved out a narrow exception to OTDP for patents with expiration dates that were extended as a result of § 156 PTEs. Appx61-63. There, the Federal Circuit held that the grant of a § 156 PTE could not cause a patent to become invalid for OTDP. *Ezra*, 909 F.3d at 1374-75 (holding that an earlier-expiring patent did not qualify as an OTDP reference where the challenged patent expired later only on account of having received a § 156 PTE). But there is no basis to extend *Ezra*'s narrow exception for § 156 PTEs to § 154(b) PTAs.

1. Sections 154(b) and 156 Are Not Analogous

The district court wrongly treated § 154(b) as analogous to § 156. Appx64-66. As this Court has recognized, they are very different statutes, particularly as they concern OTDP. *See Merck*, 482 F.3d at 1322. For example, § 154(b) expressly acknowledges the rule against OTDP by barring the grant of a PTA beyond a terminally disclaimed expiration date. *Id.*; *see* 35 U.S.C. § 154(b)(2)(B). By contrast, § 156 is silent as to terminal disclaimers or other issues related to OTDP. *See Merck*, 482 F.3d at 1322 (comparing 35 U.S.C. §§ 154(b)(2)(B) and 156). These statutes should therefore have very different OTDP outcomes.

In *Merck*, this Court addressed the impact of a terminal disclaimer, filed to overcome an OTDP rejection, on a § 156 PTE. *Id.* Applying rules of statutory interpretation, this Court concluded that by expressly referring to terminal disclaimers in § 154(b) but not in § 156, Congress clearly intended for terminal disclaimers to bar patents from receiving the benefit of PTAs based on PTO delay but not prevent patents from receiving PTEs due to FDA delay. *Merck*, 482 F.3d at 1322. In support of that conclusion, this Court observed that "an action that is expressly required under one federal rule but not included among the enumerated actions from another federal rule indicates that the action is not a requirement of the later federal rule." *Id.* (citing *Leatherman v. Tarrant County Narcotics Intelligence & Coordination Unit*, 507 U.S. 163, 168 (1993)).

Whereas Congress specifically wrote § 156 to provide a branded drug patentee with freedom to select which patent in its portfolio would receive the PTE, regardless of any terminal disclaimers, Congress did not provide such flexibility in § 154(b) for PTAs. *See id.* at 1323 ("Congress chose not to limit the availability of a [§ 156] patent term extension to a specific parent or continuation patent but instead chose a flexible approach which gave the patentee the choice. We see no reason why a patentee should not have the same choice as between an earlier patent and a later patent related by a terminal disclaimer.") Rather, Congress expressly intended that patentees not benefit from PTAs when their own

patents are patentably indistinct from one another. *See* 35 U.S.C. § 154(b)(2)(B). In contrast, § 156's silence as to terminal disclaimers reflects Congress's intent that PTEs be granted and enforced regardless of any terminal disclaimers. *Merck*, 482 F.3d at 1322-24.

Ezra was merely a "logical extension of this court's holding in *Merck*." *Ezra*, 909 F.3d. at 1368; *see also id.* at 1373 ("We conclude, as a logical extension of our holding in *Merck & Co. v. Hi-Tech Pharmacal Co.*, that obviousness-type double patenting does not invalidate a validly obtained PTE in such a scenario."). But there is no parallel logical basis for extending this Court's holding in *Ezra* for § 156 PTEs to this case involving § 154(b) PTAs.

Whereas the *Merck* panel found that a terminal disclaimer filed to resolve an OTDP problem could not negate a PTE in light of the aforementioned difference in the statutory texts of § 154(b) and § 156, the *Ezra* panel found that a PTE could not in-and-of-itself create an OTDP problem. *Ezra*, 909 F.3d at 1373-74. Thus, this key textual distinction between § 154(b) and § 156 led the Court in *Ezra* to recognize a narrow exception to the rule against OTDP specifically for § 156 PTEs. *Id.* To then extend *Ezra*'s narrow exception for § 156 PTEs to apply to § 154(b) PTAs—as the district court did below—defies the very logic for creating the PTE exception in the first place and causes the exception to swallow the rule.

The district court failed to appreciate this important textual distinction between § 154(b) and § 156 or the congressional intent reflected in § 154(b)(2)(B). Instead, the district court—in a single footnote—focused only on how the two statutes were discussed in the context of *Ezra* (concerning a § 156 PTE) instead of on how § 154(b) should be interpreted and applied in the context of this case. Appx65 n.45.

2. Double Patenting and Terminal Disclaimers Are Fundamentally Intertwined

In a similar vein, the district court failed to appreciate the role of terminal disclaimers with respect to OTDP. The district court concluded its footnote by stating: "But even if the role of a terminal disclaimer affected the obviousness-type double patenting analysis, Zydus does not contend that a terminal disclaimer was required here." Appx65 n.45. The district court's statement is a non sequitur and evinces a lack of an appreciation of the intertwined relationship between terminal disclaimers and OTDP. *See, e.g.*, *Merck*, 482 F.3d at 1323 ("The purpose of the terminal disclaimer — to prevent extension of patent term for subject matter that would have been obvious over an earlier filed patent…"); *Gilead*, 753 F.3d at 1213-14 ("'[O]bviousness-type double patenting could be overcome by filing a terminal disclaimer, which had been provided for in section 253 of the 1952 Patent Act for that very purpose'" (quoting *Gen. Foods*, 972 F.2d at 1280)); *Perricone*,

432 F.3d at 1375 ("A terminal disclaimer can indeed supplant a finding of invalidity for double patenting.").

Zydus of course contends that the asserted claims of the '788 patent are invalid for OTDP. Contrary to the district court's footnote, however, a terminal disclaimer is never "required," and that is not even the operative question in dispute.[6] What matters in § 154(b) for purposes of deciding this case is whether Congress, by mandating that terminal disclaimers cut off the benefit of PTAs, intended the rule against OTDP to apply to patents extended by PTAs. By expressly restricting PTAs based on terminal disclaimers, Congress clearly intended the longstanding doctrine of OTDP to apply in full force to such patents.

Indeed, in *Ezra*, the appellee Mitsubishi (which is the same lead Appellee in this appeal) argued successfully to this Court: "*Merck* holds that a terminal disclaimer filed to overcome an OTDP rejection does not foreclose term restoration under Section 156. It logically follows that, if a terminal disclaimer does not

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[6] If the claims are deemed invalid for OTDP, Appellees may opt to file a terminal disclaimer with the PTO to "supplant [the] finding of invalidity for double patenting[,]" but that would be Appellees' voluntary, strategic choice. *See Perricone*, 432 F.3d at 1375. For instance, Appellees could opt not to terminally disclaim and allow claims 12 and 20 to remain invalid, in favor of the patenet's unasserted claims that could still potentially benefit from the 1,079-day PTA. The Court need not consider what Appellees might do, nor issue an advisory opinion on the potential impact of a hypothetical terminal disclaimer. *See id.* at 1375 (declining to "make [a] determination about the retrospective effect of … a [hypothetical] terminal disclaimer" that had not yet been filed).

foreclose a term extension, neither can OTDP."[7] So, too, here: If a terminal disclaimer ***does foreclose*** a term extension, like it does in § 154(b), then so too can OTDP.

3. Section 154(b) Does Not Absolutely "Guarantee" a Patent Term Adjustment in the Event of Patent Office Delay

Contrary to Appellees' position below, § 154(b) does not absolutely "guarantee" a PTA in the event of PTO delay. Rather, § 154(b)(2) expressly limits the "guarantee" based on certain circumstances, including the filing of a terminal disclaimer. 35 U.S.C. § 154(b)(2)(B). That is, Congress intended patentably indistinct patents to expire at the same time, notwithstanding any PTO delay. Appellees chose to file separate applications for patentably indistinct inventions, and will receive the full statutory term for the earlier-expiring '219 patent, whose prosecution was not delayed by the PTO.

In ruling that PTAs could not create OTDP problems, the district court committed legal error by either disregarding or misconstruing Congress's reference to terminal disclaimers in § 154(b)(2)(B). The district court's ruling frustrates Congress's intent that commonly-owned, patentably indistinct patents expire at the

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[7] Appellees' Corrected Brief Regarding the "One Patent Per Period" and Double Patenting Issues Raised by Ezra, at 28, *Novartis AG v. Ezra Ventures LLC,* Nos. 17-2284 & 17-2286, 2017 WL 6997987 (Fed. Cir. Jan. 9, 2019) (internal citations omitted).

same time, notwithstanding any PTO delay. Had the application for the '788 patent instead been rejected for OTDP during prosecution, the applicant could have obviated such a rejection by filing a terminal disclaimer, which indisputably would have barred the '788 patent from receiving the benefit of the PTA under the plain language of § 154(b)(2)(B). But that is not what happened.

Rather, the OTDP problem between the '788 and '219 patents did not become apparent until this civil litigation. It would defy logic to permit patentably indistinct claims to benefit from a PTA simply because their OTDP problem was not discovered until after the patents were already granted. As opposed to such an incongruous result, invalidity grounds like OTDP should be treated consistently during prosecution and post-issuance. *See, e.g., Perricone*, 432 F.3d at 1375 ("[T]he pre-issuance timing requirement of a terminal disclaimer to overcome a double patenting rejection does not dictate a prohibition on post-issuance terminal disclaimers."); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371-72 (Fed. Cir. 1999) (holding that the enablement analysis is the same in prosecution and post-issuance litigation).

The district court improperly considered § 154(b) only through the lens of *Ezra*, which carved out a narrow exception to OTDP for § 156 PTEs. Through that misguided analysis, the district court extended *Ezra*'s narrow exception to swallow

the well-established, broadly applicable rule against OTDP. The district court should be reversed.

B. The District Court Was Unduly "Swayed" by the Inapplicable "Observation" in *Ezra* That "a Judge-Made Doctrine" Should Not "Cut Off a Statutorily-Authorized Time Extension"

In rejecting Zydus's OTDP challenge, the district court was unduly "swayed by the Federal Circuit's observation [in *Ezra*] that 'a judge-made doctrine' should not be used to 'cut off a statutorily-authorized time extension.'" Appx66 (quoting *Ezra*, 909 F.3d at 1375). That "observation" in *Ezra* is inapplicable here and, as broadly applied by the district court, is contrary to Supreme Court precedent.

1. Congress Intended Obviousness-Type Double Patenting to Broadly Apply to Commonly-Owned Patents Having Different Expiration Dates, with Only Narrow Exceptions That Are Inapplicable Here

Extending *Ezra*'s narrow exception for § 156 PTEs to § 154(b) PTAs, as the district court has done, is contrary to this Court's precedent. *Ezra*'s stated concern about permitting "a judge-made doctrine [to] cut off a statutorily-authorized time extension"—while it perhaps makes sense in the context of § 156—is plainly inapplicable to § 154(b) in light of the differences between the statutes.

As this Court has recognized, "Congress is understood to legislate against a background of common-law adjudicatory principles." *Arista*, 908 F.3d at 802 (quoting *Astoria Fed. Sav. & Loan Ass'n v. Solimino*, 501 U.S. 104, 108 (1991)). "Thus, where a common-law principle is well established, the courts may take it as

given that Congress has legislated with an expectation that the principle will apply except 'when a statutory purpose to the contrary is evident.'" *Id.* (quoting *Isbrandtsen Co. v. Johnson*, 343 U.S. 779, 783 (1952)).

In that regard, the federal courts recognize many well-established judge-made doctrines that can materially limit statutorily authorized patent rights or defenses. For example, notwithstanding the statutory mandates that "[a] patentee shall have remedy by civil action for infringement of his patent" (35 U.S.C. § 281) and that noninfringement and invalidity "shall be defenses in any action involving the validity or infringement of a patent" (35 U.S.C. § 282(b)), courts have limited the availability of such remedies and defenses based on a variety of well-established, longstanding common-law doctrines. *See, e.g., SCA Hygiene Prod. Aktiebolag v. First Quality Baby Prod., LLC*, 137 S. Ct. 954, 967 (2017) (recognizing equitable estoppel as a defense to patent infringement); *Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U.S. 313, 335 (1971) (recognizing *res judicata* and collateral estoppel in patent cases); *Mars Inc. v. Nippon Conlux Kabushiki-Kaisha*, 58 F.3d 616, 620 (Fed. Cir. 1995) (upholding the application of claim preclusion in a patent case).

Indeed, the Supreme Court reaffirmed this legal principle just last week, when it upheld the continued viability of the common-law doctrine of assignor estoppel in patent cases. *See Minerva Surgical, Inc. v. Hologic, Inc.*,

594 U.S. ____, No. 20-440, slip op. at 10 (2021). Recognizing "a whole host of common-law preclusion doctrines" that apply in patent cases, the Court held that eliminating the common-law doctrine of assignor estoppel "would subvert congressional design" because "Congress legislates against a background of common-law adjudicatory principles, and it expects those principles to apply except when a statutory purpose to the contrary is evident." *Id.* (quotation marks and citation omitted)).[8]

It is beyond dispute that OTDP is a well-established common-law doctrine that the federal courts have applied since long before Congress first enacted § 154(b). "While often described as a court-created doctrine," OTDP is "a bedrock principle of our patent system," a "longstanding" common-law doctrine "grounded in the text of the Patent Act." *AbbVie*, 764 F.3d at 1372 (discussing OTDP's roots in § 101); *Gilead*, 753 F.3d at 1212-14 (discussing history of OTDP, dating back to 19th century case law). Although judge-created, the rule against OTDP can negate the validity of patents that would otherwise be valid under the express terms of the

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[8] While the Supreme Court did place some limits on the applicability of assignor estoppel, slip op. at 14 ("Assignor estoppel should apply only when its underlying principle of fair dealing comes into play."), that has no impact on this case. As this Court already held in *AbbVie*, applying OTDP to patents with § 154(b) PTAs "ensures that a particular invention (and obvious variants thereof) does not receive an undue patent term extension" and solves a "crucial purpose of the doctrine … to prevent an inventor from securing a second, later expiring patent for the same invention." *AbbVie*, 764 F.3d at 1373.

Patent Act. Accordingly, the Patent Act should be interpreted with the understanding that when Congress wrote and amended it, including § 154(b), Congress embraced the common-law rule against OTDP with the knowledge and foresight that the federal courts would continue to apply it, unless clearly prohibited by statute. Nothing in § 154(b) excludes or limits OTDP. To the contrary, the statute expressly contemplates the doctrine's applicability to patents subject to PTAs by limiting PTAs based on terminal disclaimers. 35 U.S.C. § 154(b)(2)(B).

Although Congress "shed little light on exactly why [it] enacted" the terminal disclaimer statute, 35 U.S.C. § 253(b), this Court and its predecessor have since recognized terminal disclaimers to have been authorized to be an effective means for removing OTDP problems. *See Application of Robeson*, 331 F.2d 610, 613-15 (C.C.P.A. 1964) ("[T]he only real objection to granting appellant's application is an extension of the monopoly. The terminal disclaimer, which Congress has expressly provided, removes any danger of such result[.]); *Gilead*, 753 F.3d at 1213-14 ("'[O]bviousness-type double patenting could be overcome by filing a terminal disclaimer, which had been provided for in section 253 of the 1952 Patent Act for that very purpose'" (quoting *Gen. Foods*, 972 F.2d at 1280)).

Congress, too, has since acknowledged the role of terminal disclaimers in obviating OTDP problems. For example, in connection with enacting the Patent

Law Amendments Act of 1984, Congress recognized OTDP's applicability and the use of terminal disclaimers to remove OTDP problems:

> The Committee expects that the Patent and Trademark Office will reinstitute in appropriate circumstances the practice of rejecting claims in commonly owned applications of different inventive entities on the ground of double patenting. This will be necessary in order to prevent an organization from obtaining two or more patents with different expiration dates covering nearly identical subject matter. In accordance with established patent law doctrines, double patenting rejections can be overcome in certain circumstances by disclaiming the terminal portion of the term of the later patent, thereby eliminating the problem of extending patent life.

Section-by-Section Analysis: Patent Law Amendments of 1984, 130 Cong. Rec. 28065, 28071 (1984), *reprinted in* 1984 U.S.C.C.A.N. 5827, 5834 (capitalization revised for clarity of reading).

Nothing in the Patent Act suggests that Congress intended to reduce the applicability of OTDP against patents that are otherwise eligible for § 154(b) PTAs. Congress enacted § 154(b) in 1994 to authorize PTAs except to the extent a patent was "subject to a terminal disclaimer," and then amended § 154(b) in 1999 to expand the availability of PTAs while still maintaining terminal disclaimers as a barrier to receiving their benefit. *See supra* at 25-26. Congress was plainly aware at the time of the courts' longstanding applications of the rule against OTDP and terminal disclaimers to resolve OTDP problems. Had Congress intended to exempt patents with PTAs from having to comply with the rule against OTDP, it

could have done so, but clearly it did not. *See Lorillard v. Pons*, 434 U.S. 575, 580 (1978) ("Congress is presumed to be aware of an administrative or judicial interpretation of a statute and to adopt that interpretation when it re-enacts a statute without change.").

Unlike § 156, where Congress's comparative silence about terminal disclaimers in the statute evinced "a statutory purpose to the contrary" of allowing terminal disclaimers to constrain PTEs, § 154(b) is unequivocal that terminal disclaimers can constrain PTAs. *See Arista*, 908 F.3d at 802; *Merck*, 482 F.3d at 1322 ("§ 154(b)(2)(B) expressly excludes patents in which a terminal disclaimer was filed from the benefit of a term adjustment for PTO delays. There is no similar provision that excludes patents in which a terminal disclaimer was filed from the benefits of Hatch-Waxman extensions.").

Furthermore, beyond § 156 PTEs, there are other statute-based exceptions to the applicability of OTDP, such as patents protected by the safe-harbor of 35 U.S.C. § 121,[9] and situations involving both pre-URAA and post-URAA patents.[10]

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[9] *See supra* § I.C.

[10] *See Novartis Pharm. Corp. v. Breckenridge Pharm. Inc.*, 909 F.3d 1355, 1366-67 (Fed. Cir. 2018) (holding that a later-issuing, earlier-expiring post-URAA patent was not a proper OTDP reference against the challenged pre-URAA patent because the post-URAA patent expired earlier only due to the intervening change in patent term law imposed by the URAA).

None of these exceptions apply here though.[11] To the contrary, by expressly imposing terminal disclaimers as a bar to patents receiving the benefit of PTAs, Congress embraced the applicability of OTDP to such patents. Absent anything in the Patent Act that constrains the reach of OTDP to patents with § 154(b) PTAs, the Court should assume that Congress intended the doctrine to apply to such patents in full force, without restriction.

2. The "Observation" in *Ezra* Arose from a Wholly Unrebutted, One-Sided Argument and Should Not Be Broadly Applied

In *Ezra*, as an ancillary basis for rejecting the appellant's argument that a § 156 PTE could create an OTDP problem, the Court noted that it had previously "described obviousness-type double patenting as a 'judge-made doctrine' that is intended to prevent extension of a patent beyond a 'statutory time limit.'" *Ezra*, 909 F.3d at 1375 (quoting *In re Berg*, 140 F.3d 1428, 1431–32 (Fed. Cir. 1998)). The Court "declined" to agree with the appellant because to do so "would mean that a judge-made doctrine would cut off a statutorily-authorized time extension." *Ezra*, 909 F.3d at 1375.

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[11] *See infra* § III.

This paragraph in the *Ezra* opinion, however, arose from the appellee's[12] wholly unrebutted argument that "no 'judicially crafted exception' can subvert the 'statutory text'; 'so long as the [statutory] elements are met,' the applicant is entitled to a patent term extension." Appellees' Corrected Brief Regarding the "One Patent Per Period" and Double Patenting Issues Raised by Ezra, at 28, *Novartis AG v. Ezra Ventures LLC,* No. 17-2284, 2017 WL 6997987 (Fed. Cir. Jan. 9, 2018) (citing *United States v. Gilbert*, 430 F.3d 215, 216, 218-19 (4th Cir. 2005).

The proposed "judicially crafted exception" in *Gilbert*, however, was the polar opposite of the well-established, more-than-century-old common-law doctrine of OTDP. In *Gilbert*, a criminal defendant attempted "to overturn his conviction as a felon in possession of a firearm by invoking an affirmative defense of 'innocent possession'" that was "wholly absent from the statutory text." *Gilbert*, 430 F.3d at 216. In rejecting the defense, the Fourth Circuit reasoned that there was no "common law" basis for an "innocent possession" defense, and the closest common law defense of "justification" was to be construed "very narrowly." *Id.* at 219 ("Thus, unlike justification, the innocent possession defense could create an exception that swallows the rule."). For whatever reason, the

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[12] The appellee in *Ezra* was Mitsubishi Tanabe Pharma Corporation, the lead Appellee in the instant appeal.

appellant in *Ezra* never directly responded to the appellee's reliance on *Gilbert* or argument that no judicially crafted exception can subvert the statutory text.[13]

In stark contrast to the essentially novel proposed criminal defense in *Gilbert*, "[t]he prohibition against double patenting is a longstanding doctrine of patent law" that "[f]ederal courts for over a century have applied . . . as a means to preserve the public's right to use not only the exact invention claimed by an inventor when his patent expires, but also obvious modifications of that invention that are not patentably distinct improvements." *Gilead*, 753 F.3d at 1212-13. Thus, the panel's "observation" in *Ezra* was made in response to a one-sided, incomplete picture of the case law, and should not be applied broadly outside of the specific circumstances of that case. While the panel's reasoning made sense in the context of § 156, which does not mention OTDP, the district court erred in adopting the "observation" as an essentially all-encompassing statement of the law and extending it to § 154(b) despite the statute's unequivocal recognition of OTDP.

C. Public Policy Favors Applying the Rule Against Double Patenting to Patents with § 154(b) Patent Term Adjustments

In rejecting Zydus's OTDP defense, the district court found that, "[u]nlike in *Gilead*, the granting of a PTA does not present the potential for gamesmanship by

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[13] *See generally* Reply Brief of Defendant-Appellant Ezra Ventures LLC (ECF No. 74), at 28, *Novartis AG v. Ezra Ventures LLC,* No. 17-2284 (Fed. Cir. Jan. 24, 2018).

inventors to secure a second, later expiring patent for the same invention." Appx65 (citing *Ezra*, 909 F.3d at 1374-75). As an initial matter, "gamesmanship" is not a requisite element of an OTDP defense. Furthermore, allowing a patent to benefit from a PTA while simultaneously shielding it from an OTDP challenge from a related patent, as the district court has done, presents the opportunity for gamesmanship.

1. Double Patenting Has No "Gamesmanship" Requirement

Contrary to the district court's suggestion, "gamesmanship" is not a requisite element of OTDP. OTDP does not require a showing of an inappropriate prosecution strategy, deceptive intent, or any other mental state. In *AbbVie*, this Court expressly rejected the notion that OTDP's main goal is to "curb abuses" in patent prosecution strategy. *AbbVie*, 764 F.3d 1373. Rather, the Court held that OTDP "is designed to prevent an inventor from securing a second, later expiring patent for the same invention" and "ensures that the public gets the benefit of the invention after the original period of monopoly expires." *Id.* To that end, the Court noted that this "problem still exists" in the post-URAA world, citing § 154(b) PTAs as an example of a problematic situation. *Id.* The Court concluded that "[w]hen such situations arise, the doctrine of obviousness-type double patenting ensures that a particular invention (and obvious variants thereof) does not receive an undue patent term extension." *Id.* Thus, applying OTDP to § 154(b)

PTA furthers the doctrine's key public policy goals, regardless of any gamesmanship.

In addition, the "second justification for obviousness-type double patenting—harassment by multiple assignees"—can occur regardless of any gamesmanship or ill intent. *In re Fallaux*, 564 F.3d 1313, 1319 (Fed. Cir. 2009).

Moreover, requiring an element of subjective intent to prove OTDP would unnecessarily increase the costs of litigation by impelling defendants to take fact discovery of patent prosecutors and others to discern the patentees' specific patenting strategies, much of which would likely be shielded by privilege or lead to extensive discovery motion practice. Unlike equitable defenses like inequitable conduct, unclean hands, and waiver, OTDP is not grounded in equity and the specific patentee's subjective intent should be irrelevant. Rather, OTDP is "grounded in public policy" "to preserve that bargained-for right held by the public" so that the "public is free to use" a patented invention and patentably indistinct variants upon expiration. *AbbVie*, 764 F.3d at 1372; *Gilead*, 753 F.3d at 1214.

2. Allowing a Patent to Benefit from a Patent Term Adjustment While Simultaneously Shielding It from an Double Patenting Challenge Is Contrary to Public Policy

Relying on *Ezra* and *Breckenridge*, the district court concluded that the situation presented in this case does not present any "potential for gamesmanship." Appx64-65. That is wrong.

Unlike in the situations presented in *Ezra* (§ 156 PTEs) and *Breckenridge* (intervening change in law), a patent applicant is generally aware of PTO delays during prosecution and therefore can readily determine during prosecution whether and to what extent a resulting patent will qualify for a § 154(b) PTA and plan accordingly. Section 154(b) lays out how PTAs should be calculated, which a patent practitioner can readily track during prosecution. 35 U.S.C. § 154(b)(1); *see, e.g., Pfizer, Inc. v. Lee*, 811 F.3d 466, 468-69 (Fed. Cir. 2016); *Novartis AG v. Lee*, 740 F.3d 593, 595-97 (Fed. Cir. 2014). Thus, during prosecution, a reasonable applicant should be well-aware of which applications in a patent family are most likely to receive the longest PTAs, and can use that information to orchestrate prosecution in a manner that selectively obtains PTAs and avoids OTDP rejections for specific applications to maximize the terms of the desired patents beyond what the applicant is entitled to due to OTDP problems.

The PTO's Manual of Patent Examining Procedure ("MPEP") provides guidance for how examiners should deal with OTDP issues between co-pending

applications. *See* MPEP § 804(I)(B), at 800-26–28 (9th ed., 10.2019 rev., June 2020).[14] The MPEP instructs examiners to issue a "provisional" OTDP rejection in each co-pending application, to make the "applicant aware of the potential double patenting problem if one of the applications became a patent." *Id.* at 800-26. The MPEP further provides that where "both applications are actually filed on the same day, or are entitled to the same earliest effective filing date[,] … the provisional nonstatutory double patenting rejection made in each application should be maintained until the rejection is overcome." *Id.* § 804(I)(B)(1)(b)(ii), at 800-27–28. The applicant can overcome such a rejection "by either filing a reply showing that the claims subject to the provisional nonstatutory double patenting rejections are patentably distinct or filing a terminal disclaimer in the pending application." *Id.* Thus, where claims in co-pending applications are not patentably distinct, an applicant needs to either file a terminal disclaimer or amend or cancel the claims. Because a terminal disclaimer during prosecution will cut off any PTA that the resulting patent might otherwise receive, there can be considerable value in avoiding OTDP rejections (provisional or otherwise) and terminal disclaimers during prosecution.[15]

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[14] Available at https://www.uspto.gov/web/offices/pac/mpep/mpep-0800.pdf.

[15] Indeed, the pharmaceutical legal community has written much on strategies for avoiding OTDP rejections and terminal disclaimers during prosecution and maximizing PTAs. *See, e.g.*, Rob Sahr & Kady Bruce, *Protecting pharmaceutical*

Under the district court's ruling, a patent applicant has even greater incentive to orchestrate prosecution in a manner that prevents the PTO from recognizing OTDP problems during prosecution and thereby avoids terminal disclaimers. For example, an applicant could strategically stagger the filing of its patentably indistinct continuing applications—as Appellees did here by filing the application for the '219 patent only after the '788 patent had already issued—which would avoid the risk of OTDP rejections in the earlier application based on the patentably indistinct continuing applications and the resulting need to file a terminal disclaimer during prosecution. Such a strategy would allow the resulting patent to benefit from a PTA and be shielded from OTDP challenge from its patentably indistinct family members during post-issuance litigation.

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exclusivity: Avoiding the hidden dangers of double patenting, Pharmaceutical Commerce, Jan. 27, 2021, available at https://www.pharmaceuticalcommerce.com/view/protecting-pharmaceutical-exclusivity-avoiding-the-hidden-dangers-of-double-patenting (last visited July 6, 2021); Leslie A. McDonell & Christina M. Rodrigo, *Practice Tips for Avoiding Terminal Disclaimers and Maintaining PTA*, Landslide, Nov./Dec. 2017, available at https://www.finnegan.com/en/insights/articles/practice-tips-for-avoiding-terminal-disclaimers-and-maintaining-pta.html (last visited July 6, 2021); Alicia Russo, *Defeating Double Patenting: Strategies For Maximizing Patent Term*, American Conference Institute, at 36-38 (Feb. 27, 2017), available at https://www.americanconference.com/life-sciences-patents/wp-content/uploads/sites/1728/2017/02/Day1_4.45_Lowe.Russo_.Todaro.Combined.pdf (last visited July 6, 2021); Courtenay C. Brinckerhoff, *Patent Term Adjustment and Double Patenting*, PharmaPatents Blog (Mar. 4, 2014), available at https://www.foley.com/en/insights/publications/2014/03/patent-term-adjustment-and-double-patenting (last visited July 6, 2021).

On a similar note, the district court's ruling also puts immense pressure on the PTO to catch each and every potential OTDP problem during prosecution. If the PTO inadvertently overlooks a true OTDP problem based on a related patentably indistinct patent and the application issues with a § 154(b) PTA, the resulting patent would then be immune from an OTDP challenge based on that same patentably indistinct patent.

To allow a PTA to immunize a granted patent against an OTDP challenge based on a patentably indistinct related patent, as the district court seems to have done, would incentivize applicants to serially file applications for patentably indistinct inventions, with the hope that the PTO will miss the OTDP problems[16] and thereby allow further extension of the patentably indistinct inventions' term though additional PTAs. Such a result would be directly contrary to the "bedrock principle" of OTDP that, upon patent expiration, "the public is free use" to the patented invention and its patentably indistinct variants, and contrary to "the fundamental reason for the rule of [OTDP] … *to prevent unjustified timewise extension of the right to exclude* granted by a patent no matter how the extension is

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[16] "The examiners of the Patent Office are highly qualified for the work performed by them, but they are not infallible, and it is conceivable that sometimes relevant references may be overlooked by them." *In re Lee*, 139 F.2d 717, 720 (C.C.P.A. 1943). As evidenced by the plethora of cases in which patents have been found invalid for OTDP in post-issuance litigation, the PTO may overlook OTDP problems during prosecution from time to time.

brought about." *Gilead*, 753 F.3d at 1214; *Boehringer*, 592 F.3d at 1347-48 (emphasis in original; quotation marks and citation omitted).

Congress could not have intended to allow patent applicants to so easily circumvent the express terminal disclaimer bar to PTAs in § 154(b)(2)(B) simply by timing prosecution in a way that prevents the PTO from discovering OTDP problems or by lucking out with the PTO not noticing an OTDP problem during prosecution.

Along those same lines, the district court's ruling is contrary to public policy because it creates a major incentive for patentees to conceal potential OTDP problems from the PTO in hopes of obtaining a valuable PTA that could otherwise be unavailable. If a patent applicant is aware of a potential OTDP problem based on a related patent but conceals it to avoid filing a terminal disclaimer during prosecution, the applicant can obtain a highly valuable § 154(b) PTA of the resulting patent and the resulting patent would then be immune to being challenged based on that OTDP problem in a subsequent litigation. If, however, the applicant were to disclose the OTDP issue to the examiner during prosecution, the applicant could need to file a terminal disclaimer during prosecution to resolve the OTDP problem, which would then bar the resulting patent from receiving the benefit of a PTA by operation of § 154(b)(2)(B). Congress could not have intended such an incongruous result that discourages open disclosure to the PTO. *See* 37 C.F.R.

§ 1.56 (establishing duty to disclose information material to patentability to the PTO); 35 U.S.C. § 2(b) (conveying to the PTO the power to promulgate regulations not inconsistent with law).

The incentive to avoid terminal disclaimers during prosecution is even more pronounced in the pharmaceutical field, where the initial patent applications for a new drug are typically filed many years before the New Drug Application ("NDA") is filed and approved.[17] Applicants for new drug patents therefore often have little reason to rush to get their application granted. Instead, they benefit significantly from PTO delay since it accumulates PTA at the end of the patents' terms, when the drugs are on the market and the value of the patents is at its highest because they can be used to stave off potential competition.

With regard to *Ezra*, the Court there found "no potential gamesmanship issue" in a patentee's selection of which one patent covering its FDA-approved drug should receive the § 156 PTE. *Ezra*, 909 F.3d at 1374. Unlike with § 154(b), "Congress chose not to limit the availability of a patent term extension to a specific parent or continuation patent but instead chose a flexible approach which gave the patentee the choice." *Id.* at 1369-70 (quoting *Merck*, 482 F.3d at 1323). As the

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[17] For example, in this case, Appellees filed their initial patent application for canagliflozin in 2005, but did not file their NDA until 2012 or for receive FDA-approval for INVOKANA® until 2013. Appx6; Appx8-9; Appx1732 (trial testimony of Dr. Williams).

Court recognized in *Merck*, "[t]he legislative history of § 156 indicates that Congress was aware of concerns over the effects of extending related patents—at least as to parent, continuation, and continuation-in-part patents—and chose to provide the patentee with the option to select to extend the term of only one of either the parent patent or a continuation patent." *Merck*, 482 F.3d at 1323 (citing 130 Cong. Rec. 23765, 24444 (1984)). But in enacting § 154(b), Congress did not intend to grant applicants a similar flexibility in choosing which patents to extend.

Breckenridge is also inapposite. There, the Court was dealing with a completely different situation—a pre-URAA patent and post-URAA patent with divergent terms due to the intervening change in law defining patent term. *Breckenridge*, 909 F.3d at 1355. Indeed, the Court in *Breckenridge* found *Gilead* and *AbbVie* to be "inapposite because [they both] involved two post-URAA patents." *Breckenridge*, 909 F.3d at 1364-65. Like in *Gilead* and *AbbVie*, the '788 and '219 patents in this case are both post-URAA. In addition, the *Breckenridge* panel found that "the present facts do not give rise to similar patent prosecution gamesmanship" because the challenged patent expired later "only due to happenstance of an intervening change in patent term law." *Id.* at 1364. There is no parallel change in law or "happenstance" here.

Ultimately, Appellees chose to file serial applications for patentably indistinct inventions, and timed their filings so that the applications for the '788

and '219 patents were never co-pending before the PTO.[18] Appellees will receive a full statutory term based on the earlier-expiring '219 patent, whose prosecution was not delayed by the PTO. Consistent with the foundational principles of OTDP, when the '219 patent expires, the public should be free to use its claimed inventions and all patentably indistinct variations thereof, including claims 12 and 20 of the '788 patent. *Gilead*, 753 F.3d at 1214. When the '219 patent for the use of canagliflozin expires, the public should be free to use canagliflozin, as claimed in the '788 patent.

III. THE § 121 SAFE-HARBOR IS INAPPLICABLE

The district court expressly declined to rule on Appellees' argument below that the safe-harbor provision of 35 U.S.C. § 121 shields the '788 patent from Zydus's OTDP challenge. Appx66. The Court should reverse the district court's OTDP ruling and need not remand this appeal for the district court to decide whether the § 121 safe-harbor applies because Appellees failed to even meet their burden of production to trigger potential application of the safe-harbor.

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[18] *See Application of Simmons*, 312 F.2d 821, 825 (C.C.P.A. 1963) ("The mere fact that [applicant] filed two separate applications in the considered belief that two patentable inventions were present does not entitle him to two patents. [Applicant] suggests that he is being 'penalized' for not consolidating the copending applications. If [applicant] is penalized, it is his own doing.")

Although Zydus ultimately bears the burden of proof to show invalidity for OTDP, once Zydus established that an OTDP issue existed between the commonly-owned, patentably-indistinct '788 and '219 patents, the burden of production shifted to Appellees to go forward with rebuttal evidence. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008) ("A quite different burden is that of going forward with evidence—sometimes referred to as the burden of production—a shifting burden the allocation of which depends on where in the process of trial the issue arises."); *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305-06 (Fed. Cir. 2008) ("Once [defendant] established by clear and convincing evidence that the [reference] was § 102(b) prior art to the asserted claims of the [asserted] patents, the burden was on [plaintiff] to come forward with evidence to the contrary.").

Accordingly, at trial, Appellees bore the burden of production to establish the applicability of the § 121 safe-harbor. *See Bristol-Myers Squibb Co. v. Pharmachemie B.V.*, 361 F.3d 1343, 1347-48 (Fed. Cir. 2004) ("As section 121 has been interpreted by this court, [the patentee] is entitled to invoke the statutory [safe-harbor]"); *Geneva*, 349 F.3d at 1381 (holding that the patentee "d[id] not meet its burden to show" the applicability of the § 121 safe-harbor).

Among other requirements, § 121 authorizes safe-harbor protection only where the divisional application was filed "as a result of" a restriction requirement

and "before the issuance of the patent on the other application." 35 U.S.C. § 121. Plaintiffs failed to go forward with evidence sufficient to establish these statutory requirements.

The '219 patent's application was filed as a purported divisional of the '757 application (which issued as the '984 patent), which in turn was a purported divisional of the '788 patent's application. *See supra* at 11-13. Thus, the '788 patent's application is the grandparent of the '219 patent's application, with an intermediate application between them. It is undisputed that the PTO issued a restriction requirement in the '788 patent's prosecution on March 24, 2008. Appx16802-16823. It is also undisputed, however, that '219 patent's application was not filed until July 1, 2011, which is after the application for the '788 patent had already issued on May 17, 2011. Appx60-61; Appx2246-2247. Thus, Appellees never went forward with evidence that "the divisional application [wa]s filed before the issuance of the patent on the other application," as required by § 121.

Relatedly, to establish that the '219 patent's application was filed "as a result of" the restriction requirement in the '788 patent's application, Appellees bore the burden of production to go forward with evidence sufficient to show that the restriction requirement "carried forward" to the '219 patent. *See G.D. Searle LLC v. Lupin Pharm., Inc.*, 790 F.3d 1349, 1356-58 (Fed. Cir. 2015) (holding that the

patentee failed to establish the "as a result of" prong of § 121 because there was "[n]o evidence show[ing] that the PTO intended the restriction requirement to carry forward to the [later] application" or "that the examiner made any reference to the restriction requirement [imposed in the grandparent application] at all during prosecution of the [challenged patent] application."). Appellees, however, failed to link the restriction requirement in the '788 patent's application to the filing of its grandchild, the '219 patent's application.

More specifically, Appellees did not offer any evidence that that the PTO intended the restriction requirement to survive beyond the '788 patent's issuance or to carry forward to or be reinstated in the grandchild application for the '219 patent. *See, e.g.*, Appx20405 (Oct. 15, 2010 Notice of Allowance in '788 patent prosecution) ("Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on March 24, 2008 is hereby withdrawn**." (emphasis in original)). No divisional applications were filed until after the March 24, 2008 restriction requirement had already been withdrawn. *See Application of Ziegler*, 443 F.2d 1211, 1215-16 (C.C.P.A. 1971) ("[T]he restriction requirement was withdrawn and the withdrawal of the restriction requirement deprived appellants of any possible benefit from § 121."). Moreover, nothing in the prosecution of the '219 patent's application refers back to the March 24, 2008 restriction requirement.

Even to the extent Appellees contend that the restriction requirement carried forward to the '219 patent by way of the intermediate '757 application, they failed to go forward with evidence supporting that. Appellees bore the burden of production, but they did not offer the '757 application into evidence and even objected to having the district court consider its prosecution history. Appx132-134. Thus, Appellees did not meet their burden of production to establish a link between the filing of the '219 patent and the restriction requirement in its grandparent application.

Because Appellees failed to go forward with evidence sufficient to establish that the '219 patent's application was filed "as a result of" the restriction requirement in the '788 patent,[19] they never triggered any potential application of the § 121 safe-harbor. The Court can reverse the district court, without remand.

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[19] The trial record further established the '219 patent's application was in fact not filed "as a result of" any administrative requirements imposed by the PTO because, after the restriction requirement issued (Appx16802-16823), the applicants affirmatively and voluntarily "cancelled" the method of treatment claims in the '788 patent's application "in order to expedite prosecution," despite the claims being withdrawn and there being no requirement to cancel them. Appx16938-16942 (Mar. 3, 2009 Amendment); Appx20407 (Index of Claims); Appx2000-2019 (trial testimony of Mr. Carmichael). Some of these facts, however, were disputed between the parties' experts, and the district court did not make complete findings in that regard.

IV. CONCLUSION

For these reasons, the Court should reverse the district court's judgment regarding the '788 patent. Claims 12 and 20 of the '788 patent are invalid for OTDP over claim 22 of the '219 patent.

Dated: July 6, 2021

Respectfully submitted,

By: /s/ Jay Deshmukh

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ADDENDUM

Document Name	Appendix Pages
Final Judgment, dated Apr. 5, 2021 (ECF No. 247)	Appx1-3
Redacted & Amended Opinion, dated Apr. 7, 2021 (ECF No. 249)	Appx4-66
Order, dated Mar. 22, 2021 (ECF No. 244)	Appx67-68
Letter Order, dated Dec. 8, 2020 (ECF No. 230)	Appx132-134
U.S. Patent No. 7,943,788 to Nomura et al. (DTX-001)	Appx182-299
U.S. Patent No. 8,222,219 to Nomura et al. (DTX-002)	Appx300-415
U.S. Patent No. 8,785,403 to Nomura et al. (DTX-003)	Appx416-531

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, *et al.*, Plaintiffs, v. SANDOZ INC., *et al.*, Defendants.	Civil Action No. 17-5319 (FLW) (DEA) (CONSOLIDATED) (Filed Electronically)

FINAL JUDGMENT

NOW THEREFORE, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. This Court has jurisdiction over Plaintiffs Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International (collectively, "Plaintiffs") and Defendant Zydus Pharmaceutical (U.S.A.) Inc. ("Zydus") and the subject matter of this action.

2. For the reasons set forth in the Court's March 22, 2021 Memorandum Opinion (D.I. 243), Final Judgment is entered in favor of Plaintiffs and against Zydus on all claims and counterclaims with respect to United States Patent No. 7,943,788 ("the '788 patent"), United

States Patent No. 8,222,219 ("the '219 patent"), and United States Patent No. 8,785,403 ("the '403 patent"). The manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Zydus's Abbreviated New Drug Application ("ANDA") products that are the subject of ANDA Nos. 210541 and 210542 before the expiration of these patents would infringe claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent. Claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent are not invalid.

3. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Zydus's ANDA Nos. 210541 and 210542 shall be no earlier than the latest date of expiration of the '788, '219, and '403 patents (currently July 14, 2027), including any periods of regulatory exclusivity, such as pediatric exclusivity under 21 U.S.C. § 355a, that the U.S. Food and Drug Administration ("FDA") may deem to apply in the future.

4. Pursuant to 35 U.S.C. § 271(e)(4)(B), Zydus and its affiliates, successors, partners, officers, agents, servants, employees, and attorneys, and other persons or entities in active concert or participation with any of them, are hereby enjoined from commercially manufacturing, using, offering to sell, or selling within the United States, or importing into the United States, the products that are the subject of ANDA Nos. 210541 and 210542 until the latest date of expiration of the '788, '219, and '403 patents (currently July 14, 2027). If Plaintiffs become entitled to new regulatory exclusivities, such as pediatric exclusivity under 21 U.S.C. § 355a, Plaintiffs may apply to the Court for further relief as may be appropriate, without prejudice to Zydus's right to object to such further relief. For the sake of clarity, nothing in this Judgment prohibits activity that falls within the 35 U.S.C. § 271(e)(1) safe harbor.

5. Within five days of the entry of this Final Judgment, Zydus shall inform the FDA of this Final Judgment and that, for ANDA Nos. 210541 and 210542, a Final Judgment has been entered that claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent are infringed and not invalid. Zydus shall provide confirmation of such communication to Plaintiffs within seven days thereof.

6. As the prevailing parties in this action, Plaintiffs may seek their costs subject to Paragraphs 7 and 8 in an amount to be determined by the Clerk of Court.

7. In the event that a party appeals this Final Judgment, any motion for attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after final disposition of any such appeal. The responding party shall have 45 days after filing and service of any such motion to respond, and the moving party shall have 21 days thereafter to file and serve a reply.

8. In the event that no party appeals this Final Judgment, any motion for attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4. The responding party shall have 45 days after filing and service of any such motion to respond, and the moving party shall have 21 days thereafter to file and serve a reply.

9. All pending motions and other outstanding requests for relief not specifically addressed herein are DENIED. This is a final, appealable judgment.

IT IS SO ORDERED this 5th day of April 2021.

/s/ Freda L. Wolfson
FREDA L. WOLFSON
United States Chief District Court Judge

FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARAMCEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT, LLC, and CILAG GMBH INTERNATIONAL, Plaintiffs, v. SANDOZ, INC., et al., Defendants.	Civil Action No. 17-5319 (FLW) (DEA) **REDACTED & AMENDED OPINION**

WOLFSON, Chief Judge:

This consolidated action was filed by Plaintiffs, Mitsubishi Tanabe Pharma Corp. ("MTPC"), Janssen Pharmaceuticals, Inc. ("JPI"), Janssen Pharmaceutica NV ("JNV"), Janssen Research and Development, LLC ("JRD"), and Cilag GmbH International ("Cilag")[1] (collectively, "Plaintiffs") against Defendant Zydus Pharmaceuticals (U.S.A.) Inc. ("Zydus" or "Defendant") for patent infringement in violation of section 271(e)(2) of Title 35 of the United States Code. In response, Zydus has filed a counterclaim seeking a declaratory judgment against Plaintiffs that the patents-in-suit are invalid.

Defendant is alleged to infringe the following claims of the corresponding United States Patents held by Plaintiffs: (1) claims 12 and 20 of United States Patent Number 7,943,788 ("the '788 Patent"); (2) claim 22 of United States Patent Number 8,222,219 ("the '219 Patent"); and (3)

[1] The Court refers to JPI, JNV, JRD, and Cilag, collectively, as "Janssen."

claim 26 of United States Patent Number 8,785,403 ("the '403 Patent") (collectively, the "asserted claims").[2] The patents-in-suit relate to the pharmaceutical composition and method of treatment encompassed by the drugs "Invokana" and "Invokamet" (together "the Invokana Products"), which are used to treat type 2 diabetes. Plaintiffs' infringement claims are based on Zydus's filing of Abbreviated New Drug Applications ("ANDA") with the Food and Drug Administration ("FDA") seeking approval to commercially manufacture and market generic versions of the Invokana Products prior to the expiration of the patents-in-suit.[3] Zydus has stipulated that its submission of the ANDAs and any commercial manufacture, use, offer for sale, sale, or importation of the ANDA products before expiration of the patents-in-suit would infringe the asserted claims. As its defense, Zydus contends that (1) the asserted claims of patents-in-suit are invalid as obvious; and (2) claims 12 and 20 of the '788 Patent are invalid under the doctrine of obviousness-type double patenting.

The Court conducted a six-day bench trial,[4] during which numerous experts testified as to the issues of obviousness and obviousness-type double patenting. In accordance with Federal Rule of Civil Procedure 52(a), the Court sets forth herein its findings of facts and conclusions of law. After consideration of all the evidence, the Court finds that the patents-in-suit are not invalid as obvious and that claims 12 and 20 of the '788 Patent are not invalid under the doctrine of

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2 The Court refers to the '788, '219, and '403 Patents, collectively, as the "patents-in-suit."

3 Zydus has agreed not to launch the products within the scope of the ANDAs at issue, *i.e.*, the generic equivalents of Invokana and Invokamet, until four months after the parties submitted their Proposed Findings of Fact and Conclusions of Law. (ECF No. 206.) The parties submitted their Proposed Findings of Fact and Conclusions of Law on November 23, 2020. (*See* Zydus Proposed Findings of Fact and Conclusions of Law ("DFOF"), ECF No. 221; Plaintiffs' Proposed Findings of Fact and Conclusions of Law ("PFOF"), ECF No. 220.)

4 In light of the ongoing COVID-19 pandemic, the bench trial was held remotely via Zoom.

obviousness-type double patenting. Based on Zydus's concession, the Court further concludes that the filed ANDAs infringe upon the patents-in-suit.

I. OVERVIEW

A. Parties

MTPC is the lawful assignee of the patents-in-suit. (Pretrial Order, Stipulation of Facts ("SOF") ¶ 1, ECF No. 144.) JPI, JRD, and Cilag are the exclusive licensees of the patents-in-suit, and JNV is an exclusive sublicensee of the patents-in-suit. (*Id.* ¶ 8.) JPI holds approved New Drug Application ("NDA") No. 204042 for canagliflozin tablets, which are prescribed and sold as Invokana, and approved NDA No. 204353 for canagliflozin and metformin hydrochloride tablets, which are prescribed and sold as Invokamet. (*Id.* ¶ 9.) Canagliflozin is in a class of compounds known as SGLT-2 inhibitors which are used in the treatment of type 2 diabetes.

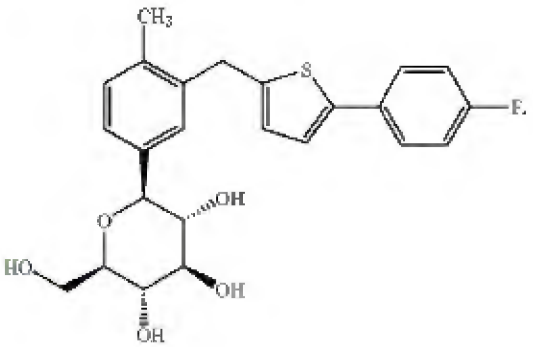
Zydus is a manufacturer and distributor of generic drugs. Zydus filed ANDA Nos. 210541 and 210542 with the FDA, seeking approval to commercially manufacture and market generic versions of the Invokana Products prior to the expiration of the patents-in-suit. (*Id.* ¶ 14.)

B. The Patents-in-Suit

1. The '788 Patent

The '788 Patent was issued by the United States Patent and Trademark Office ("USPTO") on May 17, 2011, and is entitled "Glucopyranoside Compound." (*Id.* ¶ 22; DTX-001.) The '788 Patent lists Sumihiro Nomura, Eiji Kawanishi, and Kiichiro Ueta as the named inventors. (SOF ¶ 23.) The '788 Patent was issued in connection with U.S. Patent Application No. 11/045,446 (the "'446 application"), which was filed on January 31, 2005, and was a continuation of International Application No. PCT/JP2004/011312, which was filed on July 30, 2004. (*Id.* ¶¶ 24–25.) Asserted claims 12 and 20 of the '788 Patent are directed to the compound now known as canagliflozin.

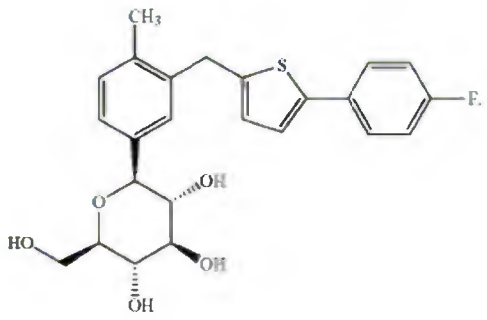
(*Id.* ¶¶ 26–27.) Specifically, claim 12 recites "1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene," which is the chemical name for canagliflozin. (*Id.* ¶ 26.) Claim 20 of the '788 Patent recites "[a] compound having the following structure," and depicts the chemical structure of canagliflozin:



(DTX-001, at 224:40-55.)

2. The '219 Patent

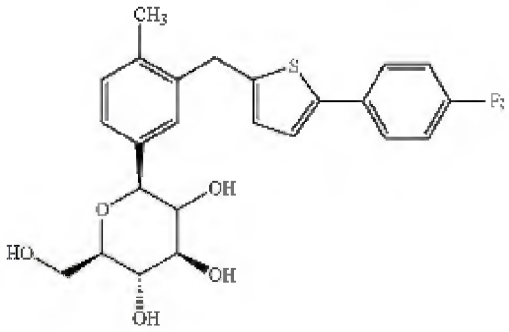
The '219 Patent was issued by the USPTO on July 17, 2012, and is titled "Glucopyranoside Compound." (SOF ¶ 28; DTX-002.) Like the '788 Patent, the listed inventors of the '219 Patent are Drs. Nomura, Kawanishi, and Ueta. (*Id.* ¶ 29.) The '219 Patent was issued in connection with U.S. Patent Application No. 13/174,814 ("the '814 application"), which was filed on July 1, 2011. (*Id.* ¶ 30.) The '814 application was filed as a division of U.S. Patent Application No. 13/005,757 ("the '757 application"), which was filed on January 13, 2011. (*Id.* ¶ 31.) The '757 application was filed as a division of the '446 application, which was issued as the '788 Patent. (*Id.*) Asserted claim 22 of the '219 Patent is directed to a method of treating or delaying the progression or onset of type 2 diabetes with the compound of the following structure, which is now known as canagliflozin:



(SOF ¶ 32; DTX-002, at 220:43-46.)

3. The '403 Patent

The '403 patent is titled "Glucopyranoside Compound" and was issued by the USPTO on July 22, 2014. (SF ¶ 33; DTX-003.) The '403 Patent lists Drs. Nomura, Kawanishi, and Ueta as the inventors. (SF ¶ 34.) The '403 Patent was issued in connection with U.S. Patent Application No. 13/494,602 (the "'602 application"), which was filed on June 12, 2012. (*Id.* ¶ 35.) The '602 application was a continuation of the '814 application. (*Id.* ¶ 36.) Asserted claim 26 of the '403 Patent is directed to a pharmaceutical composition comprising a biguanide compound and the compound of the following structure, which is now known as canagliflozin:



(SOF ¶ 37; DTX-003, at 221:25–26.)

C. The Invokana Products

Invokana, with canagliflozin as its active ingredient, was approved for use by the FDA in

March 2013. (PTX-1086.) It was the first SGLT[5] inhibitor to be approved in the United States.[6] (Williams Tr., at 1055:23–25.)[7] Invokamet was approved for use by the FDA in August 2014, and combines canagliflozin with metformin. (Brennan Dep. Tr., at 71:2–3; PTX-1085.) The Invokana Products act by inhibiting SGLT2 in the kidneys and suppressing glucose reabsorption. (*See* Bannister Demonstrative, at 7.) This leads to glucose being excreted in the urine in greater amounts, reducing blood glucose levels. (PTX-1086, at 7.) The Invokana Products also have the ability to inhibit SGLT1 and reduce the uptake of glucose from the gut. (Gavin Tr., at 757:–21.)

Clinical data has demonstrated that Invokana significantly reduces A1C, fasting plasma glucose levels, body weight, and systolic blood pressure in diabetic patients and that it is generally well tolerated. (*Id.* at 746:3–23; PTX-1086, at 9–14.) The Invokana Products are currently indicated: (1) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes; (2) to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease; and (3) to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria. (Gavin Tr., at

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[5] SGLT refers to a sodium glucose transporter. (Bannister Tr., at 112:19–22.) SGLTs are present in the kidneys, which filter blood for the human body. (*Id.* at 112:23–24.) Waste filtered by the kidneys is generally shunted to the bladder and excreted in urine. (*Id.* at 112:25–113:3.) However, SGLTs reabsorb—or transport—glucose initially filtered by the kidney back into the blood. (*Id.* at 113:8–25.) There are two types of SGLTs—SGLT1 and SGLT2. SGLT2s are only present in the kidneys, while SGLT1s are responsible for shunting glucose in other parts of the body, including the gut and heart. (*Id.* at 114:17–22.)

[6] The FDA has since approved three additional SGLT inhibitors for use. In 2014, the FDA approved both dapagliflozin, marketed as Farxiga, and empagliflozin, marketed as Jardiance. (Williams Tr., at 1056:6–14.) In 2017, the FDA approved ertugliflozin. (*Id.* at 1056:14–16.)

[7] For ease of reference, the Court refers to the trial transcripts by the name of the expert testifying during that portion of the transcript.

743:10–19; PTX-1086, at 1; PTX-1085, at 1.)

D. Procedural History

On July 20, 2017, Plaintiffs filed the instant patent infringement action against Zydus arising from Zydus's filing of ANDA Nos. 210541 and 210542.[8] (SOF ¶ 14; ECF No. 1.) Zydus has stipulated that its submission of ANDA Nos. 210541 and 210542 to the FDA and any commercial manufacture, use, offer for sale, sale, or importation of Zydus's ANDA Products before the expiration of the patents-in-suit would infringe on the asserted claims, to the extent they are not found invalid. (SOF ¶ 17; ECF No. 100, at 2–3.) Rather, Zydus maintains that the patents-in-suit are invalid as obvious. As such, the sole issues presented at trial were (1) whether the patents-in-suit are invalid as obvious and (2) whether claims 12 and 20 of the '788 Patent are invalid for obviousness-type double patenting.

The Court held a six-day bench trial on September 24, 25, and 30; October 1 and 2; and November 5, 2020. At trial, Defendant presented four expert witnesses: Thomas T. Bannister, Ph.D.; DeForest McDuff, Ph.D.; Jonathan S. Williams, M.D., M.M.Sc.; and James T. Carmichael, Esq. Dr. Bannister was accepted without objection as an expert in molecular medicine and chemistry, drug discovery, and medicinal chemistry. (Bannister Tr., at 106:9–12, 107:18–22.) Dr. McDuff was accepted without objection as an expert in economics and commercial success. (McDuff Tr., at 406:1–3.) Dr. Williams was accepted without objection as an expert in the field

[8] This consolidated matter initially included as defendants Sandoz, Inc. ("Sandoz"), InvaGen Pharmaceuticals, Inc. ("InvaGen"), Aurobindo Pharma USA Inc. ("Aurobindo"), and Prinston Pharmaceutical Inc. ("Prinston"). The Court entered Consent Judgments of infringement with permanent injunctions lasting through patent expiration with respect to InvaGen, Prinston, and Aurobindo. (*See* ECF Nos. 99, 102, 172.) Sandoz was dismissed from this matter pursuant to a stipulation between Plaintiffs and Sandoz after Sandoz abandoned its last-remaining defense. (*See* ECF No. 129.) Sandoz, however, continues to challenge other patents covering the Invokana Products in a separate matter also proceeding in this District.

of clinical management and development of type 2 diabetes. (Williams Tr., at 1036:21–1037:24.) Mr. Carmichael was accepted as an expert in USPTO procedure. (Carmichael Tr., at 1274:19–1280:21.)

Plaintiff also presented four expert witnesses: Stephen G. Davies, Ph.D.; Raymond Sims; James R. Gavin III, M.D.; and Robert Stoll, Esq. Dr. Davies was accepted as an expert in medicinal chemistry. (Davies Tr., at 502:22–503:14.) Mr. Sims was accepted as an expert in intellectual property research and analysis regarding whether a patented product is a commercial success. (Sims Tr., at 935:14–23.) Dr. Gavin was accepted as an expert in the field of clinical management and development of type 2 diabetes treatment. (Gavin Tr., at 728:16–729:15.) Mr. Stoll was accepted as an expert in USPTO procedures, practices, and policy. (Stoll Tr., at 1194:21–1196:1.) Plaintiffs also presented testimony from Dr. Kawanishi, who is identified as the inventor of canagliflozin. (Kawanishi Tr., at 893:17–25.)

During trial, the Court denied Plaintiffs' motion for judgment as a matter of law pursuant to Federal Rule of Civil Procedure 52(c). (Trial Tr., at 432:2–3.) Limited closing arguments were presented on December 22, 2020.

II. OBVIOUSNESS

A. Findings of Fact

Because the question of obviousness is a factual question that is guided by legal principles, I make certain factual findings before setting forth my conclusions of law, *infra*. As such, this section contains the relevant factual background necessary for the Court to conduct its obviousness analysis. To the extent any finding of fact below is a conclusion of law, it is also adopted as a conclusion of law.

1. Medicinal Chemistry & Drug Discovery

Medicinal chemistry is a multidisciplinary approach which uses molecular biology, biochemistry, pharmacology, medicine, analytical chemistry, and organic chemistry to identify organic compounds that may treat diseases in humans. (Davies Tr., at 502:3–10.) In other words, the study of medicinal chemistry seeks "to understand how drug substances work." (Bannister Tr., at 112:9–11.) In that connection, the drug discovery process "is a data-driven, iterative process," that typically involves: (1) analyzing biological targets and known compounds in the prior art for a particular disease area; (2) selecting lead compounds for improvement based on known data; (3) identifying assays that can verify whether the compounds being developed have the desired effect; (4) identifying one portion of each selected compound to modify; (5) synthesizing, testing, and analyzing each modification to the selected lead compounds; (6) identifying a potentially promising compound for further biological development based on the testing results; (7) conducting further studies on that promising compound; and (8) advancing that compound to clinical development, if appropriate. (Davies Tr., at 511:4–514:9.)

The second step of that process, the selection of a lead compound, involves a discrete number of biological targets and their corresponding compounds because of limited time and resources. (*Id.* at 512:4–7, 650:15–24.) Once a lead compound is selected, the medicinal chemist investigates the effect of various structural modifications upon biological activity, usually through a lengthy, iterative, and labor-intensive program with the goal of finding an improved candidate molecule for further evaluation. (*Id.* at 512:4–513:18; Bannister Tr., at 313:21–315:8 (agreeing that "drug compound discovery is a highly iterative process" in which a medicinal chemist would "try [to] improve [a] starting compound").) The drug development process is "lengthy" because, *inter alia*, it is necessary to make modifications to one portion of the compound at a time to

determine if the change was helpful, harmful, or neutral. (Davies Tr., at 512:4–10, 514:14–21; Bannister Tr., at 314:23–315:18 (agreeing that "the goal of a medicinal chemist would be to try [to] improve [a] starting compound" by changing "one area of the molecule at a time").)

Bioisosterism, a relevant principle of medicinal chemistry, is the observation that, in certain cases, "one group of atoms take[s] the place of another group of atoms in a biologically active molecule [resulting in] roughly the same biological activity." (Bannister Tr., at 181:3–10; Davies Tr., at 655:19–25 (explaining that bioisosterism is a concept that permits you to "swap groups around in order to keep biological activity and change the other properties").) In other words, bioisosterism is the "idea that one substructure can be swapped out for another." (Bannister Tr., at 181:12–14.) The "two different collections of atoms [that can be swapped] are called bioisosteres." (*Id.* at 181:11–12.)

2. Type 2 Diabetes and its Treatment History

Diabetes mellitus, commonly referred to as "diabetes," is "a very complex and progressive metabolic disease." (Gavin Tr.,731:10.) There are four types of diabetes, the most common of which is type 2 diabetes. (*Id.* 731:11–12.) Type 2 diabetes is characterized by a state of insulin insensitivity and resistance. (Williams Tr., at 1040:25–1041:9.) While a person with type 2 diabetes may be able to produce a reduced amount of insulin, he or she will, over time, experience resistance to insulin's blood sugar-lowering action and/or inadequate functioning of β cells.[9]

Doctors diagnose type 2 diabetes through a variety of tests, including measuring blood sugar under certain conditions, such as fasting, or monitoring glycemic control "A1C" test. (Gavin Tr., at 732:17–25; Williams Tr., at 1044:9–13.) A1C is a measurement of the average blood glucose level in a patient over the previous few months. (Gavin Tr., at 732:12–736:3.)

[9] β cells are responsible for the production and release of insulin. (Gavin Tr., at 731:10–17.)

Once diagnosed, type 2 diabetes is generally treated in a stepwise manner. (Gavin Tr., at 736:9–19.) Typically, the initial recommendation is to incorporate diet and exercise into the patient's daily lifestyle. (*Id.*) Then, if necessary, a drug would be administered to control the patient's glucose levels. (*Id.*) A healthcare provider would introduce one drug at a time, beginning with metformin and then including additional agents, as necessary. (*See id.* at 736:9–737:16.) In the 2003 time-period, the most commonly used type 2 diabetes drugs included biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones ("TZDs"), and meglitinides. (PTX-176, at 48–51.) However, the FDA-approved compounds in these classes of drugs each had certain shortcomings, including administration difficulties, weight gain, hypoglycemia, gastrointestinal side effects, negative psychological impact, and/or efficacy issues. (*See id.*) Accordingly, in 2003, additional tools were required to adequately manage type 2 diabetes and its complications. (*See id.*)

3. The POSA and the Problem to be Solved

The parties agree that the person of ordinary skill in the art (the "POSA") in this case would have had a graduate degree in medicinal chemistry, pharmacology, and/or a related field, with experience in the development of pharmaceutical compositions and an awareness of the antidiabetic drug field. (Bannister Tr., at 163:11–22; Davies Tr., at 516:17–21.) Additionally, a POSA would have had a "relatively low" level of creativity and would have had access to individuals having skills in chemistry and pharmacology, and would collaborate with them, as necessary. (*See* Bannister Tr., at 101:2224, 334:16–335:18; Davies Tr., at 502:510.)

Dr. Bannister and Dr. Davies further agreed that a POSA in this case would be "looking to positively alter the options for treating diabetes." (*See* Bannister Tr., at 280:11–14; Davies Tr., at 518:1–4 (explaining that the problem facing a POSA was "[t]o find an improved treatment, a better

drug, for the treatment of type 2 diabetes).)

4. Prior Art References

For the purpose of determining whether the patents-in-suit are obvious, the Court finds that the date of invention of the patents-in-suit occurred no later than October 29, 2003. (Kawanishi Tr., at 861:16–23.) October 29, 2003 is, therefore, the relevant date for determining the scope of prior art under 35 U.S.C. §§ 102(a), (e).[10] July 30, 2004, the earliest effective filing date for the patents-in-suit, is the relevant date for determining the scope of prior art under § 102(b).[11] In other words, references filed prior to July 30, 2003 may be considered prior art. *See* §§ 102(a), (b), (e). In this section, the Court discusses the key prior art references in this matter.

a) T-1095

In the 1990s, Tanabe Seiyaku ("Tanabe"), MTPC's predecessor, developed an analog of

[10] Because the patents-in-suit stem from patent applications that were filed before March 16, 2013, *i.e.*, before the passage of the Leahy-Smith America Invents Act ("AIA"), the Court refers to the pre-AIA version of 35 U.S.C. § 102. Pre-AIA section 102(a) provided that "[a] person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a) (2002). Pre-AIA section 102(e) provided that a person was not entitled to a patent if "the invention was described in (1) an application for a patent . . . by another filed in the United States before the invention by the applicant for a patent or (2) a patent granted on an application by another filed in the United States before the invention by the applicant for patent." *Id.* § 102(e).

[11] Pre-AIA section 102(b) provided that a person was not entitled to a patent if "the invention was patented or described in a printed publication in this or a foreign country or in a public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b) (2002).

phlorizin,[12] known as T-1095, a potential anti-diabetic agent.[13] (Bannister Tr., at 125:23–26.) T-1095 is an O-glucoside, meaning that glucose is "attached through an oxygen atom to the rest of the molecule." (*Id.* at 126:3–18; *see also* Bannister Demonstrative, at 16.) According to Dr. Bannister, T-1095 was a "much improved phlorizin analog" because it remained metabolically stable. (*See* Bannister Tr., at 130:5–131:5.) As T-1095 was shown to be absorbed through the stomach, it could be given to animals orally. (*Id.* at 131:15–17.) Accordingly, "it actually became a clinical compound to be tested in humans and potentially be developed as a drug." (*Id.* at 131:17–19.)

Dr. Davies specifically observed that the T-1095 references highlighted two compounds: T-1095 and T-1095A. (Davies Tr., at 538:19–22.) Dr. Davies explained that:

> T-1095 is a prodrug for T-1095A. A prodrug is a derivative of a drug that is converted in the body to the drug itself. So where you have a compound that has good biological pharmaceutical activity but doesn't have, for example, good absorption profile, you can form what is called a prodrug. You can attach, temporarily, a group to that drug molecule that improves the, in this case, the absorption. But the body is able to, using its enzymes, take off that extra unit you put on, that temporary group you put on, to release the drug

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[12] Phlorizin is a natural compound that was shown to lower blood glucose in the 1930s. (*See* Bannister Tr., at 115:23–116:3.) Phlorizin, however, had certain limitations for use as an antidiabetic agent. (*Id.* at 118:14–17.) Notably, it needed to be injected into the blood, rather than be orally ingested, to have biological effect, and it was known to be metabolically unstable. (*Id.* at 118:14–120:15.)

[13] Tanabe's findings with respect to T-1095 are set forth in several publications, including Akira Oku, et al., *Antidiabetic ϵ¡fect ϲf T-1095, an inhibitor ϲf Na+-glucose cotransporter in neonatally strϵptozotocin-treated rats*, 391 Eur. J. Pharmacol. 183 (2000); Akira Oku, et al., *T-1095, an Inhibitor ϲf Renal Na+-Glucose Cotransporters, May Provide a Novel Approach to Treating Diabetes*, 48 Diabetes 1794 (1999); Kenji Tsujihara, et al., *Na+-Glucose Cotransporter (SGL1) Inhibitors as Antidiabetic Agents. 4. Synthesis and Pharmacological Properties ϲf 4'-Dehydroxyphlorizin Derivatives Substituted on the B Ring*, 42 J. Med. Chem. 5311 (1999); and Kenji Tsujihara et al., *Na+-Glucose Cotransporter Inhibitors as Antidiabetics. I. Synthesis and Pharmacological Properties ϲf 4'Dehydroxyphlorizin Derivatives Based on a New Concept*, 44 Chem. Pharm. Bull. 1174 (1996). The Court refers to these publications, collectively, as the "T-1095 references."

> inside the body.
>
> So in this case it shows the prodrug and the actual compound through oral administration. . . . It shows that they both induce urinary glucose excretion, and the prodrug increases it over the parent drug. So 1095 is better than 1095A, but the actual active species is the same.

(*Id.* at 538:22–539:12.) Tanabe, therefore, selected T-1095, the prodrug, "as a promising [candidate] for the treatment of diabetes." (*Id.* at 539:19–20; PTX-122, at 5314.) Indeed, as Dr. Davies observed, "[Tanabe] scientists had demonstrated that . . . long term treatment with T-1095 restored deterioration of diabetic states." (*Id.* at 633:2–6.) Further, "T-1095A had been selected for further evaluation and as a potential anti-diabetic agent and was expected to be used as therapy for patients with type 2 diabetes." (*Id.* at 636:3–12.)

b) Link

The Link reference[14] was published in 2000 and explored whether phlorizin can be made more stable by transforming it from an O-glucoside, a glucose with an oxygen linker, to a C-glucoside, a glucose with a carbon linker. (*See* Bannister Tr., at 132:9–133:8.) Link found, however, the C-glucosides were weaker than O-glucosides in terms of efficacy. (Davies Tr., at 545:14–16; *see also* Bannister Tr., at 133:21–134:1.) Accordingly, the Link authors concluded that the O-glucoside linkage was important to SGLT-inhibition activity. (Davies Tr., at 545:3–12.)

While the parties agree that the Link reference demonstrates that O-glucosides were more effective compounds, there is some disagreement as to whether Link demonstrates that C-glucosides are more metabolically stable than O-glucosides. Dr. Bannister testified that Link

[14] Link & Sorensen, *A method for preparing C-glycosides related to phlorizin*, 41 Tetrahedron Letts 9213 (2000).

demonstrated that C-glucosides were more stable because replacing an oxygen bond with a carbon bond, generally, makes the molecule more stable. (Bannister Tr., Vol. 1., at 133:12–20.) However, Dr. Bannister admitted that Link only "made what [are] presumably stable compounds" and that Link "doesn't describe the stability." (*Id.* at 136:16–18.) In that regard, Dr. Davies explained that "[t]here are many instances where replacing a CO bond with a CC bond will improve stability . . . it's not a given. It depends on what carbon bond you've made and where – where in the body you're putting the drug." (Davies Tr., at 662:14–17.) As such, the Court finds that the Link reference demonstrates only that O-glucosides were more effective at inhibiting SGLT activity. The Link reference would not, however, have taught a POSA that C-glucosides are more stable than O-glucosides as Link made no specific findings with respect to stability.

c) US '674

In 2001, U.S. Patent Application Publication No. 2001/0041674 ("US '674") disclosed that C-glucosides are metabolically stable and could have "potent anti-diabetic activities." (DTX-172, at 1 ¶ 14.) US '674 recognized that O-glucosides are subject to glucosidases when administered orally. (*Id.* at 1 ¶ 8.) Thus, US '674 posited that C-glucosides could "overcome the stability against glycosidases" and further observed that "it is not reported that C-glycosides [have] strong SGLT [inhibition], so far." (*Id.* at 1 ¶ 10.)

US '674 confirmed the findings of Link—that replacing the oxygen with a carbon atom does not produce a potent compound. (*See* Bannister Tr., at 141:22–142:3.) The compound disclosed in US '674 instead omitted a "spacer" in the carbon bond between the glucose and the A ring for a direct carbon-to-carbon bond, which permitted the compound to remain "biologically active." (*Id.* at 141:22–142:23.) The potency of the compounds disclosed in US '674 was supported with biological data showing an increase in "the amount of glucose that was going out

in the urine which necessarily means it decreases the amount of glucose in the blood." (*Id.* at 138:21–139:4.) However, as Dr. Davies highlighted, the biological activity reported in US '674 was based only on administration by intraperitoneal injection, not oral administration. (Davies Tr., at 669:1–670:80.)

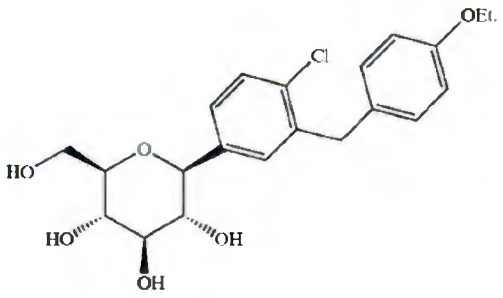
d) The BMS Patents

i. The '126 Patent

On July 2, 2002, US Patent No. 6,414,126 ("the '126 Patent") was issued to Ellsworth, *et al.*, and assigned to the Bristol Myers Squibb Company ("BMS"). (DTX-084.) The '126 Patent describes a family of C-glucoside compounds, which maintained the direct carbon link set forth in US '674, but modified the B and C rings of the molecule to attempt to formulate C-glucosides with greater potency. (*See* Bannister Tr., at 144:4–19.) Specifically, the '126 Patent states that "[t]he present invention relates to C-aryl glucosides which are inhibitors of sodium dependent glucose transporters found in the intestine and kidney (SGLT2) and to a method for treating diabetes, especially type II diabetes." (DTX-084 at 1.) The '126 Patent disclosed approximately 80 examples of C-glucosides and made "some broad claims about what different variables can be on different rings." (Bannister Tr., Vol.1, at 144:20–145:4.) The '126 Patent further provides a detailed description of a cell-based SGLT-2 inhibition assay. (DTX-084, at 35–36.)

ii. The '117 Patent

On February 4, 2003, US Patent No. 6,515,117 ("the '117 Patent") was issued to Ellsworth, *et al.*, with BMS as the assignee. (DTX-087.) The '117 Patent disclosed a single C-glucoside compound within the family reported in the '126 Patent, having the following structure:



(*Id.* at Abstract.) The '117 Patent described this structure as "[a]n SGLT2 inhibiting compound."[15] (*Id.*) The '117 Patent further set forth "[a] method for treating diabetes and related diseases employing an SGLT2 inhibiting amount of the above compound alone or in combination with another antidiabetic agent or other therapeutic agent." (*Id.*)

e) Patani

The Patani reference[16] was published in 1996, and reviews certain principles of bioisosterism. (*See* DTX-208.) Patani reviews "bioisosteric replacements which have been used to advance drug development." (*Id.* at 3148.) Specifically relevant here are Patani's teachings with respect to chloride and methyl groups, benzene rings and thiophene rings, and fluorine atoms and hydrogen atoms.

First, Patani states that "[w]hile the chlorine atom is often viewed to be isosteric[17] and

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15 Zydus refers to this structure as "dapagliflozin," which is the compound's marketing name. While a POSA at the time of invention would not have known the compound as dapagliflozin, the Court refers to the structure as its marketing name throughout the Opinion for ease of reference.

16 Patani & LaVoie, *Bioisosterism: A Rational Approach in Drug Design*, 96 Chem Rev. 3147 (1996).

17 Isosteric means that the molecules are the same size. (*See* Bannister Tr., at 207:3–5.)

isolipophilic[18] with the methyl group, it is very often selected as a bioisosteric replacement because of its ability to alter the metabolism." (*Id.* at 3154.) In that regard, Dr. Bannister testified that Patani "teaches us that chlorine and methyl are used interchangeably." (Bannister Tr., 193:25–194:2.) However, while Patani recognizes that chlorine and methyl are isoteric, it further states that "[t]he methyl substituents provide a site which is susceptible to metabolic degradation." (DTX-208, at 3154.) In other words,

> Patani is saying [that] it can be a good idea to change a methyl group to a chlorine, but it is not necessarily a good idea to change a chlorine to a methyl group, because a methyl group is susceptible to metabolic degradation, so you don't want to make a change that introduces instability into your molecule.

(Davies Tr., at 560:14–21; *see also* Bannister Tr., at 325:15–23 (agreeing that "[i]f there is a metabolic degradation, that means that the metabolic stability of the compound is adversely affected").)

Patani also teaches bioisosterism for benzene (methyl) rings and thiophene rings, observing that "[t]he classical bioisosteres benzene, thiophene, and pyridine resulted in analogues with retention of biological activity within different series of pharmacological agents." (DTX-208, at 3158.) Moreover, Patani states that fluorine and hydrogen atoms are often interchangeable as substituents: "[t]he substitution of hydrogen by fluorine is one of the more commonly employed monovalent isoteric replacements." (*Id.* at 3149.)

f) Sheridan

The Sheridan reference[19] was published in January 2002. (DTX-210.) Sheridan discloses

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[18] Dr. Bannister explained that "isolipophilic means greasy versus not greasy versus water-like." (Bannister Tr., at 207:6–7.)

[19] Robert P. Sheridan, *The Most Common Chemical Replacements in Drug-Like Compounds*, 42 J. Chem. Inf. Comput. Sci. 103 (2002).

a computation-based analysis of bioisosterism to "systematically identify candidate bioisosteres." (*Id.*) Graphically, Sheridan shows many "fragment pairs" and quantifies how well-matched they are, indicating the likelihood for successful replacement of one with the other. (*Id.* at 105–06.)

5. The Invention Story[20]

Dr. Kawanishi, an inventor of canagliflozin, testified at trial.[21] In December 2002, Dr. Kawanishi joined MTPC's "T-1095 backup project." (Kawanishi Tr., at 825:9–12.) The T-1095 backup project was a joint project with Janssen and sought an improved SGLT compound based on T-1095's poor performance in clinical trials. (*Id.* at 825:11–19.) During this project, MTPC scientists performed numerous modifications to both C-glucosides and O-glucosides to find a better SGLT inhibitor. (*See id.* at 843:9–848:23.) During this process, Dr. Kawanishi testified that MTPC would use other compounds from the literature as "reference compounds" to benchmark the progress of MTPC's own work. (*Id.* at 903:1–907:9.)

Dr. Kawanishi testified that around the fall of 2003, he began "making a plan to introduce to the aglycon portion of the molecule, a ring in addition to the A ring and B ring." (*Id.* at 853:5–9.) On or about, October 29, 2003, Dr. Kawanishi prepared a "Chem Draw" that memorialized his plan to synthesize and test forty analogs, which ultimately led to the discovery of canagliflozin. (*Id.* at 877:22–23.) Dr. Kawanishi shared his idea to add a third aryl ring to the compound with

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[20] The Court makes the following findings regarding the discovery of canagliflozin as useful background information. The Court does not, however, rely on Dr. Kawanishi's testimony in conducting its obviousness analysis because "[p]atentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103; *see also Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight.").

[21] Dr. Kawanishi was originally called to testify because, prior to trial, Zydus contested the date of invention. However, at trial, Zydus's counsel did not question Dr. Kawanishi regarding the date of invention nor does Zydus continue to contest the October 29, 2003 invention date.

his colleagues, who did not think that the SGLT activity would be maintained with this modification. (*Id.* at 856:19–25.) However, Dr. Kawanishi "felt strongly that SGLT activity is maintained, that a compound introducing a third ring maintains SGLT activity." (*Id.* at 857:18–21.) Based on this strong personal conviction, Dr. Kawanishi and two other researchers, Mr. Sugama and Mr. Yanagisawa, were permitted to implement Dr. Kawanishi's plan. (*Id.* at 857:19–58:5.) Thereafter, on November 13, 2003, Mr. Sugama first synthesized the compound known today as canagliflozin. (*Id.* at 859:16–22.)

B. Conclusions of Law

Zydus contends that the patents-in-suit are obvious over the compound disclosed in the '117 Patent, now known as dapagliflozin. Specifically, Zydus posits that a POSA would have selected dapagliflozin as a lead compound and would have been motivated to modify it to arrive at a "me too" drug. (DFOF ¶¶ 1–4.) Based on the principles of bioisosterism, Zydus maintains that a POSA would have had a reasonable expectation of success in modifying dapagliflozin to reach canagliflozin. (*Id.* ¶ 3.) Plaintiffs, on the other hand, argue that Zydus has failed to show, by clear and convincing evidence, that a POSA (1) would have selected dapagliflozin as a lead compound or (2) would have been motivated to modify dapagliflozin to reach canagliflozin.

1. The Legal Standard

35 U.S.C. § 103 provides that a patent may be invalidated if its claims are obvious in light of the prior art. More specifically, the pre-AIA version of section 103 provides that "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). As issued patents are entitled to a presumption of validity, 35

U.S.C. § 282(a), the party seeking to invalidate a patent must demonstrate obviousness by clear and convincing evidence. *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008). Moreover, where, as here, "the examiner considered the asserted prior art and basis for the validity challenge during patent prosecution, that burden becomes particularly heavy."[22] *Id.* Whether a patent is invalid as obvious "is a question of law, based on the underlying factual findings." *K/S Himpp v. Hear-Wear Techs., LLC*, 751 F.3d 1362, 1364 (Fed. Cir. 2014).

The obviousness determination is centered on four factual inquiries, known as the *Graham* factors: "(1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations such as commercial success and satisfaction of a long-felt need." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966). The Federal Circuit has explained that:

> Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.

Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1353, 1360–61 (Fed. Cir. 2011) (citations omitted).

Where the claims at issue involve a chemical compound, "*prima facie* obviousness under the third *Graham* factor generally turns on the structural similarities and differences between the claimed compound and the prior art compounds." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678

[22] There is no dispute that the examiner considered the relevant prior art in the prosecution of the asserted claims.

F.3d 1280, 1291 (Fed. Cir. 2012). Indeed, Federal Circuit "case law demonstrates that whether a new chemical compound would have been *prima facie* obvious over particular prior art compounds typically follows a two-part inquiry." *Id.* "First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* (citing *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)). Second, the court must determine "whether the prior art would have supplied one of ordinary skills in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.* at 1292 (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). Importantly, when conducting this analysis, courts must avoid improperly relying on hindsight. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070–71 (Fed. Cir. 2012).

2. Selection of a Lead Compound

The Federal Circuit has explained that a lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Otsuka Pharm. Co.*, 678 F.3d at 1291 (alteration in original) (quoting *Takeda Chem. Indus.*, 492 F.3d at 1357). However, "[a]bsent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Id.* Rather, "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). Moreover, "the attribution of a compound as a lead compound must avoid hindsight bias; it must look at the state of that art *at the time the invention was made* to find a motivation to

select and then modify a lead compound to arrive at the claimed invention." *Id.* (emphasis in original). Indeed, "proving a reason to select a compound as a lead compound depends on more than just structural similarly, but also knowledge in the art of the functional properties and limitations of the prior art compounds." *Id.* In that regard, "[p]otent and promising activity in the prior art trumps mere structural relationships." *Id.* Thus, in determining whether a POSA would select a compound as a lead compound, the court must be "guided by evidence of the compound's pertinent properties," including "positive attributes such as activity and potency, adverse effects such as toxicity, and other relevant characteristics in evidence." *Otsuka Pharm.*, 678 F.3d at 1292 (citations omitted).

a) Testimony at Trial

Dr. Bannister, Zydus's medicinal chemistry expert, opined that a POSA would have selected the structure disclosed in the '117 Patent, otherwise known as dapagliflozin, as a lead compound. Dr. Bannister testified that a POSA would be interested in SGLT inhibition because it was a "promising biological mechanism" that had shown "promise in animals and even in people [of] lowering blood sugar." (*Id.* at 165:2–20.) In that connection, while Dr. Bannister understood there to be significant biological data concerning SGLT inhibitors in 2002 to 2003, there were no such existing drugs on the market. (*Id.* at 165:12–166:6.) Thus, in 2003, SGLT inhibitors were "just right" for development, meaning that there were "a lot of scientific advances to be made, lots of patients to be helped, [and] lots of money to be made."[23] (*Id.* at 168:2–5.)

Dr. Bannister opined that, among the SGLT-2 inhibitors known in 2003, a POSA would

[23] In explaining his analysis of lead compound selection, Dr. Bannister employed what he called "the Goldilocks principle." (Bannister Tr., at 166:21.) In other words, he testified that a POSA did not "want something that is . . . too hot, its already been explored exhaustively, not too cold, it's not some pie-in-the-sky idea." (*Id.* at 167:2–6.)

have selected dapagliflozin as a lead compound because, as a C-glucoside, it was not subject to the metabolic instability problem that had "plagued all the best compounds to date."[24] (*Id.* at 170:21–171:6.) While Dr. Bannister "admit[ted] that the BMS patents don't have numbers for a POSA to say . . . that compound is that potent," he noted that "a POSA knows how to test for the potency, based on the prior art or based upon the teachings of the '117 [Patent], with their assay." (*Id.* at 171:10–19.) Moreover, because the '117 Patent is only one compound, a POSA knows that "the chemistry works." (*Id.*) Most notably, Dr. Bannister concluded that because the '117 Patent focused on one compound, as opposed to the '126 Patent, a POSA would know that it is the best compound of those disclosed in the '126 Patent. (*Id.* at 172:4–14.)

Plaintiffs, however, contend that Dr. Bannister's opinion that a POSA would select dapagliflozin as a lead compound is based solely on hindsight. In that regard, Plaintiffs argue that Dr. Bannister provided no support for his "Goldilocks approach" to selecting a lead compound. Indeed, Plaintiffs' expert, Dr. Davies, provided a different perspective. Dr. Davies explained that

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[24] Zydus contends in its Proposed Findings of Fact and Conclusions of Law that MTPC's "internal documents dispel any doubt as to how [MTPC] identified dapagliflozin as a lead compound." (DFOF ¶ 107.) The Court, however, cannot consider such evidence in conducting its obviousness analysis because, as previously explained, "'[p]atentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103. Recognizing this, Zydus argues there are several reasons why the Court may consider these internal documents, including to impeach the credibility of Dr. Kawanishi, to challenge the testimony of an alleged inventor concerning the conception date, or as evidence of inherency. (*See* DFOF ¶¶ 332–34.) Nevertheless, Zydus does not rely on any MTPC documents to support any challenge to the date of invention. Nor does Zydus make any legal argument regarding inherency. With respect to inherency, the Federal Circuit has explained that "the concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the 'natural result' of the combination of prior art elements." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). Zydus contends that SGLT inhibition activities of a compound are "inherent properties" and, therefore, "a POSA can easily ascertain such activity using routine prior art assay methods without undue experimentation." (DFOF ¶ 79.) However, as discussed *infra*, there is no dispute that a POSA would know how to conduct the assays necessary to determine the potency of dapagliflozin. Accordingly, to the extent Zydus relied on such materials at trial, the Court considers them only to weigh Dr. Kawanishi's credibility as a witness.

there were three categories of potential antidiabetic treatment options a POSA would have considered in selecting a lead compound at that time: (1) compounds that have been approved by a regulatory authority, such as the FDA; (2) compounds that had a demonstrated efficacy in humans, and (3) compounds for which there was preliminary activity data at the biological target. (Davies Demonstrative, at 10.) Dr. Davies opined that each of these categories of compounds would have been "just right" for development by a POSA. (*See* Davies Tr., at 519:9.)

Expanding on these three categories, Dr. Davies identified several FDA-approved therapies that existed in 2003 for treating type 2 diabetes, including α-glucosidase inhibitors, thiazolidinediones ("TZDs"), and meglitinides. (*Id.* at 520:3–524:8; Davies Demonstrative, at 12–15.) Dr. Davies highlighted that a POSA would continue to look in these areas, despite FDA approval, because the FDA-approved compounds did not solve all the problems, and "[t]here was still an unmet need to treat type 2 diabetes." (*Id.* at 524:3–8.) Next, the doctor highlighted that a POSA could have explored compounds that were in clinical trials and had shown some efficacy in humans, including non-TZD dual PPAR agonists, GLP-1 agonists, and DPP-4 inhibitors. (Davies Tr., at 524:17–530:3.) Third, the doctor explained that there were other type 2 diabetes treatment targets and mechanisms of action that were being actively pursued by the pharmaceutical industry during the relevant time-period, including protein-tyrosine phosphatase inhibitors, retinoid X receptor modulators, glycogen phosphorylase inhibitors, glucokinase activators, and glucocorticoid receptor antagonists. (*Id.* at 530:4–25.) Moreover, Dr. Davies identified certain compounds that would have been of greater interest to a POSA than dapagliflozin. (*See id.* at 540:3–541:10.)

Indeed, Dr. Davies observed that in 2003, while there was some data indicating that SGLT inhibitors were a potential treatment for type 2 diabetes, there was no clinical data demonstrating

such. (*See id.* at 531:12–25.) In that connection, the doctor testified that he reviewed articles from 2000 to 2003 regarding potential type 2 diabetes targets and found that they did not discuss SGLT inhibitors among promising examples being explored at the time. (*Id.* at 532:1–21.) Dr. Davies further explained that the literature from the relevant time-period that focused on SGLT inhibitors was more focused on the T-1095 compound. (*Id.* at 533:3–10.) In that regard, Dr. Davies disagreed with Dr. Bannister's opinion that a POSA would select dapagliflozin as a lead compound. Dr. Davies highlighted that the '117 Patent did not include the data necessary for a POSA to assess dapagliflozin's SGLT-2 inhibitor activity. (*Id.* at 541:17–24.) Notably, the doctor emphasized that in order to obtain the data, a POSA would have to make the '117 compound and set up the assay for SGLT2 activity, which "would take a significant amount of time." (*Id.* at 542:8–17.) In other words, if a POSA were focused on the '117 Patent, "they would need to first set up, validate, and run the tests just to find out what the potency was of the '117 Patent compound." (*Id.* at 542:24–543:6.)

b) A POSA Would Not Have Selected Dapagliflozin as a Lead Compound

Zydus contends that a POSA would have (1) understood that SGLT inhibitors were a promising class of compounds, and (2) would have selected dapagliflozin as a lead compound based on its stability and potency. As such, the Court first turns to whether a POSA would have pursued working with SGLT inhibitors as opposed to other classes of antidiabetic compounds. Dr. Bannister testified that SGLT inhibitors were a promising class of anti-diabetic agents because they were known to lower blood sugar in both humans and animals and, further, because there was biological data regarding both the T-1095 and US '674 compounds. (*See* Bannister Tr., at 165:1–15.) Moreover, Dr. Bannister opined that a POSA would be interested in SGLT-2 inhibitors because they presented a "huge commercial opportunity." (*Id.*) Thus, under Dr. Bannister's

"Goldilocks" approach, SGLT-2 inhibitors were "just right" for development because "nobody has done it . . . , there are scientific advances to be made, lots of patients to be helped, [and] lots of money to be made," if done right. (*Id.* at 168:2–5.)

This approach, however, fails to consider other compounds that were, in the 2002 to 2003 time-period, "just right" for further development. Put differently, there were several categories of compounds that a POSA would have been aware of in the relevant time-period and, further, that were "just right" for further development. For example, both Dr. Davies and Dr. Bannister agreed that "a POSA faced with a problem of trying to make an improved antidiabetic medication could also pursue an improvement against an existing therapy." (Bannister Tr., at 283:5–18; Davies Tr., at 519:18–524:8.) Notably, in 2003, there were several FDA-approved therapies that a POSA would be interested in improving. (*See* Davies Tr., at 519:18–524:8.) A POSA would have also been interested in compounds that had a demonstrated efficacy in humans, including dual PPAR agonists, GLP-1 receptor agonists, and DPP-4 inhibitors. (*See id.* at 524:14–16; Bannister Tr., at 281:1–283:4.)

While Dr. Bannister acknowledged that these different categories of compounds would have interested a POSA seeking to develop an improved antidiabetic agent, he failed to explain any reason why a POSA would solely focus on SGLT inhibitors. Indeed, Dr. Bannister admitted on cross examination that SGLT inhibitors would not have been the only focus of a POSA:

> Q: You agree that in the 2003, 2004 time period there were a number of ways to try and treat type 2 diabetes, correct?
>
> A: Yes.
>
> Q: For this reason, in deciding amongst the different targets that were possible for treating diabetes, SGLT compounds wouldn't necessarily be the only focus of a POSA. Do you agree?
>
> A: I would agree that there are other options, yes.

(*See* Bannister Tr., at 280:15–281:3.) When pressed as to whether he considered other categories of mechanisms in his lead compound selection analysis, Dr. Bannister stated that he did consider them, but found SGLT inhibitors to be more appealing and that some of the other compounds "fall into the too-hot-versus-too-cold concept." (*Id.* at 285:8–15.) The Court, however, finds this testimony lacks credibility as Dr. Bannister did not refer to any of those potential mechanisms during his direct testimony, nor did he indicate why those compounds were "too hot" or "too cold." (*See id.* at 280:15–285:19.) More importantly, Dr. Bannister does not give any cogent reason as to why other feasible compounds would have been less appealing that SGLT inhibitors.

Further, there was not a clear focus on SGLT inhibitors in the early 2000s that would have prompted a POSA to select an SGLT inhibitor as a lead compound. As Dr. Davies, who I find more credible, explained, his analysis of review articles from 2000 to 2003 regarding potential type 2 diabetes targets revealed that the industry did not discuss SGLT inhibitors among the numerous other compounds being explored at the time. (*See* Davies Tr., at 532:121, 534:4–12.)[25] In response, Zydus emphasizes that the prior art may point to more than one lead compound. (*See* Davies Tr., at 650:10–14); *see also Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 923 F. Supp. 2d 602, 654 (D. Del. 2013) ("[T]he Federal Circuit has rejected the notion that the 'prior art must point only to a single lead compound for further development efforts.'") (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009))). It is true that a lead compound "may be one of a number of compounds that the [POSA] would have been motivated to select from the panoply of known compounds in the prior art, based on the lead

[25] For example, Dr. Davies highlighted three review articles in his trial testimony that made no mention of SGLT inhibitors: the Zhang reference, published in 2000, (PTX-240); the Sarabu reference, published in July 2003, (PTX-119); and the Morral reference, published in May 2003, (PTX-113).

compound's promising useful properties." *Bristol-Myers Squibb Co.*, 923 F. Supp. 2d at 654. On this point, however, Zydus has failed to show—by clear and convincing evidence—that a POSA would have been motivated to select SGLT inhibitors from the "panoply" of known antidiabetic agents that were in development in the early 2000s. *Accord id.*

Even assuming that a POSA would have selected an SGLT inhibitor as a lead compound, the Court further finds that Zydus has failed to show that a POSA would have selected dapagliflozin. There is no dispute that dapagliflozin is a C-glucoside compound that "possesses activity as inhibitors of [SGLT] found in the intestine and kidney of mammals and is useful in the treatment of diabetes." (DTX-087, at 4.) In other words, the "'117 Patent suggested that there was some biological activity against SGLT." (Davies Tr., at 645:25–646:3.) Zydus thus contends that a POSA would have selected dapagliflozin as a lead compound, because a POSA would have known that dapagliflozin was not subject to the metabolic instability problem that plagued other SGLT inhibitor compounds and would have surmised that dapagliflozin was potent. (Bannister. Tr., at 171:1–6.) I disagree.

First, it was Dr. Bannister's opinion that a POSA would know that dapagliflozin, as a C-glucoside, was not subject to the metabolic instability problem that had "plagued all the best compounds to date, save many [of] the '674 C-glucosides." (Bannister Tr., at 171:1–6.) In that connection, Dr. Bannister maintained that a POSA would not have selected an O-glucoside because, he concluded, all the O-glucosides in the prior art suffered from metabolic stability issues that would disrupt activity after oral administration. (*See, e.g.*, Bannister Tr., at 130:5–131:24.) However, that opinion is not supported by the prior art, which demonstrates that companies that were investigating SGLT inhibitors in the early 2000s, such as BMS, were, in fact, focused on O-glucosides during the relevant time-period. (*See* Davies Tr., at 550:18–551:5.) Indeed, Dr.

Bannister acknowledged that BMS described the efficacy of its O-glucosides and C-glucosides using the same disclosures in both sets of patents.[26] (*See* Bannister Tr., at 308:20–309:14; PTX-340.) Accordingly, it is not clear that a POSA would have been able to effectively distinguish BMS's C-glucoside and O-glucoside compounds to determine that the C-glucosides were more stable.

While Dr. Bannister opined that a POSA would have understood that C-glucosides had improved activity after oral administration compared to O-glucosides based on the findings of Link, US '674, and the BMS patents, (*see* Bannister Tr., at 141:15–144:3), none of those references disclosed activity data after oral administration. Notably, Link did not describe the stability of the tested C-glucosides and, further, showed that the tested C-glucosides were weaker than their corresponding O-glucosides. (Davies Tr., at 544:24–545:17; Bannister Tr., at 136:16–21; PTX-112.) US '674 also did not disclose improved oral activity since the *in vivo* experiment set forth in the patent application involved intraperitoneal administration of the compound.[27] (Davies 543:7–544:15.) Nor did US '674 compare its C-glucoside compounds to O-glucosides; that is, a POSA could not have known whether the C-glucoside compounds had improved activity. Moreover, there was no basis for Dr. Bannister's testimony that the BMS Patents were a "breakthrough" in solving the stability problems that had plagued SGLT-2 inhibitors; indeed, as Dr. Bannister admitted, "no prior art reference . . . calls BMS's C-glucoside work a breakthrough."

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[26] BMS disclosed a family of O-glucosides compounds in International Patent Application No. WO 2003/020737 ("WO '737"). (PTX-089.) WO '737 disclosed that the O-glucoside compounds reported by the application "are inhibitors of sodium dependent glucose transporters found in the intestine and kidney (SGLT2)" and included "a method for treating diabetes." (*Id.*)

[27] Intraperitoneal administration is done via injection into the body cavity and bypasses key metabolic processes implicated in oral administration, including those which occur in the gastrointestinal tract. (Davies Tr., at 543:7–544:15; Williams Tr., at 1091:2–14.)

(Bannister Tr., at 305:18–24.)

Second, a POSA similarly would have not known that dapagliflozin was a potent compound. Zydus contends that "[a] POSA would know, based on the compound synthesis and assays described in detail in the BMS Patents, how to make and test the potency of dapagliflozin." (DFOF ¶ 193.) The BMS Patents, however, do not actually disclose any information regarding the potency of dapagliflozin. (*See* Bannister Tr., at 289:2–21 (confirming that the '117 Patent did not disclose any *in vitro* data, selectivity data, or metabolic stability data).) Rather, a POSA would have had to run the assays set forth in the '117 Patent to test the potency of dapagliflozin. (*See* Bannister Tr., at 171:10–19.) Dr. Bannister testified that POSA would know how to follow the steps of the assay to test the biological activity of dapagliflozin and that the test would take a week or two. (*Id.* at 148:22–149:20.) However, in offering his opinion, Dr. Bannister seemingly failed to take into account that running such an assay would take "a significant amount of time" and resources for a POSA to make and test the compound. (Davies Tr., at 542:6–17.) In that regard, the Court does not find that a POSA would know that dapagliflozin was a potent compound, contrary to Dr. Bannister's opinion, without expending a significant amount of time and resources.

For these reasons, the Court finds that Zydus has not shown, by clear and convincing evidence, that a POSA would have selected dapagliflozin as a lead compound. While there is no dispute that dapagliflozin and canagliflozin are structurally similar, "[p]otent and promising activity in the prior art trumps mere structural relationships." *See Daiichi*, 619 F.3d at 1354. Here, a review of dapagliflozin's functional properties do not demonstrate that a POSA would have known that it was a promising SGLT-2 inhibitor or that it was especially potent in comparison to other known SGLT-2 inhibitors in the art, such as T-1095/T-1095A, for which there was considerably more available biologic activity data. More likely, a POSA at the time would have

had limited information as to the functional properties of dapagliflozin as the BMS Patents did not actually disclose the potency of the compound and, rather, simply suggested it had potential to act as an SGLT-2 inhibitor. Accordingly, the Court finds that the "lack of [available] pharmaceutical data" would not have led a POSA to select dapagliflozin as a lead compound, particularly under the clear and convincing standard. *See Merck Sharp & Dohme Corp. v. Sandoz Inc.*, No. 12-3289, 2015 WL 5089543, at *43 (D.N.J. Aug. 27, 2015) (citing *Daiichi*, 619 F.3d at 1354).[28]

3. Motivation to Modify & Reasonable Expectation of Success

Because Zydus has not shown by clear and convincing evidence that a POSA would select dapagliflozin as a lead compound, it has not set forth a *prima facie* case of obviousness. Nevertheless, for the sake of completeness, the Court will consider whether a POSA would have been motivated to modify dapagliflozin to arrive at canagliflozin. The relevant question on this inquiry is "whether the prior art would have supplied [a POSA] with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292. "The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). Rather, the motivation to modify "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007) (quoting *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

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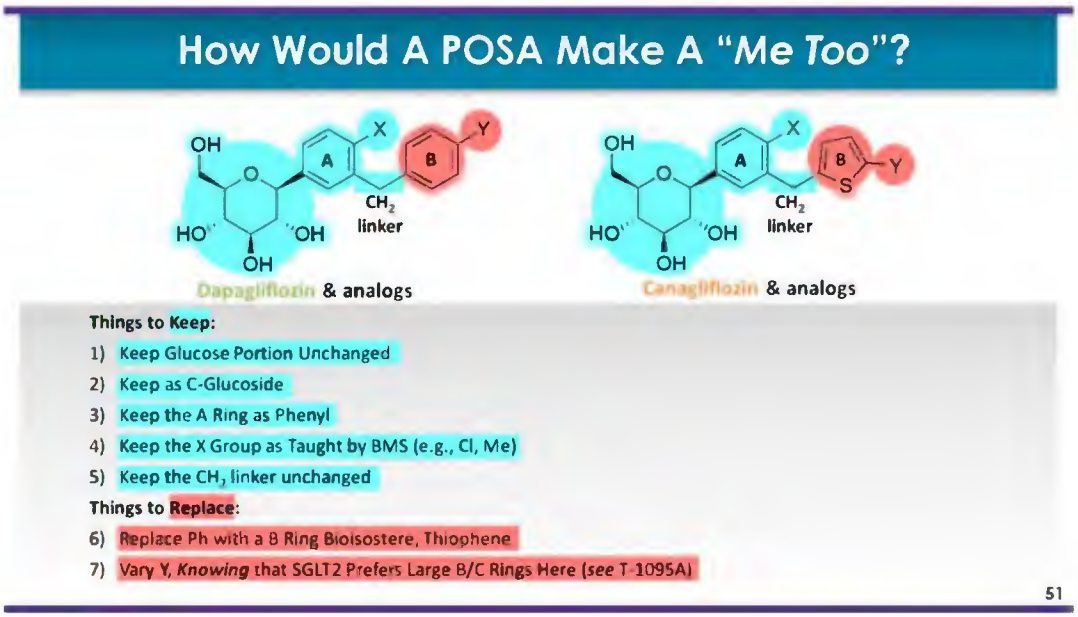
[28] Zydus contends that the fact that BMS took the extra effort to file a single compound patent covering dapagliflozin would suggest to a POSA that BMS considered dapagliflozin to be the "best" of the compounds covered by the '126 Patent. (DFOF ¶ 294.) That is not a reasonable inference, however, because the '117 Patent simply did not disclose the type of biologic activity data that would have prompted a POSA to choose dapagliflozin as a lead compound.

With respect to a reasonable expectation of success, "[i]t is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Bristol Myers Squibb*, 752 F.3d at 973 (omission in original) (quoting *Otsuka Pharm.*, 678 F.3d at 1293). The prior art need not, however, contain "an explicit teaching that the claimed compound will have a particular utility." *Aventis Pharma*, 499 F.3d at 1301. Thus, in some circumstances, "[s]tructural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1096 (Fed. Cir. 1986) (quoting *In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 19789)).

a) Testimony at Trial

Dr. Bannister testified that a POSA would have a commercial "motivation to find something that would be comparable to" dapagliflozin, "this all-star of a compound that had just shown up." (*Id.* at 175:13–17.) He explained that a POSA would seek to modify dapagliflozin in a way to avoid the BMS Patents, while still maintaining its biological activity, essentially adopting the "strategy of developing a 'me too' drug." (*Id.* at 175:13–176:24.)

Fundamental to Dr. Bannister's opinion is the principle of bioisosterism, which according to Dr. Bannister, would be "well known to a POSA . . . by 2003." (*Id.* at 181:14–20.) Dr. Bannister went on to explain what parts of dapagliflozin a POSA would "keep" and what parts would be changed based on the "fundamental principles of bioisoster[ism]" to arrive at canagliflozin. (*Id.* at 189:22–25.) Dr. Bannister's analysis is described by the following demonstrative, which was presented at trial:



(Bannister Demonstrative, at 51.)

First, Dr. Bannister explained that a POSA would "keep the glucose portion [of the molecule] unchanged." (Bannister Tr., at 190:19.) A POSA would also, according to Dr. Bannister, keep the direct carbon-to-carbon bond between the glucose portion of the molecule and the A ring, keep the A ring as a phenyl, and keep the "carbon connector from the A ring to the B ring." (*Id.* at 191:1–194:17.) Once determining what to "keep" from dapagliflozin, Dr. Bannister indicated that a POSA would then make a "choice" of whether to make the "X Group" chlorine or methyl. (*Id.* at 191:19–192:25.) In that regard, Dr. Bannister testified that "chlorine and methyl are the two things you can most often swap out for one another" and that the two compounds can be used interchangeably. (*Id.* 192:24–25, 193:25–194:3.) Dr. Bannister went on to state that replacing chlorine with methyl is "not really a change. It's a choice. It's like one lump of sugar or two in your coffee this morning. Both are going to work. Both are going to give you a sweet drink." (*Id.* at 193:18–21.) Making the choice to use a 4-methyl, Dr. Bannister opined, would permit a POSA to "design around the prior art compound." (Bannister Tr., at 317:10–13.)

However, on cross examination, Dr. Bannister admitted that the BMS Patents claim dapagliflozin using both a 4-methyl and a 4-chlorine. (*Id.*)

Next, Dr. Bannister explained the steps a POSA would take to modify dapagliflozin. He opined that a POSA would not work through numerous theoretically possible options but, rather, would apply reasonable limiting principles in this process. (Bannister Tr., at 213:16–23.) Dr. Bannister suggested that the limiting principles a POSA would apply here were "obvious to try and easy to make." (*Id.* at 213:16–23.) Thus, according to the doctor, the first change the POSA would take is to do a bioisosteric swap in the B ring, because such a ring is "far away from the glucose" and the SGLT literature demonstrates that a "wide array of diversity is tolerated in the B ring." (*Id.* at 195:14–24, 217:7–10.) Based on Dr. Bannister's theory that a POSA would seek to design around the BMS Patents, he testified that "[the] best shot is to see whether something else [works] as a B ring." (*Id.* at 196:2–14.) In accordance with allegedly known bioisosteric replacements, Dr. Bannister opined that a POSA would be motivated to swap out the phenyl B ring in dapagliflozin for a thiophene B ring. (*Id.* at 184:2–13, 195:2–4.) A POSA would also be motivated to swap out the phenyl B ring because it was "easy to try" as the chemistry was known and laid out in the BMS Patents. (*Id.* at 185:16–187:17.)

According to Dr. Bannister, a POSA would next replace the ethoxy substituent on the thiophene B ring. (*Id.* at 196:15–24.) He emphasized that a POSA would need to replace the ethoxy substituent based on his knowledge that "multiple drugs [had] been withdrawn from the market that had a thiophene in them because of toxicity." (*Id.* at 242:2–7.) Dr. Bannister concluded that the solution to this issue is to add a substituent from a limited group at the Y position of the thiophene B ring. (*Id.* at 242:16–21.) In that regard, the doctor pointed out that the BMS Patents taught that 4-phenyl groups were suitable alternatives to 4-ethoxy groups as B ring

substituents. (*See* Bannister Demonstrative, at 74.)

The final change a POSA would make, according to Dr. Bannister, would be to add one or more fluorine (F) atoms to biologically active substances. (Bannister Tr., at 223:19–224:16.) Specifically, Dr. Bannister explained that a POSA would probably run a "fluorine scan," in which a fluorine is added to every possible position of a ring and tested for improvements. (*Id.* at 246:18–25.) Moreover, Dr. Bannister observed that the prior art would have motivated a POSA to add one or more F atoms to biologically active substances, given that the presence of the electron-withdrawing F atom often leads to improved drug-like properties. (*Id.* at 223:19–224:16.)

Finally, Dr. Bannister concluded that a POSA would have had a reasonable expectation that the modifications to dapagliflozin necessary to arrive at canagliflozin would result in a metabolically stable SGLT-2 inhibitor. (*Id.* at 163:5–10.) In explaining this conclusion, the doctor noted that while there is no guarantee that swapping out one bioisostere for another would not change the biological activity, a POSA "can have some confidence that it is likely or not likely to work depending on how often it has worked in the literature as a whole in the past." (*Id.* at 182:7–10.) Here, based on the "rank ordering of bioisosteres taught by Sheridan, [and] Patani," a POSA would have known whether the bioisosteres he planned to use would work. (*Id.* at 183:3–9.)

In contrast, Dr. Davies opined that a POSA would not "have been motivated to modify [dapagliflozin] to get to canagliflozin." (*Id.* at 555:14–17.) Specifically, Dr. Davies explained:

> I don't think a POSA would simply try to design around patents while maintaining activity. A POSA is in the business of finding an improved compound, not in finding a compound that just maintains activity. I don't think – Dr. Bannister proposes modifications that are not supported by his own prior art references. He ignores numerous other options that would have been considered by a POSA. And Dr. Bannister fails to identify prior art supporting a reasonable expectation of success, especially given the fact that he's proposing multiple simultaneous modifications with no testing of intermediates.

(*Id.* at 555:16–556:2.)

b) A POSA Would Not Have Been Motivated to Modify Dapagliflozin to Make Canagliflozin

i. A POSA Would Not Have Been Motivated to Design Around the BMS Patents

The Court begins with Zydus's contention that a POSA would have been motivated "to modify dapagliflozin in such a way as to avoid infringing the BMS Patents, while maintaining its biological activity." (DFOF ¶¶ 199–200.) In other words, Zydus maintains that a POSA would have been motivated to develop a "me too" drug. (*Id.*) Dr. Bannister described the "me too" strategy as taking a compound and "chang[ing] something that is relatively minor but is arguably not covered by [the patent] . . . and find out that it does exactly the same things." (Bannister Tr., at 175:22–176:6.) This approach, Dr. Bannister explained, does not necessarily result in a "better" compound but still makes a "new discovery" that can be taken to market and potentially be a commercial success. (*Id.* at 176:3–6.) To implement this strategy, Dr. Bannister concluded that a POSA would employ principles of bioisosterism to "circumvent a patent situation with potential competitors." (*Id.* at 177:11–22.) In support of this approach, Dr. Bannister relied on the Böhm reference,[29] which was a review article published in March 2002, and stated that bioisosteric replacements "could be attempted for various reason[s]," including "to circumvent a conflicting patent situation with potential competitors."[30] (DTX-192, at 43307.)

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[29] Böhm & Klebe, *Development of New Hydrogen-Bond Descriptors and Their Application to Comparative Molecular Field Analyses*, 45 J. Med. Chem. 1585 (2002). Dr. Bannister confirmed on cross-examination that he relied on the Böhm reference solely for the "fact that bioisosterism is a field of interest in the relevant time period." (Bannister Tr., at 318:1–20.)

[30] Dr. Bannister also pointed to the Nogrady reference for the general principle that "[v]ariations in ring structure are endless in drug synthesis, and are often used in the service of some other change or are introduced simply for patent-right purposes." (DTX-202, at 45945.) The

However, this theory of modification relies on a far too limited framing of the problem sought to be solved by the POSA. Indeed, Zydus's argument that a POSA would have wanted to make a "me too" compound is based on its underlying assumption that the problem the POSA sought to solve was to make a metabolically stable SGLT inhibitor. (DFOF ¶ 303.) However, both Dr. Davies and Dr. Bannister testified that the problem faced by a POSA was broader than seeking a stable SGLT-2 inhibitor; rather, a POSA would have been seeking to develop an improved antidiabetic agent. *See supra* § II.A.3. The Federal Circuit has explained that "[i]n considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). Indeed. "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Id.* Here, by framing the problem to be solved by a POSA as finding a metabolically stable SGLT-2 inhibitor with "roughly equal" properties to dapagliflozin, Zydus too narrowly focuses on the problem that was solved by the patents-in-suit and improperly relies on hindsight to suggest that a POSA would have been motivated to "circumvent" the BMS Patents. Thus, Zydus has failed to convince the Court that a POSA would have been motivated to "design around" the BMS Patents. Nevertheless, while the Court finds that Zydus has not shown that a POSA would have been motivated to design around the BMS Patents, I will briefly address each proposed change Zydus contends a POSA would have been motivated to make to dapagliflozin to reach canagliflozin.

Nogrady reference, however, was published in 2005, and therefore, does not reflect whether a POSA would have been motivated to make such replacements to design around a patent during the relevant time period.

ii. The Methyl to Chlorine Change

The first change that Dr. Bannister contends a POSA would have made to transform dapagliflozin to canagliflozin is to make the A ring substituent (denoted in Dr. Bannister's demonstrative as "X") a methyl, rather than a chlorine. Dr. Bannister testified that the Patani and Sheridan references taught that "chlorine and methyl are used interchangeably." (Bannister Tr., at 193:25–194:2.) Moreover, Dr. Bannister highlighted that the '126 Patent additionally taught that chlorine and methyl can be used "interchangeably" in the family of SGLT-2 inhibitors described in the '126 Patent. (*Id.* at 194:2–11, 192:16.) Indeed, while Dr. Davies contended that a POSA would not have known that methyl and chlorine could be used interchangeably because there was "no biological activity" disclosed in the '126 Patent, he agreed that the '126 Patent discloses "some examples that have the methyl and some that have chloro." (Davies Tr., at 698:16–20.)

Nevertheless, Plaintiffs maintain that a POSA would not have changed the A ring substituent to a methyl because the Patani reference specifically taught that switching a chlorine atom to a methyl may result in metabolic instability. (*See id.* at 559:23–561:2; Bannister Tr., at 325:20–23.) The Federal Circuit has explained that "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The Court, however, does not find that the Patani reference would have taught a POSA away from making the A ring substituent a methyl. The '126 Patent disclosed several compounds that used methyl in this manner. As Dr. Bannister explained at trial, these disclosures would suggest to a POSA that methyl may work in this location. The Court agrees. While there is some risk that switching a chlorine to a methyl *could* cause some instability, that instability is not a guarantee. Even so, a POSA would have seen the change used in the '126 Patent and reasonably surmised that, in this

context, chlorine and methyl could be used interchangeably. As such, the Court finds that Zydus has shown that a POSA would be motivated to change the A ring substituent from a chlorine to a methyl.

iii. The Thiophene to Phenyl Change

Zydus has not, however, shown that a POSA would have been motivated to change the phenyl B ring in dapagliflozin to a thiophene B ring. Dr. Bannister testified that the Sheridan reference taught that "thiophene is a[bio]isostere for phenyl, and the best one." (Bannister Tr., at 184:15–17.) Plaintiffs, however, argue that Dr. Bannister's alleged change of phenyl to thiophene does not have any support in the relevant prior art. Indeed, Plaintiffs highlight that Dr. Bannister failed to provide any prior art examples of thiophene being considered a bioisostere in the SGLT context and, further, Dr. Bannister admitted that none of the C-glucoside references, *i.e.*, the BMS Patents, describe a C-glucoside SGLT inhibitor that contains a thiophene ring at any location. (*Id.* at 336:21–25, 344:4–8.)

On that basis, the Court agrees that a POSA would not have been motivated to substitute the phenyl B ring in dapagliflozin with a thiophene B ring. Dr. Bannister's only support for this change is the "principles of bioisosterism." Fatally, Dr. Bannister referred to no prior art that would have suggested that replacing the phenyl with thiophene would have made a better compound, or that the new compound would have similar activity compared to the previous compound.[31] *See, e.g.*, *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, No. 08-335, 2011 WL

[31] Zydus contends that the proposed bioisosteric modifications provide clear and convincing evidence of motivation to modify because "the '126 Patent taught that certain known bioisosteres were, in fact, bioisosteric *in the context of the particular molecule being modified*." (DFOF ¶ 299 n.42 (citing *Mylan Pharm. Inc. v. Research Corp. Techs., Inc.*, 914 F.3d 1366, 1376 (Fed. Cir. 2019).) However, Zydus presented no evidence that a POSA would have known that thiophene is bioisosteric in the context of SGLT inhibitors, as no prior art taught as such, and *none* of the

3236037, at *4 (D. Del. July 28, 2011) (rejecting arguments "regarding the bioisosterism of thienyl and phenyl because bioisosterism gives no indication about whether the new compound will be better or worse than the previous compound, how well it will bind to the enzyme, or what the overall effect of the binding will be" (footnote omitted)), *aff'd* 689 F.3d 1368 (Fed. Cir. 2012). Put differently, a POSA would not have been motivated to make this change because he or she could not have predicted the effect the change would have on the compound without any indications from the prior art. As the Federal Circuit has emphasized, "predictability is a vital consideration in the obviousness analysis." *Otsuka*, 678 F.3d at 1298. Notably, "[i]n the context of drug development, data is a necessary prerequisite to predicting the impact of modifying a chemical compound." *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 531 (D. Del. 2016), *aff'd*, 890 F.3d 1313 (Fed. Cir. 2018). In that regard, Zydus has not offered any evidence that shows a POSA would have been able to predict that replacing the phenyl B ring with a thiophene B ring would have improved the compound, let alone maintained the sought-after biological activity.

iv. The 4-Phenyl to 4-Ethoxy Change and Fluorination of the B Ring Substituent

The Court next considers the final two modifications proposed by Dr Bannister: (1) replacing the ethoxy substituent on the thiophene B ring to solve the toxicity problem created by adding thiophene to the compound; and (2) fluorinating the B ring substituent to "further mitigate the metabolic, toxicity, and oxidization issues associated with thiophene." (DFOF ¶ 304.) I reject both modifications proposed by Dr. Bannister in this context, because they are proposed solely to solve problems created by the addition of the thiophene B ring. In other words, these issues were

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compounds disclosed by the BMS Patents included thiophene. (*See* Davies Tr., at 612:12–21 ("The phenyl B ring is required in every single example in the '126 Patent.").)

not present in the dapagliflozin compound. As such, there is no reason a POSA would have made these modifications because he "would not have recognized the problem[s]," as they did not exist in the alleged lead compound. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013); *see also Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087 (Fed. Cir. 2019) (affirming no error in determination "that a person of ordinary skill would not have [made proposed modification] "to solve an undefined problem").

c) A POSA Would Not Have Had a Reasonable Expectation of Success

Finally, Zydus has not demonstrated by clear and convincing evidence that a POSA would have had a reasonable expectation of success that the modification proposed by Dr. Bannister would have yielded an improved antidiabetic agent. Zydus contends that the principle of bioisosterism, by definition, supports a reasonable expectation that the "new compound will have *similar properties* to the old." (DFOF ¶ 299 (quoting *Bristol Myers Squibb*, 752 F.3d at 972).) However, Zydus cannot rely on that principle here. As the Court discussed above, Zydus failed to show that a POSA would have known that thiophene is a bioisostere for phenyl *in the context of SGLT inhibitors* and, therefore, a POSA would not have had a reasonable expectation that making that replacement would have led to a stable and potent SGLT-2 inhibitor. Moreover, any reasonable expectation of success is belied by the fact that Dr. Bannister's analysis requires a POSA to have made multiple allegedly bioisosteric modifications to dapagliflozin. Dr. Bannister himself admitted that the prior art did not support making multiple, simultaneous bioisosteric changes to a compound. (*See* Bannister Tr., at 340:13–25, 341:8–17.) Accordingly, I find that Zydus has neither shown that a POSA would have been motivated to modify dapagliflozin to reach canagliflozin, nor that a POSA would have had a reasonable expectation of success. As such, Zydus has failed to make out a *prima facie* case of obviousness.

4. Objective Considerations

In determining whether a patent is invalid as obvious, a court must also consider secondary considerations of nonobviousness.[32] *KSR Int'l Co.*, 550 U.S. at 406–07. The Supreme Court has explained that this inquiry is broad and "invite[s] courts, where appropriate, to look at any secondary considerations that would prove instructive." *Id.* at 415. A court's evaluation of objective indicia of nonobviousness "is not just a cumulative or confirmatory part of the obviousness calculus but [rather] constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Indeed, consideration of these criteria "help[s] inoculate the obviousness analysis against hindsight." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). As the obviousness inquiry is "expansive and flexible," *KSR Int'l Co.*, 550 U.S. at 419, there are a variety of secondary considerations that may be "utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented," including, but not limited to, "commercial success, long felt but unsolved needs, [and] failure of others." *Graham*, 383 U.S. at 17–18. In that regard, a court need not find that all factors are present to determine that the objective considerations support

[32] While the Court finds that Zydus has not met its burden of proving obviousness, I must still consider the secondary considerations of nonobviousness. *See Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered."); *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666–66 (Fed. Cir. 2000) ("[S]econdary considerations, when present, *must* be considered in determining obviousness." (emphasis added)); *Cephalon, Inc. v. Slayback Pharma Limited Liab. Co.*, 456 F. Supp. 3d 594, 601–02 (D. Del. 2020) (noting that "the safer course for a district court faced with an obviousness challenge (and looking to avoid reversal by the Federal Circuit) is to treat *Graham*'s 'invitation' to look at secondary considerations like a subpoena"). However, a failure to show that the objective considerations support a finding of nonobviousness, will not overcome a defendant's failure to make out a *prima facia* case of obviousness. *See Cephalon, Inc.*, 456 F. Supp. 3d at 611, 621 (finding that failure to show objective indicia of nonobviousness did not undermine conclusion that the asserted claims are not obvious).

a finding of nonobviousness. *See id.*

"Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Apotex, Inc.*, 480 F.3d at 1372 (citing *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988)). Indeed, the Federal Circuit has "often held [that] evidence of secondary considerations does not always overcome a strong prima facie showing of obviousness." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion in this case that the secondary considerations cannot overcome the strong evidence of obviousness presented.").

Here, the parties presented evidence as to unexpected properties, skepticism, long-felt, unmet need and failure of others, copying and acquiescence, and commercial success. In addition to finding that Zydus has failed to establish a prima facia case of obviousness, I further find that skepticism and commercial success support a finding of non-obviousness here.

a) Unexpected Properties

The Federal Circuit has explained that "[u]nexpected results are useful to show the improved properties provided by the claimed compositions are much greater than would have been predicted." *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (quoting *Leo Pharm. Prods., Ltd.*, 726 F.3d at 1358). Thus, nonobvious may be demonstrated "when an invention 'yield[ed] more than predictable results.'" *Id.* (alteration in original) (quoting *Crocs, Inc. v. Intl Trade Comm'n*, 598 F.3d 1294, 1309 (Fed. Cir. 2010)). To that end, "the results must be shown to be unexpected compared with the closest prior art." *Id.* (quoting *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). However, unexpected results "do not necessarily guarantee that a new compound is nonobvious." *Bristol-Myers Squibb*, 752 F.3d at

977. In that connection, "[w]hile a 'marked superiority' in an expected property may be enough in some circumstances to render a compound patentable, a 'mere difference in degree' is insufficient." *Id.*

At trial, Plaintiff's expert Dr. Gavin opined that canagliflozin "has superior benefit compared to dapagliflozin." (Gavin Tr., at 750:13–17.) Specifically, Dr. Gavin testified that three studies demonstrated that canagliflozin has superior glycemic control, evidenced by reduced blood glucose levels upon oral administration:

(1) The peer-reviewed Zaccardi meta-analysis, which analyzed data from 38 randomized controlled clinical trials involving more than 23,000 participants, "to assess the comparative efficacy and safety of [SGLT-2] inhibitors in adults with type 2 diabetes." (PTX-238, at 783; Gavin Tr., at 763:7–764:17.) The data showed that the highest FDA-approved dose of canagliflozin reduced A1C and fasting plasma glucose levels to a statistically significant greater extent that the highest FDA-approved dose of dapagliflozin.[33] (Gavin Tr., at 763:7–764:17, 806:25–807:8; PTX-238 at 783, 791.) Based on this data, the Zaccardi meta-analysis concluded that "SGLT2 inhibitors improve cardiometabolic markets in patients with type 2 diabetes, with canagliflozin 300 mg generally performing better than other inhibitors." (PTX-238, at 791.)

(2) The Blonde cohort study, which analyzed data from type 2 diabetes patients taking either dapagliflozin or canagliflozin at their highest FDA-approved dosages. (PTX-182, at 1–2, 9.) The study concluded that patients taking canagliflozin had larger A1C reduction after six months and better A1C goal attainment. (Gavin Tr., at 762:9–24.) Moreover,

[33] Zydus suggests the fact that canagliflozin is used at a higher dose than dapagliflozin is relevant in determining whether there were unexpected results. (*See* DFOF ¶¶ 253–54.) Zydus, however, provides no scientific explanation for this assertion.

patients in the study who received 300 mg of canagliflozin were less likely to discontinue their treatment than those on 10 mg of dapagliflozin, which is critical for disease management. (*Id.* at 762:20–24.)

(3) Sha, a head-to-head Phase I study comparing canagliflozin and dapagliflozin, (Gavin Tr., at 751:16–18; PTX-231), which demonstrated that while both drugs "had similar effects on glucose excretion after dosing in the four-hour time frame, but canagliflozin was associated with a higher urinary glucose excretion and a greater renal threshold for glucose lowering for the rest of the day." (Gavin Tr., at 752:1–6.) Notably, the Sha study additionally found that canagliflozin provided the added benefit of delayed and reduced postprandial glucose excursion (change in blood glucose levels after a meal is consumed), while dapagliflozin did not. (Gavin Tr., at 752:7–15, 753:1–10, 757:10–25.)

Furthermore, Plaintiffs presented additional head-to-head studies between canagliflozin and other antidiabetic drugs, including sitagliptin, a DPP-4 inhibitor.[34] (Gavin Tr., at 758:11–25, 759:1–5, 760:7–10; PTX-1086.) This study showed that canagliflozin was statistically superior in lowering A1C levels in type 2 diabetes patients. (Gavin Tr., at 760:5–10.) In contrast, "dapagliflozin . . . was found to be inferior to sitagliptin." (*Id.* at 760:13–17.)

While the evidence highlighted by Plaintiffs demonstrates that canagliflozin has some benefits over dapagliflozin in the clinical setting, these benefits do not demonstrate a "marked superiority" over dapagliflozin. Rather, the differences between canagliflozin and dapagliflozin are one of degree. Canagliflozin and dapagliflozin, expectedly, have the same type of biologic activity. *See In re Merck & Co.*, 800 F.2d at 1099. In that connection, "[u]nexpected results that

[34] Because dapagliflozin was not approved by the FDA until after canagliflozin, it could not be used as the direct head-to-head comparator to demonstrate the efficacy of canagliflozin in a clinical trial. (Gavin Tr., at 750:18–751:6.)

are probative of nonobviousness are those that are 'different in kind and not merely in degree from the results of the prior art.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (quoting *Grip Barbell Co. v. USA Sports, Inc.*, 393 F.3d 1317, 1322 (Fed. Cir. 2004)). Here, the difference between canagliflozin and dapagliflozin is one of efficacy and is not substantial. Accordingly, the Court does not find that this consideration does not support a finding of nonobviousness.

b) Skepticism

A court may also consider "[g]eneral skepticism of those in the art" as "'relevant and persuasive' evidence of nonobviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998) (quoting *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 726 (Fed. Cir. 1990)). In other words, "[p]roceeding contrary to the accepted wisdom is . . . strong evidence of [non]obviousness." *Ruiz.*, 234 F.3d at 668. On this factor, Plaintiffs rely on the testimony of Dr. Gavin and Dr. Davies to support their assertion that "clinicians and researchers in the diabetes field were skeptical of the use of SGLT inhibitors as a potential type 2 diabetes treatment and, instead, focused on other drug categories." (PFOF ¶ 155.) In that regard, Dr. Gavin testified that in the 2003-time frame, a treatment "that depended on increasing the amount of glucose in the urine . . . was viewed generally as a counterintuitive approach" because clinicians had been taught "that the appearance of glucose in the urine was a sign of poor control in diabetes." (Gavin Tr., at 741:2–10.) Drs. Davies and Gavin additionally pointed to review articles from 2000 to 2003 documenting viable type 2 diabetes treatment targets which made no mention of SGLT inhibitors. (*See* Davies 532:1–21; Gavin Tr., at 738:1–740:18.)

Zydus, however, maintains that the research community was not skeptical of SGLT-2 inhibitors and argues that it was "a validated mechanism of action and promising treatment option

of type 2 diabetes." (DFOF ¶ 255.) Dr. Williams, Zydus's diabetes treatment expert, testified that "the research community had . . . validated SGLT as an important way of lowering blood sugar" and "that if you impaired SGLT, you could cause excretion of a greater amount of glucose into the urine, and at the same time lower blood glucose levels." (Williams Tr., at 1048:23–1049:3.) Thus, Dr. Williams opined that SGLT-2 inhibition was "an attractive area of research interest at that time." (*Id.* at 1049:4–6.) Moreover, Dr. Williams disagreed with Dr. Gavin's opinion that causing excretion of glucose in the urine would be viewed as counterintuitive. Rather, Dr. Williams observed that "people [who] have poorly controlled diabetes usually have higher glucose excretion in the urine," and the use of SGLT-2 inhibitors "take[s] advantage of that known physiologic phenomenon and . . . exploit[s] it to actually treat our patients with type 2 diabetes." (*Id.* at 1053:13–20.) Indeed, Dr. Williams opined that SGLT inhibition was an "attractive target" because it took "advantage of the knowledge and experience that you can get rid of glucose by using the kidney." (*Id.* at 1053:21–24.) Further, Zydus contends that the lack of skepticism was demonstrated by the medicinal chemistry community's exploration of SGLT inhibitors throughout the 1990s and 2000s, including Tanabe's work on T-1095 and BMS's development of dapagliflozin. (DFOF ¶ 257.)

Having heard competing testimony on this issue, I find that there was skepticism in the medicinal chemistry community regarding the development of SGLT inhibitors in the 2003 time-period. Drs. Davies and Gavin presented credible testimony that researchers in the type 2 diabetes community did not view SGLT inhibitors as a promising mechanism for treatment. (*See* Davies Tr., at 532:1–21, 534:4–12; Gavin Tr., at 738:1–140:18.) Most tellingly, Dr. Bannister, who had previously worked in the development of antidiabetic agents and kept up with relevant medicinal chemistry literature during 2003, could not recall whether he was aware of SGLT inhibitors during

the 2003 time-period. (*See* Bannister Tr., at 285:21–286:15.) Moreover, Dr. Williams lacked credibility on this issue. While the doctor claimed that SGLT inhibition was an "attractive" area of research, he pointed to no references to support that statement and admitted that the only SGLT inhibitor he was aware of during the relevant time period was T-1095; in fact, he was unaware of any companies that were developing SGLT-2 inhibitors prior to 2004. (*See* Williams Tr., at 1101:1–1102:5.)

Industry doubts about "whether or how a problem could be solved or the workability of the claimed solution" favors non-obviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016). Here, the prior art presented at trial demonstrates that, in 2003, Plaintiffs and BMS were focused on SGLT inhibitors while others in the industry primarily focused on other compounds. Accordingly, the Court finds that there was, at the very least, some skepticism of SGLT inhibitors as antidiabetic agents, and that this consideration supports a finding of nonobviousness.

c) Long-Felt Need and Failure of Others

"Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1082–83. To show "satisfaction of long-felt need, one must establish that (1) a POSA recognized a problem that existed for a long period of time without a solution, (2) the long-felt need had not been satisfied by another before the claimed invention, and (3) the invention in fact satisfied the long-felt need." *Immunex Corp. v. Sandoz Inc.*, 395 F. Supp. 3d 366, 405 (D.N.J. 2019).

The parties do not dispute that in 2003, there was a "long-felt unmet need" for a metabolically stable SGLT-2 inhibitor. (*See* DFOF ¶ 259; PFOF ¶ 158.) There is similarly no

dispute that researchers studying SGLT inhibitors encountered many issues and dead ends and, furthermore, there were "a significant number[] of companies that did not achieve the goal of introducing a useful SGLT inhibitor." (Bannister Tr., at 249:10–19, 287:5–8.) However, the evidence presented by Plaintiffs does not demonstrate that this long-felt need was satisfied by canagliflozin. Indeed, there is no dispute that the '117 Patent, which disclosed the structure for dapagliflozin, was published on February 4, 2003, prior to the invention of canagliflozin and the filing of the patents-in-suit. (Bannister Tr., at 248:8–20.) In that regard, while there was an unmet need for an SGLT2 inhibitor, that need had been met by dapagliflozin prior to the invention of canagliflozin. As such, this consideration does not support a finding of nonobviousness.[35]

d) Copying & Acquiescence

Copying of an invention can also indicate nonobviousness. However, evidence of copying "in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *see also Janssen Prods., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 671–72 (D.N.J. 2014). Plaintiff, nevertheless, contends that the fact that at least 14 generic pharmaceutical companies are seeking to market generic Invokana Products may be considered objective evidence of nonobviousness. (PFOF ¶ 243.) In support of that contention, Plaintiffs cite *Metabolite Laboratories., Inc. v. Laboratory Corp. of America Holdings*, wherein the Federal Circuit found that extensive licensing of an invention supported a finding of nonobviousness. 370 F.3d 1354, 1368 (Fed. Cir. 2004). That case, however, is inapposite because it did not involve

[35] Plaintiffs' argument with respect to this factor highlights that canagliflozin was the first SGLT-2 inhibitor approved by the FDA for the treatment of type 2 diabetes. (PFOF ¶ 159.) However, it is of no moment that canagliflozin was approved for use before dapagliflozin. The Court's analysis of this factor, rather, focuses on whether there was already *an invention* that satisfied the unmet need.

pharmaceuticals or any ANDA. *See id.* at 1357. As such, I find that this consideration does not support a finding of nonobviousness.

e) Commercial Success

Commercial success is relevant to the obvious determination because "the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Thus, evidence of commercial success, along with "some casual relation or 'nexus' between an invention and commercial success of a product embodying that invention" is "probative of whether an invention was non-obvious." *Id.* However, if the commercial success is due to a feature "known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

The Court begins with several undisputed facts. The Invokana Products were launched in March 2013. [redacted]

Relevant to the parties' different interpretations of this data are several events that occurred following the launch of the Invokana Products. In 2014, the FDA approved additional SGLT-2 inhibitors: dapagliflozin, marketed as Farxiga, and empagliflozin, marketed as Jardiance.

(Williams Tr., at 1056:6–14.) In 2017, the FDA approved ertugliflozin. (*Id.* at 1056:14–16.) In 2016, Jardiance gained a new indication for treating patients with cardiovascular disease, which gave it a competitive advantage over the other SGLT-2 inhibitors on the market. (Sims. Tr., at 944:25–945:7.) Then, in May 2017, the FDA placed a black box warning, which is the strictest warning that can be put on a prescription drug product, about amputation risk, on the Invokana Products. (McDuff Tr., at 412:5–413:6.)[36] Finally, in 2018 and 2019, the Invokana Products received two new indications for cardiovascular disease and renal disease, respectively. (Sims Tr., at 947:24–948:10.)

In terms of raw sales revenue figures, the Invokana Products have been commercially successful. Federal Circuit case law provides that commercial success is "usually shown by significant sales in a relevant market." *Ecolochem, Inc. v. So. Cal. Edison, Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). [redacted] The fact that the Products have seen some decrease in sales as a result of the Black Box warning does not detract from these significant earnings. Indeed, in comparison to other products that courts have found to be a commercial success, the net sales of the Invokana Products are on par. *See Bristol-Myers Squibb*, 923 F. Supp. 2d at 677 (finding that $835 million of total revenue from sales in the United States and $3.8 billion in worldwide sales were "clearly not small numbers"). Moreover, as one court has aptly observed, "'[s]trong evidence of commercial success is not surprising in a case under the Hatch-Waxman Act,' because if the patented drug were not a commercial success, at

[36] The FDA removed the black box warning on August 26, 2020. (McDuff Tr., at 472:18–473:6.)

least to some degree, 'generic manufacturers would have little interest in offering their own versions of the drug.'" *Id.* (quoting *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, No. 99-38, 2001 WL 1397304, at *12 (S.D. Ind. Oct. 29, 2001)).

Nevertheless, Zydus further submits that the Invokana Products are not commercially successful because they have a low market share and have, allegedly, not been profitable for Janssen. Looking first to the question of market share, the testimony at trial demonstrated that in the branded market for second-line diabetes treatments, *i.e.*, excluding metformin, Invokana held a high of 15 percent market share, that eventually declined to 9 percent, which Mr. Sims testified was "still a significant share of that segment of the market." (Sims Tr., at 962:20–963:8.) Within the SGLT-2 inhibitor drug class, the Invokana Products have maintained a significant portion of the market as additional approved SGLT inhibitors have been launched. (Sims Tr., at 963:9–964:5; McDuff Tr., at 460:2–7.)

Finally, Dr. McDuff testified that the Invokana Products have only a one percent share of the non-insulin anti-diabetes drug products ("NIAD market") and a two percent share of the NIAD market excluding metformin. (McDuff Tr., at 423:20–426:7.) Zydus contends that the NIAD market figures should govern this Court's determination of market share in assessing the commercial success of the Invokana Products. I disagree. Zydus points to no case law, Federal Circuit or otherwise, to suggest that commercial success of a product is determined by the NIAD market, as a whole, as opposed to smaller subsets of the market. (DFOF ¶ 237.) Rather, I find that each of these figures is relevant to my determination of commercial success. *See Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 386 (S.D.N.Y. 2006) (considering product's market share of oral antidiabetic drugs, as a whole, and smaller subset of TZD drug class). There is no dispute that at the time of the launch of the Invokana Products, and continued

to this day, the NIAD market is a crowded field. (*See* McDuff Tr., at 461:4–24.) Relative to that crowded market, the Invokana Products have maintained a strong market share among other SGLT-2 inhibitors.

The Court additionally heard evidence as to whether the Invokana Products have been profitable. At the outset, while evidence of profitability may be an indication of commercial success, *see Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 386 (D.N.J. 2009), the Court does not find that the analysis of profitability factors heavily into the commercial success analysis. In that connection, evidence of a product's sales and market share weighs more heavily on whether the product is obvious in light of the prior art. That is because the question of profitability depends on a number of internal factors, rather than a comparison to other similar products. For this reason, even if the Court were to consider the parties' positions with respect to profitability,[37] I do not find the argument persuasive.

Finally, Zydus contends that the Invokana Products are not successful because there is no nexus between the Product's performance and the patents-in-suit. The Federal Circuit has explained that "there is a presumption of nexus for objective considerations when the patentee

37 [redacted]

shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). Here, there is no dispute that the Invokana Products are the embodiment of the invention disclosed in the patents-in-suit, *i.e.*, canagliflozin, and as such the presumption of nexus applies.[38]

However, the presumption of nexus may be rebutted by "evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention," including "additional features and external factors, such as improvements in marketing." *Id.* Zydus first contends that the discounting and marketing of the Invokana Products "demonstrate a lack of differentiation and lack of connection to the Patents-in-Suit." (DFOF ¶ 242.) While Dr. McDuff stated that the marketing spend for the Invokana Products was high "compared to typical drugs," he "did not do any comparison between the marketing and sales of Invokana compared to any other branded type 2 diabetes treatment." (McDuff Tr., at 463:16–464:5.) Moreover, Mr. Sims highlighted that the marketing for the Invokana Products has been "education related" and focused on risk/benefit profiles and clinical data, "rather than factors unrelated to the patent features of canagliflozin and its use in treating type 2 diabetes." (PFOF ¶ 172; Sims Tr., at 966:12–967:18.)

Next, Zydus contends that discounts and rebates for the Invokana Products substantially increased over time as the sales for the Products decreased relative to other SGLT-2 inhibitors on the market. (McDuff Tr., at 441:3–443:1.) Dr. McDuff testified that the discounting and pricing

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[38] Zydus, nevertheless, argues that Plaintiffs "fails to show how the Invokana Products' supposed success can be tied to anything particular about canagliflozin." (DFOF ¶ 240.) This argument, however, does not reflect Federal Circuit law which plainly provides that a nexus is presumed where, as here, the commercial products are the embodiment of the patents-in-suit. *See WBIP, LLC*, 829 F.3d at 1329.

data "shows that Invokana is not able to maintain its share of the market even though it is cutting prices [a]nd that indicates a lack of differentiation of the product compared to these competitors." (*Id.* at 442:23–443:1.) I do not find that this evidence overcomes the presumption of a nexus. While marketing and discounting may have played a role in the success of the Invokana Products, Zydus has "not negated the possibility that the merits of the claimed composition also drive prescriptions and sales," especially in light of the competitive nature of the diabetes prescription market. *See Intendis GMBH & Co. KG v. Glenmark Pharms. Ltd.*, 117 F. Supp. 3d 549, 593 (D. Del. 2015).

Ultimately, I find that the Invokana Products were commercially successful. The totality of the evidence presented on this issue demonstrates that the Invokana Products have been a commercial success for Janssen, and the products have made significant sales since their launch, despite the crowded market and the sales ramifications of the FDA's black box warning. Accordingly, this factor supports a finding of nonobviousness. While Zydus attempts to undermine the success of the Products, "[t]here is no requirement that the invention be the only successful product in its market niche or the most successful." *Takeda Chem. Indus.*, 417 F. Supp. 2d at 386. Accordingly, commercial success supports a finding of nonobviousness.

In sum, the Court finds that Zydus has not shown, by clear and convincing evidence, that the patents-in-suit are invalid as obvious. Zydus has failed to show, by clear and convincing evidence, that a POSA would have selected dapagliflozin as a lead compound or that a POSA would have been motivated to modify, or a reasonable expectation of modifying, dapagliflozin to reach canagliflozin. Moreover, objective indicia of nonobviousness, notably skepticism and commercial success, support the Court's finding of nonobviousness.

III. OBVIOUSNESS TYPE DOUBLE PATENTING

Finally, Zydus contends that claims 12 and 20 of the '788 Patent are invalid for obviousness-type double patenting because they are anticipated by, or obvious in view of, claim 22 of the earlier-expiring '219 Patent. Plaintiffs, however, maintain that the '219 Patent cannot serve as an obviousness-type double patenting reference and, even if it could, claims 12 and 20 of the '788 Patent are protected by the safe harbor set forth in 35 U.S.C. § 121. In support of its arguments on obviousness-type double patenting, Zydus relied on the testimony of Mr. Carmichael, an experienced patent examiner. Plaintiffs relied on the testimony of Mr. Stoll, also an experienced patent examiner.

A. The Relevant Prosecution History

The application that led to the '788 Patent was filed on January 31, 2005, claimed priority to an application filed on July 30, 2004, and was issued as the '788 Patent on May 17, 2011. (PTX-001.) On March 24, 2008, the PTO imposed a "restriction requirement," in which the PTO grouped the asserted claims into categories and directed MTPC to "elect" the category of claims to be examined first. (DTX-004, at 2464–79.) The PTO divided the claims into the following categories: (1) compounds, (2) methods of treatment, (3) processes for preparing/making the compounds, and (4) compositions comprising compounds and another therapeutic agent. (*Id.*; *see also* Stoll Demonstrative, at 703.) On April 24, 2008, MTPC responded to the restriction requirement and elected, with traverse,[39] the compound claim (canagliflozin, claim 10); the remaining claims were either cancelled or withdrawn.[40] (Stoll Tr., at 1210:1–1211:5.) On March

[39] Mr. Stoll explained that by filing the election "with traverse," MTPC indicated that it "does not agree with the restriction requirement." (Stoll Tr., at 1210:22–1211:1.)

[40] The examination of "unelected" or "withdrawn" claims is suspended until further notice but remain pending in the action. (Stoll Tr., at 1259:23–1260:4.) Conversely, a cancelled claim

3, 2009, MTPC cancelled the method of treatment claims in the '788 Patent application. (Stoll Tr., at 1248:4–11.) On May 17, 2011, the '788 Patent was issued. (DTX-001.) While, based on the date the application was filed, the '788 Patent would have expired on July 30, 2024, the PTO granted a priority term adjustment ("PTA") of 1,079 days pursuant to 35 U.S.C. § 154(b), based on delays caused by the USPTO during prosecution. (*See id.*) The '788 Patent, therefore, is set to expire on July 14, 2027.

The application that led to the '219 Patent was filed on July 1, 2011, claimed priority to the same application as the '788 Patent, and was issued as the '219 Patent on July 17, 2012. (PTX-002.) The '219 Patent had a shorter prosecution and, therefore, it was issued without a PTA. (*Id.*) Because the '219 Patent claimed priority to the same July 30, 2004 application as the '788 Patent, the '219 Patent will expire on April 11, 2025.[41] (PTX-005, at 698.)

B. Discussion

The doctrine of obviousness-type double patenting is a judicially created doctrine which "prohibits an inventor from obtaining a second patent for claims that are not patentably distinct from the claims of the first patent." *UCB, Inc.*, 890 F.3d at 1323 (quoting *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997)). The doctrine, thus, "prevent[s] the extension of the term of a patent, even where an express statutory basis for the rejection is missing, by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Id.*

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is removed from the application entirely. (*Id.* a 1259:15–17; Carmichael Tr., at 1284:17–1285"3 ("A cancelled claim is no longer in the application, and it is not going . . . [to] have the same treatment as a withdrawn claim.").) Mr. Carmichael further expanded on the difference between withdrawn and cancelled claims, noting that the examiner must consider a withdrawn claim for rejoinder, "whereas the examiner does not need to consider a cancelled claim for rejoinder." (Carmichael Tr., at 1285:4–17.)

[41] The '219 Patent was granted a 256-day patent term extension under 35 U.S.C. § 156, based on regulatory review delay. (PTX-005, at 698.)

(quoting *Otsuka Pharm. Co.*, 678 F.3d at 1297). In other words, "[p]rohibiting double patenting prevents a patentee from obtaining sequential patents on the same invention and obvious variants, to thereby effectively manufacture a timewise extension of its patent exclusivity through a later-expiring patent." *Novartis Pharms. Corp. v. Breckenridge Pharm. Inc.*, 909 F.3d 1355 (Fed. Cir. 2018). "The key purpose of obviousness-type double patenting is thus to prevent a patent owner from controlling the public's right to use the patented invention beyond the statutorily allowed patent term of that invention." *Id.*

At the outset, Plaintiffs contend that "the '219 Patent cannot serve as a proper basis for invalidating the '788 Patent's PTA under the judicially created obviousness-type double patenting doctrine." (PFOF ¶ 245.) Zydus, on the other hand, maintains that the Federal Circuit's decision in *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014), supports application of obviousness-type double patenting to this matter.

In *Gilead*, the Federal Circuit considered the narrow question of whether "a patent that issues after but expires before another patent qualif[ies] as a double patenting reference for that other patent." *Id.* at 1211–12. There, the plaintiff owned two patents, the written descriptions of which were substantially similar. *Id.* at 1210. Despite these similarities, the two patents were "not part of the same family of patents[,] were not before the same patent examiner," and had different priority dates. *Id.* The district court concluded that "'a later-issued but earlier-expiring patent' cannot 'serve as a double-patenting reference against an earlier issued but later-expiring patent.'" *Id.* at 1211. The Federal Circuit reversed, holding that "an earlier-expiring patent can qualify as an obviousness-type double patenting reference for a later-expiring patent *under the circumstances here*." *Id.* at 1217 (emphasis added). In that regard, the Federal Circuit highlighted that if the obviousness-type double patenting analysis was "limited by issuance date, inventors could

routinely orchestrate patent term extensions by (1) filing serial applications on obvious modifications of an invention, (2) claiming priority to different applications in each, and then (3) arranging for the application claiming the latest filing date to issue first." *Id.* at 1215. In that regard, the Federal Circuit was concerned that "the terms of such patents could be subject to significant gamesmanship during prosecution." *Id.* In other words, if such conduct were permitted, "inventors could potentially obtain additional patent term exclusivity for obvious variants of their inventions while also exploring the value of an earlier priority date during prosecution." *Id.*

Zydus contends that *Gilead* provides a bright-line rule: the expiration date of a patent governs the obviousness-type double patenting analysis. (*See* DFOF ¶ 340; Closing Statement, at 1355:5–15.) However, the Federal Circuit has since limited the holding of *Gilead*. In *Novartis AG v. Ezra Ventures LLC*, the court considered the question of whether an earlier issued patent that received a patent term extension ("PTE"), that caused it to expire after a later issued patent, was invalid for obviousness-type double patenting. 909 F.3d 1367 (Fed. Cir. 2018).[42] In *Ezra*, the plaintiff had received a PTE of the earlier-issued patent under § 156 for regulatory delays that prevented the patented product from entering the market. *See id.* at 1372–73. The *Ezra* Court determined "that obviousness-type double patenting does not invalidate a validly obtained PTE" where it is the "earlier-filed, earlier-issued [patent], not the later-filed, later-issued [patent], that has the later expiration date, due to a statutorily-allowed term extension under § 156." *Id.* at 1373,

[42] The Federal Circuit also limited the so-called "*Gilead* rule" in *Breckenridge Pharmaceutical Inc.*, 909 F.3d 1355. That case involved two patents, one issued before the Uruguay Round Agreements Act of 1994 ("URAA") and one issued after the URAA. The URAA changed how patent terms are calculated. In that regard, the earlier filed, pre-URAA patent expired *after* the later filed, post-URAA patent. *See id.* at 1357–58. Inherent in the *Breckenridge* decision is that "a change in patent term law should not truncate the term *statutorily assigned* to the pre-URAA" patent. *Id.* at 1357.

1374. In so holding, the court distinguished *Gilead*, noting that there was "no potential gamesmanship issue through structuring of priority claims" as there was in that case, and observed that *Gilead* was intended to prevent inventors from improperly securing a second, later expiring patent for the same invention. *Id.* at 1374–75. Finally, the *Ezra* court declined to permit "a judge-made doctrine" to "cut off a statutorily-authorized time extension." *Id.* at 1375.[43]

The Federal Circuit has not, however, had occasion to consider the instant situation: whether a later-filed, later-issued patent that expires before the earlier-filed, earlier-issued patent due to a statutorily allowed term extension under § 154(b), can act as an obviousness-type double patenting reference.[44] However, in light of the Federal Circuit's decisions in *Ezra* and *Breckenridge*, I find that the '219 Patent is not a proper reference to invalidate the '788 Patent under the principles of obviousness-type double patenting. Specifically, I find that, as in *Ezra*,

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[43] The Federal Circuit also considered the scope of *Gilead*'s holding in *AbbVie Inc. v. Mathilda & Terence Kennedy Institute of Rheumatology Trust*, 764 F.3d 1366, 1368 (Fed. Cir. 2014). *AbbVie*, however, has limited application here because, there, "the earlier-filed patent had an earlier issuance date and earlier expiration date." *Breckenridge*, 909 F.3d at 1366; *see also AbbVie*, 764 F.3d at 1368–70. *AbbVie* does, however, contain language that would suggest that obviousness-type double patenting does apply where the earlier-filed, but later-issued patent is extended based on a PTA. Indeed, in setting forth the principles underlying the doctrine, the *AbbVie* court noted that "[i]t is designed to prevent an inventor from securing a second, later expiring patent for the same invention." *Id.* at 1373. Thus, the *AbbVie* court stated that the doctrine still has continuing viability post-URAA because "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO." *Id.* (citing 35 U.S.C. § 154(b)). This, however, was dicta and, further, did not impact the court's analysis as there was no PTA at issue in *AbbVie*. Moreover, the Federal Circuit has since, in *Ezra* and *Breckinridge*, distinguished the *AbbVie* decision. *See Breckenridge*, 909 F.3d at 1365–66; *Ezra*, 909 F.3d at 1375.

[44] The Court is only aware of one district court opinion addressing this issue: *Magna Electronics., Inc. v. TRW Automotive Holdings Corp.*, No. 12-654, 2015 WL 11430786 (W.D. Mich. Dec. 10, 2015). While the *Magna Electronics* court held that the "*Gilead*-rule" was applicable where an earlier-filed, earlier-issued patent expired after the later-filed, later-issued patent due to a PTA under § 154, that decision was rendered before the Federal Circuit decided *Ezra*. I therefore do not find *Magna Electronics* persuasive on this issue.

"[t]his case does not raise the traditional concern with obviousness-type double patenting of a patent owner 'extending his exclusive rights to an invention through claims in a later-filed patent that are not patentably distinct from claims in the earlier filed patent.'" *Ezra*, 909 F.3d at 1374. Here, both the '788 and '219 Patents are part of the same patent family and were filed as continuations of the '312 Application, which was filed on July 30, 2004. (*See* DTX-001; DTX-002.) Accordingly, absent the PTA granted to the '788 Patent, both the '788 Patent and the '219 Patent would have the same expiration date. (PFOF ¶ 188.) However, due to delays in the prosecution of the '788 Patent, it was extended by 1,079 days pursuant to section 154(b). (*See* DTX-001.) There is no dispute that this PTA was properly granted under section 154(b).[45] Unlike in *Gilead*, the granting of a PTA does not present the potential for gamesmanship by inventors to secure a second, later expiring patent for the same invention.[46] *See Ezra*, 909 F.3d at 1374–75. In

[45] Zydus attempts to distinguish *Ezra* because PTAs under section 154, unlike PTEs under section 156, are subject to terminal disclaimers. (DFOF ¶ 345.) In other words, if a patent is subject to a terminal disclaimer, a PTA cannot extend the patent's term beyond the terminal disclaimer. *See* 35 U.S.C. § 154(b)(2)(B). In that regard, Zydus suggests that the *Ezra* decision distinguishes PTEs and PTAs in the context of obviousness-type double patenting. This, however, is an incorrect reading of *Ezra*. The only mention of PTAs in *Ezra* is in the context of discussing an earlier decision that noted the different statutory conditions for granting these extensions and, further, that a PTA cannot extend the statutory term of a patent if a terminal disclaimer had previously been filed. *Ezra*, 909 F.3d at 1374 (citing *Merck & Co. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317, 1321–23 (Fed. Cir. 2007)). But even if the role of a terminal disclaimer affected the obviousness-type double patenting analysis, Zydus does not contend that a terminal disclaimer was required here.

[46] Zydus, in its post-trial submission, raised for the first time the issue of gamesmanship, contending that Plaintiffs engaged in gamesmanship by waiting to file the application for the '219 Patent after the '788 Patent had been issued. (DFOF ¶ 347.) The Court does not find that any gamesmanship was present here and, moreover, that gamesmanship does not factor into the application of the obviousness-type double patenting analysis. Rather, it is the "potential for gamesmanship" that courts have considered in determining whether the obviousness-type double patenting analysis applies in a certain situation. *See Ezra*, 909 F.3d at 1374 (noting that "[t]his case does not present the concerns that drove recent decisions of this court regarding obviousness-type double patenting in the post-URAA context").

other words, there is no concern that MTPC "sought to subsequently 'secur[e] a second, later expiring patent for the same invention" after the issuance of the '788 Patent. *See id.* at 1375. In that connection, but for the § 154(b) PTA, the '788 Patent would have expired before the '219 Patent. *See id.* Perhaps more importantly, however, the Court is swayed by the Federal Circuit's observation that "a judge made doctrine" should not be used to "cut off a statutorily-authorized time extension." *Id.* Agreeing with Zydus's position would mean just that.

In conclusion, the Court finds that the '219 Patent cannot be used as a reference against the '788 Patent for the purpose of obviousness-type double patenting analysis. Because I find that the '788 Patent is not invalid for obviousness-type double patenting, I need not consider the parties' argument with respect to whether the 25 U.S.C. § 121 safe harbor applies.

IV. CONCLUSION

For the foregoing reasons, the Court finds that (1) the patents-in-suit are not invalid as obvious and (2) that the '788 Patent is not invalid under the doctrine of obviousness-type double patenting. An appropriate Order follows.

DATED: March 22, 2021

/s/ Freda L. Wolfson
Freda L. Wolfson
U.S. Chief District Judge

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARAMCEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT, LLC, and CILAG GMBH INTERNATIONAL, Plaintiffs, v. SANDOZ, INC., et al., Defendants.	Civil Action No. 17-5319 (FLW) (DEA) **ORDER**

THIS MATTER comes before the Court upon the filing of a Complaint by Charles M. Lizza, Esq., counsel for Plaintiffs Mitsubishi Tanabe Pharma Corp, Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International (collectively, "Plaintiffs"), against Defendant Zydus Pharmaceutical (U.S.A.) Inc. ("Defendant") for patent infringement in violation of 35 U.S.C. § 271(e)(2); it appearing that Plaintiffs allege that Defendant has infringed the following claims of United States Patents held by Plaintiffs: (1) claims 12 and 20 of United States Patent Number 7,943,788 ("the '788 patent"); (2) claim 22 of United States Patent Number 8,222,219 ("the '219 patent"); and (3) claim 26 of United States Patent Number 8,785,403 ("the '403 patent") (collectively, "the patents-in-suit"); it appearing that Defendant, through its counsel Sean R. Kelly, Esq., stipulates to infringement of the patents-in-suit, but, in its defense, contends that (1) the asserted claims of the patents-in-suit are invalid as obvious, and (2) the asserted claims of the '788 patent are invalid under the doctrine of obviousness-type double patenting; it appearing that the Court held a six-day bench trial on the issues of obviousness and obviousness-type double patenting; the Court having stated its findings of fact and conclusions of law, pursuant to Federal Rule of Civil Procedure 52(a), in the Opinion also filed on this date, and for good cause shown,

IT IS on this 22nd day of March, 2021,

ORDERED that Judgment on Defendant's affirmative defense to infringement, asserting the invalidity of claims 12 and 20 of the '788 Patent, claim 22 of the '219 Patent, and claim 26 of the '403 Patent based on obviousness, is hereby entered in Plaintiffs' favor; and it is further

ORDERED that Judgment on Defendant's affirmative defense to infringement, asserting the invalidity of claims 12 and 20 of the '788 Patent based on obviousness-type double patenting, is hereby entered in Plaintiffs' favor; and it is further

ORDERED that Defendant's filing of ANDA Nos. 210541 and 210542 constitutes an act of infringement of claims 12 and 20 of the '788 Patent, claim 22 of the '219 Patent, and claim 26 of the '403 Patent, and Judgment on Plaintiffs' claims of infringement, set forth in the Complaint in Civil Action No. 17-5319, is hereby entered in Plaintiffs' favor, and it is further

ORDERED that the effective date of any approval of the drug that is the subject of ANDA Nos. 210541 and 210542 may not be earlier than the date of the expiration of the patents-in-suit; and it is further

ORDERED that the parties shall submit a joint, proposed Final Judgment within 10 days of the date of this order; and it is further

ORDERED that an unredacted version of this Court's Opinion shall be filed under temporary seal and that, in accordance with Local Civil Rule 5.3, the parties shall submit a joint submission indicating the portions of this Court's Opinion that they seek to have redacted, as well as a statement of reasons as to why each redaction is necessary, within 30 days of the date of this Order.

/s/ Freda L. Wolfson
Freda L. Wolfson
U.S. Chief District Judge

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
(609) 989-2182

CHAMBERS OF
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RE: ***Mitsubishi Tanabe Pharma Corporation, et al. v. Sandoz, Inc., et al.***
Civil Action No. 17-5319 (consolidated) (FLW) (DEA)

Counsel:

This matter comes before the Court on correspondence from the parties regarding closing arguments in this matter. The Court previously scheduled closing arguments for December 22, 2020, and directed the parties to inform the Court whether they wished to proceed with closing arguments following submission of their respective Proposed Findings of Fact and Conclusions of Law. Defendant Zydus Pharmaceuticals (USA), Inc. ("Zydus") has expressed, through its counsel, that it does not believe closing argument is necessary and will rest on its submissions.

Plaintiffs, on the other hand, contend that Zydus sets forth entirely new arguments related to its obviousness-type double patenting defense in its post-trial submission that were neither made at trial nor set forth in the Final Pretrial Order. Plaintiffs request that the Court strike these

arguments or, if the Court is inclined to consider the arguments, request that the Court proceed with closing arguments. Zydus objects to Plaintiffs' request to strike, and contends that the arguments it makes in its post-trial submission are based on facts within the scope of the record as presented at trial.[1]

Plaintiffs specifically assert that Zydus raises the following arguments for the first time in its post-trial submissions: (1) that Plaintiffs engaged in "gamesmanship" by filing its patent applications to avoid a "provisional double patenting rejection during the prosecution of the '788 patent; (2) that the 35 U.S.C. § 121 safe harbor cannot protect the '788 patent because the '219 patent was filed after the issuance of the '788 patent; and (3) that a restriction requirement in the '984 patent prosecution prevents application of the safe harbor. Zydus responds that its arguments are properly made as it has asserted an obvious-type double patenting defense since the beginning of this litigation, including in the Final Pretrial Order. Having considered the submissions of the parties, the Court makes the following findings.

First, the Court will consider Zydus's argument that Plaintiffs engaged in gamesmanship in the filing of the '788 patent. In Plaintiffs' opening argument on the issue of obviousness-type double patenting, Plaintiffs argued that they did not engage in any gamesmanship. (*See* Trial Tr., Vol. 6, at 1174.) It is, therefore, appropriate for Zydus to respond to that argument in its post-trial submissions. The Court will similarly consider Zydus's argument that the safe harbor cannot protect the '788 patent because the '219 was filed after the issuance of the '788 patent. While this exact argument was not previously raised, Zydus argued in its Trial Brief that the '219 patent was not filed as a result of a restriction requirement imposed on the '788 and, therefore, the § 121 safe

[1] In their correspondence, the parties raise other extraneous issues regarding Zydus's alleged attempt to belatedly impeach Dr. Kawanishi, one of Plaintiffs' expert witnesses, in its post-trial submissions. The Court to declines to address this issue at this time.

harbor does not apply. While Zydus did not precisely raise the issue of timing of the filing of the '219 patent, the Court finds these arguments are sufficiently related such that Plaintiffs would not be prejudiced by consideration of this argument.

The Court will, however, strike Zydus's argument that a restriction requirement in the '984 patent prosecution prevents application of the safe harbor. This argument was not raised at trial or in any of the pre-trial submissions. Tellingly, Zydus requests that the Court take judicial notice of the prosecution history records for the '984 patent to support this argument. (*See* ECF No. 221, at 99 n.48.) The prosecution history of the '984 patent was not made part of the trial record nor does it appear that the patent was mentioned in any way during trial.[2] Because Plaintiffs have not had any meaningful opportunity to address the merits of this argument, it is stricken and will not be considered by the Court. *See Mannarino v. Morgan Twp.*, 64 F. App'x 844, 846–47 (3d Cir. 2003) (finding that defendant could not raise defense not identified in pre-trial order for first time on appeal).

In light of the Court's ruling on these issues, the parties are directed to inform the Court, in writing, by December 11, 2020, whether closing arguments remain necessary.

/s/ Freda L. Wolfson
Freda L. Wolfson
U.S. Chief District Judge

[2] In support of its request that the Court take judicial notice of the prosecution history of the '984 patent, Zydus points to *Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948 (Fed. Cir. 1993). In that case, however, the Federal Circuit determined that it could take judicial notice of the publicly accessible patent prosecution history where it was referred to at the argument. *Id.* at 954 n.27.

US007943788B2

(12) **United States Patent**
Nomura et al.

(10) **Patent No.: US 7,943,788 B2**
(45) **Date of Patent: May 17, 2011**

(54) **GLUCOPYRANOSIDE COMPOUND**

(75) Inventors: **Sumihiro Nomura**, Kawaguchi (JP); **Eiji Kawanishi**, Kitamoto (JP); **Kiichiro Ueta**, Wako (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-shi (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1079 days.

(21) Appl. No.: **11/045,446**

(22) Filed: **Jan. 31, 2005**

(65) **Prior Publication Data**

US 2005/0233988 A1 Oct. 20, 2005

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/JP2004/011312, filed on Jul. 30, 2004.

(60) Provisional application No. 60/491,534, filed on Aug. 1, 2003.

(51) **Int. Cl.**

C07D 409/00	(2006.01)
A01N 43/04	(2006.01)
C07D 277/04	(2006.01)
C07D 277/08	(2006.01)
C07D 487/00	(2006.01)
C07D 257/04	(2006.01)
C07D 257/10	(2006.01)
C07D 403/00	(2006.01)

(52) **U.S. Cl.** **549/60**; 514/23; 548/146; 548/250

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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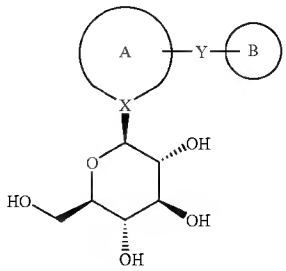
Primary Examiner — Layla Bland
(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

A compound of the formula:

(I)



wherein Ring A and Ring B are: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring or an optionally substituted unsaturated fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, and Ring B are independently an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring;
X is a carbon atom or a nitrogen atom;
Y is $—(CH_2)_n—$ (n is 1 or 2);
a pharmaceutically acceptable salt thereof, or a prodrug thereof.

26 Claims, No Drawings

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GLUCOPYRANOSIDE COMPOUND

This application is a Continuation-In-Part of co-pending PCT International Applications No. PCT/JP2004/011312 filed on Jul. 30, 2004, which designated the United States and on which priority is claimed under 35 U.S.C. §120, which claims priority of Provisional Application No. 60/491,534 filed Aug. 1, 2003, the entire contents of which are hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to a novel compound having an inhibitory activity against sodium-dependent glucose transporter (SGLT) being present in the intestine or kidney.

BACKGROUND ART

Diet therapy and exercise therapy are essential in the treatment of diabetes mellitus. When these therapies do not sufficiently control the conditions of patients, insulin or an oral antidiabetic agent is additionally used for the treatment of diabetes. At the present, there have been used as an antidiabetic agent biguanide compounds, sulfonylurea compounds, insulin resistance improving agents and α-glucosidase inhibitors. However, these antidiabetic agents have various side effects. For example, biguanide compounds cause lactic acidosis, sulfonylurea compounds cause significant hypoglycemia, insulin resistance improving agents cause edema and heart failure, and α-glucosidase inhibitors cause abdominal bloating and diarrhea. Under such circumstances, it has been desired to develop novel drugs for treatment of diabetes mellitus having no such side effects.

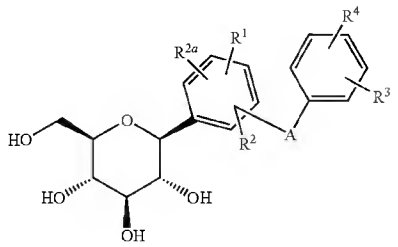
Recently, it has been reported that hyperglycemia participates in the onset and progressive impairment of diabetes mellitus, i.e., glucose toxicity theory. Namely, chronic hyperglycemia leads to decrease of insulin secretion and further to decrease of insulin sensitivity, and as a result, the blood glucose concentration is increased so that diabetes mellitus is self-exacerbated [cf., Diabetologia, vol. 28, p. 119 (1985); Diabetes Care, vol. 13, p. 610 (1990), etc.]. Therefore, by treating hyperglycemia, the aforementioned self-exacerbating cycle is interrupted so that the prophylaxis or treatment of diabetes mellitus is made possible.

As one of the methods for treating hyperglycemia, it is considered to excrete an excess amount of glucose directly into urine so that the blood glucose concentration is normalized. For example, by inhibiting sodium-dependent glucose transporter being present at the proximal convoluted tubule of kidney, the re-absorption of glucose at the kidney is inhibited, by which the excretion of glucose into urine is promoted so that the blood glucose level is decreased. In fact, it is confirmed that by continuous subcutaneous administration of phlorizin having SGLT inhibitory activity to diabetic animal models, hyperglycemia is normalized and the blood glucose level thereof can be kept normal for a long time so that the insulin secretion and insulin resistance are improved [cf., Journal of Clinical Investigation, vol. 79, p. 1510 (1987); ibid., vol. 80, p. 1037 (1987); ibid., vol. 87, p. 561 (1991), etc.].

In addition, by treating diabetic animal models with SGLT inhibitory agents for a long time, insulin secretion response and insulin sensitivity of the animals are improved without incurring any adverse affects on the kidney or imbalance in blood levels of electrolytes, and as a result, the onset and progress of diabetic nephropathy and diabetic neuropathy are prevented [cf., Journal of Medicinal Chemistry, vol. 42, p. 5311 (1999); British Journal of Pharmacology, vol. 132, p. 578 (2001), Ueta, Ishihara, Matsumoto, Oku, Nawano, Fujita, Saito, Arakawa, Life Sci., in press (2005), etc.].

From the above, SGLT inhibitors may be expected to improve insulin secretion and insulin resistance by decreasing the blood glucose level in diabetic patients and further prevent the onset and progress of diabetes mellitus and diabetic complications.

WO 01/27128 discloses an aryl C-glycoside compound having the following structure.

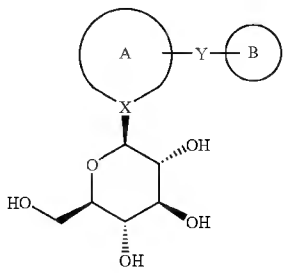


This compound is disclosed to be useful in the prophylaxis or treatment of diabetes mellitus, etc., as an SGLT inhibitor.

DISCLOSURE OF INVENTION

The present invention relates to a compound of the following formula I, or a pharmaceutically acceptable salt thereof, or a prodrug thereof:

(I)



wherein Ring A and Ring B are one of the followings: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring wherein Y is linked to the heterocyclic ring of the fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, wherein the sugar moiety X—(sugar) and the moiety —Y— (Ring B) are both on the same heterocyclic ring of the fused heterobicyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring;

X is a carbon atom or a nitrogen atom; and

Y is —$(CH_2)_n$— (wherein n is 1 or 2).

The compound of the formula I exhibits an inhibitory activity against sodium-dependent glucose transporter being present in the intestine and the kidney of mammalian species, and is useful in the treatment of diabetes mellitus or diabetic complications such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, obesity, and delayed wound healing.

BEST MODE FOR CARRYING OUT THE INVENTION

Hereinafter, the present compound (I) is illustrated in more detail.

The definitions for each term used in the description of the present invention are listed below.

The term "halogen atom" or "halo" means chlorine, bromine, fluorine and iodine, and chlorine and fluorine are preferable.

The term "alkyl group" means a straight or branched saturated monovalent hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkyl group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkyl group having 1 to 4 carbon atoms is more preferable. Examples thereof are methyl group, ethyl group, propyl group, isopropyl group, butyl group, t-butyl group, isobutyl group, pentyl group, hexyl group, isohexyl group, heptyl group, 4,4-dimethylpentyl group, octyl group, 2,2,4-trimethylpentyl group, nonyl group, decyl group, and various branched chain isomers thereof. Further, the alkyl group may optionally and independently be substituted by 1 to 4 substituents as listed below, if necessary.

The term "alkylene group" or "alkylene" means a straight or branched divalent saturated hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkylene group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkylene group having 1 to 4 carbon atoms is more preferable. Examples thereof are methylene group, ethylene group, propylene group, trimethylene group, etc. If necessary, the alkylene group may optionally be substituted in the same manner as the above-mentioned "alkyl group".

Where alkylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The term "alkenyl group" means a straight or branched monovalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. Preferable alkenyl group is a straight chain or branched chain alkenyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkenyl group having 2 to 4 carbon atoms is more preferable. Examples thereof are vinyl group, 2-propenyl group, 3-butenyl group, 2-butenyl group, 4-pentenyl group, 3-pentenyl group, 2-hexenyl group, 3-hexenyl group, 2-heptenyl group, 3-heptenyl group, 4-heptenyl group, 3-octenyl group, 3-nonenyl group, 4-decenyl group, 3-undecenyl group, 4-dodecenyl group, 4,8,12-tetradecatrienyl group, etc. The alkenyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "alkenylene group" means a straight or branched divalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. The straight chain or branched chain alkenylene group having 2 to 6 carbon atoms is preferable, and the straight chain or branched chain alkenylene group having 2 to 4 carbon atoms is more preferable.

Examples thereof are vinylene group, propenylene group, butadienylene group, etc. If necessary, the alkylene group may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary.

Where alkenylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle (e.g., a fused benzene ring) together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The term "alkynyl group" means a straight or branched monovalent hydrocarbon chain having at least one triple bond. The preferable alkynyl group is a straight chain or branched chain alkynyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkynyl group having 2 to 4 carbon atoms is more preferable. Examples thereof are 2-propynyl group, 3-butynyl group, 2-butynyl group, 4-pentynyl group, 3-pentynyl group, 2-hexynyl group, 3-hexynyl group, 2-heptynyl group, 3-heptynyl group, 4-heptynyl group, 3-octynyl group, 3-nonynyl group, 4-decynyl group, 3-undecynyl group, 4-dodecynyl group, etc. The alkynyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "cycloalkyl group" means a monocyclic or bicyclic monovalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms is more preferable. Examples thereof are a monocyclic alkyl group and a bicyclic alkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, cyclodecyl group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. The cycloalkyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the condensed unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkylidene group" means a monocyclic or bicyclic divalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 6 carbon atoms is preferable. Examples thereof are a monocyclic alkylidene group and a bicyclic alkylidene group such as cyclopropylidene group, cyclobutylidene group, cyclopentylidine group, cyclohexylidene group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkylidene group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkenyl group" means a monocyclic or bicyclic monovalent unsaturated hydrocarbon ring having 4 to 12 carbon atoms and having at least one double bond. The preferable cycloalkenyl group is a monocyclic unsaturated hydrocarbon group having 4 to 7 carbon atoms. Examples thereof are monocyclic alkenyl groups such as cyclopentenyl group, cyclopentadienyl group, cyclohexenyl group, etc.

These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkenyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkynyl group" means a monocyclic or bicyclic unsaturated hydrocarbon ring having 6 to 12 carbon atoms, and having at least one triple bond. The preferable cycloalkynyl group is a monocyclic unsaturated hydrocarbon group having 6 to 8 carbon atoms. Examples thereof are monocyclic alkynyl groups such as cyclooctynyl group, cyclodecynyl group. These groups may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkynyl group may optionally and independently be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "aryl group" means a monocyclic or bicyclic monovalent aromatic hydrocarbon group having 6 to 10 carbon atoms. Examples thereof are phenyl group, naphthyl group (including 1-naphthyl group and 2-naphthyl group). These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the aryl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "unsaturated monocyclic heterocyclic ring" means an unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the preferable one is a 4- to 7-membered saturated or unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof are pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, 4,5-dihydrooxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole, etc. Among them, pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, oxazole, and thiazole can be preferably used. The "unsaturated monocyclic heterocyclic ring" may optionally and independently be substituted by 1-4 substituents as mentioned below, if necessary.

The term "unsaturated fused heterobicyclic ring" means hydrocarbon ring comprised of a saturated or a unsaturated hydrocarbon ring condensed with the above mentioned unsaturated monocyclic heterocyclic ring where said saturated hydrocarbon ring and said unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO, or SO_2 within the ring, if necessary. The "unsaturated fused heterobicyclic ring" includes, for example, benzothiophene, indole, tetrahydrobenzothiophene, benzofuran, isoquinoline, thienothiophene, thienopyridine, quinoline, indoline, isoindoline, benzothiazole, benzoxazole, indazole, dihydro-isoquinoline, etc. Further, the "heterocyclic ring" also includes possible N- or S-oxides thereof.

The term "heterocyclyl" means a monovalent group of the above-mentioned unsaturated monocyclic heterocyclic ring or unsaturated fused heterobicyclic ring and a monovalent group of the saturated version of the above-mentioned unsaturated monocyclic heterocyclic or unsaturated fused heterobicyclic ring. If necessary, the heterocyclyl may optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "alkanoyl group" means a formyl group and ones formed by binding an "alkyl group" to a carbonyl group.

The term "alkoxy group" means ones formed by binding an "alkyl group" to an oxygen atom.

The substituent for the above each group includes, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro group, a cyano group, an oxo group. a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group. a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenyl-sulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cyclo-alkenylsulfonyl group, a cycloalkynylsulfonyl group, an aryl-sulfonyl group, and a heterocyclylsulfonyl group. Each group as mentioned above may optionally be substituted by these substituents.

Further, the terms such as a haloalkyl group, a halo-lower alkyl group, a haloalkoxy group, a halo-lower alkoxy group, a halophenyl group, or a haloheterocyclyl group mean an alkyl group, a lower alkyl group, an alkoxy group, a lower alkoxy group, a phenyl group or a heterocyclyl group (hereinafter, referred to as an alkyl group, etc.) being substituted by one or more halogen atoms, respectively. Preferable ones are an alkyl group, etc. being substituted by 1 to 7 halogen atoms, and more preferable ones are an alkyl group, etc. being substituted by 1 to 5 halogen atoms. Similarly, the terms such as

a hydroxyalkyl group, a hydroxy-lower alkyl group, a hydroxy-alkoxy group, a hydroxy-lower alkoxy group and a hydroxyphenyl group mean an alkyl group, etc., being substituted by one or more hydroxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 hydroxy groups, and more preferable ones are analkyl group, etc., being substituted by 1 to 2 hydroxy groups. Further, the terms such as an alkoxyalkyl group, a lower alkoxyalkyl group, an alkoxy-lower alkyl group, a lower alkoxy-lower alkyl group, an alkoxyalkoxy group, a lower alkoxyalkoxy group, an alkoxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, an alkoxyphenyl group, and a lower alkoxyphenyl group means an alkyl group, etc., being substituted by one or more alkoxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 alkoxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 alkoxy groups.

The terms "arylakyl" and "arylalkoxy" as used alone or as part of another group refer to alkyl and alkoxy groups as described above having an aryl substituent.

The term "lower" used in the definitions for the formulae in the present specification means a straight or branched carbon chain having 1 to 6 carbon atoms, unless defined otherwise. More preferably, it means a straight or branched carbon chain having 1 to 4 carbon atoms.

The term "prodrug" means an ester or carbonate, which is formed by reacting one or more hydroxy groups of the compound of the formula I with an acylating agent substituted by an alkyl, an alkoxy or an aryl by a conventional method to produce acetate, pivalate, methylcarbonate, benzoate, etc. Further, the prodrug includes also an ester or amide, which is similarly formed by reacting one or more hydroxy groups of the compound of the formula I with an α-amino acid or a β-amino acid, etc. using a condensing agent by a conventional method.

The pharmaceutically acceptable salt of the compound of the formula I includes, for example, a salt with an alkali metal such as lithium, sodium, potassium, etc.; a salt with an alkaline earth metal such as calcium, magnesium, etc.; a salt with zinc or aluminum; a salt with an organic base such as ammonium, choline, diethanolamine, lysine, ethylenediamine, t-butylamine, t-octylamine, tris(hydroxymethyl)aminomethane, N-methyl glucosamine, triethanolamine and dehydroabietylamine; a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; or a salt with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, etc.; or a salt with an acidic amino acid such as aspartic acid, glutamic acid, etc.

The compound of the present invention also includes a mixture of stereoisomers, or each pure or substantially pure isomer. For example, the present compound may optionally have one or more asymmetric centers at a carbon atom containing any one of substituents. Therefore, the compound of the formula I may exist in the form of enantiomer or diastereomer, or a mixture thereof. When the present compound (I) contains a double bond, the present compound may exist in the form of geometric isomerism (cis-compound, trans-compound). and when the present compound (I) contains an unsaturated bond such as carbonyl, then the present compound may exist in the form of a tautomer, and the present compound also includes these isomers or a mixture thereof. The starting compound in the form of a racemic mixture, enantiomer or diastereomer may be used in the processes for preparing the present compound. When the present compound is obtained in the form of a diastereomer or enantiomer, they can be separated by a conventional method such as chromatography or fractional crystallization.

In addition, the present compound (I) includes an intramolecular salt, hydrate, solvate or polymorphism thereof.

Examples of the optionally substituted unsaturated monocyclic heterocyclic ring of the present invention include an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxyl group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a hetero-cyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenyl-sulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group wherein each substituent may optionally be further substituted by these substituents.

Examples of the optionally substituted unsaturated fused heterobicyclic ring of the present invention include an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidene-methyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenyl-carbonyl group, a cycloalkynyl-carbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl

group, an alkynyloxy-carbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxy-carbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cyclo-alkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cyclo-alkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclyl-carbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoyl-amino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkyl-sulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cyclo-alkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group, wherein each substituent may optionally be further substituted by these substituents.

Examples of the optionally substituted benzene ring of the present invention include a benzene ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group. an alkenyloxy group, an alkynyloxy group. a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group. a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group. a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, a heterocyclylsulfonyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group wherein each substituent may optionally be further substituted by these substituents. Moreover, examples of the optionally substituted benzene ring include a benzene ring substituted with an alkylene group to form an annelated carbocycle together with the carbon atoms to which they are attached, and also includes a benzene ring substituted with an alkenylene group to form an annelated carbocycle such as a fused benzene ring together with the carbon atoms to which they are attached.

Preferable examples of the optionally substituted unsaturated monocyclic heterocyclic ring include an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group. an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

Preferable examples of the optionally substituted unsaturated fused heterobicyclic ring include an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cyclo-alkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

Preferable examples of the optionally substituted benzene ring include a benzene ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group. an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group. an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group.

In another preferable embodiment of the present invention, the optionally substituted unsaturated monocyclic heterocy-

clic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, phenylsulfonyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, a mono- or di-alkylamino group, a carboxyl group, an alkoxycarbonyl group, a phenyl group, an alkyleneoxy group, an alkylenedioxy group, an oxo group, a carbamoyl group, and a mono- or di-alkylcarbamoyl group.

In a preferable embodiment, the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group. an alkanoylamino group, an alkoxycarbonylamino group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, analkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom. a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, an alkoxycarbonyl group, a carbamoyl group and a mono- or di-alkylcarbamoyl group.

In another preferable embodiment,

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

(2) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl

group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group; or

(3) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group;

wherein each of the above-mentioned substituents on Ring A and Ring B may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, an alkoxycarbonyl group, a carbamoyl group and a mono- or di-alkylcarbamoyl group.

In a more preferable embodiment of the present invention, Ring A and Ring B are

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group;

(2) Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a phenyl group, or a lower alkenylene group, and Ring B is (a) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, or a carbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group or a carbamoyl group; (b) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected

from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or

(3) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group.

In another more preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which is substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a phenyl group, and a lower alkenylene group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxy phenyl group, a lower alkylenedioxyphenyl group, a lower alkyleneoxy phenyl group, a mono- or di-lower alkylaminophenyl group, a carbamoyl phenyl group, a mono- or di-lower alkylcarbamoylphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, a lower alkoxyheterocyclyl group, a mono- or di-lower alkylaminoheterocycyclyl group, a carbamoylheterocyclyl group, and a mono- or di-lower alkylcarbamoyl group.

In another more preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is a benzene ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, and a lower alkoxyheterocyclyl group.

Further, in another preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, and a lower alkoxyheterocyclyl group. In a more preferable embodiment of the present invention, X is a carbon atom and Y is —CH_2—.

Further, in another preferable embodiment, Ring A and Ring B are

(1) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, a phenyl group, and a lower alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, or a carbamoyl group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group or a carbamoyl roup; and an oxo group,

(2) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group, and

Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group

consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a lower alkylene group,

(3) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group;

(4) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and a lower alkylene group, or

(5) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group.

In another preferable embodiment of the present invention, Y is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group, or a phenyl group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and an oxo group.

In another more preferable embodiment of the present invention, Y is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a substituent selected from a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and a lower alkylene group.

Preferable examples of unsaturated monocyclic heterocyclic ring include a 5- or 6-membered unsaturated heterocyclic ring containing 1 or 2 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are furan, thiophene, oxazole, isoxazole, triazole, tetrazole, pyrazole, pyridine, pyrimidine, pyrazine, dihydroisoxazole, dihydropyridine, and thiazole. Preferable unsaturated fused heterobicyclic ring includes a 9- or 10-membered unsaturated fused heterocyclic ring containing 1 to 4 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are indoline, isoindoline, benzothiazole, benzoxazole, indole, indazole, quinoline, isoquinoline, benzothiophene, benzofuran, thienothiophene, and dihydroisoquinoline.

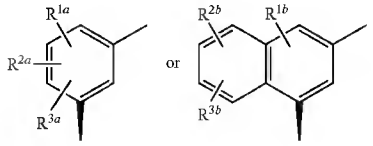
In a more preferred embodiment of the present invention, Ring A is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a phenyl group, and Ring B is a heterocyclic ring selected from the group consisting of thiophene, furan, benzofuran, benzothiophene, and benzothiazole, wherein the heterocyclic ring may optionally be substituted by a substituent selected from the following group: a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a lower alkylphenyl group, a lower alkox-

yphenyl group, a thienyl group, a halothienyl group, a pyridyl group, a halopyridyl group, and a thiazolyl group.

In yet another preferred embodiment, Y is —CH_2—, Ring A is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring selected from the group consisting of thiophene, dihydroisoquinoline, dihydroisoxazole, triazole, pyrazole, dihydropyridine, dihydroindole, indole, indazole, pyridine, pyrimidine, pyrazine, quinoline, and a isoindoline, wherein the heterocyclic ring may optionally substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

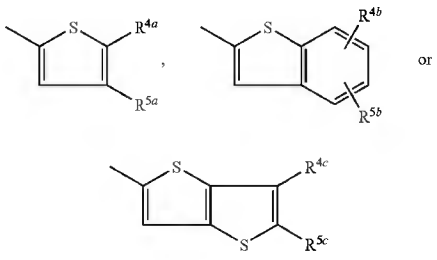
In a further preferred embodiment of the present invention, Ring A is a benzene ring which is substituted by a halogen atom or a lower alkyl group, and Ring B is thienyl group which is substituted by phenyl group or a heterocyclyl group in which said phenyl group and heterocyclyl group is substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

Further, in another aspect of the present invention, preferable examples of the compound of the formula I include a compound wherein Ring A is



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



wherein R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group. an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, a mono- or di-alkylamino group, a carbamoyl group, or a mono- or di-alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, a carbamoyl group, or a mono- or di-alkylcarbamoyl group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form an alkylene group; and

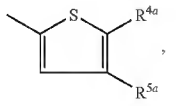
R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group or a haloalkoxy group.

More preferred is a compound wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom. a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;

R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group; and

R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

Further preferred is a compound in which Ring B is

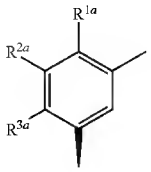


wherein R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, and

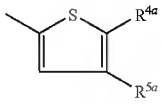
R^{5a} is a hydrogen atom, or

R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group.

Further more preferred is a compound in which Ring A is



wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is

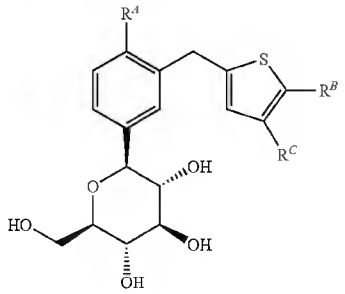


wherein R^{4a} is a phenyl group optionally substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, and R^{5a} is a hydrogen atom, and Y is —CH_2—.

In more preferable embodiment, R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

In another preferable embodiment of the present invention, a preferable compound can be represented by the following formula IA:

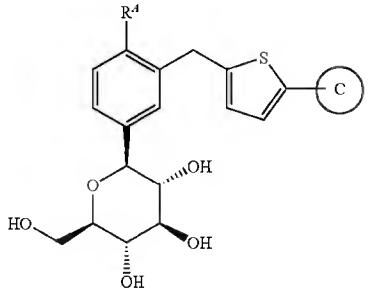
(IA)



wherein R^A is a halogen atom, a lower alkyl group or a lower alkoxy group; R^B is a phenyl group optionally substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, amono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; and R^c is hydrogen atom; or R^B and R^c taken together are a fused benzene ring which may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group.

In a preferable embodiment, R^A is a halogen atom or a lower alkyl group, R^c is hydrogen atom, and R^B is phenyl group substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group. The chemical structure of such compounds are represented by the following formula (IA')

(IA')



wherein R^A is a halogen atom, or a lower alkyl group, Ring C is a phenyl group substituted by 1-3 substituents selected

from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group.

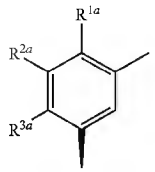
In a more preferable embodiment, Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

Among them, a compound in which Ring C is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group is preferred.

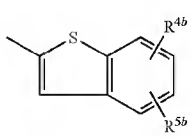
A preferred heterocyclyl group includes a 5- or 6-membered heterocyclyl group containing 1 or 2 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom, or a 9- or 10-membered heterocyclyl group containing 1 to 4 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. Specifically, a thienyl group, a pyridyl group, a pyrimidyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, a tetrazolyl group and an oxazolyl group are preferred.

In a further preferable embodiment, Ring C is a phenyl group substituted by a halogen atom or a cyano group, or a pyridyl group substituted by a halogen atom.

In another preferable embodiment of the present invention, preferred is a compound in which Ring A is



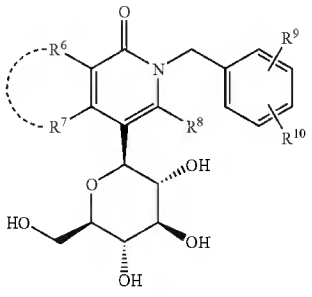
wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is



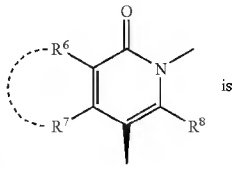
wherein R^{4b} and R^{5b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

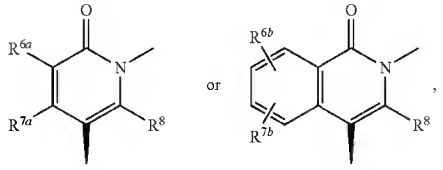
In another aspect of the present invention, preferable examples of the compound I include a compound represented by the following formula IB:

(IB)



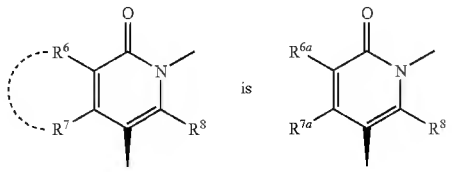
wherein R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group; and a group represented by:


is

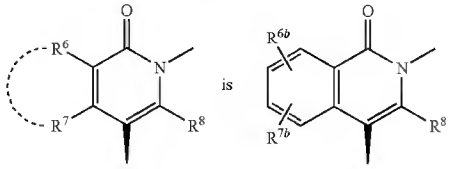


wherein R^{6a} and R^{7a} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group and R^{6b} and R^{7b} are each independently a hydrogen atom, a halogen atom, an alkyl group, a haloalkyl group, or an alkoxy group.

Among the compounds represented by the formula IB, more preferred is a compound in which R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a cycloalkoxy group, a halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, and a group represented by:



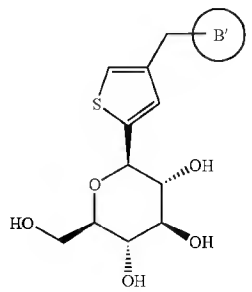
wherein R^a, R^{7a} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a cycloalkoxy group, a halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, or a group represented by:



wherein R^{6b} and R^{7b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group.

In another aspect of the present invention, preferable examples of the compound I include a compound represented by the following formula IC:

(IC)



wherein Ring B' is an optionally substituted benzene ring, an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring.

Preferable examples of Ring B' include a benzene ring and a heterocyclic ring, both of which may have a substituent (s) selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a lower alkanoyl group; a mono- or di-lower alkylamino group; a lower alkoxycarbonyl group; a carbamoyl group; a mono- or di-lower alkylcarbamoyl group; a phenyl group optionally substituted by a substituent(s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; a heterocyclyl group optionally substituted by a substituent (s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; an alkylene group; and an oxo group.

More preferable examples of Ring B' include a benzene ring which may be substituted by a substituent selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom.

Preferred compound of the present invention may be selected from the following group:

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b] thiophen-2-ylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(5-thiazolyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-(5-phenyl-2-thienylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethylphenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene;

the pharmaceutically acceptable salt thereof; and

the prodrug thereof.

Particularly Preferred compounds of the present invention include:

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof; and

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyano-phenyl)-2-thienylmethyl)benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

The compound (I) of the present invention exhibits an excellent inhibitory activity against sodium-dependent glucose transporter, and an excellent blood glucose lowering effect. Therefore, the compound of the present invention is usefule for treating or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension. In particuler, the compound of the present invention is useful in the treatment or the prophylaxis of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy) or obesity, or is useful in the treatment of postprandial hyperglycemia.

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparation for oral administration includes, for example, solid preparation such as tablets, granules, capsules, powders, etc., or solution preparations, suspension preparations, or emulsion preparations, etc. Suitable pharmaceutical preparation for parenteral administration includes, for example, suppositories; injection preparations and intravenous drip preparations using distilled water for injection, physiological saline solution or aqueous glucose solution; or inhalant preparations.

The dosage of the present compound (I) or a pharmaceutically acceptable salt thereof may vary according to the administration routes, ages, body weight, conditions of a patient, or kinds and severity of a disease to be treated, and it is usually in the range of about 0.1 to 50 mg/kg/day, preferably in the range of about 0.1 to 30 mg/kg/day.

The compound of the formula I may be used, if necessary, in combination with one or more of other antidiabetic agents, one or more agents for treating diabetic complications, and/or one or more agents for treatment of other diseases. The present compound and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The other antidiabetic agents include, for example, antidiabetic or antihyperglycemic agents including insulin, insulin secretagogues, or insulin sensitizers, or other antidiabetic agents having an action mechanism different from SGLT inhibition, and 1, 2, 3 or 4 of these other antidiabetic agents may preferably be used. Concrete examples thereof are biguanide compounds, sulfonylurea compounds, α-glucosidase inhibitors, PPARγ agonists (e.g., thiazolidinedione compounds), PPARα/γ dual agonists, dipeptidyl peptidase IV (DPP4) inhibitors, mitiglinide compounds, and/or nateglinide compounds, and insulin, glucagon-like peptide-1 (GLP-1), PTP1B inhibitors, glycogen phosphorylase inhibitors, RXR modulators, and/or glucose 6-phosphatase inhibitors.

The agents for treatment of other diseases include, for example, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an anti-atherosclerotic agent and/or a hypolipidemic agent.

The SGLT inhibitors of the formula I may be used in combination with agents for treatment of diabetic complications, if necessary. These agents include, for example, PKC inhibitors and/or ACE inhibitors.

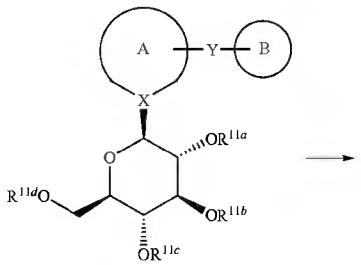
The dosage of those agents may vary according to ages, body weight, and conditions of patients, and administration routes, dosage forms, etc.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, dogs, etc., for example, in the dosage form of tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The present compound of the formula I may be prepared by the following Processes.

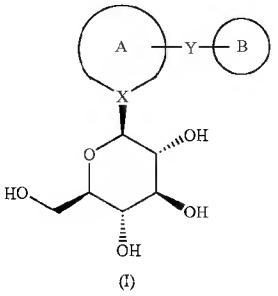
Process 1

The compound of the formula I may be prepared by a method as shown in the following scheme:



(II)

-continued



(I)

wherein R^{11a} is a hydrogen atom or a protecting group for a hydroxy group, and R^{11a}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group, and other symbols are as defined above.

The compound of the formula I may be prepared by deprotecting the compound of the formula II.

In the compound of the formula II, the protecting group for hydroxy group may be any conventional protecting groups, and a benzyl group, an acetyl group, and an alkylsily group such as a trimethylsilyl group may be used. Further, the protecting group for hydroxy group may form acetal or silylacetal together with adjacent hydroxy groups. Examples of such protecting group include an alkylidene group such as an isopropylidene group, a sec-butylidene group, etc., a benzylidene group, or a dialkylsilylene group such as di-tert-butylsilylene group, etc., which can be formed, for example, by combining R^{11c} and R^{11d} at the terminal thereof.

The deprotection can be carried out according to the kinds of protecting group to be removed, for example, by conventional processes such as reduction, hydrolysis, acid treatment, fluoride treatment, etc.

For example, when a benzyl group is to be removed, the deprotection can be carried out by (1) catalytic reduction using a palladium catalyst (e.g., palladium-carbon, palladium hydroxide) under hydrogen atmosphere in a suitable solvent (e.g., methanol, ethanol. ethyl acetate); (2) treatment with an dealkylating agent such as boron tribromide, boron trichloride, boron trichloride dimethylsulfide complex, or iodotrimethylsilane in a suitable solvent (e.g., dichloromethane); or (3) treatment with a lower alkylthiol such as ethanethiol in the presence of a Lewis acid (e.g., boron trifluoride.diethyl ether complex) in a suitable solvent (e.g., dichloromethane).

When a protecting group is removed by hydrolysis, the hydrolysis can be carried out by treating the compound of formula II with a base (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, sodium ethoxide, etc.) in a suitable solvent (e.g., tetrahydrofuran, dioxane, methanol, ethanol, water, etc.).

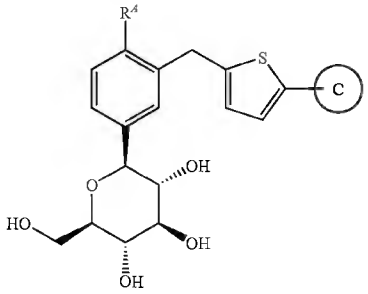
Acid treatment can be carried out by treating the compound of formula II with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

In case of the fluoride treatment, it can be carried out by treating the compound of formula II with a fluoride (e.g., hydrogen fluoride, hydrogen fluoride-pyridine, tetrabutylammonium fluoride, etc.) in a suitable solvent (e.g., acetic acid, a lower alcohol (methanol, ethanol, etc.), acetonitrile, tetrahydrofuran, etc.).

The deprotection reaction can be preferably carried out under cooling or with heating, for example, at a temperature of from 0° C. to 50° C., more preferably at a temperature of from 0° C. to room temperature.

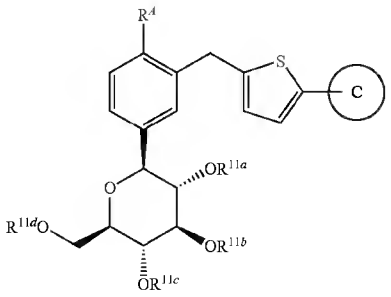
Accordingly, a compound of formula (IA'):

(IA')



wherein the symbols are the same as defined above, can be prepared by deprotecting a compound of formula (II-A):

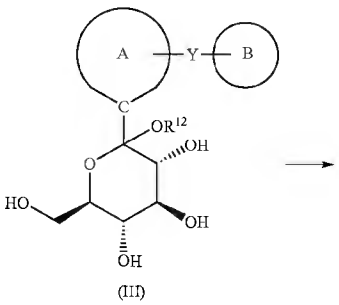
(II-A)



wherein the symbols are the same as defined above, as described above.

Process 2

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(III)

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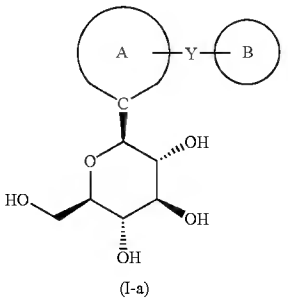


(I-a)

wherein R^{12} is a lower alkyl group, and other symbols are as defined above.

The compound of the formula I-a may be prepared by reducing the compound of the formula III.

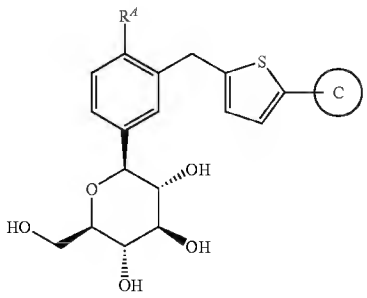
The reduction can be carried out by treatment with a silane reagent, in the presence of an acid, in a suitable solvent or in the absence of a solvent.

As the acid, for example, a Lewis acid such as boron trifluoride.diethyl ether complex, titanium tetrachloride, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc., may preferably be used.

As the silane reagent, for example, a trialkylsilane such as triethylsilane, triisopropylsilane, etc. may preferably be used.

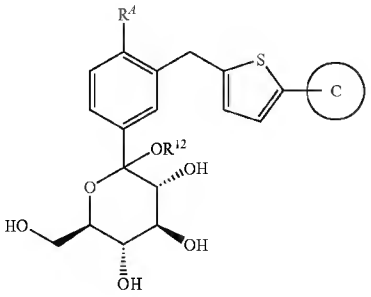
As the solvent, any kinds of solvent may be used as long as it does not affect the reaction, and for example, acetonitrile, dichloromethane, or an acetonitrile/dichloromethane mixture may preferably be used.

Accordingly, the compound of the formula (IA'):



(IA')

wherein the symbols are the same as defined above, can be prepared by reducing a compound of formula (III-A):

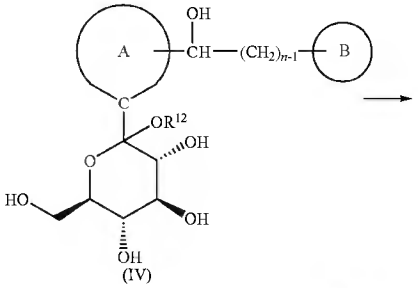


(III-A)

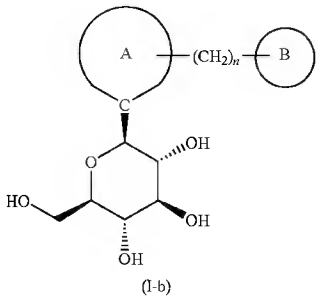
wherein the symbols are the same as defined above, as described above.

Process 3

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(IV)



(I-b)

wherein the symbols are as defined above.

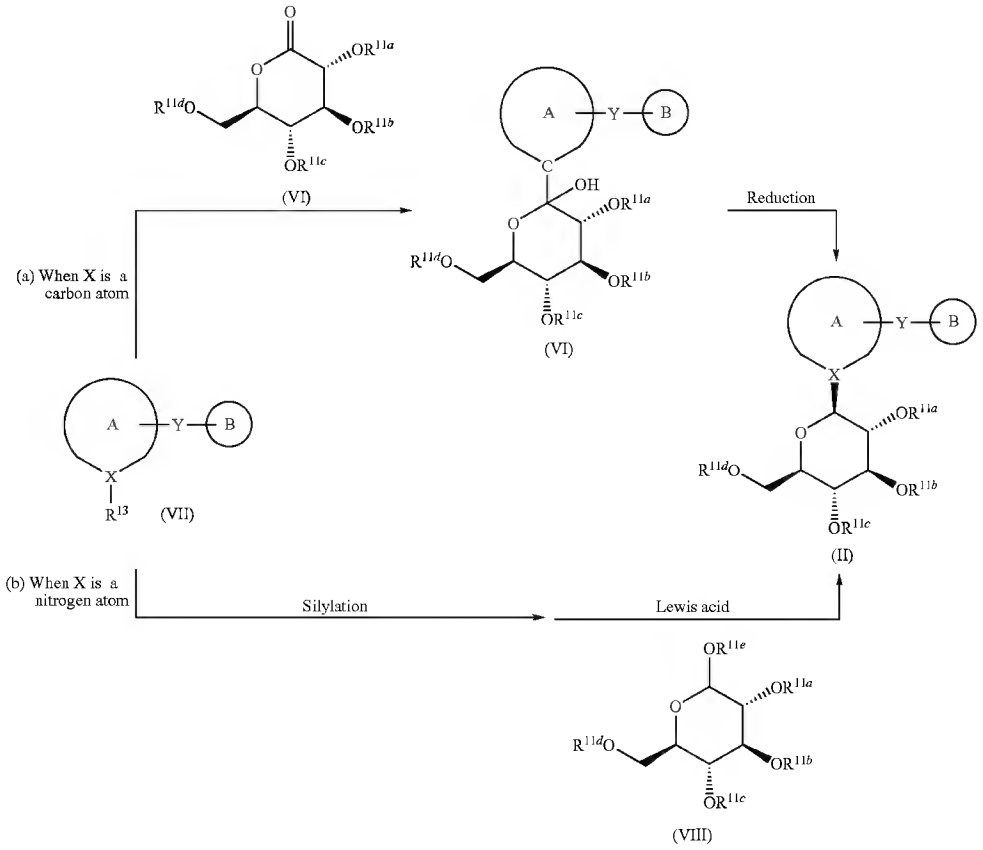
Namely, the compound of the formula I-b may be prepared by reducing the compound of the formula IV.

The reduction can be carried out in a manner similar to Process 2. In other words, it can be carried out by treatment with a silane reagent (e.g., triethylsilane, etc.), in the presence of a Lewis acid (e.g., boron trifluoride.diethyl ether complex, etc.), in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.).

The compound of the present invention thus obtained may be isolated and purified by a conventional method well known in the organic synthetic chemistry such as recrystallization, column chromatography, etc.

The starting compound represented by the formula (II), (III) or (IV) may be prepared by either one of the following steps (a)-(l).

Steps (a) and (b):



In the above scheme, R^{13} is (1) a bromine atom or an iodine atom when X is a carbon atom; or (2) a hydrogen atom when X is a nitrogen atom, R^{11e} is a protecting group for hydroxy group, and the other symbols are as defined above.

Step (a)

Among the compounds of the formula II, the compound wherein X is a carbon atom may be prepared by coupling the compound of the formula VII with the compound of the formula VI to give the compound of formula V, followed by reduction of the compound of the formula V.

The coupling reaction can be carried out by lithiating the compound of the formula VII, followed by reacting the resultant with the compound of the formula VI.

In particular, the compound of the formula VII can be treated with an alkyllithium, followed by reacting the resultant with the compound of the formula VI. As the alkyllithium, methyl lithium, n-butyl lithium, t-butyl lithium, etc. are preferably used. The solvent may be any solvent which does not disturb the reaction, and ethers such as tetrahydrofuran, diethyl ether, etc., are preferably used. This reaction can be carried out from under cooling (e.g., at −78° C.) to room temperature.

The reduction can be carried out in a manner similar to Process 2. Namely, it can be carried out by treating the compound of formula V with a silane reagent (e.g., triethylsilane, etc.) in the presence of a Lewis acid (e.g., boron trifluoride.diethyl ether complex, etc.) in a suitable solvent (e.g., acetonitrile. dichloromethane, etc.).

Step (b)

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by silylating the compound of the formula VII in a solvent, followed by reacting the resultant with the compound of the formula VIII (e.g., an α- or β-D-glucose pentaacetate, etc.) in the presence of a Lewis acid.

The silylation reaction can be carried out by treating the compound of formula VII with a silylating agent in a solvent. The silylating agent includes, for example, N,O-bis(trimethylsilyl)acetamide, 1,1,1,3,3,3-hexamethyl-disilazane, etc.

The solvent may be, for example, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, etc., ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, etc., acetonitrile, etc.

This reaction is preferably carried out under cooling or with heating, for example, at a temperature of from 0° C. to 60° C., preferably at a temperature of from room temperature to 60° C.

The reaction with the compound of the formula VIII can be carried out in a solvent in the presence of a Lewis acid.

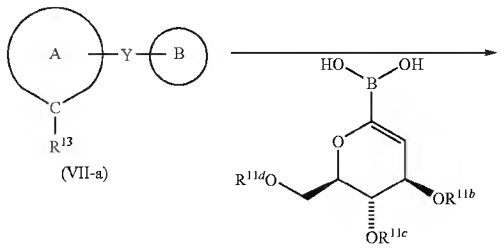
The Lewis acid includes, for example, trimethylsilyl trifluoromethanesulfonate, titanium tetrachloride, tin tetrachloride, boron trifluoride.diethyl ether complex.

The solvent may be, for example, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, etc., acetonitrile, etc.

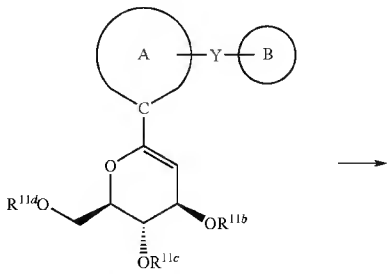
This reaction can be carried out under cooling or with heating, for example, at a temperature of from 0° C. to 100° C., preferably at a temperature of from room temperature to 60° C.

Step (c):

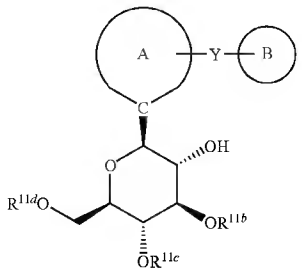
Among the compounds of the formula II, the compound wherein X is a carbon atom and R^{11a} is a hydrogen atom may be prepared by a method as shown in the following scheme:



(VII-a) (X)



(IX)

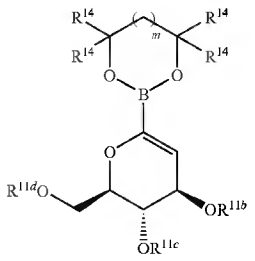


(II-a)

wherein R^{13a} is a bromine atom or an iodine atom, and the other symbols are as defined above.

Namely, the compounds of the formula II-a may be prepared by coupling the compound of the formula VII-a with the compound of the formula X or an ester thereof to give the compound of the formula IX, followed by hydrating the compound of the formula IX.

The ester of the compound of the formula X includes, for example, a lower alkyl ester thereof, and a compound represented by the formula XI:



(XI)

wherein R^{14} is a lower alkyl group, m is 0 or 1, and the other symbols are as defined above.

The coupling reaction of the compound of the formula VII-a with the compound of the formula X or an ester thereof can be carried out in the presence of a base and a palladium catalyst in a suitable solvent.

The base includes an inorganic base such as an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.) an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), potassium fluoride, potassium phosphate, etc., and an organic base such as a tri-lower alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), a cyclic tertiary amine (e.g., 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo [4.3.0]-nona-5-ene, 1,8-diazabicyclo[5.4.0]undeca-7-ene, etc.).

The palladium catalyst may be a conventional catalyst such as tetrakis(triphenyl)phosphine palladium(0), palladium(II) acetate, palladium(II) chloride, bis(triphenyl)phosphine palladium(II) chloride, palladium(II) chloride.1,1-bis(diphenylphosphino)ferrocene complex, etc.

The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., amide solvents such as N,N-dimethylformamide, 1,3-dimethyl-2-imidazolidinone, etc., aromatic hydrocarbons such as toluene, xylene, etc., dimethylsulfoxide, water, and if desired, a mixture of two or more of these solvents.

This reaction is preferably carried out with heating, for example, at a temperature of from 50° C. to a boiling point of the reaction mixture, and more preferably at a temperature of from 50° C. to 100° C.

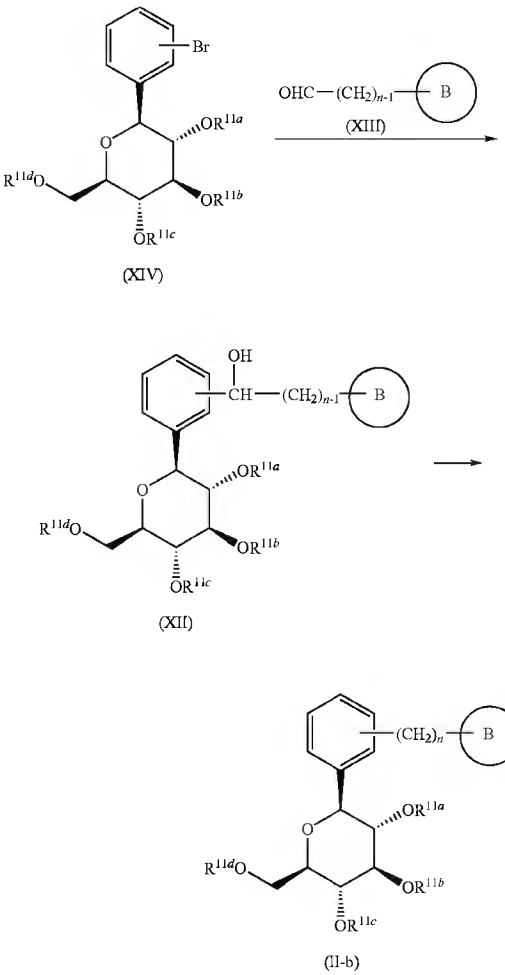
The hydration reaction of the compound of the formula IX can be carried out, for example, by hydroboration, more specifically, by reacting with diborane, borane.tetrahydrofuran complex, or 9-borabicyclononane, etc. in a suitable solvent, followed by treating with hydrogen peroxide solution in the presence of a base (e.g., an alkali metal hydroxide such as sodium hydroxide, etc.), or by treating with an oxidizing reagent such as sodium perborate, and oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) in a suitable solvent.

The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., water, and if desired, a mixture of two or more of these solvents. This reaction can be carried out at a tempera-

ture of a broad range such as under cooling or with heating, and preferably carried out at a temperature of from −10° C. to a boiling point of the reaction mixture.

Step (d):

Among the compound of the formula II, the compound wherein Ring A is a benzene ring may be prepared in a method as shown in the following scheme:



wherein the symbols are as defined above.

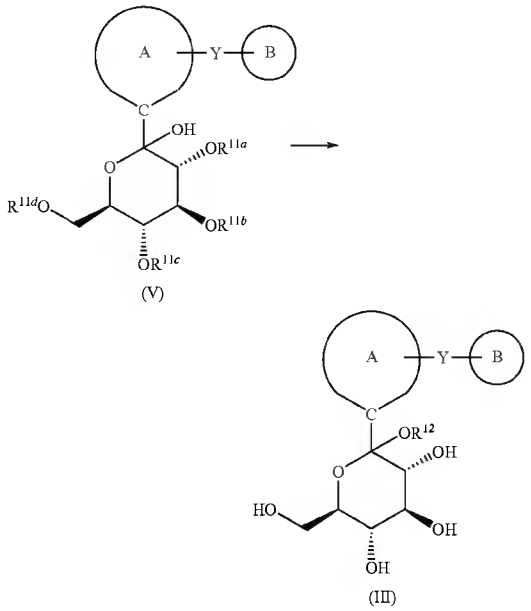
Namely, the compounds of the formula II-b may be prepared by coupling the compound of the formula XIV with the compound of the formula XIII, to give the compound of the formula XII, followed by reduction of the compound of the formula XII.

The coupling reaction can be carried out in a manner similar to Step (a). Namely, it can be carried out by lithiating the compound of formula XIV with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound (XIII).

The reduction reaction can be carried out by (1) treatment with a silane reagent (e.g., trialkyl silane such as triethyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at −30° C. to 60° C., in the presence of a Lewis acid such as boron trifluoride.diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane, or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., and a Lewis acid such as aluminum chloride, etc.).

Step (e):

The compound of the formula III may be prepared by a method as shown in the following scheme:



wherein the symbols are as defined above.

Namely, the compound of the formula III may be prepared by deprotecting the compound of the formula V which is a synthetic intermediate of Step (a), followed by treating the resultant compound with an acid in an alcohol solvent.

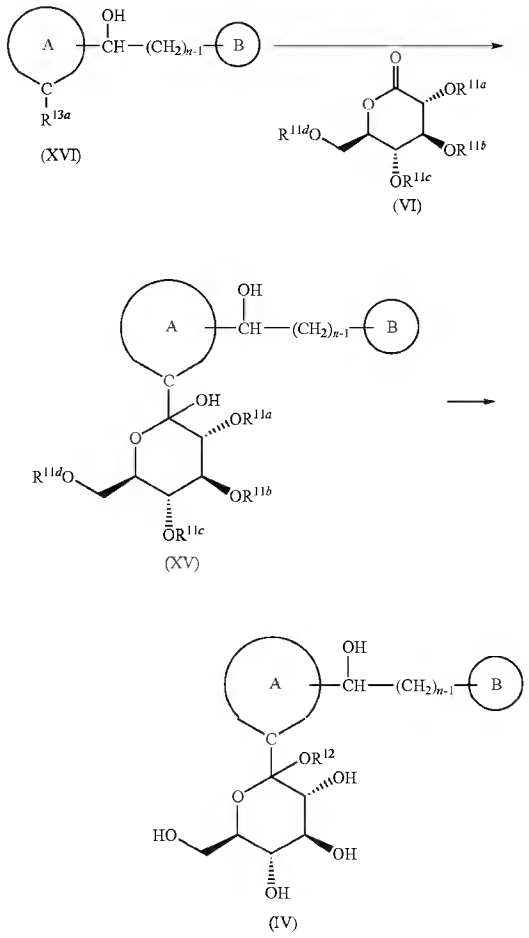
The deprotection reaction can be carried out in a manner similar to Process 1. Namely, it can be carried out by subjecting the compound V to an acid treatment, reduction, or a fluoride treatment, etc.

Following the deprotection reaction, the resultant compound is treated with an acid in a suitable alcohol. The acid includes, for example, an inorganic acid such as hydrochloric acid, nitric acid, sulfuric acid, etc., an organic acid such as p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc. The alcohol includes a conventional alkyl alcohol which does not disturb the reaction, for example, methanol, ethanol, n-propanol, i-propanol. n-butanol, etc.

Additionally, the deprotection reaction and acid treatment may be carried out in the same step, depending on the kind of the protecting group.

Step (f):

The compound of the formula IV may be prepared by a method as shown in the following scheme:



wherein the symbols are as defined as above.

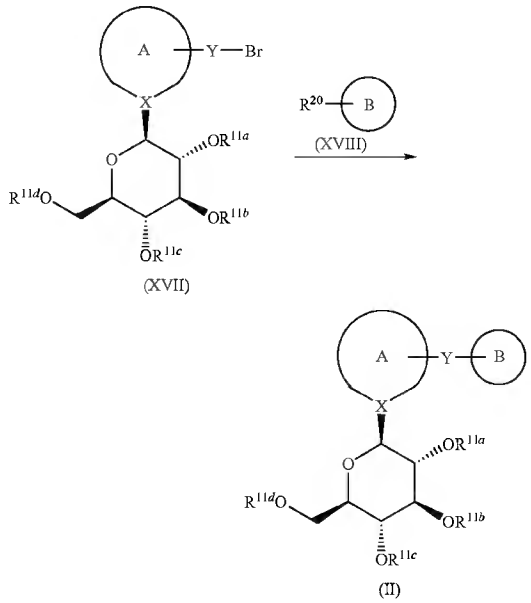
First, the compound of the formula XVI is coupled with the compound of the formula VI to give the compound of the formula XV. Then, after protecting groups are removed from the compound of the formula XV, the resultant is treated with an acid in an alcohol to give the compound of the formula IV.

The coupling reaction can be carried out in a manner similar to Step (a). Namely, the compound XVI is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc,) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound VI.

The removal of protecting groups and the acid treatment are carried out in a manner similar to Step (e). Namely, it can be carried out by subjecting the compound XV to reduction, acid treatment or fluoride treatment, depending on the kind of the protecting group to be removed, followed by treating the resultant with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

Step (g):

The compound of the formula II may be prepared by a method as shown in the following scheme:



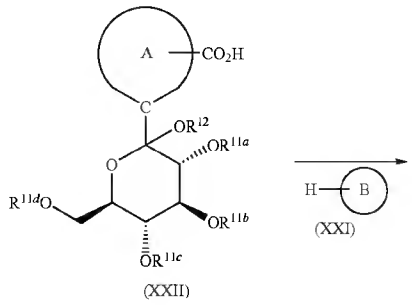
wherein R^{20} is a trialkylstannyl group, a dihydroxyboryl group or an ester thereof, and the other symbols are as defined above. Examples of esters of dihydroxyboryl group include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol.

Namely, the compound of the formula II may be prepared by coupling the compound XVII with the compound XVIII in a suitable solvent, in the presence of a palladium catalyst, and in the presence or in the absence of a base.

The coupling reaction can be carried out in a manner similar to Step (c).

Step (h):

Among the compound of the formula II, the compound wherein n is 1 and X is a carbon atom may be prepared in a method as shown in the following scheme:



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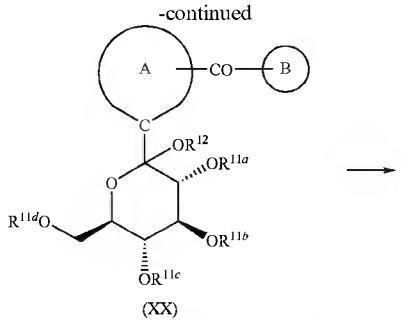
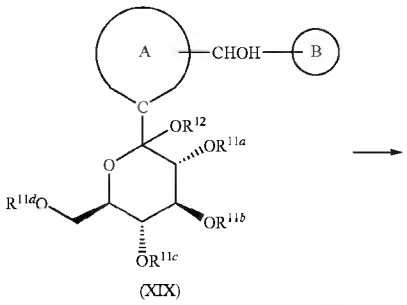
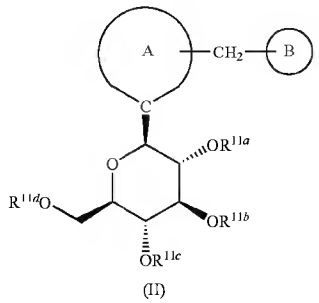


(XX)



(XIX)



(II)

wherein the symbols are as defined above.

Namely, the compound of the formula II may be prepared by the following steps: (1) treating the compound of the formula XXII with a halogenating agent in a suitable solvent or in the absence of a solvent, followed by condensation of the resultant with the compound of the formula XXI in the presence of a Lewis acid to give the compound of formula XX, (2) reducing the compound of formula XX, and (3) further reducing the compound of formula XIX.

The halogenating agent includes a conventional halogenating agent such as thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.

The solvent may be any solvent which does not disturb the reaction, and for example, dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc. may be mentioned.

Further, in the present reaction, the reaction suitably proceeds by adding a catalyst such as dimethylformamide, etc.

The condensation reaction of the compound (XXII) and the compound (XXI) can be carried out according to a conventional method as known as Friedel-Crafts reaction, in the presence of a Lewis acid and in a suitable solvent.

The Lewis acid includes aluminum chloride, boron trifluoride.diethyl ether complex, tin(IV) chloride, titanium tetrachloride, etc. which are conventionally used in Friedel-Crafts reaction.

The solvent includes halogenated hydrocarbons such as dichloromethane, carbon tetrachloride, dichloroethane, etc.

The reduction of the compound of formula XX can be carried out by treating the compound (XX) with borohydrides (e.g., sodium borohydride, sodium triacetoxyborohydride, etc.) in a suitable solvent (e.g., tetrahydrofuran, etc.).

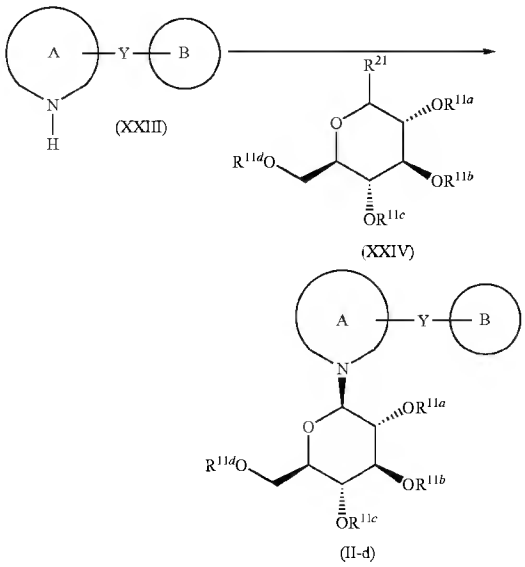
The present reaction can be carried out under cooling or with heating, for example, at a temperature of from −30° C. to 60° C.

The subsequent reduction reaction can be carried out by treating the compound of formula XIX with a silane reagent (e.g., trialkyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride.diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

The present reaction can be carried out under cooling or with heating, for example, at a temperature of from −30° C. to 60° C.

Step (i):

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by a method as shown in the following scheme:



(XXIII) (XXIV) (II-d)

wherein R^{21} is a leaving group, and the other symbols are as defined above.

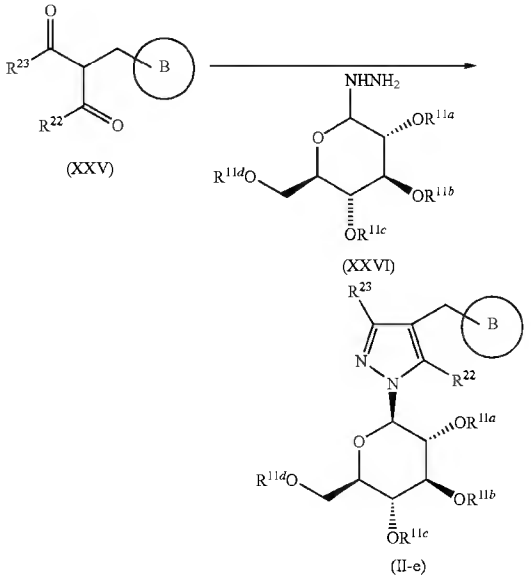
Examples of the leaving group include a halogen atom such as chlorine atom and bromine atom.

Namely, the compound of the formula II-d may be prepared by condensation of the compound of the formula XXIII with the compound of the formula XXIV.

The condensation reaction can be carried out in a suitable solvent such as acetonitrile, etc., in the presence of a base (e.g., an alkali metal hydroxide, such as potassium hydroxide, etc.).

Step (j):

Among the compound of the formula II, the compound wherein Ring A is a pyrazole substituted by a lower alkyl group, X is a nitrogen atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:



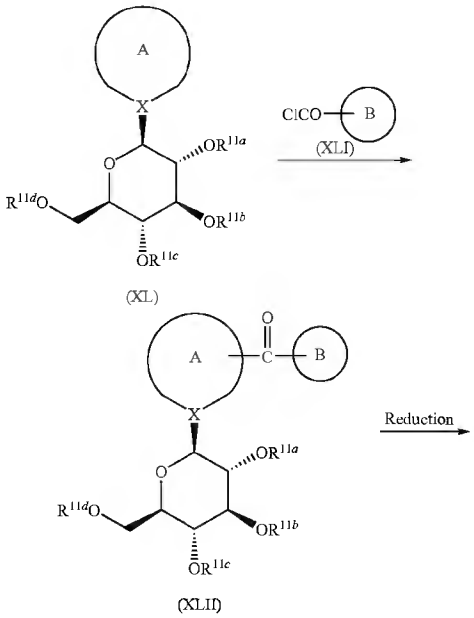
(XXV) (XXVI) (II-e)

wherein R^{22} and R^{23} are each independently a lower alkyl group, and the other symbols are as defined above.

Namely, the compound II-e may be prepared by condensation of the compound of the formula XXV with the compound of the formula XXVI in a suitable solvent (e.g., ethers such as tetrahydrofuran, etc., an aromatic hydrocarbons such as toluene, etc.).

Step (k):

Among the compounds represented by formula (II), a compound wherein Y is $—CH_2—$ group can be prepared by a method as shown in the following scheme:



(XL) (XLI) (XLII)

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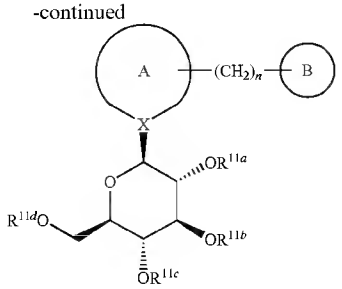


(II-f)

wherein the symbols are the same as defined above.

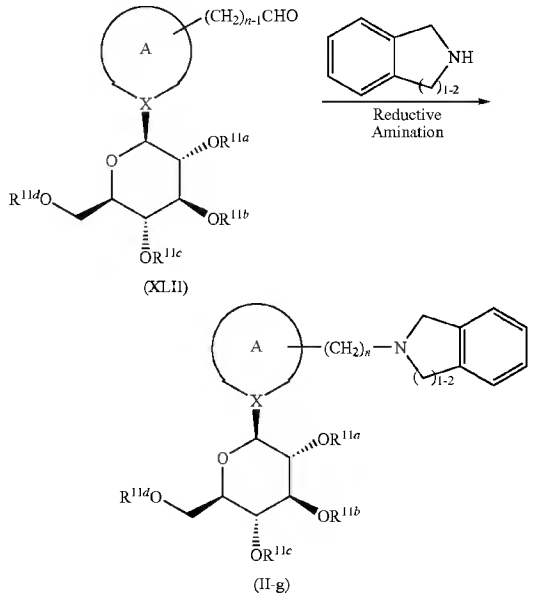
The compound (II-f) can be prepared by condensing a compound of formula (XL) with a compound of formula (XLI), and reducing a compound of formula (XLII).

The condensation reaction can be carried out in a similar manner as described in Step (h). Namely, the condensation reaction can be carried out in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, dichloroethane, etc.) in the presence of a Lewis acid (e.g., aluminum chloride, zinc chloride, titanium tetrachloride, etc.).

The reduction reaction can be carried out in a similar manner as described in Step (h).

Step (l)

Among the compounds represented by the formula (II), a compound wherein Ring B is an isoindolinyl or dihydroisoquinolinyl group can be prepared by a method as shown in the following scheme:



(XLII) (II-g)

wherein the symbols are the same as defined above.

A compound of formula (II-g) can be prepared by reductive amination of a compound of formula (XLIII) with isoindoline or dihydroisoquinoline. Reductive amination can be carried out in a suitable solvent (e.g., tetrahydrofuran, acetic acid, dichloroethane, etc.) in the presence of a reducing agent such

as borohydrides (e.g., sodium borohydride, sodium triacetoxyborohydride) and aluminum hydrides (e.g., lithium aluminum hydride).

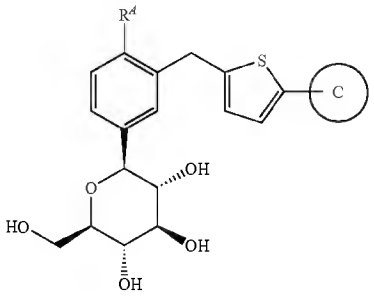
Further, the compound of the present invention may be converted to each other within the objective compounds of the present invention. Such conversion reaction may be carried out according to a conventional method, depending on the kind of the objective substituents. It may be preferable that functional groups in the compound would be protected before the conversion. The protective groups for the functional groups can be selected from conventional ones which can be removed by usual methods.

For example, a compound having as a substituent of Ring B an aryl group such as phenyl group or a heterocyclyl group may be prepared by coupling the compound in which substituents of the Ring B is a halogen atom such as a bromine atom, with a suitable phenylboronic acid, phenyltin, hetercyclylboronic acid, or heterocyclyltin.

The coupling reaction may be carried out in a manner similar to Step (c) or Step (g), or in a method as described in the following Examples.

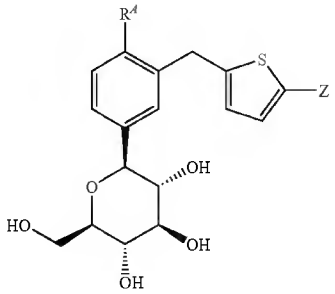
Accordingly, the compound of formula (IA'):

(IA')



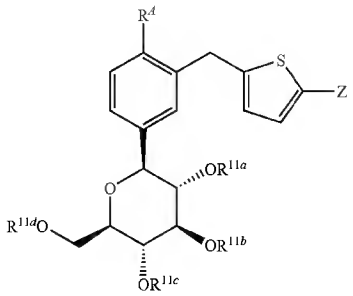
wherein the symbols are the same as defined above, can be prepared by (1) protecting a compound of formula (I-c):

(I-c)



wherein Z is a halogen atom such as chlorine, bromine and iodine atom and R^A is the same as defined above, to afford a compound of formula (II-h):

(II-h)

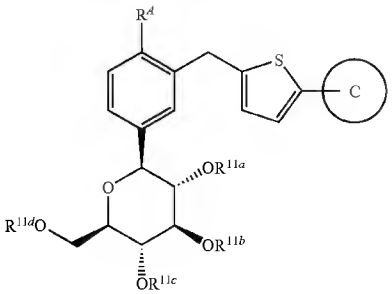


wherein the symbols are the same as defined above, (2) coupling the compound (II-h) with a compound of formula (XLIV):

(XLIV)

wherein R^x is $B(OH)_2$ or an ester thereof, or $Sn(lower\ alkyl)_3$, and Ring C is the same as defined above, to afford a compound of formula (II-A):

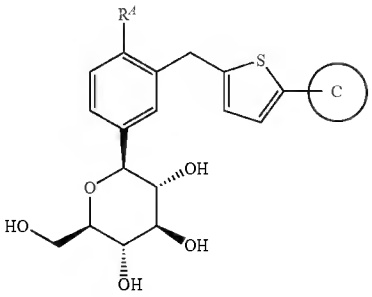
(II-A)



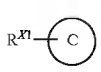
wherein the symbols are the same as defined above, and (3) removing the protecting groups. Examples of esters of $B(OH)_2$ include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol. Protection of hydroxyl groups can be carried out by conventional methods. Coupling reaction and deprotection can be carried out as described in Step (c) or (g) and Process 1, respectively.

Additionally, the compound of formula (IA'):

(IA')



wherein the symbols are the same as defined above, can be prepared by (1) converting Z group of a compound of formula (II-h) to B $(OH)_2$ or an ester thereof, (2) coupling said compound with a compound of formula (XLV):



(XLV)

wherein R^{X1} is a halogen atom such as chlorine, bromine and iodine atom and Ring C is the same as defined above, and (3) removing the protecting groups.

Examples of esters of B $(OH)_2$ include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol.

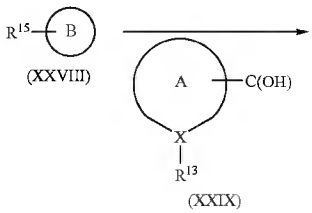
Conversion of a halogen atom to B $(OH)_2$ or an ester thereof can be carried out in a conventional method. For example, conversion of a halogen atom to B $(OH)_2$ can be carried out by treating the compound (II-h) with an alkyl lithium such as tert-butyl lithium in a suitable solvent (e.g., tetrahydrofuran), reacting the resulting compound with a tri-alkoxyborane in a suitable solvent (e.g., tetrahydrofuran), and hydrolyzing the resulting compound with an acid (such as acetic acid). And conversion of a halogen atom to an ester of $B(OH)_2$ can be carried out by treating the compound (II-h) with an alkyl lithium (such as tert-butyl lithium) in a suitable solvent (e.g., tetrahydrofuran), reacting the resulting compound with a tri-alkoxyborane in a suitable solvent (e.g., tetrahydrofuran), and reacting the resulting compound with an appropriate alcohol in a suitable solvent (e.g., tetrahydrofuran) or without solvent. Coupling reaction and deprotection can be carried out as described in Step (c) or (g) and Process 1, respectively.

In the present compound, the compound wherein heteroatom is oxidized (e.g., S-oxide, S,S-oxide, or N-oxide compounds) may be prepared by oxidizing a corresponding S-form or N-form.

The oxidation reaction can be carried out by a conventional method, for example, by treatment with an oxidizing agent (e.g., peracids such as hydrogen peroxide, m-chloroperbenzoic acid, peracetic acid, etc.) in a suitable solvent (e.g., halogenated hydrocarbons such as dichloromethane, etc.).

The starting compounds of the respective steps described above may be prepared by the methods as disclosed in Reference Examples or a process as mentioned below.

(1) Among the compounds of the formula VII, the compound wherein Y is —CH_2— may be prepared by a method as shown in the following scheme:



(XXVIII) (XXIX)

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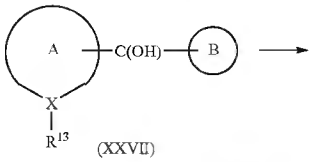
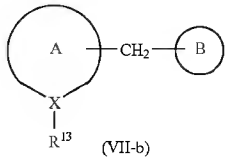


(XXVII)



(VII-b)

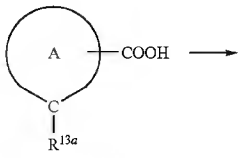
wherein R^{15} is a hydrogen atom or a halogen atom, and the other symbols are as defined above.

Namely, the compound of the formula VII-b may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXIX to give the compound of the formula XXVII, followed by reducing the obtained compound of the formula XXVII.

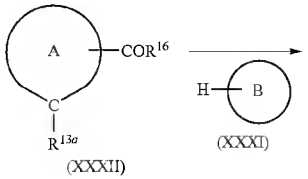
The coupling reaction of the present step may be carried out in a manner similar to Step (a). Namely, the compound of the formula XXVIII is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound of the formula XXIX.

The reduction reaction may be carried out in a manner similar to Step (d), more specifically, by (1) treatment with a silane reagent such as triethylsilane, etc., in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at −30° C. to 60° C., in the presence of a Lewis acid such as boron trifluoride.diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane, or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., a Lewis acid such as aluminum chloride, etc.).

(2) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:



(XXXIII)



(XXXII) (XXXI)

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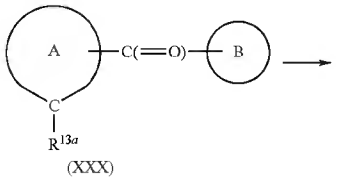
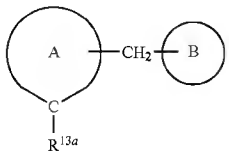


(XXX)



(VII-c)

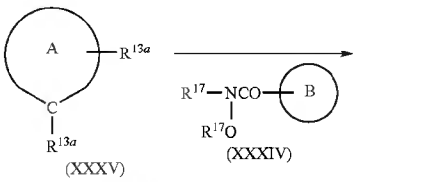
wherein R^{16} is a halogen atom, and the other symbols are as defined above.

The present process may be carried out in a manner similar to Step (h) as mentioned above.

Namely, the compound of the formula VII-c may be prepared by treating the compound of the formula XXXIII with a halogenating reagent (e.g., thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.) in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc.) or in the absence of a solvent, to give the compound of the formula XXXII, subsequently by condensing this compound with the compound of the formula XXXI in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, dichloroethane, etc.) in the presence of a Lewis acid (e.g., aluminum chloride, zinc chloride, titanium tetrachloride, etc.), to give the compound of the formula XXX, and further by reducing the obtained compound.

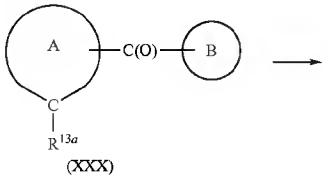
The reduction reaction can be carried out by treating with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride.diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

(3) Among the compounds of the formula VII, the compound wherein X is a carbon atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:



(XXXV)

(XXXIV)



(XXX)

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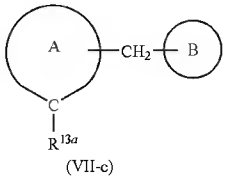


(VII-c)

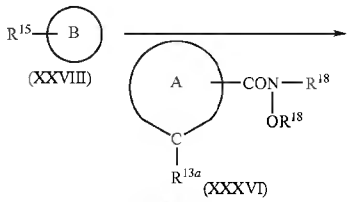
wherein R^{17} is a lower alkyl group, and the other symbols are as defined above.

The compound of the formula VII-c may be prepared by coupling the compound of the formula XXXV with the compound of the formula XXXIV to give the compound of the formula XXX, and subsequently by reducing the obtained compound.

The coupling reaction may be carried out in a manner similar to Step (a). Namely, the compound of the formula (XXV) is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the resultant with the compound (XXIV).

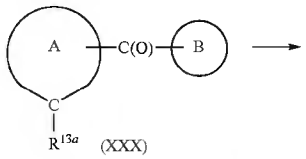
The reduction reaction may be carried out in a manner similar to Step (a). Namely, it can be carried out by treating the compound of formula XXX with a silane reagent (e.g., triethylsilane, etc.) inasuitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., boron trifluoride.diethyl ether complex, etc).

(4) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:

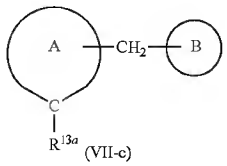


(XXVIII)

(XXXVI)



(XXX)



(VII-c)

wherein R^{18} is a lower alkyl group, and the other symbols are as defined above.

Namely, the compound of the formula VII-c may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXXVI to give the compound of the formula XXX, and subsequently by reducing the compound.

The present process may be carried out in a manner similar to Step (3). Namely, the compound of the formula (XXVIII)

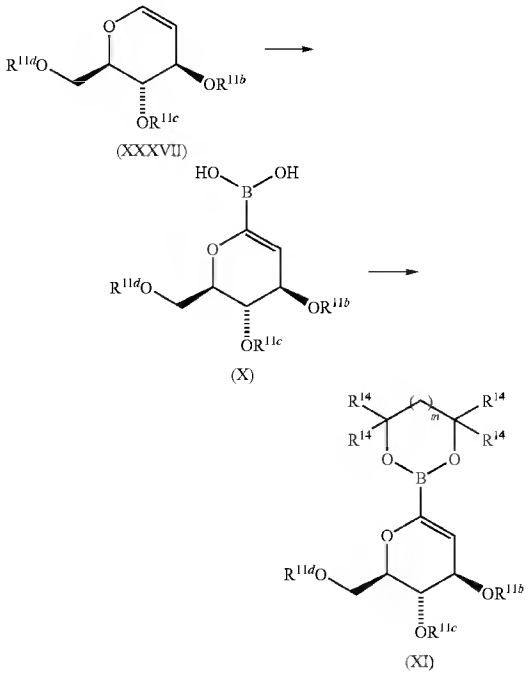
is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the resultant with the compound (**XXX**VI) to give the compound of the formula (XXX). Subsequently, the compound of the formula XXX is treated with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.) in the presence of an acid (e.g., boron trifluoride.diethyl ether complex, etc), to give the compound of the formula (VII-c).

The compound of the formula XIV wherein Ring A is a benzene ring is disclosed in WO 01/27128 pamphlet.

The compound of the formula VI is disclosed in WO 01/27128 or Benhaddu, S. Czernecki et al., Carbohydr. Res., vol. 260, p. 243-250, 1994.

The compound of the formula VIII may be prepared from D-(+)-glucono-1,5-lactone according to the method disclosed in U.S. Pat. No. 6,515,117.

The compound of the formula X and the compound of the formula XI may be prepared by the following Reaction Scheme:



wherein the symbols are as defined above.

First, the compound of the formula XXXVII is lithiated with t-butyl lithium in a suitable solvent (e.g., tetrahydrofuran, etc.) under cooling (e.g., −78° C.), followed by reacting with trimethyl borate to give the compound of the formula **X**.

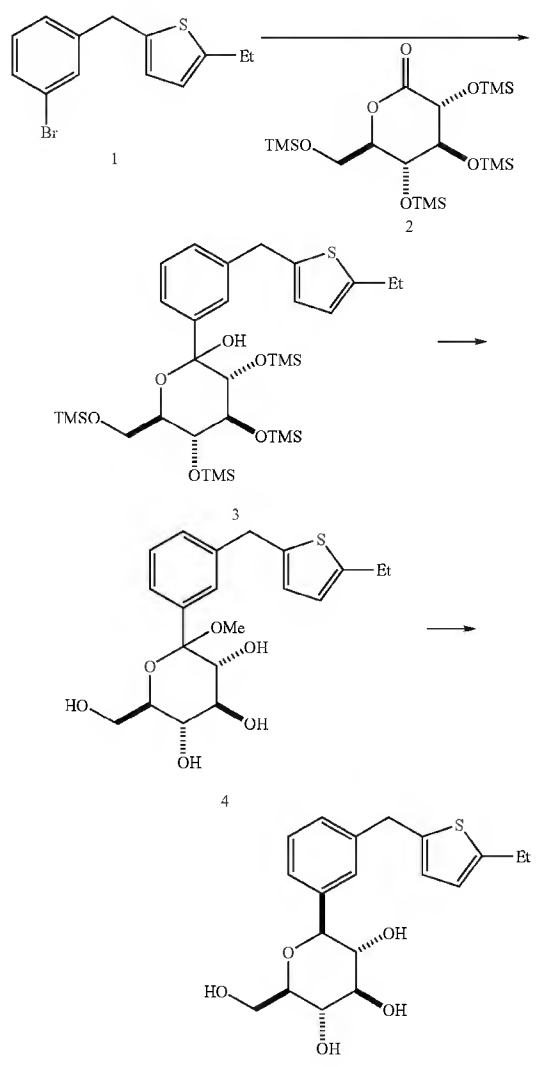
Then, the compound of the formula X is reacted with a 1,2-diol (e.g., pinacol, etc.) or 1,3-diol (e.g., 2.4-dimethyl-2, 4-pentanediol, etc.) to give the compound of the formula XI.

The other starting compounds are commercially available or are described in WO 01/27128 or WO 2004/080990, or may easily be prepared by a standard method well known to an ordinary skilled person in this field.

Hereinafter, the present invention will be illustrated by Examples and Reference Examples, but the present invention should not be construed to be limited thereto.

EXAMPLE 1

1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienyl-methyl) benzene



In the above scheme, Me is a methyl group, Et is an ethyl group, TMSO and OTMS are a trimethylsilyloxy group.

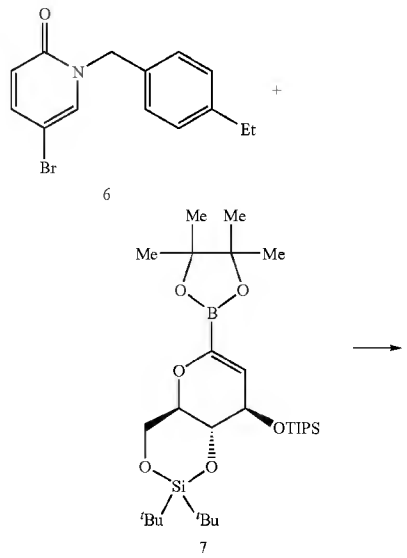
(1) 3-Bromo-(5-ethyl-2-thienylmethyl)benzene 1 (211 mg) was dissolved in tetrahydrofuran (2 ml)-toluene (4 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.29 ml), and the mixture was stirred at the same temperature for 30 minutes. Then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2

(see U.S. Pat. No. 6,515,117) (233 mg) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for one hour to give a lactol compound 3. Without isolating this compound, a solution of methanesulfonic acid (0.1 ml) in methanol (5 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give a methyl ether compound 4 (136 mg) of the lactol. APCI-Mass m/Z 412 ($M+NH_4$).

(2) A solution of the above methyl ether compound 4 (100 mg) in dichloromethane (5 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triisopropylsilane (0.16 ml), and boron trifluoride.diethyl ether complex (0.10 ml). The mixture was stirred at the same temperature for 10 minutes, and warmed. The mixture was stirred at 0° C. for 1 hour and 20 minutes, and then further stirred at room temperature for 2 hours. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienylmethyl)benzene 5 (59 mg). APCI-Mass m/Z 382 ($M+NH_4$).

EXAMPLE 2

5-(β-D-glucopyranosyl)-1-(4-ethylphenyl-methyl)-1H-pyridin-2-one



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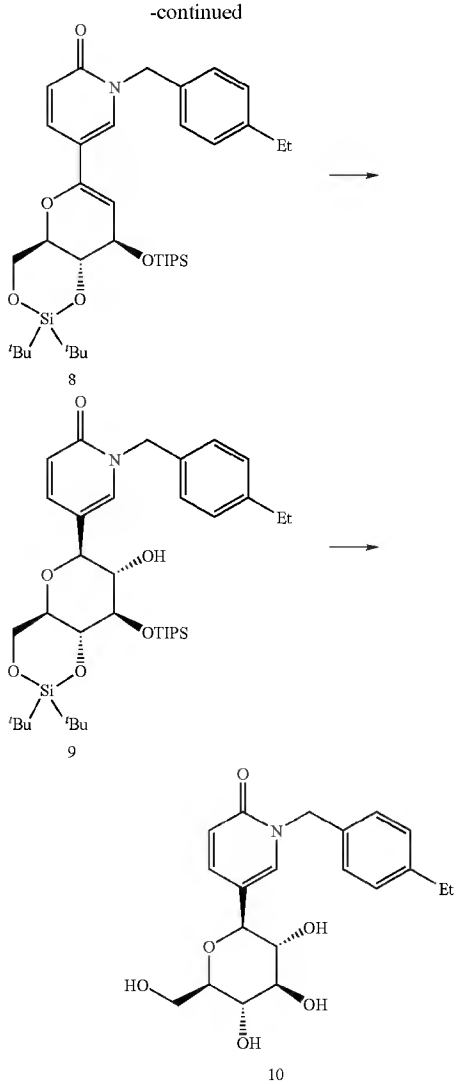


8 9 10

In the above scheme, tBu is a tert-butyl group, OTIPS is a triisopropylsilyloxy group, and the other symbols are as defined above.

(1) 5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one 6 (293 mg) and boronic acid ester of glucal 7 (1.0 g) were dissolved in dimethoxyethane (5 ml). To the mixture were added bis(triphenyl)phosphine palladium(II) dichloride (35 mg) and 2M sodium carbonate (2.5 ml), and the mixture was heated with stirring under reflux under argon atmosphere for 5 hours. The mixture was cooled to room temperature, and the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-70:30) to give glucal derivative 8 (276 mg) as colorless powder. APCI-Mass m/Z 654 (M+H).

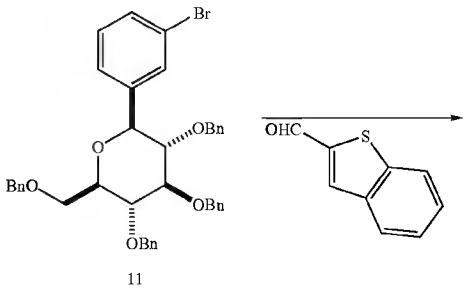
(2) A solution of glucal derivative 8 (260 mg) in tetrahydrofuran (5 ml) was cooled to 0° C. under argon atmosphere,

and thereto was added dropwise a solution of borane.tetrahydrofuran complex (1.13 M tetrahydrofuran solution, 1.06 ml), and the reaction solution was stirred at the same temperature overnight. A mixture of an aqueous hydrogen peroxide solution (31%, 5.0 ml) and 3N aqueous sodium hydroxide solution (5.0 ml) was added to the reaction solution, and the mixture was warmed to room temperature, and stirred for 30 minutes. To the mixture was added 20% aqueous sodium thiosulfate solution (30 ml), and the mixture was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=96:4-66.34) to give C-glucoside compound 9 (59 mg) as colorless powder. APCI-Mass m/Z 672 (M+H).

(3) The above C-glucoside compound 9 (55 mg) was dissolved in tetrahydrofuran (2 ml), and thereto was added tetrabutyl ammonium fluoride (1.0 M tetrahydrofuran solution, 0.41 ml). The mixture was heated with stirring under reflux for 3 hours under argon atmosphere, and the reaction solution was cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-88:12) to give the desired 5-(β-D-glucopyranosyl)-1-(4-ethylphenylmethyl)-1H-pyridin-2-one 10 (10 mg) as colorless powder. APCI-Mass m/Z 376 (M+H).

EXAMPLE 3

1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)benzene



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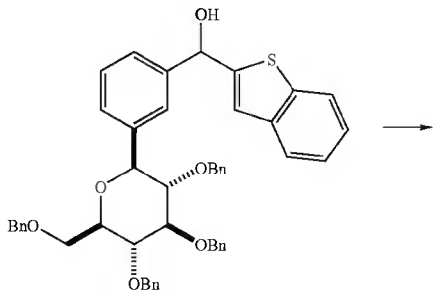

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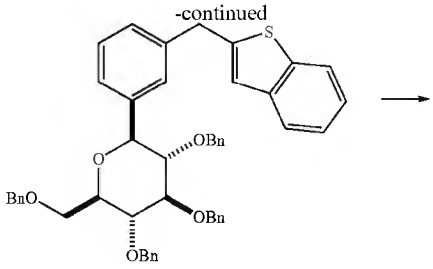

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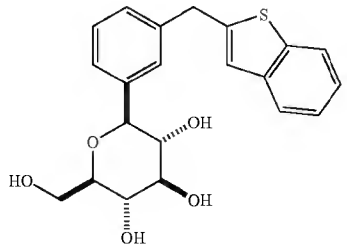


14

In the above scheme, Bn is a benzyl group.

(1) β-m-Bromophenyl-tetra-O-benzyl-C-glucoside 11 (see WO 01/27128) (1.00 g) was dissolved in diethyl ether (60 ml). and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise t-butyl lithium (1.49 M pentane solution, 0.99 ml), and the mixture was stirred at the same temperature for 10 minutes. Then, a solution of 2-formylbenzo[b]thiophene (286 mg) in diethyl ether (2 ml) was added dropwise, and the mixture was further stirred at the same temperature for 30 minutes. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was warmed to room temperature. The mixture was extracted with diethyl ether, the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-50:50) to give an alcohol compound 12 (835 mg). APCI-Mass m/Z 780 ($M+NH_4$).

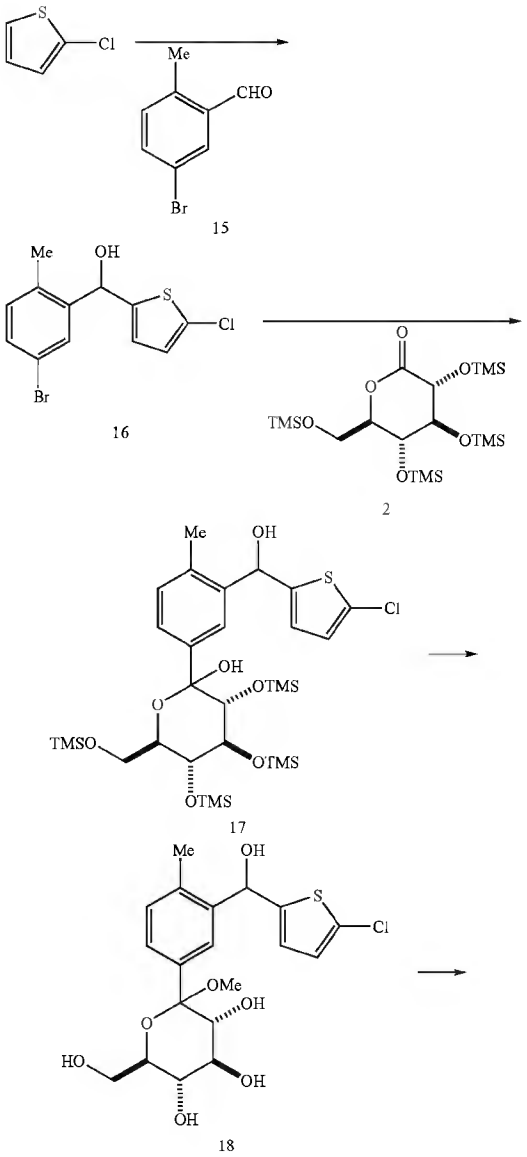
(2) A solution of the above alcohol compound 12 (820 mg) in dichloromethane (15 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (0.52 ml), and boron trifluoride.diethyl ether complex (0.20 ml). The reaction mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=94:6-75:25) to give the compound 13 (703 mg). APCI-Mass m/Z 764 ($M+NH_4$).

(3) A solution of the above compound 13 (690 mg) in dichloromethane (20 ml) was cooled to 0° C., and iodotrimethylsilane (0.66 ml) was added thereto and the mixture was stirred at room temperature for one hour. Addition of iodotrimethylsilane and stirring at room temperature were repeated in the same manner for 3 times. Total amount of the iodotrimethylsilane was summed up to 2.64 ml. Under ice-cooling, water was added to the reaction mixture, and

the mixture was extracted with diethyl ether twice, and washed with an aqueous sodium thiosulfate solution. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform: methanol=100:0-89:11) to give the desired 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)benzene 14 (180 mg). APCI-Mass m/Z 404 ($M+NH_4$)

EXAMPLE 4

1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienyl-methyl)-4-methylbenzene



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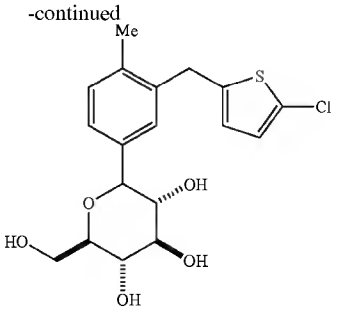


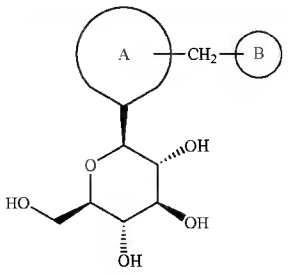
In the above scheme, the symbols are as defined above.

(1) A solution of 2-chlorothiophene (447 mg) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 2.61 ml). The mixture was stirred at the same temperature for one hour, and added dropwise thereto was a solution of 5-bromo-2-methylbenzaldehyde 15 (750 mg) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for 30 minutes to give a compound 16. Toluene (30 ml) was added, and further added dropwise thereto was n-butyl lithium (1.59 M hexane solution, 2.37 ml). The mixture was further stirred at the same temperature for 30 minutes, and a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (1.76 g) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for one and a half hours to give a lactol compound 17. Subsequently, a solution of methanesulfonic acid (1.22 ml) in methanol (25 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give a crude methyl ether compound 18, which was used in the subsequent step without further purification.

(2) A solution of the above crude methyl ether compound 18 in dichloromethane (25 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (3.01 ml), and boron trifluoride.diethyl ether complex (2.39 ml). The reaction mixture was warmed to 0° C., and stirred at the same temperature for 3 hours. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform: methanol=100:0-92:8) to give the desired 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methyl-benzene 19 (183 mg). APCI-Mass m/Z 402/404 ($M+NH_4$).

In a manner similar to the method disclosed in any of the above Examples 1 to 4, the compounds shown in Table 1 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out.

TABLE 1



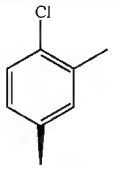
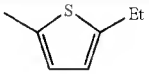
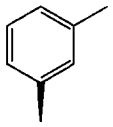
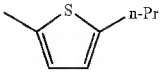
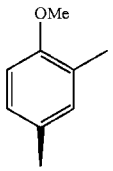
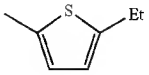
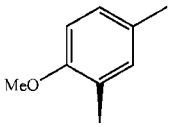
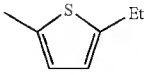
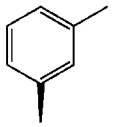
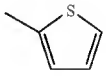
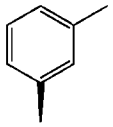
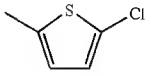
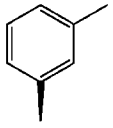
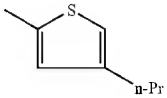
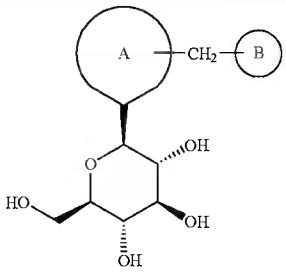
Examples	Ring A	Ring B	Prepar-ation Method	APCI-Mass (m/Z)
5			1	416/418 ($M + NH_4$)
6			1	396 ($M + NH_4$)
7			1	412 ($M + NH_4$)
8			1	412 ($M + NH_4$)
9			3	354 ($M + NH_4$)
10			3	388/390 ($M + NH_4$)
11			1	396 ($M + NH_4$)

TABLE 1-continued



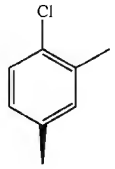
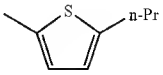
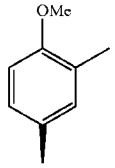
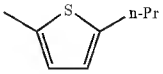
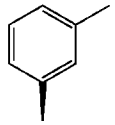
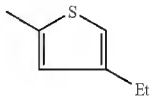
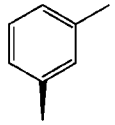
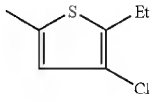
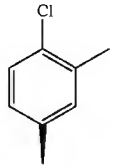
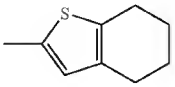
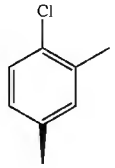
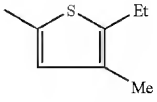
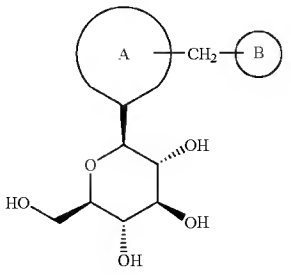
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
12			1	430/432 ($M + NH_4$)
13			1	426 ($M + NH_4$)
14			1	382 ($M + NH_4$)
15			1	416/418 ($M + NH_4$)
16			1	442/444 ($M + NH_4$)
17			1	430/432 ($M + NH_4$)

TABLE 1-continued



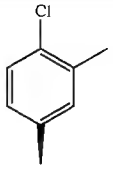
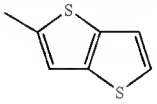
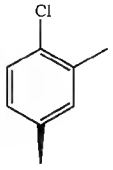
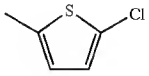
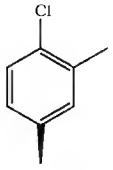
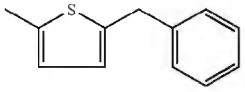
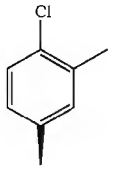
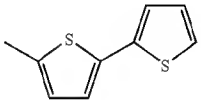
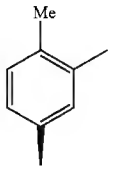
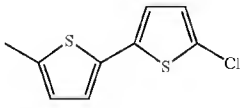
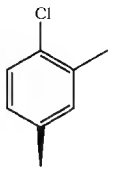
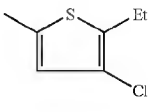
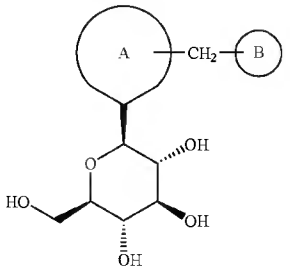
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
18			2	444/446 ($M + NH_4$)
19			1	422/424 ($M + NH_4$)
20			1	478/480 ($M + NH_4$)
21			2	470/472 ($M + NH_4$)
22			1	484/486 ($M + NH_4$)
23			1	450/452 ($M + NH_4$)

TABLE 1-continued



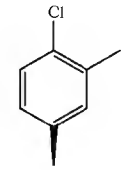
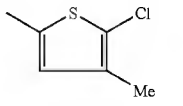
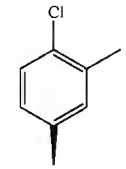
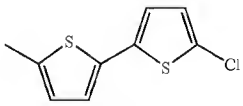
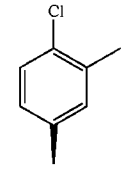
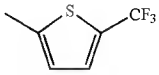
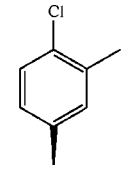
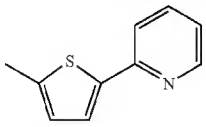
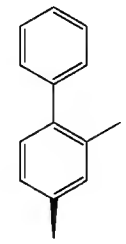
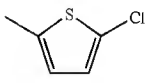
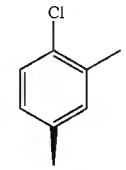
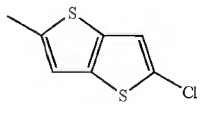
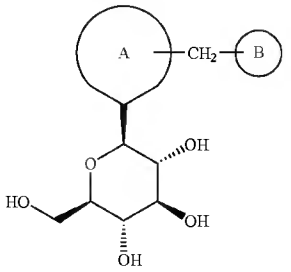
Examples	Ring A	Ring B	Prepar-ation Method	APCI-Mass (m/Z)
24			4	436/438 ($M + NH_4$)
25			1	504/506 ($M + NH_4$)
26			2	456/458 ($M + NH_4$)
27			1	448/450 ($M + NH_4$)
28			1	464/466 ($M + NH_4$)
29			4	478/480 ($M + NH_4$)

TABLE 1-continued



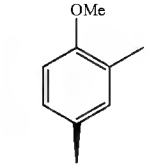
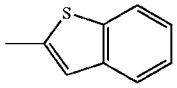
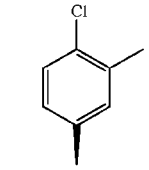
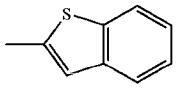
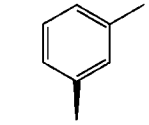
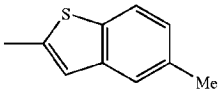
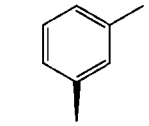
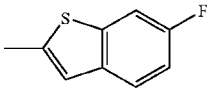
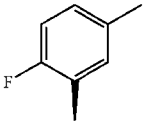
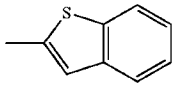
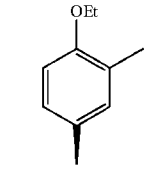
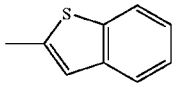
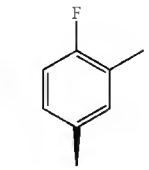
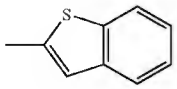
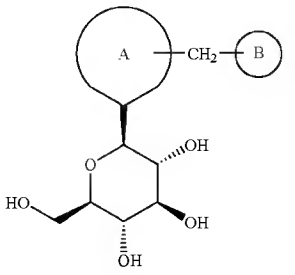
Examples	Ring A	Ring B	Prepar-ation Method	APCI-Mass (m/Z)
30			1	434 ($M + NH_4$)
31			1	438/440 ($M + NH_4$)
32			1	418 ($M + NH_4$)
33			1	422 ($M + NH_4$)
34			1	422 ($M + NH_4$)
35			1	448 ($M + NH_4$)
36			1	422 ($M + NH_4$)

TABLE 1-continued



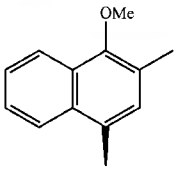
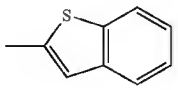
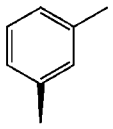
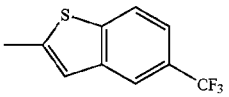
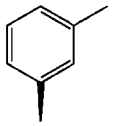
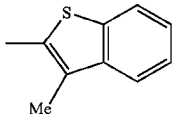
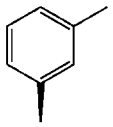
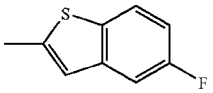
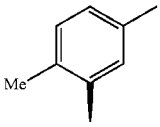
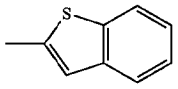
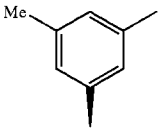
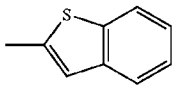
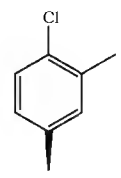
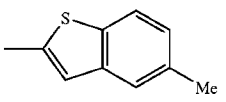
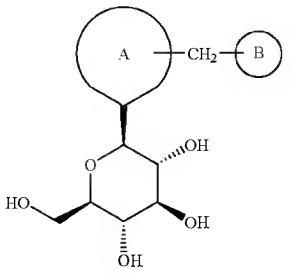
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
37			1	484 (M + NH_4)
38			1	472 (M + NH_4)
39			1	418 (M + NH_4)
40			1	422 (M + NH_4)
41			2	418 (M + NH_4)
42			1	418 (M + NH_4)
43			1	452/454 (M + NH_4)

TABLE 1-continued



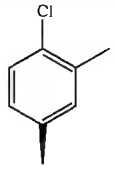
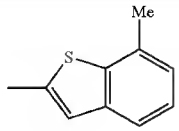
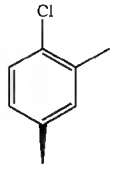
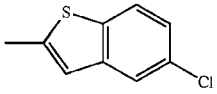
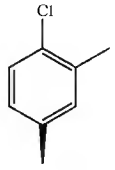
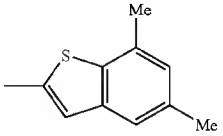
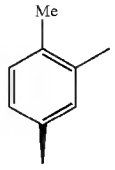
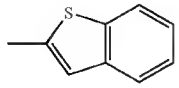
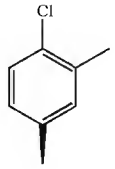
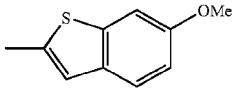
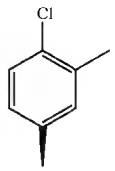
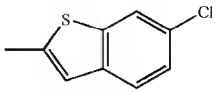
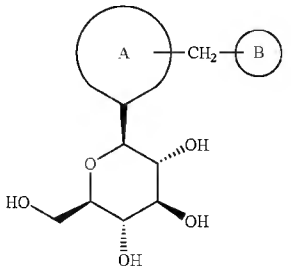
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
44			1	452/454 ($M + NH_4$)
45			1	472/474 ($M + NH_4$)
46			1	466/468 ($M + NH_4$)
47			1	418 ($M + NH_4$)
48			1	468/470 ($M + NH_4$)
49			1	472/474 ($M + NH_4$)

TABLE 1-continued



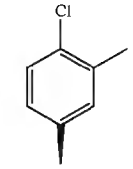
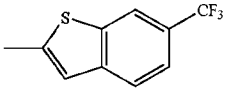
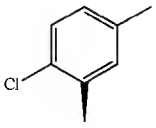
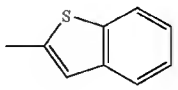
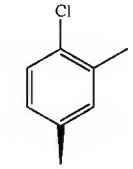
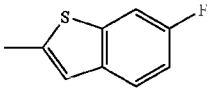
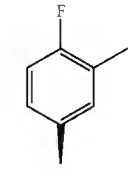
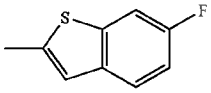
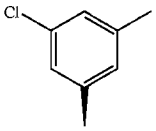
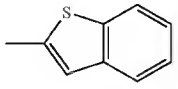
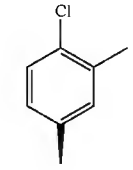
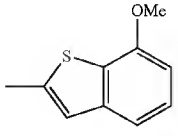
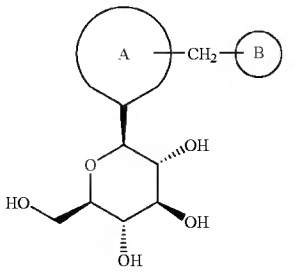
Examples	Ring A	Ring B	Prepar-ation Method	APCI-Mass (m/Z)
50			2	506/508 (M + NH_4)
51			2	438/440 (M + NH_4)
52			2	456/458 (M + NH_4)
53			2	440 (M + NH_4)
54			2	438/440 (M + NH_4)
55			1	468/470 (M + NH_4)

TABLE 1-continued



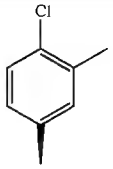
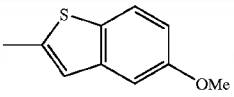
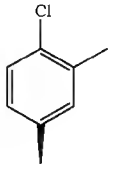
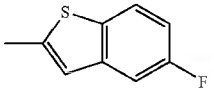
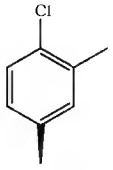
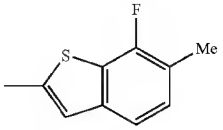
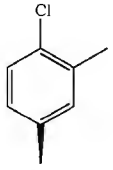
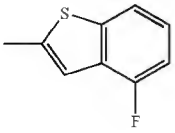
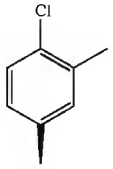
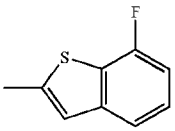
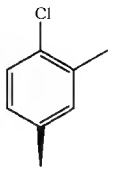
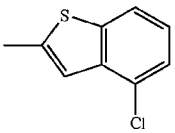
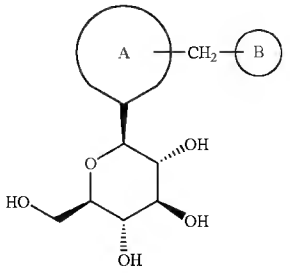
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
56			1	468/470 (M + NH_4)
57			2	456/458 (M + NH_4)
58			1	470/472 (M + NH_4)
59			2	456/458 (M + NH_4)
60			2	456/458 (M + NH_4)
61			2	472/474 (M + NH_4)

TABLE 1-continued



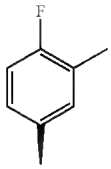
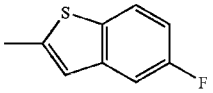
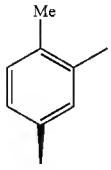
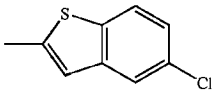
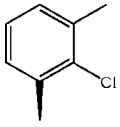
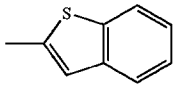
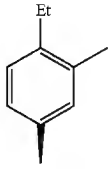
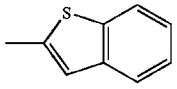
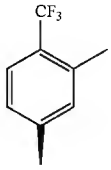
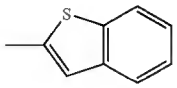
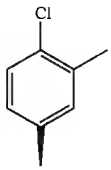
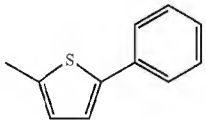
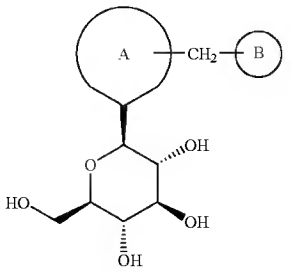
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
62			2	440 (M + NH_4)
63			4	452/454 (M + NH_4)
64			2	438/440 (M + NH_4)
65			1	432 (M + NH_4)
66			2	472 (M + NH_4)
67			1	464/466 (M + NH_4)

TABLE 1-continued



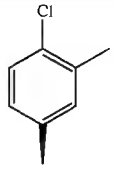
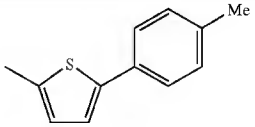
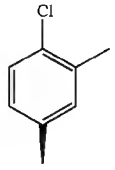
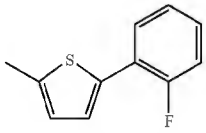
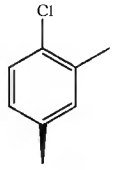
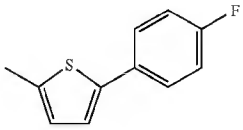
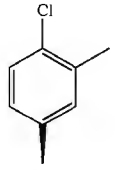
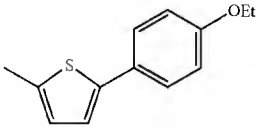
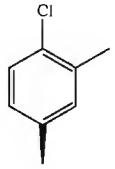
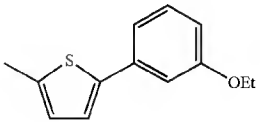
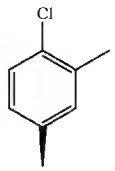
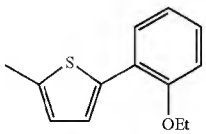
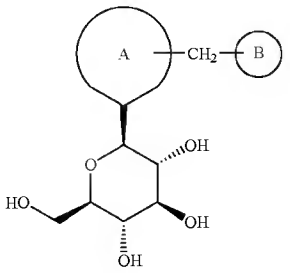
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
68			1	478/480 (M + NH_4)
69			1	482/484 (M + NH_4)
70			1	482/484 (M + NH_4)
71			1	508/510 (M + NH_4)
72			1	508/510 (M + NH_4)
73			1	508/510 (M + NH_4)

TABLE 1-continued



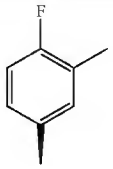
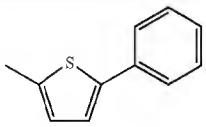
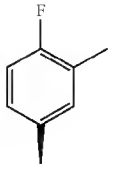
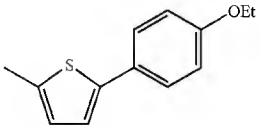
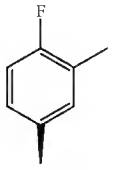
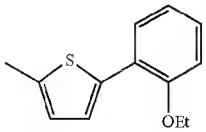
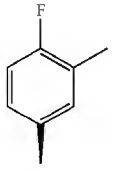
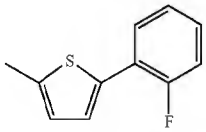
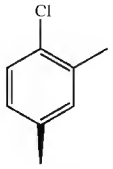
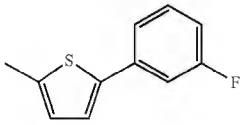
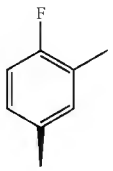
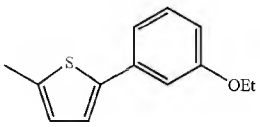
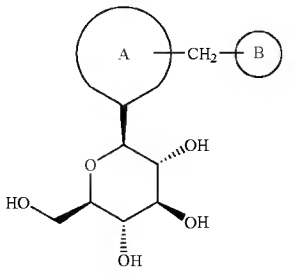
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
74			1	448 ($M + NH_4$)
75			1	492 ($M + NH_4$)
76			1	492 ($M + NH_4$)
77			1	466 ($M + NH_4$)
78			1	482/484 ($M + NH_4$)
79			1	492 ($M + NH_4$)

TABLE 1-continued



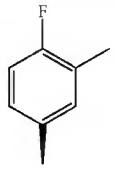
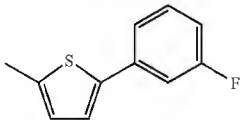
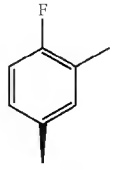
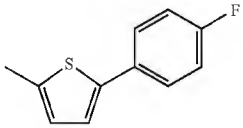
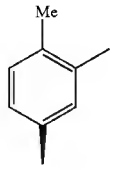
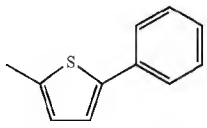
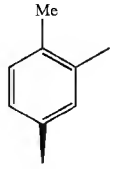
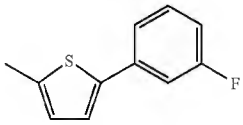
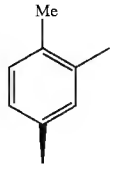
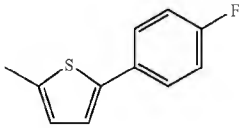
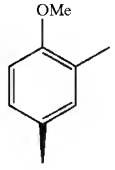
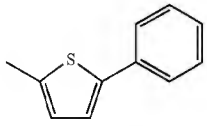
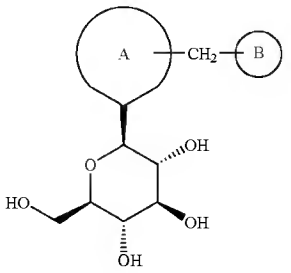
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
80			1	466 (M + NH_4)
81			1	466 (M + NH_4)
82			1	444 (M + NH_4)
83			1	462 (M + NH_4)
84			1	462 (M + NH_4)
85			2	460 (M + NH_4)

TABLE 1-continued



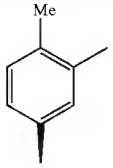
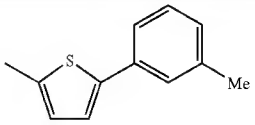
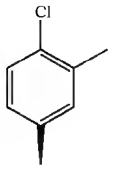
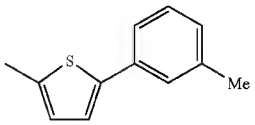
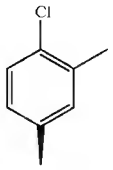
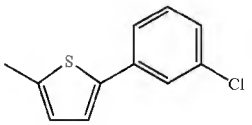
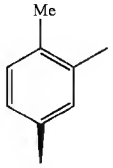
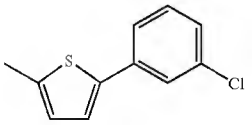
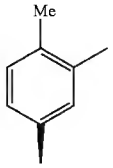
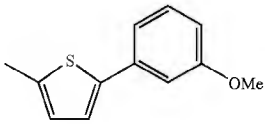
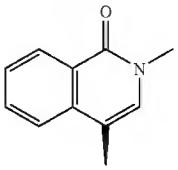
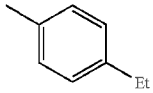
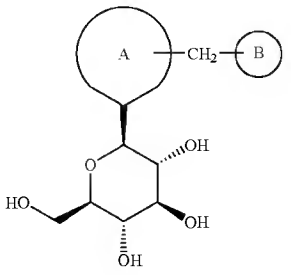
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
86			1	458 ($M + NH_4$)
87			1	478/480 ($M + NH_4$)
88			1	498/500 ($M + NH_4$)
89			1	478/480 ($M + NH_4$)
90			1	474 ($M + NH_4$)
91			2	426 (M + H)

TABLE 1-continued



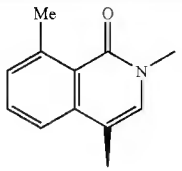
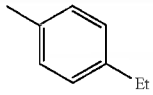
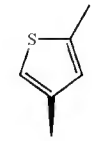
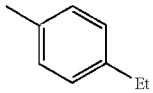
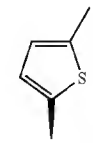
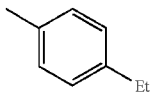
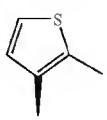
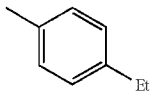
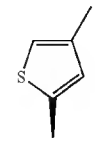
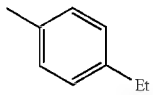
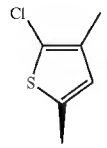
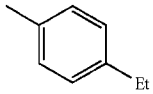
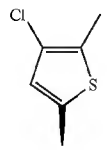
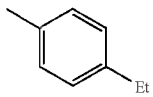
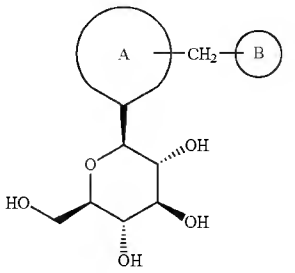
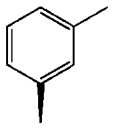
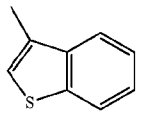
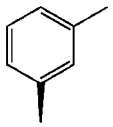
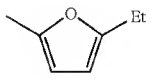
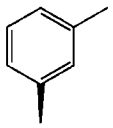
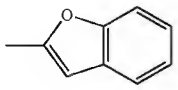
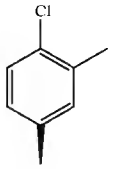
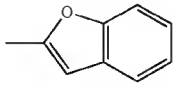
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
92			2	440 (M + H)
93			2	382 (M + NH_4)
94			2	382 (M + NH_4)
95			2	382 (M + NH_4)
96			2	382 (M + NH_4)
97			2	416/418 (M + NH_4)
98			2	416/418 (M + NH_4)

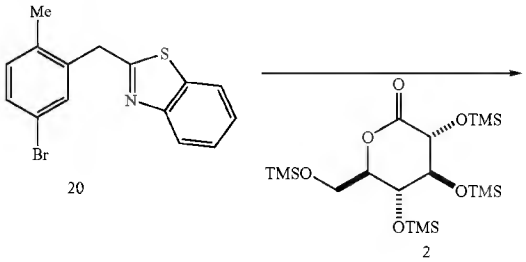
TABLE 1-continued



Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
99			1	404 (M + NH_4)
100			1	366 (M + NH_4)
101			1	388 (M + NH_4)
102			1	422/424 (M + NH_4)

EXAMPLE 103

1-(β-D-glucopyranosyl)-3-(benzothiazol-2-yl-methyl)-4-methylbenzene



20 2

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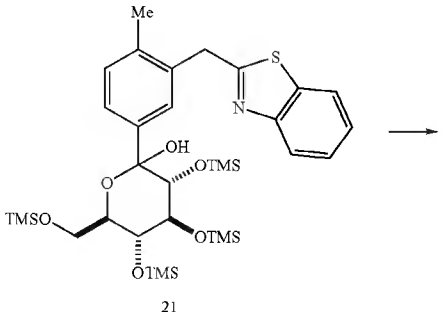

21

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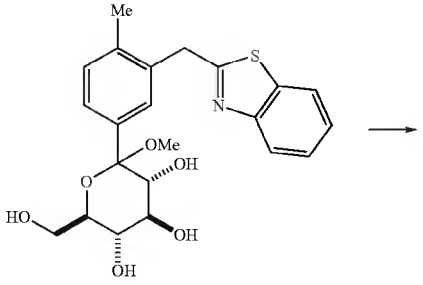
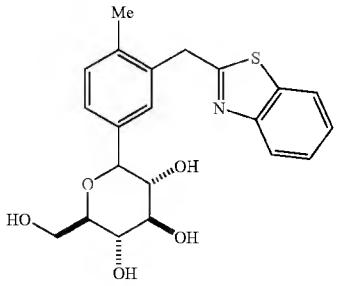


22



23

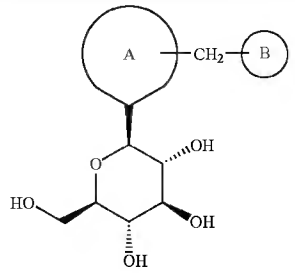
In the above scheme, the symbols are as defined above.

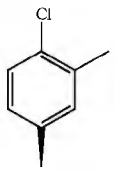
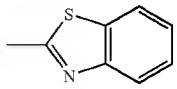
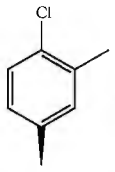
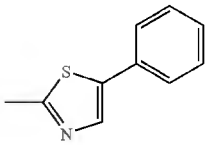
(1) 1-(benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene 20 (495 mg) was dissolved in tetrahydrofuran (5 ml)-toluene (10 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.67 ml), and successively was added dropwise t-butyl lithium (2.44 M pentane solution, 1.57 ml). The mixture was stirred at the same temperature for 10 minutes, and then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-gluconol, 5-lactone 2 (see U.S. Pat. No. 6,515,117) (2.17 g) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for 15 minutes to give a lactol compound 21. Without isolating this compound, a solution of methanesulfonic acid (1.5 ml) in methanol (25 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give a methyl ether compound 22, which was used in the subsequent step without further purification.

(2) A solution of the above methyl ether compound 22 in dichloromethane (20 ml)-acetonitrile (10 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (1.24 ml), and boron trifluoride.diethyl ether complex (0.99 ml). The mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-85:15) to give 1-(β-D-glucopyranosyl)-3-(benzothiazol-2-ylmethyl)-4-methylbenzene 23 (200 mg) as colorless powder. APCI-Mass m/Z 402 (M+H).

In a manner similar to Examples 103, the compounds shown in Table 2 below were prepared from corresponding starting materials.

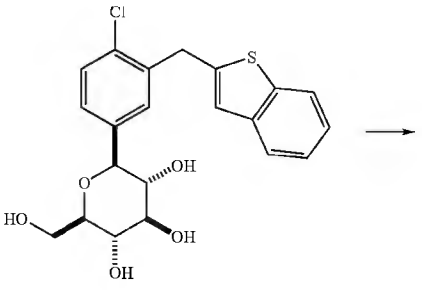
TABLE 2



Examples	Ring A	Ring B	APCI-Mass (m/Z)
104			422/424 (M + H)
105			480/482 (M + NH_4)

EXAMPLE 106

1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxy-benzo[b] thiophen-2-ylmethyl)benzene



24

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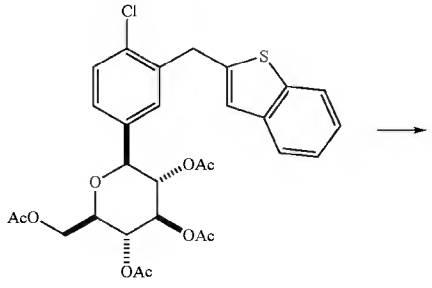
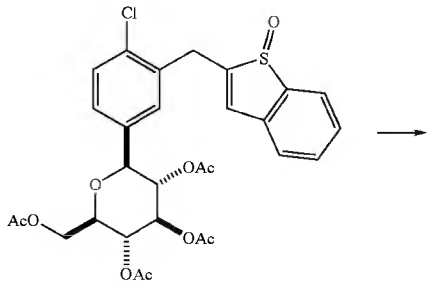
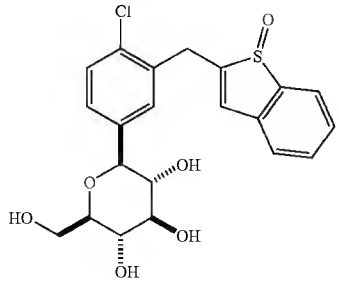


25



26



27

In the above scheme, AcO and OAc are an acetyloxy group.

(1) The compound 24 (9.61 g) obtained in Example 31 was dissolved in chloroform (100 ml), and to the mixture were added acetic anhydride (21.6 ml), pyridine (18.5 ml), and 4-dimethylaminopyridine (128 mg), and the mixture was stirred at room temperature for 3.5 days. Then, Chloroform was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (200 ml). The solution was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over magnesium sulfate, and treated with activated carbon. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol to give a tetraacetate compound 25 (6.14 g). APCI-Mass m/Z 606/608 ($M+NH_4$).

(2) The above tetraacetate compound 25 (1.00 g) was dissolved in dichloromethane (20 ml), and under ice-cooling, m-chloroperbenzoic acid (439 mg) was added thereto, and the mixture was stirred a room temperature overnight. m-Chloroperbenzoic acid was further added thereto, and the mixture was stirred again at room temperature overnight. The reaction mixture was washed successively with

10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution, and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1-1:2) to give a sulfoxide compound 26 (295 mg). APCI-Mass m/Z 622/624 ($M+NH_4$).

(3) The above sulfoxide compound 26 (293 mg) was dissolved in a mixture of methanol (10 ml)-tetrahydrofuran (5 ml), and sodium methoxide (28% methanol solution, 2 drops) was added thereto, and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give 1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxybenzo[b]thiophen-2-ylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 454/456 ($M+NH_4$).

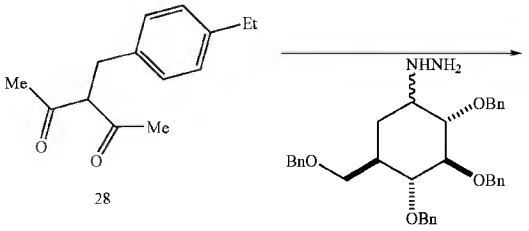
EXAMPLE 107

1-(β-D-glucopyranosyl)-4-chloro-3-(1,1-dioxybenzo[b]thiophen-2-ylmethyl)benzene

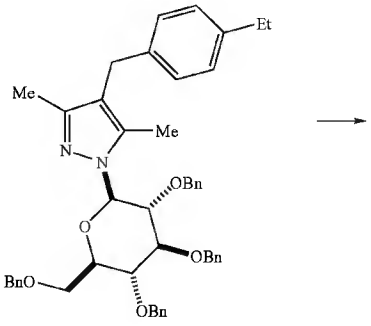
The target compound was prepared in a manner similar to Example 106. APCI-Mass m/Z 470/472 ($M+NH_4$).

EXAMPLE 108

3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole



28 29



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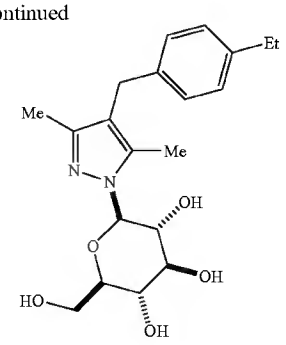


31

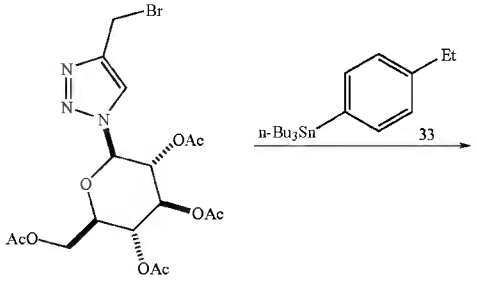
In the above scheme, the symbols are as defined above.

(1) 3-(4-ethylphenylmethyl)-2,4-pentanedione 28 (700 mg) and 2,3,4,6-tetra-O-benzyl-α,β-D-glucosehydrazone 29 (1.70 g)(See Schmidt, R. R. et al., *Liebigs Ann. Chem.* 1981, 2309) were dissolved in tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 18 hours under argon atmosphere. The solvent was evaporated under reduced pressure, and the residue was dissolved in toluene (20 ml), and the mixture was heated with stirring under reflux for 2 hours. The mixture was left alone until it was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-65:35) to give 3, 5-dimethyl-4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)pyrazole 30 (299 mg) as a pale yellow semisolid. APCI-Mass m/Z 737 (M+H).

(2) The above tetrabenzyl compound 30 (294 mg) was dissolved in a mixture of ethanol (5 ml) and tetrahydrofuran (4 ml), and added thereto was palladium hydroxide (100 mg), and the mixture was stirred at room temperature for 16 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was crystallized from diethyl ether to give the desired 3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl) pyrazole 31 (118 mg) as colorless powder. APCI-Mass m/Z 377 (M+H).

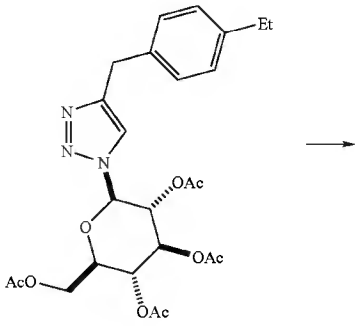
EXAMPLE 109

4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-1, 2,3-triazole

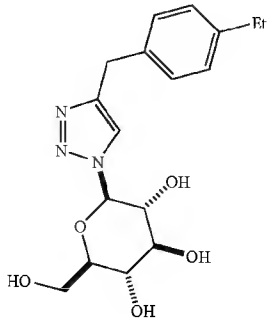


32

-continued



34



35

In the above scheme, n-Bu is n-butyl group, and other symbols are as defined above.

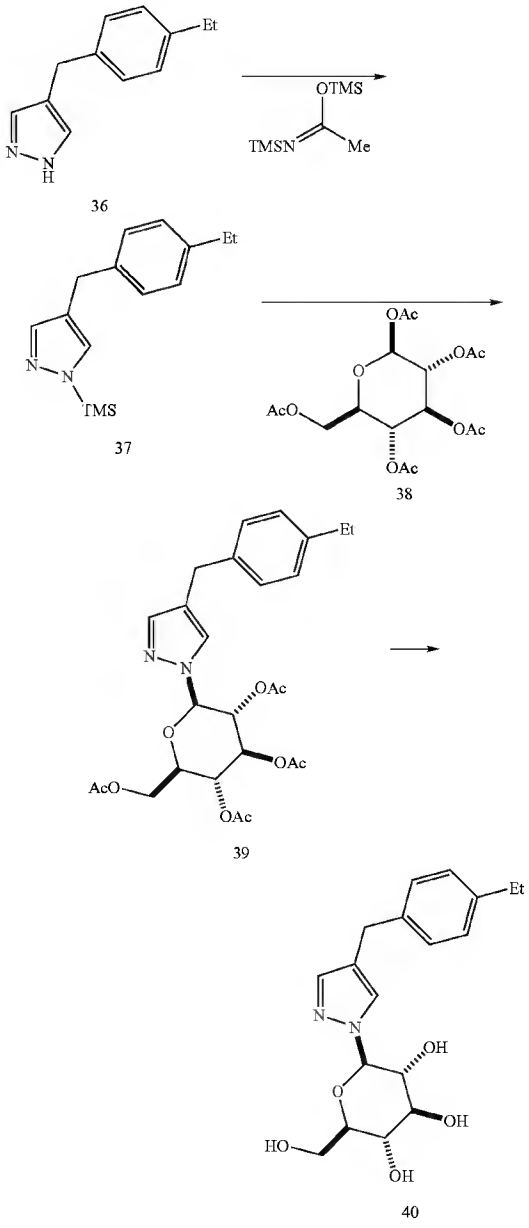
(1) A solution of 4-(bromomethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosy 1)-1,2,3-triazole 32 (500 mg) (See Federico G. H. et al., *J. Med. Chem.* (1979) 29, 496), tri-n-butyl(4-ethylphenyl)tin 33 (604 mg) and tetrakis (triphenylphosphine)palladium (0) (59 mg) in tetrahydrofuran (10 ml) was stirred under heating at 70° C. for 12 hours under argon atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and then, an aqueous potassium fluoride solution was added thereto and the mixture was stirred at room temperature for one hour. Insoluble materials were filtered off, and the filtrate was washed with water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-gluco pyranosyl)-1,2,3-triazole 34 (90 mg) as a colorless solid. APCI-Mass m/Z 518 (M+H).

(2) From the above tetraacetate compound 34, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-1,2,3-triazole 35 was prepared in a manner similar to Example 106-(3) as a colorless solid.

APCI-Mass m/Z 350 (M+H).

EXAMPLE 110

4-(4-Ethylphenylmethyl)-1-(β-D-glucopyranosyl) pyrazole



In the above scheme, TMS is a trimethylsilyl group, and other symbols are as defined above.

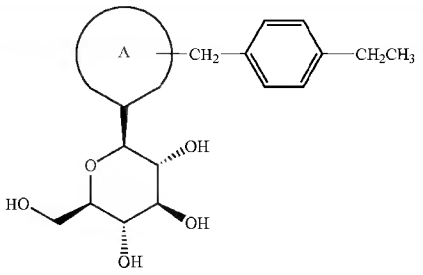
(1) To a solution of 4-(4-ethylphenylmethyl)pyrazole 36 (495 mg) in acetonitrile (2.0 ml) was added N,O-bis(trimethylsilyl)acetamide (1.05 ml), and the mixture was stirred under heating at 60° C. for 2.5 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure to give crude 4-(4-ethylphenylmethyl)-1-trimethylsilylpyrazole 37, which was used in the subsequent reaction without further purification.

(2) The above N-silyl compound 37 was dissolved in dichloroethane (7.0 ml), and added thereto were molecular sieve 4A powder (500 mg), 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose 38 (1.04 g) and trimethylsilyl trifluoromethanesulfonate (0.51 ml). The mixture was stirred under heating at heating at 80° C. for 3 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and insoluble materials were filtered off. Subsequently, the filtrate was poured into a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with dichloromethane, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20-50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-gluco pyranosyl)pyrazole 39 (610 mg) as a colorless semisolid. APCI-Mass m/Z 517 (M+H).

(3) From the above tetraacetate compound 39, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole 40 was prepared in a manner similar to Example 106-(3) as colorless oil. APCI-Mass m/Z 349 (M+H).

In a manner similar to Example 110, the compounds shown in Table 3 below were prepared from corresponding starting materials.

TABLE 3



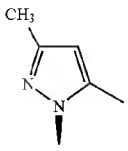
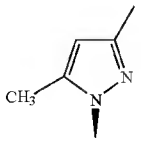
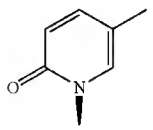
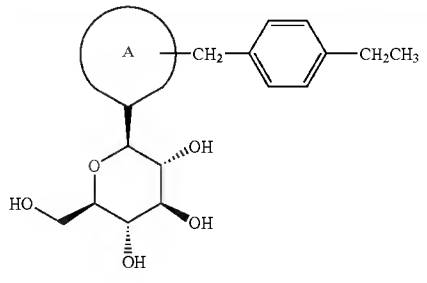
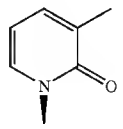
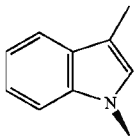
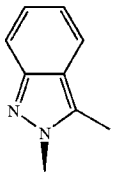
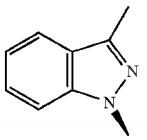
Examples	Ring A	APCI-Mass (m/Z)
111		363 (M + H)
112		363 (M + H)
113		376 (M + H)

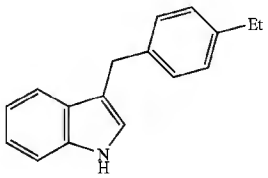
TABLE 3-continued



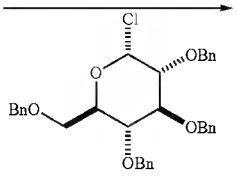
Examples	Ring A	APCI-Mass (m/Z)
114		393 (M + NH_4)
115		415 (M + NH_4)
116		399 (M + H)
117		399 (M + H)

EXAMPLE 118

3-RS-(4-ethylphenylmethyl)-1-(β-D-gluco-pyranosyl)-2,3-dihydroindole



41



42

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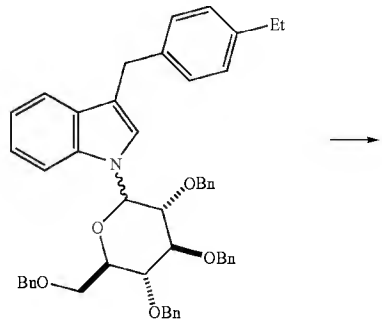
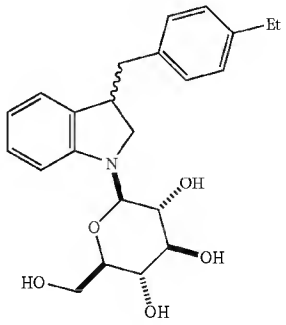


43



44

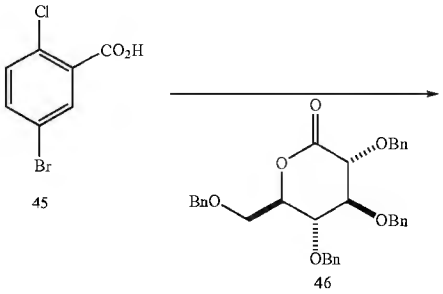
In the above scheme, the symbols are as defined above.

(1) To a suspension of potassium hydroxide power (953 mg) and sodium sulfate (6.0 g) in acetonitrile (50 ml) was added 3-(4-ethylphenylmethy)-1H-indole 41 (500 mg), and the mixture was stirred at room temperature for one hour under argon atmosphere. To the reaction mixture was added a solution of benzylchloro-α-D-glucose 42 (3.0 g) (see Cicchillo R. M. et al., *Carbohydrate Research* (2000) 328,431) in acetonitrile (20 ml), and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 2N aqueous hydrochloric acid solution, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give 3-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-αβ-D-glucopyranosyl)-1H-indole 43 (1.04 g) as a pale yellow syrup. APCI-Mass m/Z 758 (M+H).

(3) From the above tetrabenzyl compound 43, the desired 3-RS-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-2,3-dihydroindole 44 was prepared in a manner similar to Example 108-(2) as pale pink powder. APCI-Mass m/Z 400 (M+H)

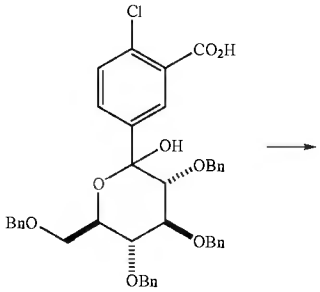
EXAMPLE 119

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene

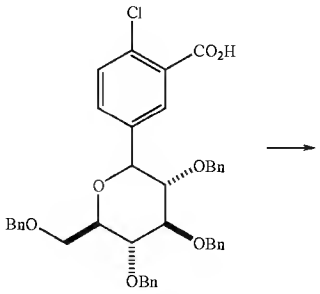


45

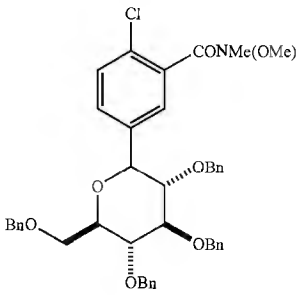
46



47



48



49

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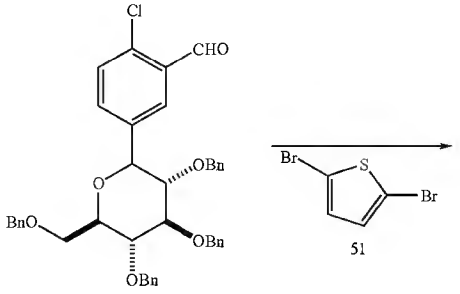
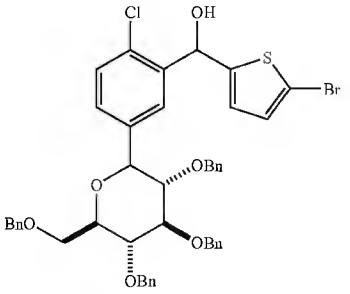


50

51



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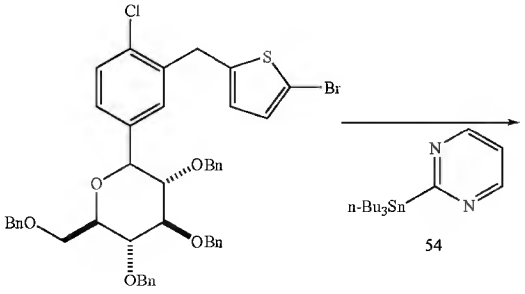
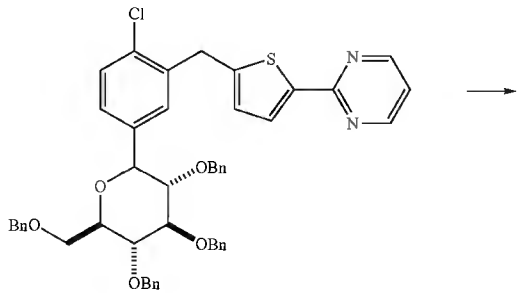


53

54



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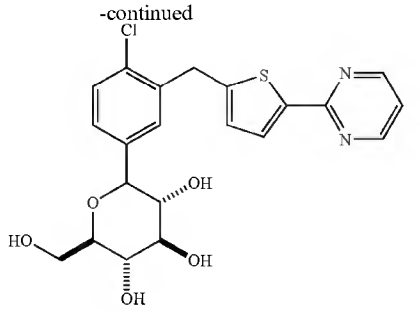


56

In the above scheme, the symbols are as defined above.

(1) To a solution of 5-boromo-2-chlorobenzoic acid 45 (1.22 g) in a mixture of tetrahydrofuran (20 ml)-toluene (20 ml) was added dropwise n-butyl lithium (2.44 M hexane solution, 4.26 ml) at −78° C. under argon atmosphere. The mixture was stirred at −78° C. for 30 minutes, and added dropwise thereto was a solution of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone 46 (2.16 g) in toluene (10 ml), and the mixture was further stirred at the same temperature for 2 hours. To the mixture was added a saturated aqueous ammonium chloride solution, and the mixture was warmed to room temperature. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude compound 47 as oil, which was used in the subsequent step without further purification.

(2) The above crude compound 47 was dissolved in dichloromethane (30 ml), and thereto were added dropwise triisopropylsilane (2.46 ml) and boron trifluoride.diethyl ether complex (1.52 ml) at −78° C. Subsequently, the mixture was stirred at 0° C. for one hour, and added there to was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was further stirred for 20 minutes. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=100:1-50:1) to give a compound 48 (1.41 g) as oil.

(3) The compound 48 (1.41 g) was dissolved in dichloromethane (10 ml), and added thereto was oxalyl chloride (2 ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The compound was dissolved in chloroform (10 ml), and added dropwise to a solution of N,O-dimethylhydroxyamine hydrochloride (390 mg) and triethyl amine (1.12 ml) in chloroform (10 ml) at 0° C. The mixture was stirred at room temperature overnight, and the reaction mixture was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-2:1) to give a compound 49 (784 mg) as pale yellow oil. APCI-Mass m/Z 739/741 ($M+NH_4$).

(4) The compound 49 (1.22 g) was dissolved in tetrahydrofuran (20 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise diisobutylaluminum hydride (1.0 M toluene solution, 4.2 ml), and the mixture was stirred at the same temperature for 3 hours. Added thereto was 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) to give a compound 50 (771 mg) as pale yellow oil. APCI-Mass m/Z 680/682 ($M+NH_4$).

(5) 2,5-dibromothiophene 51 (1.31 g) was dissolved in tetrahydrofuran (30 ml) and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.59 M hexane solution, 2.01 ml), and the mixture was stirred at the same temperature for 30 minutes. Added dropwise thereto was a solution of the above compound 50 (2.40 g) in tetrahydrofuran (15 ml), and the mixture was stirred at −78° C. for 2 hours. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate and washed with brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-4:1) to give a compound 52 (2.62 mg) as pale brown oil. APCI-Mass m/Z 842/844 ($M+NH_4$).

(6) The compound 52 was treated in a manner similar to Example 3-(2) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 as a pale yellow solid. APCI-Mass m/Z 826/828 ($M+NH_4$)

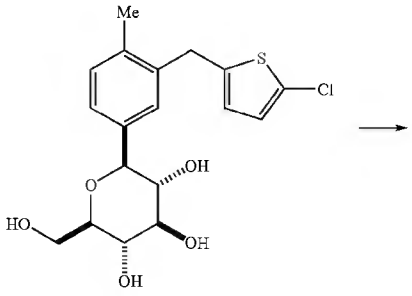
(7) A mixed solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 (200 mg), tri-n-butyl(2-pyrimidinyl)tin 54 (137 mg) and bis(triphenylphosphine)palladium (II) dichloride (9 mg) in N-methyl-2-pyrrolidinone (5 ml) was stirred at 100° C. four 7 hours under argon atmosphere. The mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethylacetate. The extract was washed with water and subsequently with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-2:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 55 (93 mg) as pale brown oil. APCI-Mass m/Z 826/828 ($M+NH_4$).

(8) To a solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5 (2-pyrimidinyl)-2-thienylmethyl)benzene 55 (90 mg) in ethanethiol (1.5 ml) was added boron trifluoride ether complex (0.42 ml) at 0° C., and the mixture was stirred at room temperature overnight. The mixture was cooled again to 0° C., and added thereto were a saturated aqueous sodium hydrogen carbonate solution and an aqueous sodium thiosulfate solution. The mixture was extracted with ethyl acetate and tetrahydrofuran, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1-9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thie-

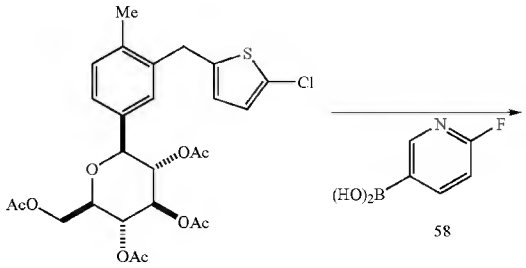
nylmethyl)benzene 56 (27 mg) as pale yellow powder. APCI-Mass m/Z 449/451 (M+H).

EXAMPLE 120

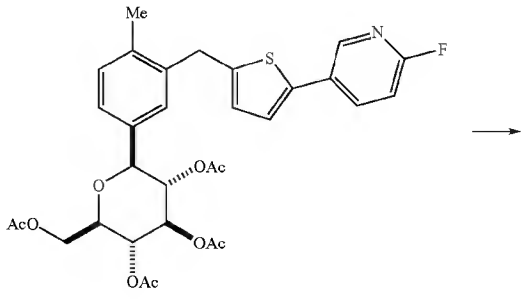
1-(β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienyl-methyl)-4-methylbenzene



19



57 58



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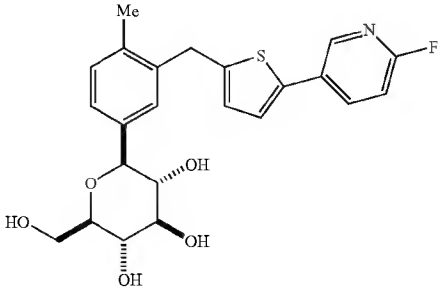


60

In the above scheme, the symbols are as defined as above.

(1) The compound 19 obtained in Example 4 was treated in a manner similar to Example 106—(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 as colorless crystals. APCI-Mass m/Z 570/572 ($M+NH_4$).

(2) A solution of the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (200 mg), 6-fluoropyridine-3-boronic acid 58 (117 mg), tri-tert-butylphosphine-tetrafluoroboric acid adduct (24 mg), potassium fluoride (80 mg) and tris(dibenzylideneacetone) dipalladium (0) (27 mg) in tetrahydrofuran (8 ml) was stirred at room temperature for 2 days under argon atmosphere. Added thereto was a saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-70:30) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59 (44 mg) as colorless crystals. APCI-Mass m/Z 631 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59 (39 mg) was dissolved in 1,4-dioxane (4 ml)-tetrahydrofuran (4 ml), and added thereto was 2N sodium hydroxide (2 ml). The mixture was stirred at room temperature for one hour. The mixture was made acidic by addition of an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and then dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the desired 1-(β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienyl-methyl)-4-methylbenzene 60 (34 mg) as colorless powder. APCI-Mass m/Z 463 ($M+NH_4$).

EXAMPLE 121

1-(β-D-glucopyranosyl)-4-chloro-3-(2-(5-phenyl-2-thienyl)-ethyl)benzene

The target compound was obtained in a manner similar to Example 1, from 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)-benzene. APCI-Mass m/Z 478/480 ($M+NH_4$).

EXAMPLE 122

1-(β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120 (1) and 3-dimethylaminophenyl boronic acid were used and treated in a manner similar to Example 120—(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methyl-benzene. APCI-Mass m/Z 638 (M+H).

(2) the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methyl-benzene was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 470 (M+H).

EXAMPLE 123

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 (1.24 g) obtained in Example 119-(6), 3-cyanophenylboronic acid (270 ml), bis(triphenylphosphine) palladium (II) dichloride (54 mg) and 2M aqueous sodium carbonate solution (2.3 ml) in 1,2-dimethoxyethane (12 ml) was heated under reflux for 4 hours. The mixture was diluted with ethyl acetate and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:1-5:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene (1.12 g) as colorless oil. APCI-Mass m/Z 849/851 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 3-(3) to give the target compound as colorless powder. APCI-Mass m/Z 489/491 ($M+NH_4$).

EXAMPLE 124

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (600 mg) obtained in Example 120-(1), tri-n-butyl (5-pyrimidinyl)tin (600 mg), tri-tert-butylphosphine.tetrafluoroboric acid adduct (116 mg), cesium fluoride (414 mg), and tris(dibenzylideneacetone) dipalladium (0) (91 mg) in 1,4-dioxane (18 ml) was heated under reflux at 100° C. for 3 hours under argon atmosphere. Insoluble materials were filtered off, and the filtrate was diluted with ethyl acetate and washed with brine. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-40:60) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5 (5-pyrimidinyl)-2-thienylmethyl)benzene (266 mg) as colorless crystals. APCI-Mass m/Z 597 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5 (5-pyrimidinyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 106-(3) to give the target compound as colorless powder. APCI-Mass m/Z 429 (M+H)

EXAMPLE 125

1-(β-D-glucopyranosyl)-4-chloro-3-(2-phenyl-5-thiazolyl-methylbenzene

The target compound was prepared in a manner similar to Example 1, starting from 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene. APCI-Mass m/Z 448/450 (M+H).

EXAMPLE 126

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-pyridyl)-2-thienyl-methyl)benzene

(1) 1-(β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene obtained in Example 19 was used and treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)$_4$-chloro-3-(5-chloro-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 590/592 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene and tri-n-butyl(3-pyridyl)tin were used and treated in a manner similar to Example 124 to give the target compound as colorless powder. APCI-Mass m/Z 448/450 (M+H)

EXAMPLE 127

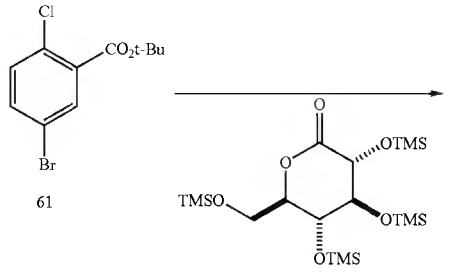
1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienyl-methyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120-(1) and 3-cyanophenylboronic acid were used and treated in a manner similar to Example 120—(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-cyano phenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 637 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-cyano phenyl)-2-thienylmethyl)-4-methylbenzene was used and treated in a manner similar to Example 106—(3) to give the target compound as colorless powder. APCI-Mass m/Z 469 ($M+NH_4$)

EXAMPLE 128

1-(β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienyl-methyl)benzene



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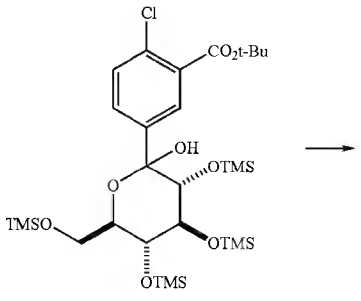

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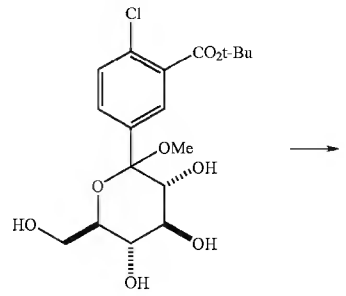

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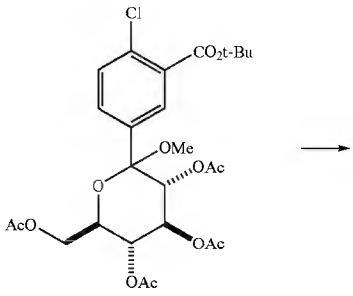

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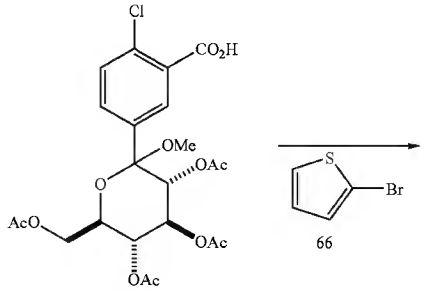

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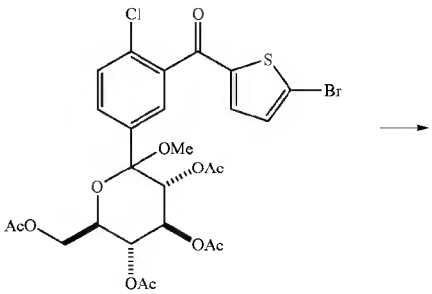

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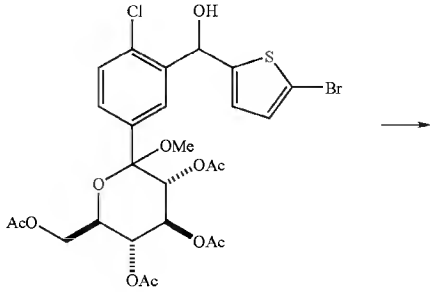

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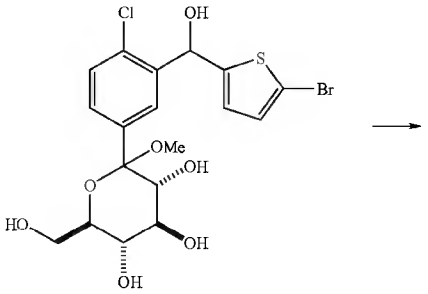

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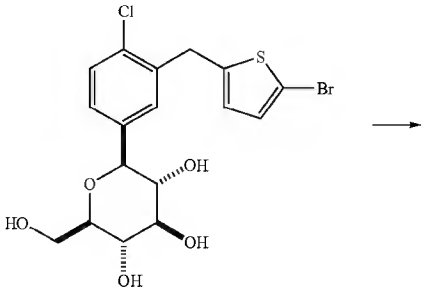

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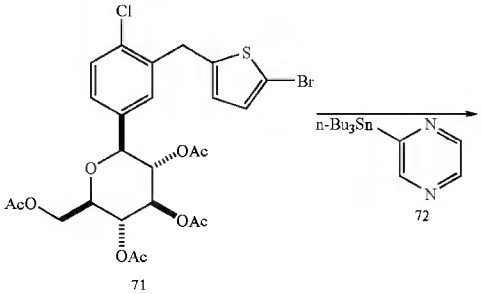

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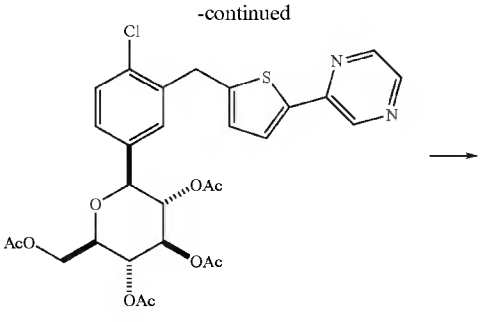

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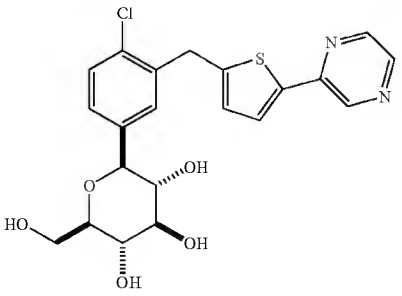


74

In the above scheme, the symbols are as defined above.

(1) A solution of mesityl bromide (4.74 g) in tetrahydrofuran (100 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise t-butyl lithium (1.43 M pentane solution, 33 ml). The mixture was stirred at −30 to −20° C. for one hour, and then, a mixed solution of t-butyl 5-bromo-2-chlorobenzoate 61 (4.94 g) and 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (11.10 g) in tetrahydrofuran (70 ml) was added dropwise thereto at −78° C. The mixture was stirred at the same temperature for one hour to give a compound 62. Without isolating this compound, a solution of methanesulfonic acid (3.75 ml) in methanol (50 ml) was added to the reaction solution, and the mixture was stirred at room temperature for 18 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution at 0° C., and the mixture was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give a methyl ether compound 63 (4.55 g) of the lactol as pale yellow powder. APCI-Mass m/Z 422/424 ($M+NH_4$).

(2) The compound 63 was treated in a manner similar to Example 106-(1) to give the compound 64. APCI-Mass m/Z 590/592 ($M+NH_4$).

(3) A solution of the above compound 64 (7.10 g) in formic acid (50 ml) was stirred at 50° C. for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene, twice, to give a compound 65 as colorless powder. Without further purification, this compound was dissolved in dichloromethane (50 ml). Added thereto were oxalyl chloride (1.3 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was dissolved in dichloroethane (50 ml), without further purification. To the solution was added 2-bromothiophene 66 (2.63 g) and the mixture was cooled to 0° C. Added gradually thereto was aluminum chloride (8.26 g), and subsequently, the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-cold water, and the mixture was extracted with ethyl acetate. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1-5:1) to give a compound 67 (7.01 g) as pale yellowish powder. APCI-Mass m/Z 678/680 ($M+NH_4$).

(4) The above ketone compound 67 (7.01 g) was dissolved in ethanol (50 ml), and thereto was added sodium borohydride (401 mg), and the mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with successively with water, 2N aqueous hydrochloride acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a compound 68 as pale yellow powder, which was dissolved in methanol (50 ml) without further purification. To the solution, sodium methoxide (28% methanol solution, 5 drops) was added, and then the mixture was stirred at room temperature for 2.5 hours. The solvent was evaporated under reduced pressure to give a deacetylated compound 69 as pale yellow powder. Without further purification, it was dissolved in dichloromethane (170 ml)-acetonitrile (70 ml), and added thereto was triethylsilane (10.2 ml), and the mixture was cooled to 0° C. Added dropwise thereto was boron trifluoride.diethyl ether complex (8.1 ml), and the mixture was stirred at room temperature for 5 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chloro benzene 70 as pale brown powder. Without further purification, this was dissolved in dichloromethane (30 ml), and added thereto were acetic anhydride (10.0 ml), pyridine (8.57 ml) and 4-dimethylaminopyridine (258 mg), and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate, and the solution was washed successively with water, 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The solution was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (3.17 g) as colorless crystals. APCI-Mass m/Z 634/636 ($M+NH_4$).

(5) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)4-chlorobenzene 71 (600 mg) was dissolved in 1,4-dioxane (11 ml). Added thereto were tri-n-butyl(pyrazinyl)tin 72 (720 mg), tetrakis (triphenylphosphine)palladium (0) (206 mg) and copper (I) iodide (51 mg), and the mixture was stirred under heating at 100° C. for 1.5 hours, under irradiation by a microwave (500 W). The mixture was diluted with ethyl acetate, the insoluble materials were filtered off, and the filtrate was washed with water. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-30:70), and crystallized from hexane-diethyl ether to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 (263 mg) as pale yellow crystals. APCI-Mass m/Z 617/619 (M+H).

(6) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 was used and treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienyl-methyl)benzene 74 as colorless powder. APCI-Mass m/Z 449/451 (M+H).

EXAMPLE 129

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethoxy-benzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)-benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482/484 ($M+NH_4$).

EXAMPLE 130

1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120—(1) and 3-formylphenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 640 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene (100 mg) was dissolved in dichloromethane (2 ml), and added thereto was (diethylamino) sulfur trifluoride (0.30 ml). The mixture was stirred at room temperature overnight. Water was added to the mixture and the mixture was extracted with chloroform. The extract was washed with brine and dried over magnesium sulfate, and then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-1:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methyl-benzene (82 mg). APCI-Mass m/Z 662 ($M+NH_4$).

(3) The above obtained 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienyl methyl)-4-methylbenzene was used and treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

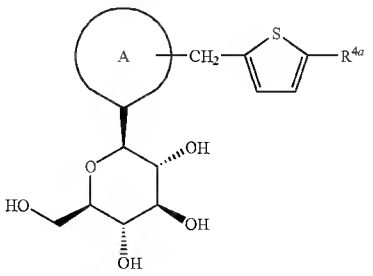
EXAMPLE 131

1-(β-D-glucopyranosyl)-4-chloro-3-(6-phenyl-3-pyridyl-methyl)benzene

5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 442/444 (M+H).

In a manner similar to the method disclosed in any of the above Examples, the compounds shown in Table 4 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out in the similar manner.

TABLE 4



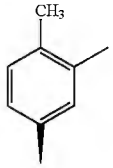
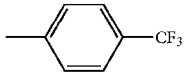
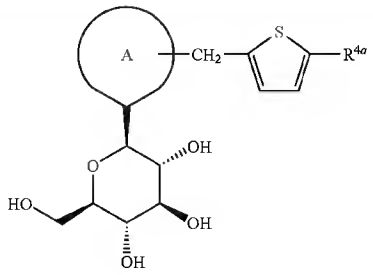
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
132			1	512 ($M + NH_4$)

TABLE 4-continued



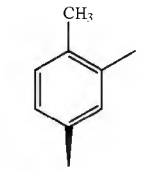
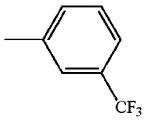
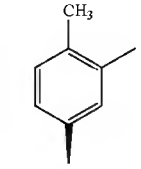
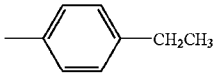
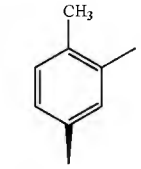
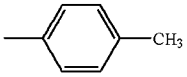
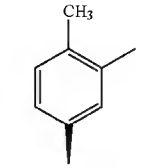
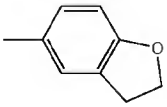
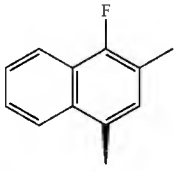
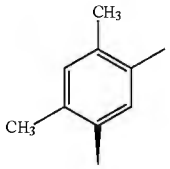
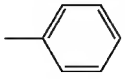
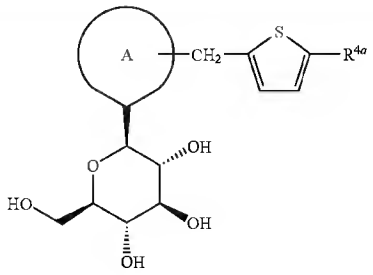
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
133			1	512 ($M + NH_4$)
134			4	472 ($M + NH_4$)
135			4	458 ($M + NH_4$)
136			4	486 ($M + NH_4$)
137		C1	1	456/458 ($M + NH_4$)
138			2	458 ($M + NH_4$)

TABLE 4-continued



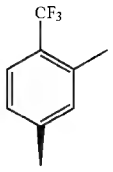
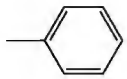
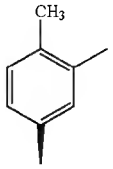
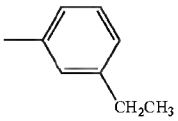
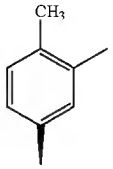
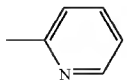
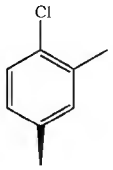
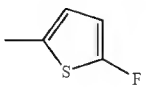
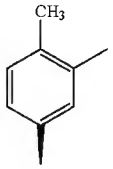
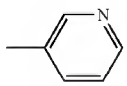
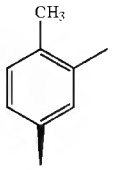
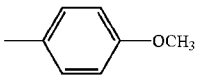
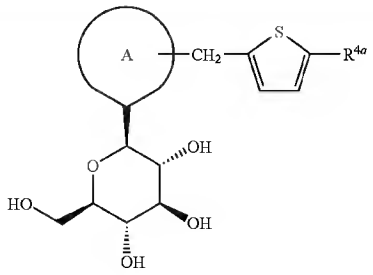
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
139			2	498 ($M + NH_4$)
140			1	472 ($M + NH_4$)
141			1	428 ($M + H$)
142			4	488/490 ($M + NH_4$)
143			1	428 ($M + H$)
144			1	474 ($M + NH_4$)

TABLE 4-continued



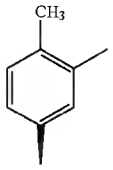
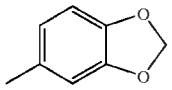
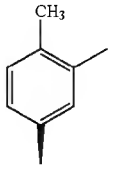
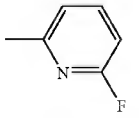
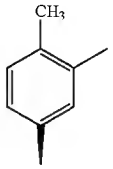
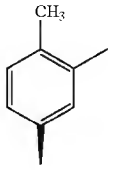
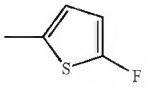
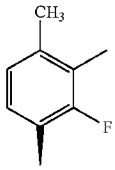
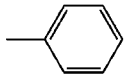
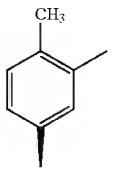
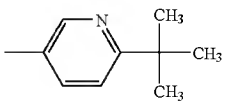
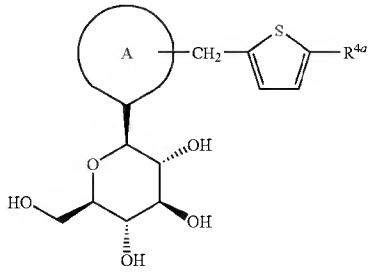
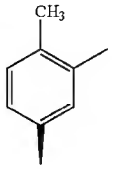
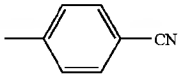
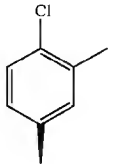
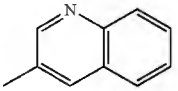
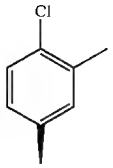
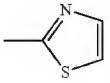
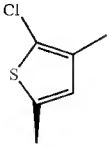
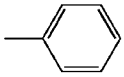
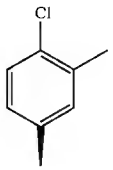
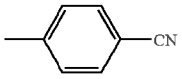
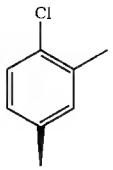
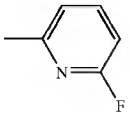
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
145			1	488 (M + NH_4)
146			1	463 (M + NH_4)
147		CF_3	1	436 (M + NH_4)
148			1	468 (M + NH_4)
149			1	462 (M + NH_4)
150			103	484 (M + H)

TABLE 4-continued



Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
151			124	469 ($M + NH_4$)
152			122	498/500 (M + H)
153			128	454/456 (M + H)
154			2	470/472 ($M + NH_4$)
155			122	489/491 ($M + NH_4$)
156			122	466/468 (M + H)

EXAMPLE 157

1-(β-D-glucopyranosyl)-4-chloro-3-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b]thiophen-2-yl-methyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 ($M+NH_4$).

EXAMPLE 158

1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (12.0 g) obtained in Example 120-(1) was dissolved in tetrahydrofuran (120 ml) and methanol (360 ml), and added thereto were triethylamine (24.2 ml) and 10% palladium carbon catalyst (wet, 3.6 g), and the mixture was stirred at room temperature for 18 hours under hydrogen atmosphere under normal pressure. The insoluble materials were filtered off, washed with tetrahydrofuran, and the filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform, washed successively with a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution and water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene (7.79 g) as colorless crystals. APCI-Mass m/Z 536 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienyl-methyl) benzene as colorless powder. APCI-Mass m/Z 368 ($M+NH_4$)

EXAMPLE 159

1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene (11.08 g) obtained in Example 158-(1) was dissolved in chloroform (100 ml), and added dropwise thereto at 0° C. was a solution of bromine (3.71 g) in chloroform (13 ml). The mixture was stirred at 0° C. for 1.5 hours, and then, at room temperature for 1 hour, and the mixture was poured into a 10% aqueous sodium thiosulfate solution and a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20-67:33) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (7.13 g) as a colorless solid. APCI-Mass m/Z 614/616 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106—(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 446/448 ($M+NH_4$).

EXAMPLE 160

1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 3-bromobenzadlehyde was treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 430 ($M+NH_4$).

EXAMPLE 161

1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (500 mg) obtained in Example 159-(1) was dissolved in N,N-dimethylacetamide (10 ml), and added thereto were zinc cyanide (98 mg), tris(dibenzylideneacetone)dipalladium(0) (77 mg), 1,1'-bis(diphenylphosphino)ferrocene (47 mg) and zinc power (14 mg). The mixture was heated under stirring at 120° C. overnight. The reaction solution was cooled, diluted with ethyl acetate and water, and the insoluble materials were filtered off. The organic layer of the filtrate was washed twice with water and successively washed with brine. After drying the same over sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-50:50) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene (207 mg) as colorless crystals. APCI-Mass m/Z 561 ($M+NH_4$)

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 393 ($M+NH_4$).

EXAMPLE 162

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(2-pyridyl)-2-thienylmethyl)naphthalene

4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl) naphthale was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482 (M+H).

EXAMPLE 163

1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 466/468 ($M+NH_4$).

EXAMPLE 164

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in

Example 159-(1) and tri-n-butyl(2-pyrimidinyl)tin 54 were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 429 (M+H).

EXAMPLE 165

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-thiazolyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and tri-n-butyl(2-thiazolyl)tin were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 434 (M+H).

EXAMPLE 166

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethyl-3-pyridylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 394/396 (M+H).

EXAMPLE 167

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b]thiophen-2-ylmethyl)benzene

6-Ethylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 466/468 (M+H).

EXAMPLE 168

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (500 mg) obtained in Example 128-(4) was dissolved in 1,2-dimethoxyethane (15 ml), and added thereto were 6-fluoropyridine-3-boronic acid 58 (228 mg), tetrakis(triphenylphosphine)palladium(0) (94 mg) and cesium fluoride (738 mg). The mixture was heated under reflux for 30 minutes. The reaction solution was poured into a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-60:40) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene (454 mg) as a colorless solid. APCI-Mass m/Z 634/636 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 106—(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 483 ($M+NH_4$), 466 (M+H).

EXAMPLE 169

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-3-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 6-methoxypyridine-3-boronic acid were treated in a manner similar to Example 168 to give the target compound. APCI-Mass m/Z 478/480 (M+H).

EXAMPLE 170

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-2-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl(6-methoxy-2-pyridyl)tin (see Gros, Philippe; Fort, Yves. Synthesis (1999), 754-756) were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 478/480 (M+H).

EXAMPLE 171

1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxo-2-isoindolinylmethyl)benzene

5-Bromo-2-chloro-1-(1-oxo-2-isoindolynilmethyl)benzene was treated in a manner similar to Example 2 to give the target compound. APCI-Mass m/Z 437/439 ($M+NH_4$).

EXAMPLE 172

1-(β-D-glucopyranosyl)-4-chloro-3-(1-phenyl-4-pyrazolylmethyl)benzene

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 431/433 (M+H).

EXAMPLE 173

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl(6-ethoxy-2-pyridyl)tin (see WO 00/74681) were treated in a manner similar to Example 128-(5) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 660/662 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene (245 mg) was dissolved in tetrahydrofuran (5 ml), added thereto was a solution of sodium hydride (oil, 9 mg) in ethanol (5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene (145 mg) as colorless powder. APCI-Mass m/Z 492/494 (M+H).

EXAMPLE 174

1-(β-D-glucopyranosyl)-4-chloro-3-(6-n-propyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b]thiophen-2-yl-methyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 ($M+NH_4$).

EXAMPLE 175

1-(β-D-glucopyranosyl)-4-chloro-3-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 500/502 ($M+NH_4$).

EXAMPLE 176

1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene from Example 159-(1) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-formylphenyl)-2-thienylmethyl)-4-methylbenzene as a colorless solid. APCI-Mass m/Z 640 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-formylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 130—(2) to give the desired 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienyl-methyl)-4-methylbenzene as colorless crystals. APCI-Mass m/Z 662 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

EXAMPLE 177

1-(β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and 3,4-difluorophenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless crystals. APCI-Mass m/Z 648 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 480 ($M+NH_4$).

EXAMPLE 178

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128—(4) and 3-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 ($M+NH_4$)

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl) benzene was treated in a manner similar to Example 130—(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl) benzene as colorless crystals. APCI-Mass m/Z 682/684 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 120—(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-benzene as colorless powder. APCI-Mass m/Z 514/516 ($M+NH_4$)

EXAMPLE 179

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl) benzene was treated in a manner similar to Example 130—(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl) benzene as colorless crystals. APCI-Mass m/Z 682/684 ($M+NH_4$)

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-benzene as colorless powder. APCI-Mass m/Z 514/516 ($M+NH_4$).

EXAMPLE 180

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethyl-3-fluorophenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and 3-fluoro-4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl) benzene as colorless foam. APCI-Mass m/Z 678/680 ($M+NH_4$).

(2) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl)-benzene was treated in a manner similar to Example 178-(2) and

(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethyl-3-fluorophenyl)-2-thienylmethyl)-benzene as a colorless foam. APCI-Mass m/Z 532/534 ($M+NH_4$)

EXAMPLE 181

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and (2-benzyloxymethyl-2H-tetrazol-5-yl)tri-n-butyltin (see *Tetrahedron Lett.* (2000) 2805) were treated in a manner similar to Example 128-(5) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-benzyloxymethyl-2H-tetrazol-5-yl)-2-thienylmethyl)-4-chlorobenzene as colorless solid. APCI-Mass m/Z 727/729 (M+H).

(2) A mixture of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-benzyloxymethyl-2H-tetrazol-5-yl)-2-thienylmethyl)-4-chlorobenzene (247 mg), 6M aqueous hydrochloric acid solution (2 ml) and methanol (20 ml) was refluxed overnight. The solvent was evaporated under reduced pressure and the residue was triturated with diethyl ether to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2-thienylmethyl)benzene (172 mg) as colorless powder. ESI-Mass m/Z 437/439 (M−H)

EXAMPLE 182

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methyl-2H-tetrazol-5-yl)-2-thienylmethyl)benzene

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2thienylmethyl)benzene (140 mg) obtained in Example 181 was dissolved in dimethylformamide (5 ml) and added thereto were methyl iodide (100 μl) and potassium carbonate (220 mg). The mixture was stirred at room temperature overnight. The reaction solution was poured into water and the mixture was extracted with ethylacetate. The extract was washed with brine and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methyl-2H-tetrazol-5-yl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 470/472 ($M+NH_4$).

EXAMPLE 183

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene

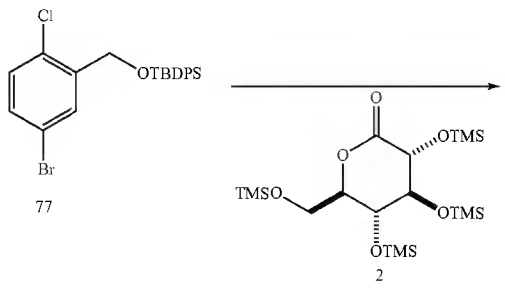
(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl) benzene (272 mg) obtained in Example 180-(1) was dissolved in N-methyl-2-pyrrolidone (10 ml) and added thereto was hydroxylamine hydrochloride (34 mg). The mixture was heated under stirring at 117° C. overnight. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethylacetate=3:1-2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxyimino-3-fluorophenyl)-2-thienylmethyl) benzene (177 mg) as colorless caramel. APCI-Mass m/Z 693/695 ($M+NH_4$).

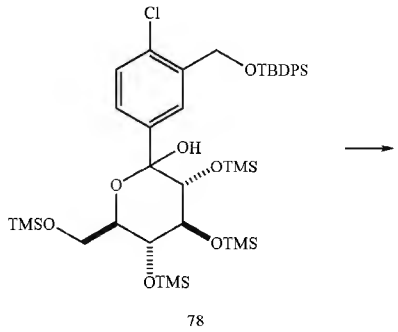
(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxyimino-3-fluorophenyl)-2-thienyl-methyl) benzene (175 mg) was dissolved in chloroform (5 ml) and added thereto was 1,1'-carbonyldiimidazole (46 mg). The mixture was stirred at room temperature overnight. 1,1'-Carbonyl-diimidazole (92 mg) was further added thereto, and the mixture was stirred at 40° C. for 6 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was separated and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene (158 mg) as colorless caramel. APCI-Mass m/Z 675/677 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)-benzene was treated in a manner similar to Example 106-(3) to give desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 507/509 ($M+NH_4$).

EXAMPLE 184

1-(β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene





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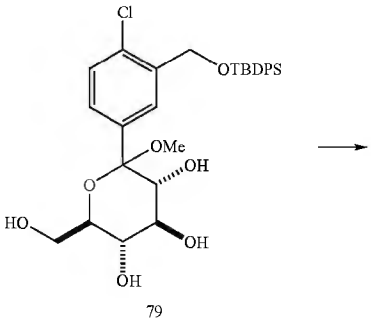

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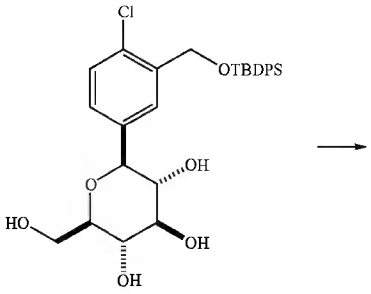

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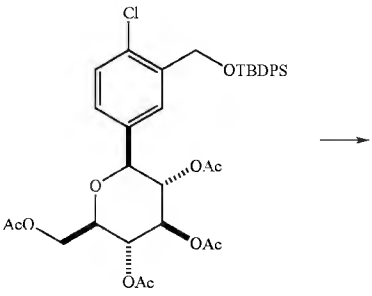

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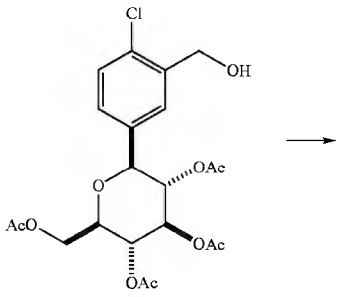

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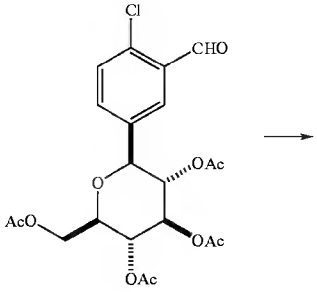

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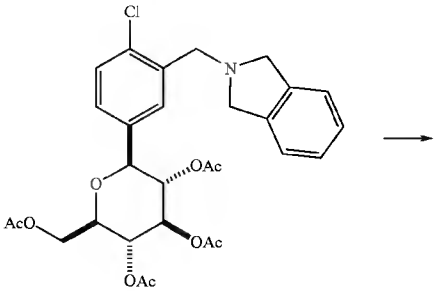

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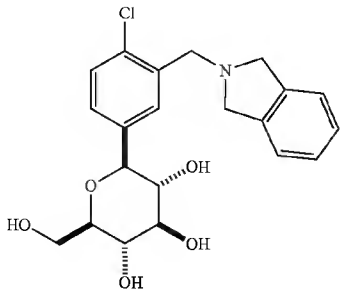


85

(In the above scheme, OTBDPS is a tert-butyldiphenylsilyloxy group, and the other symbols are the same as defined above.)

(1) A mixed solution of 5-bromo-2-chloro-1-(tert-butyldiphenylsilyloxymethyl)benzene 77 (10.83 g) and 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (13.2 g) in tetrahydrofuran (400 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise tert-butyl lithium (1.60 M pentane solution, 30.9 ml), and the mixture was stirred at the same temperature for 30 minutes to give a compound 78. Without isolating this compound, a solution of methanesulfonic acid (6.12 ml) in methanol (200 ml) was added to the reaction solution, and the reaction mixture was warmed to room temperature, and stirred at the same temperature for 15 hours. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=93:7) to give a

methyl ether compound 79 (9.71 g) as colorless powder. APCI-Mass m/Z 590/592 ($M+NH_4$).

(2) A solution of the above methyl ether compound 79 (3.46 g) in dichloromethane (70 ml) was cooled to 0° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (2.89 ml) and boron trifluoride.diethyl ether complex (2.28 ml). The mixture was stirred at the same temperature for 1 hour. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-94:4) to give 1-(β-D-glucopyranosyl)-4-chloro-3-(tert-butyldiphenylsilyloxymethyl)benzene 80 (2.52 g) as colorless powder. APCI-Mass m/Z 560/562 ($M+NH_4$).

(3) The above compound 80 (4.12 g) was treated in a manner similar to Example 106-(1) to give the compound 81 (5.44 g). APCI-Mass m/Z 728/730 ($M+NH_4$).

(4) A mixed solution of the above compound 81 (5.44 g), acetic acid (1.29 ml) in tetrahydrofuran (60 ml) was cooled to 0° C. under argon atmosphere, and thereto was added tetrabutyl ammonium fluoride (1.0 M tetrahydrofuran solution, 8.43 ml). The mixture was stirred at the same temperature for 30 minutes, and then further stirred at room temperature for 15 hours. The mixture was diluted with ethyl acetate and washed successively with 0.4 M aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-1:1) to give the compound 82 (2.97 g) as a colorless solid. APCI-Mass m/Z 490/492 ($M+NH_4$).

(5) A solution of the above compound 82 (1.60 g) in dichloromethane (50 ml) was cooled to 0° C. under argon atmosphere, and thereto was added Dess-Martin periodinane (1.58 g). The mixture was warmed to room temperature and stirred at the same temperature for 3 hours. The mixture was diluted with ethyl acetate, and insoluble materials were filtered off. The filtrate was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1-1:1) to give 5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-chloro-benzaldehyde 83 (1.35 g) as colorless crystals. APCI-Mass m/Z 488/490 ($M+NH_4$).

(6) To a mixed solution of the above 5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-chlorobenzaldehyde 83 (325 mg), 2,3-dihydro-1H-isoindole (98 mg), acetic acid (82 mg) in 1,2-dichloroethane (5 ml) was added sodium triacetoxyborohydride (219 mg). The mixture was stirred at room temperature for 3 hours, and cooled to 0° C. A saturated aqueous sodium hydrogen carbonate solution was added thereto to basify the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:0-1:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 84 (234 mg) as a colorless solid. APCI-Mass m/Z 574/576 (M+H).

(7) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-yl-methyl)benzene 84 was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 85 as colorless powder. APCI-Mass m/Z 406/408 (M+H).

EXAMPLE 185

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(3-cyano-4-fluorophenyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159—(1) and 4-fluoro-3-formylphenylboronic acid were used and treated in a manner similar to Example 177-(1) and Example 183 to give the title compound as colorless powder. APCI-Mass m/z 487 ($M+NH_4$).

EXAMPLE 186

1-(β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (597 mg) obtained in Example 159—(1) was dissolved in N-methyl-2-pyrrolidone (10 ml) and added thereto were tri-n-butyl (2-cyano-5-pyridyl)tin (590 mg), dichlorobis(triphenylphosphine)palladium(II) (70 mg) and copper(I)iodide (19 mg). The mixture was heated under stirring at 100° C. for 4 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (351 mg) as colorless powder. APCI-Mass m/Z 621 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (62 mg) was dissolved in a mixture of tert-butanol (3 ml)-tetrahydrofuran (3 ml) and added thereto was sodium tert-butoxide (48 mg). The mixture was stirred at room temperature for 3.5 hours. Sodium tert-butoxide (19 mg) was further added thereto, and the mixture was stirred at room temperature for 1 hour. To the mixture was added a saturated aqueous ammonium chloride solution at 0° C., and the mixture was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (23 mg) as colorless powder. APCI-Mass m/Z 470 ($M+NH_4$)

EXAMPLE 187

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) was treated in a manner similar to

Example 186-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 641/643 (M+H).

(2) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 186-(2) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 490/492 ($M+NH_4$).

EXAMPLE 188

1-(β-D-glucopyranosyl)-3-(5-(2-carbamoyl-5-pyridyl)-2-thienylmethyl)-4-chlorobenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene obtained in Example 187-(1) was treated in a manner similar to Example 106—(3) to give the mixture of 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene and 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene. This mixture was dissolved in methanol, and sodium methoxide (28% methanol solution, 1 drop) was added thereto, and the mixture was stirred at 60° C. for 6 hours. The reaction solution was cooled and the solvent was evaporated under reduced pressure to give pure 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene. APCI-Mass m/Z 505/507 (M+H).

(2) The above 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene was suspended in tetrahydrofuran, and sodium hydride (60% mineral oil suspension, 2 equivalent) was added thereto, and the mixture was stirred under reflux for 3 hours. The reaction solution was cooled and to the mixture was added a saturated aqueous ammonium chloride solution at 0° C., and the mixture was extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1-5:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(2-carbamoyl-5-pyridyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow powder. APCI-Mass m/Z 491/493 (M+H).

EXAMPLE 189

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene

(1) 5-bromo-2-fluorobenzaldehyde and 2-chlorothiophene were used and treated in a manner similar to Example 4 and Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 574/576 ($M+NH_4$). mp 130-131° C.

(2) The above compound was treated in a manner similar to EXAMPLE 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 540 ($M+NH_4$). mp 119-121° C.

(3) The above compound was treated in a manner similar to Example 159—(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 618/620 ($M+NH_4$). mp 127-129° C.

(4) The above compound and 3-cyanophenylboronic acid were used and treated in a manner similar to Example 168 to give the title compound as colorless powder. APCI-Mass m/z 473 ($M+NH_4$).

EXAMPLE 190

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(2-thiazolyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluorobenzene obtained in Example 189-(3) and tri-n-butyl(2-thiazolyl)tin were used and treated in a manner similar to Example 128 to give the title compound as colorless crystals. APCI-Mass m/z 438 ($M+NH_4$). mp 161.5-162° C.

EXAMPLE 191

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-ethoxycarbonylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128—(4) and 4-cyanophenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 657/659 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (128 mg) was suspended in ethanol (2 ml) and added thereto was a concentrated hydrochloric acid aqueous solution (1 ml). The mixture was heated reflux for 8.5 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-ethoxycarbonylphenyl)-2-thienylmethyl)benzene (39 mg) as pale yellow foam. APCI-Mass m/Z 536/538 ($M+NH_4$).

EXAMPLE 192

1-(β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (128 mg) obtained in Example 191—(1) was dissolved in acetic acid (2 ml) and added thereto was a concentrated hydrochloric acid aqueous solution (2 ml). The mixture was refluxed for 6.5 hours. To the mixture was added a 10% aqueous sodium hydroxide solution at 0° C., and the mixture was washed with ethyl acetate. The aqueous layer was acidified by adding concentrated hydrochloric acid, and extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was dried

over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by washing with a mixture of ethyl acetate and diethyl ether to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (49 mg) as pale brown powder. ESI-Mass m/Z 489/491 (M−H).

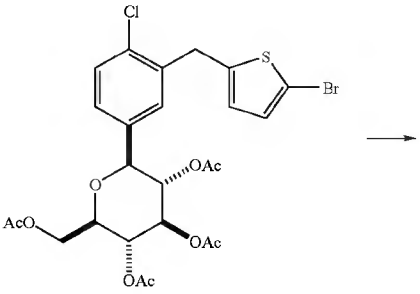
EXAMPLE 193

1-(β-D-glucopyranosyl)-3-(5-(4-carbamoylphenyl)-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (282 mg) obtained in Example 191-(1) was suspended in ethanol (5 ml) and added thereto was a 6N aqueous sodium hydroxide solution (0.37 ml). The mixture was stirred at room temperature for 10 minutes. To the mixture was added a 30% aqueous hydrogen peroxide solution (0.2 ml), and the mixture was stirred at room temperature for 1.5 hours and at 45° C. for 3 hours. To the mixture was added water (20 ml) and the mixture was cooled. The powder was collected by filtration and washed with diethyl ether and dried to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-carbamoyl-phenyl)-2-thienylmethyl)-4-chlorobenzene (176 mg) as colorless powder. APCI-Mass m/Z 507/509 ($M+NH_4$).

EXAMPLE 194

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene



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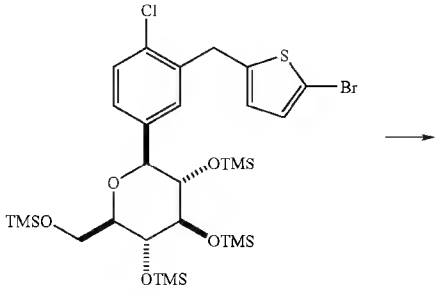

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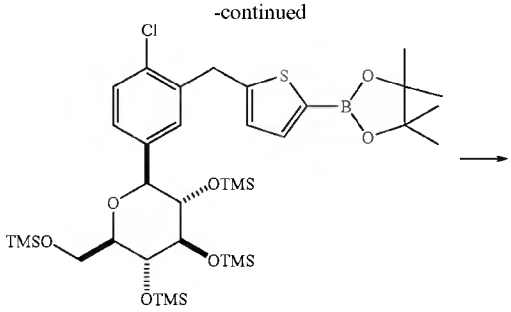

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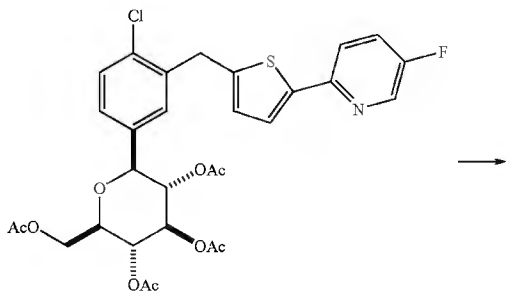

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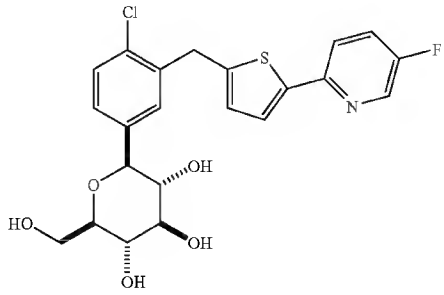


89

In the above scheme, the symbols are defined as above.

(1) The 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)$_4$-chlorobenzene 71 (750 mg) obtained in Example 128-(4) was dissolved in a mixture of methanol (8 ml)-tetrahydrofuran (8 ml), and sodium methoxide (28% methanol solution, 1 drop) was added thereto, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 ml), and thereto were added pyridine (0.69 ml) and 4-dimethylaminopyridine (15 mg). The mixture was cooled to 0° C., and thereto was added trimethylsilyl trifluoromethanesulfonate (1.54 ml). The mixture was stirred at room temperature for 3 days. To the mixture was added water, and the mixture was extracted with diethyl ether. The extract was washed with successively with water, a saturated aqueous ammonium chloride solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the compound 86 (900 mg) as colorless oil.

(2) A mixed solution of the above compound 86 (900 mg), triisopropoxyborane (252 mg) in tetrahydrofuran (22 ml) was cooled to −78° C. under argon atmosphere. Thereto was added dropwise tert-butyl lithium (1.46 M pentane

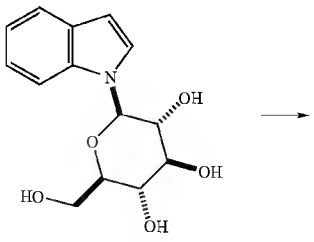
solution, 0.9 ml), and the mixture was stirred at the same temperature for 1 hour. The mixture was warmed to room temperature, and thereto was added pinacol (2.24 g). The mixture was stirred at the same temperature overnight. The mixture was diluted with ethyl acetate, and washed successively with water and brine. The solvent was evaporated under reduced pressure to give the compound 87, which was used in the subsequent reaction without further purification.

(3) The whole amount of the above compound 87 was dissolved in dimethoxyethane (20 ml), and thereto were added 2-bromo-5-fluoropyridine (460 mg), tetrakis(triphenylphosphine)palladium(0) (150 mg) and cesium fluoride (1.4 g). The mixture was stirred at 80° C. for 3 hours. The mixture was cooled to room temperature, acidified with 2 M aqueous hydrochloric acid solution, and stirred at the same temperature overnight. Under ice-cooling, the reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was passed through silica gel column chromatography (chloroform:methanol=100:0-88:12) to give crude oil, which was dissolved in dichloromethane (20 ml). To the mixture were added acetic anhydride (0.71 ml), pyridine (0.61 ml), and 4-dimethylaminopyridine (13 mg), and the mixture was stirred at room temperature for 1 hour. Then, dichloromethane was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed successively with 2 M aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:0-3:2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene 88 (218 mg) as a colorless solid. APCI-Mass m/Z 634/636 (M+H)

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienyl-methyl)benzene 88 was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene 89 as a colorless solid. APCI-Mass m/Z 466/468 (M+H).

EXAMPLE 195

1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)-indole



90

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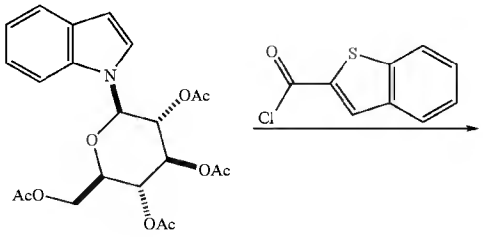

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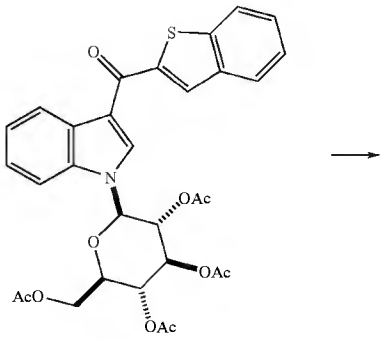

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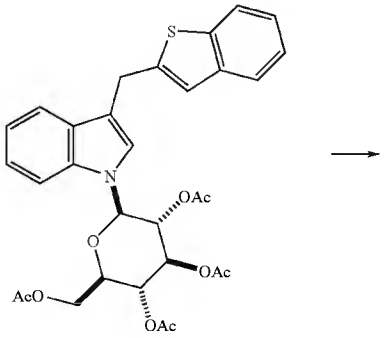
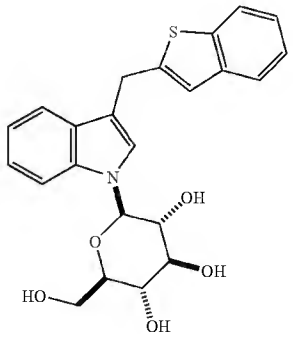


93



94

In the above scheme, the symbols are defined as above.

(1) 1-(β-D-glucopyranosyl)indole 90 (see *Eur. J. Med. Chem.* (2004) 39, 453-458) was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indole 91 as colorless crystals. APCI-Mass m/Z 465 ($M+NH_4$).

(2) Benzo[b]thiophene-2-carboxylic acid (598 mg) was suspended in dichloromethane (10 ml). Added thereto were oxalyl chloride (0.39 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was dissolved in dichloroethane (30 ml). To the solution was added 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)indole 91 (1 g) obtained above, and the mixture was cooled to 0° C. Added gradually thereto was aluminum chloride (2.09 g), and subsequently, the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-cold water, and the mixture was extracted with chloroform. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-5:4) to give Benzo[b] thiophen-2-yl(1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-indol-3-yl) ketone 92 (570 mg) as colorless crystals. APCI-Mass m/Z 608 (M+H).

(3) The above Benzo[b]thiophen-2-yl(1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-indol-3-yl) ketone 92 (440 mg) was dissolved in tetrahydrofuran (6 ml) and ethanol (3 ml). To the solution was added sodium borohydride (137 mg), and the mixture was stirred at room temperature for 60 minutes. The reaction mixture was quenched with cold aqueous HCl solution (0.5 N), and extracted with ethyl acetate. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The resultant residue was dissolved in dichloromethane (8 ml) and acetonitrile (4 ml), and the mixture was cooled to 0° C. under argon atmosphere. To the mixture were added triethylsilane (0.58 ml) and boron trifluoride.diethyl ether complex (0.46 ml). After 30 minutes, the mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the organic layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The resultant residue was dissolved in chloroform (20 ml), and to the mixture were added acetic anhydride (0.16 ml), triethylamine (0.2 ml), and 4-dimethylaminopyridine (15 mg), and the mixture was stirred at room temperature for 30 minutes. Then, the solution was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (hexane:ethyl acetate=8:2-6:4) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(benzo-[b]thiophen-2-yl-methyl)indole 93 (290 mg). APCI-Mass m/Z 611 ($M+NH_4$).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)indole 93 (336 mg) was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-yl-methyl) indole 94 (208 mg) as a colorless powder. APCI-Mass m/Z 443 ($M+NH_4$)

EXAMPLE 196

1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienyl-methyl)-4-fluoronaphthalene

(1) The 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienyl-methyl)-4-fluoronaphthalene obtained in Example 137 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 624/626 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienyl-methyl)-4-fluoronaphthalene. APCI-Mass m/Z 590 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-3-(2-thienylmethyl)-4-fluoronaphthalene was treated in a manner similar to Example 159-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 668/670 ($M+NH_4$).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluoronaphthalene and 3-cyanophenylboronic acid were treated in a manner similar to Example 168 to give 1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienyl-methyl)-4-fluoronaphthalene. APCI-Mass m/Z 523 ($M+NH_4$).

EXAMPLE 197

1-(β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienyl-methyl)-4-chlorobenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in EXAMPLE 128-(4) and 4-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)aniline were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow powder. APCI-Mass m/Z 630/632 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow foam. APCI-Mass m/Z 479/481 ($M+NH_4$).

EXAMPLE 198

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoyl-phenyl)-2-thienylmethyl)benzene

(1) 1-(β-D-Glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (637 mg) obtained in Example 192 was dissolved in a mixture of dichloromethane (10 ml)-tetrahydrofuran (5 ml) and added thereto were acetic anhydride (1.22 ml), pyridine (1.05 ml) and 4-dimethylaminopyridine (32 mg). The mixture was stirred at room temperature overnight. The solvents were evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 2N hydrochloric acid aqueous solution and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:1-50:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (687 mg) as pale yellow powder. ESI-Mass m/Z 657/659 (M−H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chloro

benzene (198 mg) was dissolved in dichloromethane (5 ml) and added thereto were oxalyl chloride (1 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature for 3.5 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was suspended in tetrahydrofuran (4 ml), without further purification. To the suspension was added a 2.0 M solution of methylamine in tetrahydrofuran (1.5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)-benzene (218 mg) as pale yellow powder. APCI-Mass m/Z 689/691 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)-benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 521/523 ($M+NH_4$).

EXAMPLE 199

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonyl-aminophenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene (126 mg) obtained in Example 197-(1) was dissolved in dichloromethane (3 ml) and added thereto were methanesulfonyl chloride (48 mg) and pyridine (48 mg). The mixture was stirred at room temperature for 3.5 hours. To the mixture was added 2N hydrochloric acid aqueous solution at 0° C. and extracted with ethyl acetate. The organic layer was washed with water, aqueous sodium hydrogen carbonate solution and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1-1:2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylamino-phenyl)-2-thienylmethyl)benzene (154 mg) as yellow caramel. ESI-Mass m/Z 706/708 (M−H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 106—(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienyl-methyl)benzene as yellow foam. ESI-Mass m/Z 538/540 (M−H).

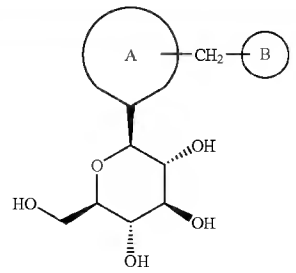
EXAMPLE 200

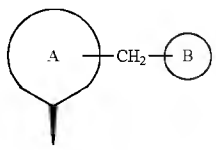
1-(β-D-glucopyranosyl)-3-(5-(4-acetylaminophenyl)-2-thienyl methyl)-4-chlorobenzene

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene (126 mg) obtained in Example 197-(1) was treated in a manner similar to Example 106—(1) and (3) to give the target compound as colorless powder. APCI-Mass m/Z 521/523 ($M+NH_4$).

The compounds shown in Table 5 below were prepared in a manner similar to one of the above Examples from the corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out.

TABLE 5





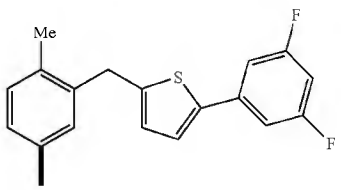
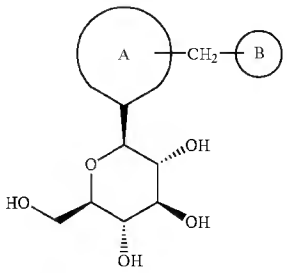
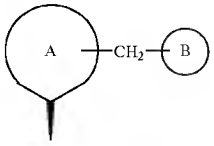
Examples		Preparation Method	APCI-Mass (m/Z)
201		177	480 ($M + NH_4$)

TABLE 5-continued





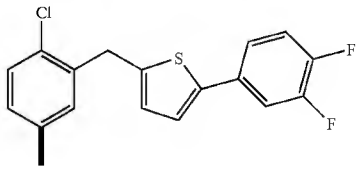
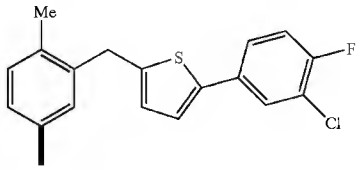
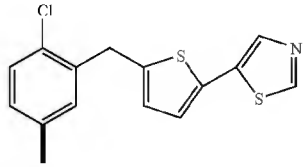
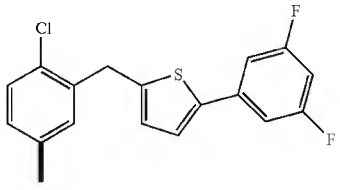
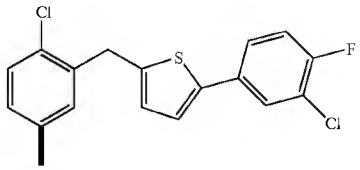
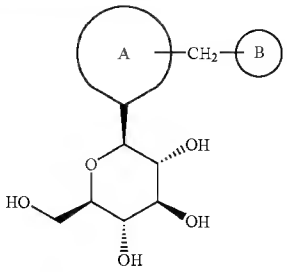
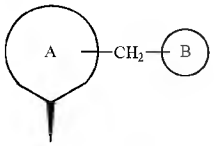
Examples		Preparation Method	APCI-Mass (m/Z)
202		168	500/502 ($M + NH_4$)
203		177	496/498 ($M + NH_4$)
204		128	454/456 ($M + H$)
205		168	500/502 ($M + NH_4$)
206		168	516/518 ($M + NH_4$)

TABLE 5-continued





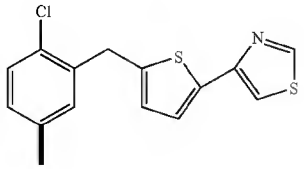
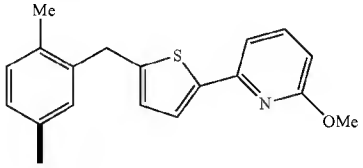
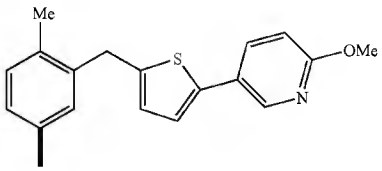
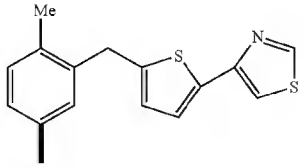
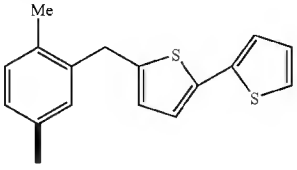
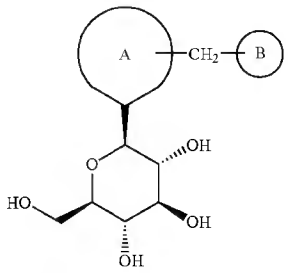
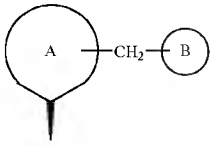
Examples		Preparation Method	APCI-Mass (m/Z)
207		128	454/456 (M + H)
208		164	458 (M + H)
209		177	458 (M + H)
210		164	434 (M + H)
211		177	450 (M + NH_4)

TABLE 5-continued





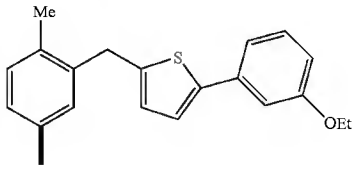
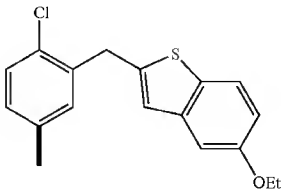
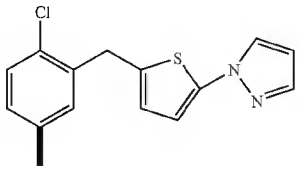
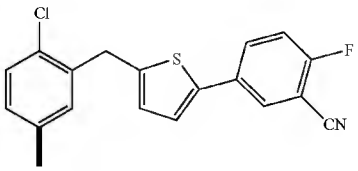
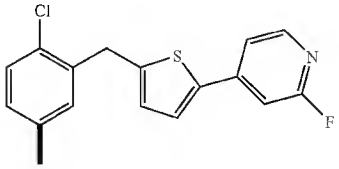
Examples		Preparation Method	APCI-Mass (m/Z)
212		177	488 ($M + NH_4$)
213		1	482/484 ($M + NH_4$)
214		2	437/439 (M + H)
215		183	507/509 ($M + NH_4$)
216		168	466/468 (M + H)

TABLE 5-continued

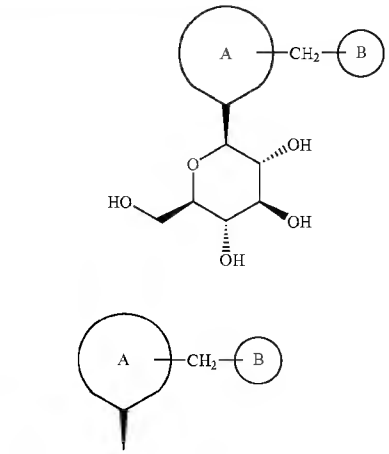
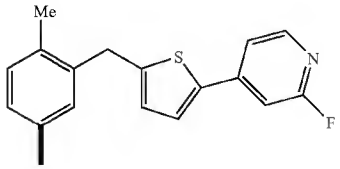
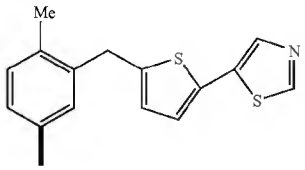
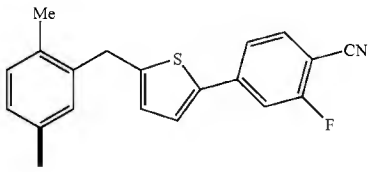
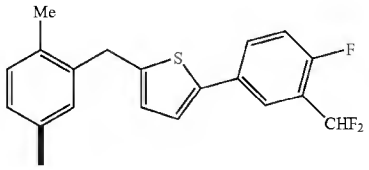
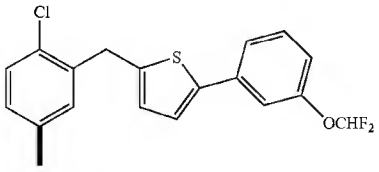
Examples		Preparation Method	APCI-Mass (m/Z)
217		177	446 (M + H)
218		164	434 (M + H)
219		185	487 (M + NH_4)
220		176	512 (M + NH_4)
221		168	530/532 (M + NH_4)

TABLE 5-continued

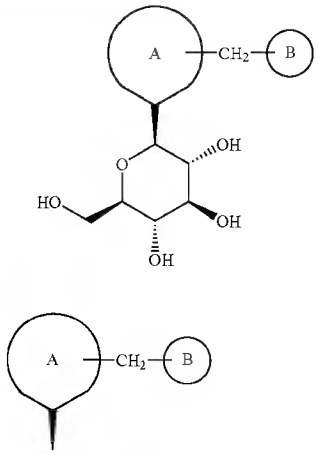
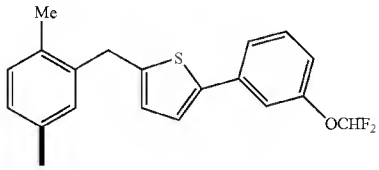
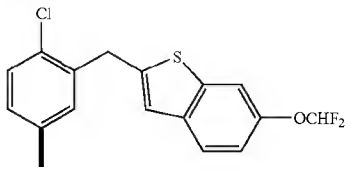
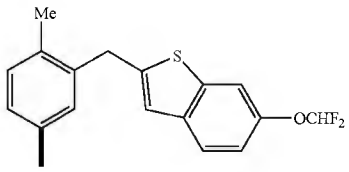
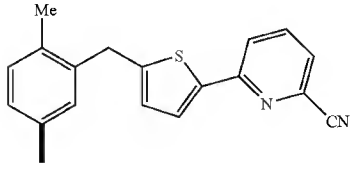
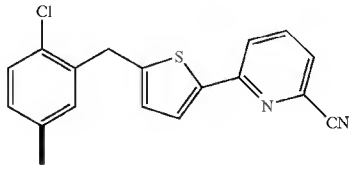
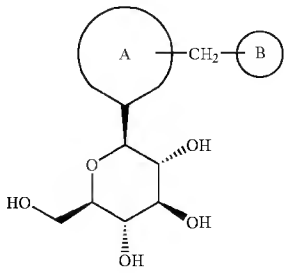
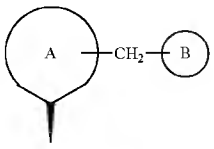
Examples		Preparation Method	APCI-Mass (m/Z)
222		177	510 (M + NH_4)
223		2	504/506 (M + NH_4)
224		2	484 (M + NH_4)
225		186	470 (M + NH_4)
226		187	490/492 (M + NH_4)

TABLE 5-continued





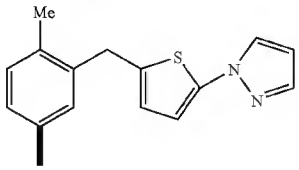
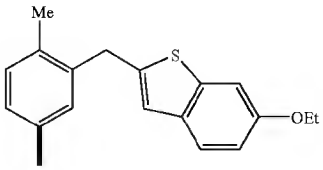
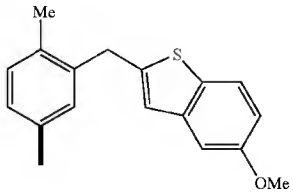
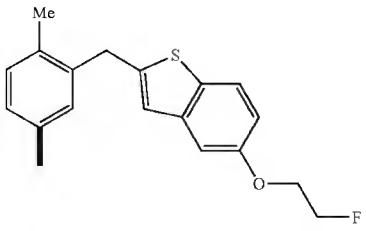
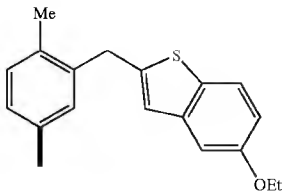
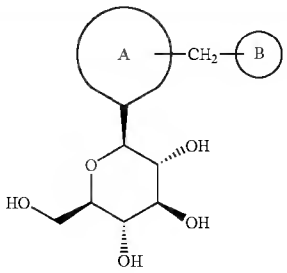
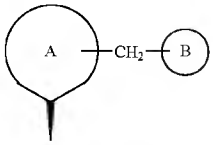
Examples		Preparation Method	APCI-Mass (m/Z)
227		2	417 (M + H)
228		1	462 (M + NH_4)
229		1	448 (M + NH_4)
230		1	480 (M + NH_4)
231		1	462 (M + NH_4)

TABLE 5-continued





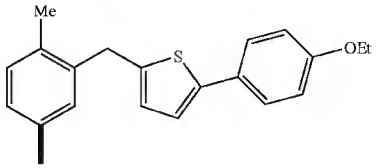
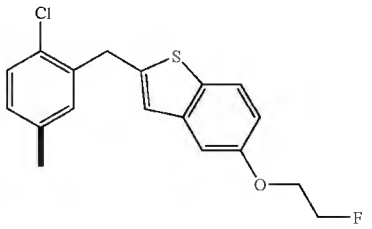
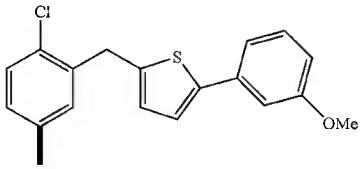
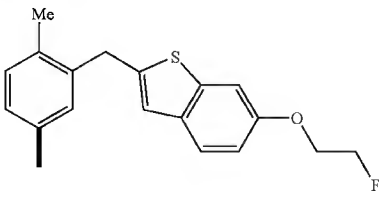
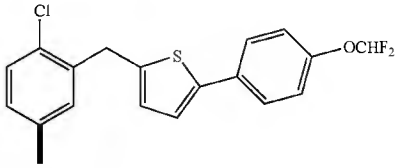
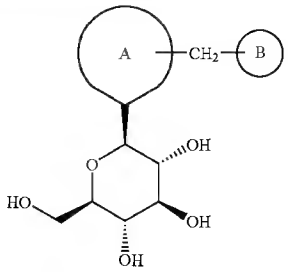
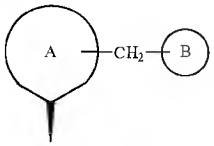
Examples		Preparation Method	APCI-Mass (m/Z)
232		177	488 ($M + NH_4$)
233		1	500/502 ($M + NH_4$)
234		168	494/496 ($M + NH_4$)
235		1	480 ($M + NH_4$)
236		168	530/532 ($M + NH_4$)

TABLE 5-continued





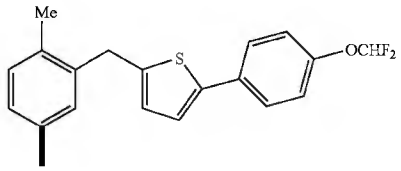
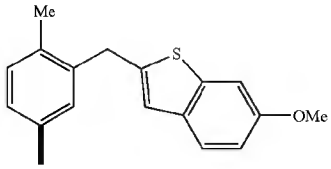
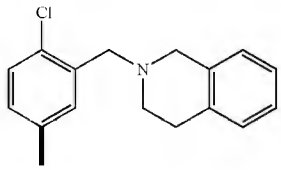
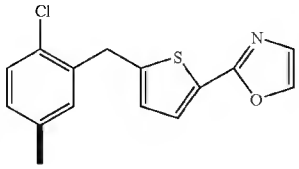
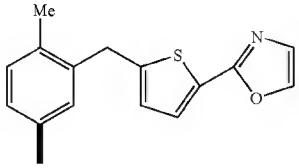
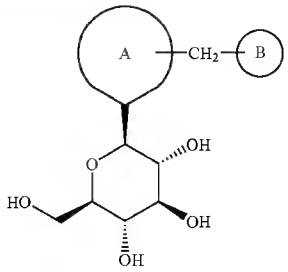
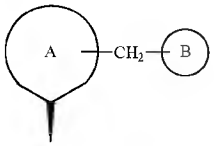
Examples		Preparation Method	APCI-Mass (m/Z)
237		177	510 (M + NH_4)
238		1	448 (M + NH_4)
239		184	420/422 (M + H)
240		128	438/440 (M + H)
241		164	418 (M + H)

TABLE 5-continued





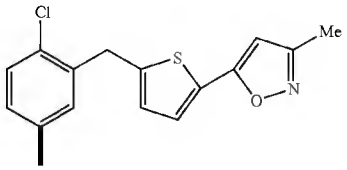
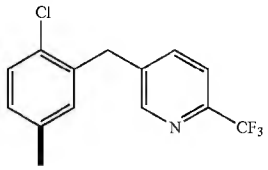
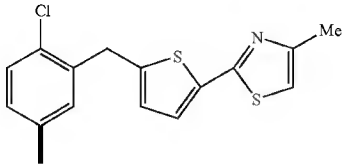
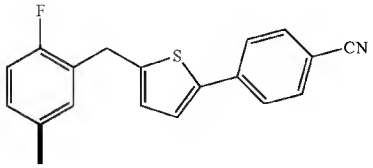
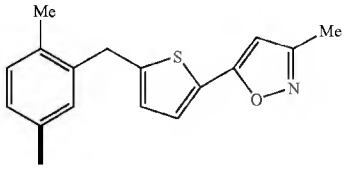
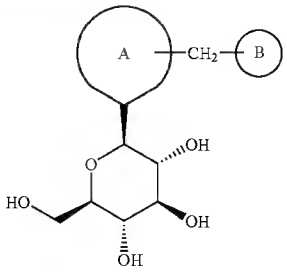
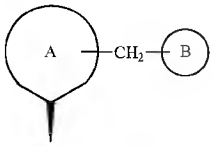
Examples		Preparation Method	APCI-Mass (m/Z)
242		128	469/471 ($M + NH_4$)
243		1	434/436 (M + H)
244		128	468/470 (M + H)
245		189	473 ($M + NH_4$)
246		164	449 ($M + NH_4$)

TABLE 5-continued





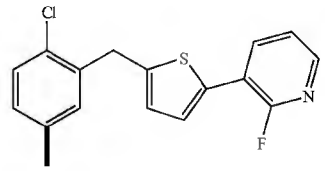
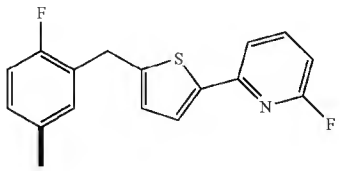
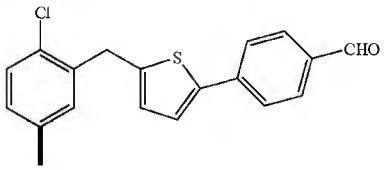
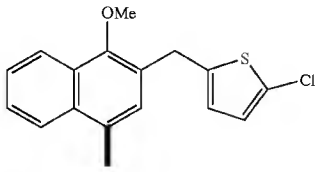
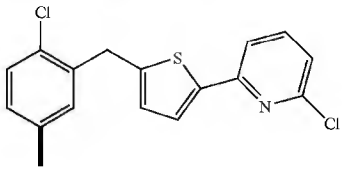
Examples		Preparation Method	APCI-Mass (m/Z)
247		168	483/485 ($M + NH_4$)
248		189	467 ($M + NH_4$)
249		168	492/494 ($M + NH_4$)
250		1	468/470 ($M + NH_4$)
251		168	499/501 ($M + NH_4$)

TABLE 5-continued

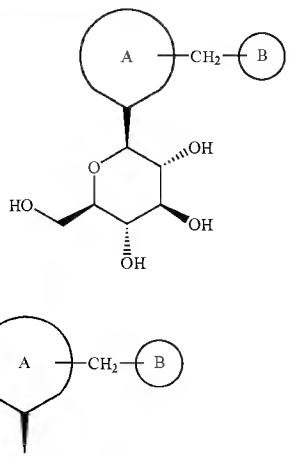
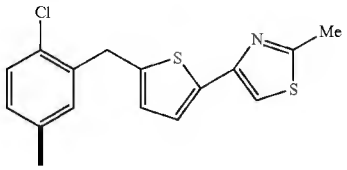
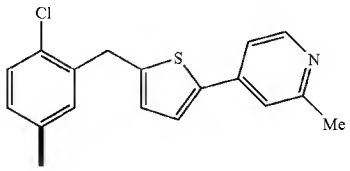
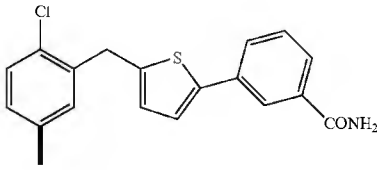
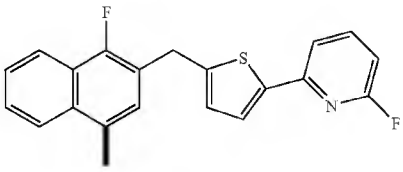
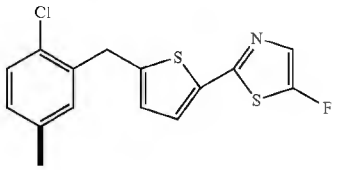
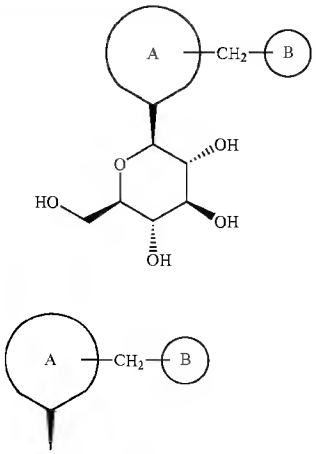
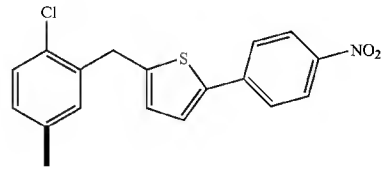
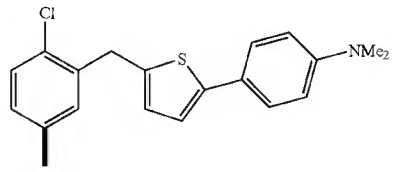
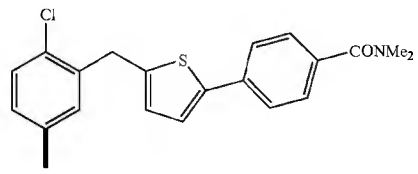
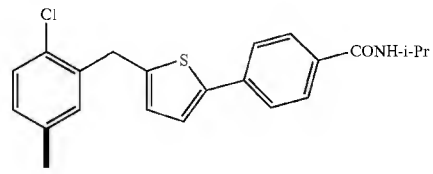
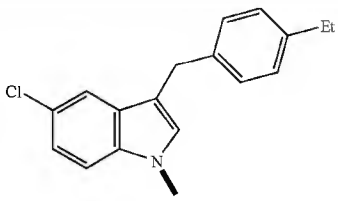
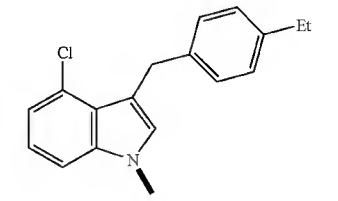
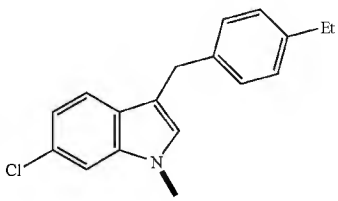
Examples		Preparation Method	APCI-Mass (m/Z)
252		128	468/470 (M + H)
253		168	462/464 (M + H)
254		193	507/509 ($M + NH_4$)
255		196	517 ($M + NH_4$)
256		1	472/474 (M + H)

TABLE 5-continued

Examples		Preparation Method	APCI-Mass (m/Z)
257		168	509/511 ($M + NH_4$)
258		168	490/492 (M + H)
259		198	535/537 ($M + NH_4$)
260		198	549/551 ($M + NH_4$)

The compounds shown in Table 6 below were prepared in a manner similar to Example 195 from the corresponding starting materials.

TABLE 6

Examples		APCI-Mass (m/Z)
261		449/451 (M + NH_4)
262		432/434 (M + H)
263		449/451 (M + NH_4)

EXAMPLE 264

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxymethyl-phenyl)-2-thienylmethyl)benzene

1-(β-D-Glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene (84 mg) obtained in Example 249 was dissolved in a mixture of ethanol (2 ml)-tetrahydrofuran (2 ml) and added thereto was sodium borohydride (7 mg). The mixture was stirred at room temperature for 1 hour. The mixture was quenched by 2N hydrochloric acid aqueous solution (3 drops) at 0° C., and the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxymethylphenyl)-2-thienylmethyl)benzene (82 mg) as colorless foam. APCI-Mass m/Z 494/496 (M+NH_4).

EXAMPLE 265

1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)-4-methoxynaphthalene

(1) 1-(β-D-Glucopyranosyl)-3-(5-chloro-2-thienyl-methyl)-4-methoxynaphthalene obtained in Example 250 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 636/638 (M+NH_4).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-3-(5chloro-2-thienylmethyl)-4-methoxynaphthalene was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienyl-methyl)-4-methoxynaphthalene. APCI-Mass m/Z 602 (M+NH_4).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-3-(2-thienylmethyl)-4-methoxynaphthalene was treated in a manner similar to Example 159-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 680/682 (M+NH_4).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxynaphthalene and phenylboronic acid were treated in a manner similar to Example 168 to give the desired 1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienyl-methyl)-4-methoxynaphthalene. APCI-Mass m/Z 510 (M+NH_4).

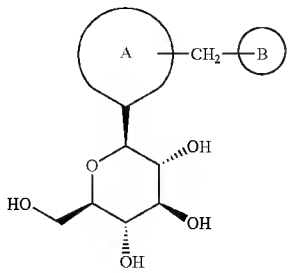
EXAMPLE 266

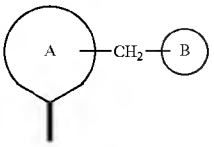
1-(β-D-glucopyranosyl)-3-(5-(2-pyrimidinyl)-2-thienylmethyl)-4-methoxynaphthalene

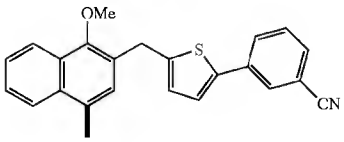
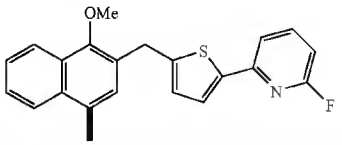
1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxylnaphthalene obtained in Example 265-(3) and 2-tributylstannylpyrimidine were treated in a manner similar to Example 128-(5) and (6) to give 1-(β-D-glucopyranosyl)-3-(5-(2-pyrimidinyl)-2-thienyl-methyl)-4-methoxylnaphthalene. APCI-Mass m/Z 495 (M+H).

The compounds shown in Table 7 below were prepared in a manner similar to Example 265 from the corresponding starting materials.

TABLE 7





Examples		APCI-Mass (m/Z)
267		535 ($M + NH_4$)
268		529 ($M + NH_4$)

REFERENCE EXAMPLE 1

3-Bromo-1-(5-ethyl-2-thienylmethyl)benzene

(1) A solution of 1,3-dibromobenzene (3.7 g) in tetrahydrofuran (25 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.55 ml). The reaction mixture was stirred at the same temperature for 10 minutes, and thereto was added dropwise a solution of 5-ethyl-2-thiophenecarboxaldehyde (2.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated ammonium chloride solution, and the reaction mixture was warmed to room temperature. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=97:3-85:15) to give 3-bromophenyl-5-ethyl-2-thienylmethanol (2.97 g) as a pale yellow syrup. APCI-Mass m/Z 279/281 ($M+H—H_2O$).

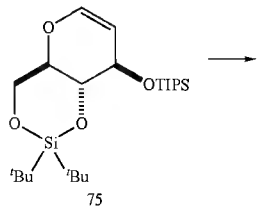
(2) The above 3-bromophenyl-5-ethyl-2-thienylmethanol (2.90 g) was dissolved in dichloromethane (38 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture were added triethylsilane (6.18 ml) and boron trifluoride.diethyl ether complex (2.45 ml), and the mixture was gradually warmed to room temperature over a period of one hour. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the dichloromethane layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give the desired 3-bromo-(5-ethyl-2-thienylmethyl)benzene (2.57 g) as a colorless syrup. APCI-Mass m/Z 281/283 (M+H)

REFERENCE EXAMPLE 2

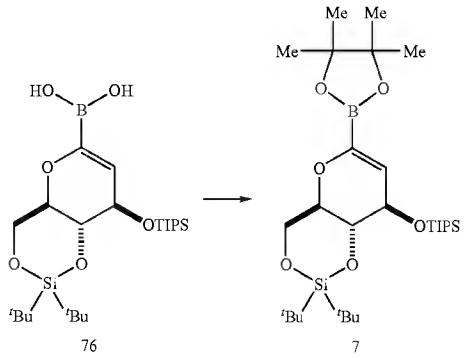
5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one

5-Bromo-1H-pyridin-2-one (1.04 g) and 4-ethylbenzyl bromide (1.43 g) were dissolved in N,N-dimethylformamide (15 ml), and thereto was added potassium carbonate (1.66 g). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and washed successively with water and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1-3:1) to give 5-bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one (1.58 g) as colorless crystals. APCI-Mass m/Z 292/294 (M+H).

REFERENCE EXAMPLE 3



75



76 7

In the above scheme, the symbols are as defined above.

(1) A solution of silylated glucal 75 (see Parker et al., Org. Lett. 2000, 2, 497-499) (7.00 g) in tetrahydrofuran (70 ml) was cooled to −78° C. under argon atmosphere. Thereto was added dropwise t-butyl lithium (1.45 M pentane solution, 49.0 ml) over a period of 10 minutes. The mixture was stirred at the same temperature for 15 minutes, and then warmed to room temperature, and further stirred for 30 minutes. The mixture was cooled again to −78° C., and thereto was added trimethyl borate (8.90 ml) in one portion. After 15 minutes, the reaction solution was warmed to room temperature over a period of one hour, and thereto was added water (100 ml) at 0° C. The mixture was stirred for 30 minutes, and extracted twice with diethyl ether. The extract was washed with water, and then washed with brine. The resultant was dried over magnesium sulfate, and

the solvent was evaporated under reduced pressure to give the compound 76, which was used in the subsequent reaction without further purification.

(2) The whole amount of the above compound 76 was dissolved in toluene (65 ml), and thereto was added pinacol (2.24 g). The mixture was stirred at room temperature under argon atmosphere for 17 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, and the extract was washed with brine, dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the compound 7 (10.4 g) as a yellow semisolid, which was used in the subsequent reaction without further purification. APCI-Mass m/Z 569 (M+H).

REFERENCE EXAMPLE 4

5-Bromo-2-methylbenzaldehyde

(1) Methyl 5-bromo-2-methylbenzoate (see Japanese Unexamined Patent Publication No. 9-263549) (16.12 g) was dissolved in methanol (100 ml), and thereto was added 10% aqueous sodium hydroxide solution (50 ml). The mixture was stirred at 50° C. for 40 minutes. Under ice-cooling, the mixture was adjusted to pH 1 by addition of 10% aqueous hydrochloric acid solution, and diluted with water. Precipitated powder was collected by filtration, and dried to give 5-bromo-2-methylbenzoic acid (14.1 g). ESI-Mass m/Z 213/215 (M−H).

(2) The above 5-bromo-2-methylbenzoic acid (10.0 g) was suspended in dichloromethane (100 ml), and thereto were added oxalyl chloride (8.1 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-methylbenzoyl chloride. This benzoyl chloride was dissolved in dichloromethane (200 ml), and thereto was added N,O-dimethylhydroxylamine hydrochloride (12.3 g). To the mixture was added dropwise triethylamine (20 ml) at 0° C., and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate, and washed successively with water, 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.25 g) as oil. APCI-Mass m/Z 258/260 (M+H).

(3) A solution of the above N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.2 g) in tetrahydrofuran (100 ml) was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise diisobutyl aluminum hydride (1.0 M toluene solution, 75 ml), and the mixture was stirred at the same temperature for one hour. 10% aqueous hydrochloric acid solution (50 ml) was added thereto, and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate twice, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was solidified to give 5-bromo-2-methylbenzaldehyde (8.73 g). APCI-Mass m/Z 213/215 (M+H+ MeOH—H_2O).

REFERENCE EXAMPLE 5

5-Bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene

(1) 5-Bromo-2-chlorobenzoic acid (5.00 g) was suspended in dichloromethane (10 ml), and thereto were added oxalyl chloride (2.2 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 6 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzoyl chloride. This compound and 2-ethylthiophene (2.38 g) were dissolved in dichloromethane (20 ml), and thereto was added aluminum chloride (3.11 g) at 0° C. The mixture was stirred at the same temperature for one hour. The reaction mixture was poured into a cold 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:1) to give 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) as an oil. APCI-Mass m/Z 329/331 (M+H).

(2) A solution of the above 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) in dichloromethane (50 ml)—acetonitrile (50 ml) was cooled under ice-cooling, and thereto were added dropwise triethylsilane (7.69 ml) and boron trifluoride.diethyl ether complex (6.1 ml). Subsequently, the mixture was stirred at room temperature for 3.5 hours, and was cooled again under ice-cooling. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene (4.52 g) as a colorless liquid.

REFERENCE EXAMPLE 6

3-Bromo-1-(5-n-propyl-2-thienylmethyl)benzene

3-Bromobenzoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

REFERENCE EXAMPLE 7

5-Bromo-(5-ethyl-2-thienylmethyl)$_2$-methoxybenzene

(1) A solution of 2-ethylthiophene (3.00 g) in tetrahydrofuran (36 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.56 M hexane solution, 17.1 ml). The mixture was stirred at the same temperature for 30 minutes, and cooled to −78° C., and thereto was added dropwise a suspension of 5-bromo-2-methoxybenzaldehyde (5.74 g) in tetrahydrofuran (60 ml). The mixture was stirred at the same temperature for 2 hours, warmed to 0° C., and thereto was added a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol (5.99 g) as a pale yellow syrup. APCI-Mass m/Z 309/311 (M+H—H_2O)

(2) The above 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol was treated in a manner similar to Reference

Example 1-(2) to give 5-bromo-(5-ethyl-2-thienylmethyl)-2-methoxybenzene as oil. APCI-Mass m/Z 311/313 (M+H).

REFERENCE EXAMPLE 8

3-Bromo-1-(5-ethyl-2-thienylmethyl)-4-methoxybenzene

2-Ethylthiophene and 3-bromo-4-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 9

3-Bromo-1-(4-n-propyl-2-thienylmethyl)benzene

(1) 3-n-Propylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 7-(1) to give 3-bromophenyl-4-n-propyl-2-thienyl methanol. APCI-Mass m/Z 293/295 (M+H—H_2O).

(2) A solution of the above 3-bromophenyl-4-n-propyl-2-thienyl methanol (2.4 g) in acetonitrile (10 ml) was added dropwise to a mixed solution of chlorotrimethylsilane (4.54 ml) and sodium iodide (5.36 g) in acetonitrile (10 ml) at 0° C., over a period of 2 hours. The mixture was further stirred at room temperature for 5 minutes, and cooled again to 0° C. An aqueous solution (10 ml) of sodium hydroxide (1.0 g) was added thereto, and the mixture was stirred at 0° C. for 0.5 hours. The mixture was extracted with ethyl acetate, washed successively with an aqueous sodium thiosulfate solution, water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-1-(4-n-propyl-2-thienyl)benzene (1.97 g) as colorless oil.

REFERENCE EXAMPLE 10

5-Bromo-2-chloro-1-(5-n-propyl-2-thienylmethyl) benzene

5-Bromo-2-chlorobenozoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

REFERENCE EXAMPLE 11

5-Bromo-2-methoxy-1-(5-n-propyl-2-thienylmethyl) benzene

2-n-Propylthiophene and 5-bromo-2-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 325/327 (M+H)

REFERENCE EXAMPLE 12

3-Bromo-1-(4-ethyl-2-thienylmethyl)benzene

3-Ethylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 281/283 (M+H).

REFERENCE EXAMPLE 13

3-Bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene

(1) To a solution of 5-ethyl-2-thiophenecarboxaldehyde (6.0 g) in N,N-dimethylformamide (60 ml) was added N-chlorosuccinimide (8.57 g), and the mixture was stirred at room temperature for 2 hours, and subsequently stirred under heating at 60° C. for 2 hours. N-chlorosuccinimide (4.00 g) was further added thereto, and the mixture was further stirred under heating at 60° C. for 2 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=33:1) to give 4-chloro-5-ethyl-2-thiophenecarboxaldehyde (3.1 g) as colorless oil.

(2) The above 4-chloro-5-ethyl-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 1 to give 3-bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene as yellow oil. APCI-Mass m/Z 347/349 (M+H+ MeOH)

REFERENCE EXAMPLE 14

5-Bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b] thiophen-2-ylmethyl)benzene

(1) To a solution of 4-keto-4, 5, 6, 7-tetrahydrothianaphthene (9.83 g) in ethylene glycol (100 ml) were added hydrazine hydrate (10.4 ml) and potassium hydroxide (13.0 g), and the mixture was stirred under argon atmosphere at 190° C. for 4 hours. The reaction mixture was cooled to room temperature, and poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 4,5,6,7-tetrahydrothianaphthene (2.75 g) as colorless oil.

(2) The above 4,5,6,7-tetrahydrothianaphthene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl methyl)benzene as a colorless solid. APCI-Mass m/Z 341/343 (M+H).

REFERENCE EXAMPLE 15

5-Bromo-2-chloro-1-(5-ethyl-4-methyl-2-thienylmethyl)-benzene

(3) 2-Acetyl-3-methylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 329/331 (M+H).

REFERENCE EXAMPLE 16

5-Bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl) benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chlorobenzaldehyde. APCI-Mass m/Z 233/235 (M+H+ MeOH—H_2O).

(2) The above 5-bromo-2-chlorobenzaldehyde and thieno[3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans* 1 1997, 3465-3470) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 343/345 (M+H).

REFERENCE EXAMPLE 17

5-Bromo-2-chloro-1-(5-chloro-2-thienylmethyl)benzene

2-Chlorothiophene was treated in a manner similar to Reference Example 5 to give the target compound.

REFERENCE EXAMPLE 18

5-Bromo-2-chloro-1-(5-phenylmethyl-2-thienylmethyl)benzene

2-Benzoylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 377/379 (M+H).

REFERENCE EXAMPLE 19

5-Bromo-2-chloro-1-(5-(2-thienyl)-2-thienylmethyl) benzene

2,2'-Bithiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

REFERENCE EXAMPLE 20

5-Bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methylbenzene

(1) To a solution of 2-bromo-5-chlorothiophene (4.11 g), thiophene-2-boronic acid (4.00 g), tetrakis(triphenylphosphine)palladium (0) (1.20 g) and 2M aqueous sodium carbonate solution (31.3 ml) in dimethoxyethane (100 ml) was heated under reflux under argon atmosphere for 2.5 hours. The reaction mixture was cooled, and extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-chloro-2-thienyl) thiophene (3.37 g) as pale yellow oil.

(2) The above 2-(5-chloro-2-thienyl)thiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were used and treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methyl benzene as a colorless solid. APCI-Mass m/Z 383/385 (M+H).

REFERENCE EXAMPLE 21

5-Bromo-2-chloro-1-(4-chloro-5-ethyl-2-thienylmethyl)-benzene

2-Acetyl-3-chlorothiophene (see Japanese Unexamined Patent Publication No. 2000-34230) was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

REFERENCE EXAMPLE 22

5-Chloro-4-methylthiophene

The target compound was prepared according to a method described in Japanese Unexamined Patent Publication No. 10-324632.

REFERENCE EXAMPLE 23

5-Bromo-2-chloro-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl) benzene

2-(5-Chloro-2-thienyl)thiophene and 5-bromo-2-chlorobenzoic acid were treated in a manner similar to Reference Example 5 to give the target compound.

REFERENCE EXAMPLE 24

5-Bromo-2-chloro-1-(5-trifluoromethyl-2-thienylmethyl)-benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 25

5-Bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl) benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16—(1) were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol as colorless powder. APCI-Mass m/Z 380/382 (M+H)

(2) A solution of the above 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol (3.52 g) in trifluoroacetic acid (45 ml) was added to a solution of sodium borohydride (1.75 g) in trifluoroacetic acid (45 ml), and the mixture was stirred at room temperature for 4 hours. Trifluoroacetic acid was evaporated under reduced pressure. The residue was basified with an aqueous potassium hydroxide solution, and extracted with diethyl ether. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-4:1) to give 5-bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl) benzene (2.42 g) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

REFERENCE EXAMPLE 26

5-Bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) and 2-chlorothiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene as colorless oil.

(2) To a solution of the above 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene (1.0 g) in dimethoxyethane (10 ml) were added phenylboronic acid (310 mg), bis(triphenylphosphine)palladium (II) dichloride (85 mg) and 2M

aqueous sodium carbonate solution (3.8 ml), and the mixture was stirred at 50° C. overnight. Added thereto was a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene (683 mg) as oil.

REFERENCE EXAMPLE 27

2-Chlorothieno[3,2-b]thiophene

(1) A solution of thieno[3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans* 1 1997, 3465-3470) (1.27 g) in tetrahydrofuran (30 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 5.70 ml). The mixture was stirred at 0° C. for 30 minutes, and cooled again to −78° C. Added thereto was a solution of hexachloroethane (2.14 g) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for one hour, and warmed to 0° C. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give 2-Chlorothieno[3,2-b]thiophene (1.19 g) as a solid.

REFERENCE EXAMPLE 28

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methoxybenzene

Thianaphthene was treated in a manner similar to Reference Example 7 to give the target compound. ESI-Mass m/Z 331/333 (M−H).

REFERENCE EXAMPLE 29

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-chlorobenzene

Thianaphthene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 30

3-Bromo-1-(5-methylbenzo[b]thiophen-2-ylmethyl) benzene

5-Methylbenzo[b]thiophene and 3-bromobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 31

3-Bromo-1-(6-fluorobenzo[b]thiophen-2-ylmethyl) benzene

(1) To a solution of 2,4-difluorobenzaldehyde (5.0 g) in dimethylsulfoxide (100 ml) were added methyl thioglycolate (3.45 ml) and triethylamine (10 ml), and the mixture was stirred at 80° C. overnight. The reaction mixture was poured into ice-cold water. The mixture was extracted with ethyl acetate, washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:1) to give 6-fluoro-2-methoxycarbonylbenzo[b]thiophene (1.32 g) as colorless powder. GC-EI-Mass m/Z 210 (M).

(2) The above 6-fluoro-2-methoxycarbonylbenzo[b] thiophene was treated in a manner similar to Reference Example 4-(1) to give 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid as colorless powder. ESI-Mass m/Z 195 (M−H).

(3) The above 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 4-(2) to give 6-fluoro-2-(N-methoxy-N-methylcarbamoyl) benzo[b]thiophene as colorless powder. APCI-Mass m/Z 240 (M+H).

(4) A solution of 1,3-dibromobenzene (493 mg) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 0.86 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of the above 6-fluoro-2-(N-methoxy-N-methylcarbamoyl)benzo[b] thiophene (500 mg) in tetrahydrofuran (3 ml). The mixture was warmed to room temperature, and added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-85:15) to give 3-bromophenyl 6-fluorobenzo[b]thiophen-2-yl ketone (479 mg) as a pale yellow solid. APCI-Mass m/Z 335/337 ($M+NH_4$).

(5) The above 3-bromophenyl 6-fluorobenzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 3-bromo-1-(6-fluorobenzo[b] thiophen-2-ylmethyl)benzene as a colorless solid.

REFERENCE EXAMPLE 32

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-fluorobenzene

Thianaphthene and 3-bromo-4-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 33

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethoxybenzene

Thianaphthene and 5-bromo-2-ethoxybenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 34

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-fluorobenzene

Thianaphthene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 35

2-(Benzo[b]thiophen-2-ylmethyl)-4-bromo-1-methoxy-naphthalene

2,4-Dibromo-1-methoxynaphthalene (see J. Clayden, et al. *Org. Lett.*, 5, (2003) 831) and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

REFERENCE EXAMPLE 36

3-Bromo-1-(5-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

5-Trifluoromethylbenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 31-(3), (4), and (5) to give the target compound.

REFERENCE EXAMPLE 37

3-Bromo-1-(3-methylbenzo[b]thiophen-2-ylmethyl) benzene

3-Methylbenzo[b]thiophene-2-carboxaldehyde was treated in a manner similar to Reference Example 1 to give the target compound.

REFERENCE EXAMPLE 38

3-Bromo-1-(5-fluorobenzo[b]thiophen-2-ylmethyl) benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 31 to give the target compound.

REFERENCE EXAMPLE 39

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene

(1) 3-Bromo-4-methylbenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 3-bromo-4-methylbenzaldehyde as colorless crystals. APCI-Mass m/Z 213/215 (M+H+MeOH).
(2) The above 3-bromo-4-methylbenzaldehyde and thianaphthene were treated in a manner similar to Reference Example 7 to give (Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene as a colorless solid.

REFERENCE EXAMPLE 40

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-methylbenzene

3,5-Dibromotoluene and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

REFERENCE EXAMPLE 41

5-Bromo-2-chloro-1-(5-methylbenzo[b]thiophen-2-ylmethyl)benzene

5-Methylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 42

5-Bromo-2-chloro-1-(7-methylbenzo[b]thiophen-2-ylmethyl)benzene

7-Methylbenzo[b]thiophene (see Tilak, B. D. *Tetrahedron* 9 (1960) 76-95)and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 43

5-Bromo-2-chloro-1-(5-chlorobenzo[b]thiophen-2-ylmethyl)benzene

5-Chlorobenzo[b]thiophene (see Tilak, B. D. Tetrahedron 9 (1960) 76-95)and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 44

5-Bromo-2-chloro-1-(5,7-dimethylbenzo[b]thiophen-2-ylmethyl)benzene

5,7-Dimethylbenzo[b]thiophene (see Yoshimura, Y. et al., *J. Med. Chem.* 43 (2000) 2929-2937) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 45

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene

(1) A solution of thianaphthene (543 mg) in diethyl ether (20 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 1.74 ml). The reaction mixture was stirred at the same temperature for 3 hours. The reaction mixture was added dropwise to a solution of N-methoxy-N-methyl-5-bromo-2-methylbenzamide (1.15 g) obtained in Reference Example 4-(2) in diethyl ether (10 ml) cooled to −78° C. The mixture was warmed to room temperature and stirred for one hour. Added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-95:5) to give 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone (995 mg) as a pale yellow syrup. APCI-Mass m/Z 331/333 (M+H).
(2) The above 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 1-(benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene as colorless oil.

REFERENCE EXAMPLE 46

5-Bromo-2-chloro-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)-benzene

6-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference

Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 47

5-Bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)-benzene

(1) 4-Chloro-2-fluorobenzaldehyde was treated in a manner similar to Reference Example 31-(1) and (2) to give 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid as colorless crystals. ESI-Mass m/Z 211/213 (M−H).

(2) A solution of the above 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid (3.0 g) and copper powder (1.2 g) in quinoline (20 ml) was stirred at 210° C. for 40 minutes. The mixture was cooled to room temperature and diluted with diethyl ether, and insoluble materials were filtered off. The filtrate was washed successively with 10% aqueous hydrochloric acid solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 6-chlorobenzo[b]thiophene (1.79 g) as colorless crystals.

(3) The above 6-chlorobenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give 5-bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)-benzene as colorless crystals.

REFERENCE EXAMPLE 48

5-Bromo-2-chloro-1-(6-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

2-Fluoro-4-trifluoromethylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

REFERENCE EXAMPLE 49

1-Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-chlorobenzene

3-Bromo-4-chlorobenzoic acid was treated in a manner similar to Reference Example 39 to give the target compound.

REFERENCE EXAMPLE 50

5-Bromo-2-chloro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,4-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

REFERENCE EXAMPLE 51

5-Bromo-2-fluoro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

6-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 50 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 52

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-chlorobenzene

1-Chloro-3,5-dibromobenzene and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

REFERENCE EXAMPLE 53

5-Bromo-2-chloro-1-(7-methoxybenzo[b]thiophen-2-ylmethyl)-benzene

7-Methoxybenzo[b]thiophene (see WO 02/094262) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

REFERENCE EXAMPLE 54

5-Bromo-2-chloro-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-benzene

5-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

REFERENCE EXAMPLE 55

5-Bromo-2-chloro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

REFERENCE EXAMPLE 56

5-Bromo-2-chloro-1-(7-fluoro-6-methylbenzo[b]thiophen-2-ylmethyl)benzene

2,3-Difluoro-4-methylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

REFERENCE EXAMPLE 57

5-Bromo-2-chloro-1-(4-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,6-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

REFERENCE EXAMPLE 58

5-Bromo-2-chloro-1-(7-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,3-difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

REFERENCE EXAMPLE 59

5-Bromo-2-chloro-1-(4-chlorobenzo[b]thiophen-2-ylmethyl)-benzene

2-Chloro-6-fluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

REFERENCE EXAMPLE 60

5-Bromo-2-fluoro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

5-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 55 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 61

3-Bromo-2-chloro-1-(benzo[b]thiophen-2-ylmethyl) benzene

(1) 3-Bromo-2-chlorobenzoic acid (see Frederic Gohier et al., *J. Org. Chem.* (2003) δ 2030-2033.) was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-3-bromo-2-chlorobenzamide as oil. APCI-Mass m/Z 278/280/282 (M+H).

(2) The above N-methoxy-N-methyl-3-bromo-2-chlorobenzamide was treated in a manner similar to Reference Example 45 to give 3-bromo-2-chloro-1-(benzo[b] thiophen-2-ylmethyl)benzene as a colorless solid.

REFERENCE EXAMPLE 62

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethyl-benzene

(1) To a solution of 2-ethylbenzoic acid (10.0 g) in dichloromethane (50 ml) were added oxalyl chloride (7.0 ml) and N,N-dimethylformamide (3 drops) and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The acid chloride was dissolved in methanol (60 ml) and the mixture was stirred at room temperature for 3 hours, and then, the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give methyl 2-ethylbenzoate, which was used in the subsequent step without further purification.

(2) The above methyl 2-ethylbenzoate was mixed with molecular sieve 13× (powder, 70 g), and while stirring the mixture, bromine (5.2 ml) was added dropwise thereto at 80° C. The mixture was further stirred at the same temperature for 1.5 hours. The mixture was cooled to room temperature, and added thereto were potassium carbonate (7.4 g), water (70 ml) and methanol (350 ml), and the mixture was stirred for 8 hours. Insoluble materials were filtered off, and suspended in a mixed solution of methanol (500 ml)-water (500 ml), and the mixture was stirred at room temperature overnight. Insoluble materials were filtered off and the filtrate was combined with the previously obtained filtrate, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was distilled under reduced pressure, to give methyl 5-bromo-2-ethylbenzoate (2.44 g). APCI-Mass m/Z 260/262 ($M+NH_4$).

(3) The above methyl 5-bromo-2-ethylbenzoate was treated in a manner similar to Reference Example 4-(1) and (2) to give N-methoxy-N-methyl-5-bromo-2-ethylbenzamide as colorless oil. APCI-Mass m/Z 272/274 (M+H).

(4) The above N-methoxy-N-methyl-5-bromo-2-ethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give 1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethylbenzene as oil.

REFERENCE EXAMPLE 63

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-trifluoromethyl-benzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-iodobenzamide as a pale yellow solid. APCI-Mass m/Z 370/372 (M+H).

(2) To a solution of the above N-methoxy-N-methyl-5-bromo-2-iodobenzamide (2.67 g) in N-methyl-2-pyrrolidinone (12 ml) were added copper (I) bromide (124 mg) and methyl fluorosulfonyl(difluoro)acetate (1.34 ml), and the mixture was stirred under heating for 1.5 hours. The reaction mixture was cooled to room temperature, and then, a diluted aqueous ammonia was added thereto, and the mixture was extracted with ethylacetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide (1.59 g) as colorless oil. APCI-Mass m/Z 312/314 (M+H).

(3) The above N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give 1-(Benzo[b] thiophen-2-ylmethyl)-5-bromo-2-trifluoromethylbenzene as a colorless solid. ESI-Mass m/Z 369/371 (M–H).

REFERENCE EXAMPLE 64

5-Bromo-2-chloro-1-(5-phenyl-2-thienylmethyl) benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 363/365 (M+H).

REFERENCE EXAMPLE 65

5-Bromo-2-chloro-1-(5-(4-methylphenyl)-2-thienyl-methyl)-benzene

(1) 2-Iodothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(4-methylphenyl)thiophene as colorless crystals. APCI-Mass m/Z 175 (M+H).

(2) The above 2-(4-methylphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-

2-chloro-1-(5-(4-methylphenyl)-2-thienylmethyl)-benzene as colorless crystals. APCI-Mass m/Z 377/379 (M+H)

REFERENCE EXAMPLE 66

5-Bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)-benzene

(1) 2-Fluorobromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-fluorophenyl)thiophene as a colorless liquid. (2) The above 2-(2-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)-benzene as a colorless solid. APCI-Mass m/Z 381/383 (M+H)

REFERENCE EXAMPLE 67

5-Bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)-benzene

(1) 2-Iodothiophene and 4-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(4-fluorophenyl)thiophene as colorless powder.
(2) The above 2-(4-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)-benzene as colorless powder.

REFERENCE EXAMPLE 68

5-Bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 4-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-ethoxyphenyl)thiophene as a colorless solid. APCI-Mass m/Z 205 (M+H).
(2) The above 2-(4-ethoxyphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)-benzene as a colorless solid. APCI-Mass m/Z 407/409 (M+H)

REFERENCE EXAMPLE 69

5-Bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 3-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethoxyphenyl)thiophene as colorless oil. APCI-Mass m/Z 205 (M+H).
(2) The above 2-(3-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)-benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H).

REFERENCE EXAMPLE 70

5-Bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)-benzene

(1) 2-Iodothiophene and 2-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-ethoxyphenyl)thiophene as a pale yellow solid.
(2) The above 2-(2-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)-benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H)

REFERENCE EXAMPLE 71

5-Bromo-2-fluoro-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

REFERENCE EXAMPLE 72

5-Bromo-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(4-Ethoxyphenyl)thiophene obtained in Reference Example 68—(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

REFERENCE EXAMPLE 73

5-Bromo-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(2-Ethoxyphenyl)thiophene obtained in Reference Example 70-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

REFERENCE EXAMPLE 74

5-Bromo-2-fluoro-1-(5-(2-fluorophenyl)-2-thienylmethyl)-benzene

2-(2-Fluorophenyl)thiophene obtained in Reference Example 66-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 365/367 (M+H)

REFERENCE EXAMPLE 75

5-Bromo-2-chloro-1-(5-(3-fluorophenyl)-2-thienylmethyl)-benzene

(1) 2-Iodothiophene and 3-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-fluorophenyl)thiophene as oil.
(2) The above 2-(3-fluoropheny)thiophene was treated in a manner similar to Reference Example 5 to give the target compound as powder.

REFERENCE EXAMPLE 76

5-Bromo-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(3-Ethoxyphenyl)thiophene obtained in Reference Example 69-(1) and 5-bromo-2-fluorobenzaldehyde were

treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

REFERENCE EXAMPLE 77

5-Bromo-2-fluoro-1-(5-(3-fluorophenyl)-2-thienylmethyl)-benzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 78

5-Bromo-2-fluoro-1-(5-(4-fluorophenyl)-2-thienylmethyl)-benzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 79

5-Bromo-2-methyl-1-(5-phenyl-2-thienylmethyl) benzene

2-Phenylthiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 343/345 (M+H).

REFERENCE EXAMPLE 80

5-Bromo-1-(5-(3-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75—(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

REFERENCE EXAMPLE 81

5-Bromo-1-(5-(4-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

REFERENCE EXAMPLE 82

5-Bromo-2-methoxy-1-(5-phenyl-2-thienylmethyl) benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 359/361 (M+H).

REFERENCE EXAMPLE 83

5-Bromo-2-methyl-1-(5-(3-methylphenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 3-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methylphenyl)thiophene as colorless oil.

(2) The above 2-(3-methylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 357/359 (M+H)

REFERENCE EXAMPLE 84

5-Bromo-2-chloro-1-(5-(3-methylphenyl)-2-thienylmethyl)-benzene

2-(3-Methylphenyl)thiophene obtained in Reference Example 83-(1) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16—(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 377/379/381 (M+H).

REFERENCE EXAMPLE 85

5-Bromo-2-chloro-1-(5-(3-chlorophenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 3-chlorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-chlorophenyl)thiophene as colorless oil.

(2) The above 2-(3-chlorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give the target compound as colorless oil.

REFERENCE EXAMPLE 86

5-Bromo-1-(5-(3-chlorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Chlorophenyl)thiophene obtained in Reference Example 85-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound as colorless oil.

REFERENCE EXAMPLE 87

5-Bromo-1-(5-(3-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) 3-Methoxybromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methoxyphenyl)thiophene as a yellow liquid. APCI-Mass m/Z 191 (M+H).

(2) The above 2-(3-methoxyphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound as yellow oil. APCI-Mass m/Z 373/375 (M+H)

REFERENCE EXAMPLE 88

4-Bromo-2-(4-ethylphenylmethyl)-2H-isoquinolin-1-one

4-Bromo-2H-isoquiolin-1-one (see EP0355750) was treated in a manner similar to Reference Example 2 to give the target compound. APCI-Mass m/Z 342/344 (M+H).

REFERENCE EXAMPLE 89

4-Bromo-2-(4-ethylphenylmethyl)-8-methyl-2H-isoquinolin-1-one

(1) To a solution of 8-methyl-2H-isoquiolin-1-one (1.15 g) in dichloromethane (20 ml) was added dropwise a solution of bromine (1.26 g) in dichloromethane (4 ml) at room temperature. The mixture was stirred at the same temperature for one hour, and the solvent was evaporated under reduced pressure. The residue was crystallized from ether to give 4-bromo-8-methyl-2H-isoquinolin-1-one (1.86 g) as colorless crystals. APCI-Mass m/Z 238/240 (M+H).
(2) The above 4-bromo-8-methyl-2H-isoquinolin-1-one was treated in a manner similar to Reference Example 2 to give the target compound as colorless crystals. APCI-Mass m/Z 356/358M+H).

REFERENCE EXAMPLE 90

4-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) A solution of 4-bromo-2-thiophenecarboxaldehyde (4.78 g) in tetrahydrofuran (40 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise 4-ethylphenylmagnesium bromide (0.5 M tetrahydrofuran solution, 50 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethylacetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=97:3-84:16) to give 4-bromo-2-thienyl-4-ethylphenylmethanol (5.37 g) as colorless oil. APCI-Mass m/Z 279/281 (M+H—H_2O).
(2) The above 4-bromo-2-thienyl-4-ethylphenylmethanol was treated in a manner similar to Reference Example 1-(2) to give the target compound as colorless oil.

REFERENCE EXAMPLE 91

5-Bromo-2-(4-ethylphenylmethyl)thiophene

5-Bromo-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound. ESI-Mass m/Z 279/281 (M−H).

REFERENCE EXAMPLE 92

3-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) 2,3-Dibromothiophene and 4-ethylbenzaldehyde were treated in a manner similar to Reference Example 1-(1) to give 3-bromo-2-thienyl-4-ethylphenylmethanol as yellow oil. APCI-Mass m/Z 279/281 (M+H—H_2O).
(2) A solution of the above 3-bromo-2-thienyl-4-ethylphenylmethanol (12.4 g) in diethyl ether (10 ml) was added dropwise into a suspension of lithium aluminum hydride (2.6 g) and aluminum chloride (9.0 g) in diethyl ether (35 ml) at 0° C. Subsequently, the mixture was stirred at room temperature overnight, and then poured onto ice. The mixture was extracted with diethyl ether, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-2-(4-ethylphenylmethyl)thiophene (8.77 g) as colorless oil. APCI-Mass m/Z 279/281 (M+H).

REFERENCE EXAMPLE 93

5-Bromo-3-(4-ethylphenylmethyl)thiophene

5-Bromo-3-thiophenecarboxaldehyde (see Amishiro, N. et al., *Chem. Pharm. Bull.* 47 (1999) 1393-1403.) was treated in a manner similar to Reference Example 90 to give the target compound.

REFERENCE EXAMPLE 94

5-Bromo-2-chloro-3-(4-ethylphenylmethyl)thiophene

(1) 5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chloro-3-thiophenecarboxaldehyde as pale yellow oil. APCI-Mass m/Z 239/241/243 (M+H+MeOH—H_2O).
(2) The above 5-bromo-2-chloro-3-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound as colorless oil.

REFERENCE EXAMPLE 95

5-Bromo-3-chloro-2-(4-ethylphenylmethyl)thiophene

(1) A solution of diisopropylamine (6.8 ml) in tetrahydrofuran (75 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 30.5 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 3-chloro-2-thiophenecarboxylic acid (3.92 g) in tetrahydrofuran (40 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise 1,2-dibromo-1,1,2,2-tetrafluoroethane (6.0 ml). The mixture was stirred at the same temperature for one hour, and then, warmed to room temperature. The mixture was poured into a diluted aqueous hydrochloric acid solution, and the solution was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was crystallized from a mixed solvent of diisopropyl ether and hexane to give 5-bromo-3-chloro-2-thiophenecarboxylic acid (3.79 g) as a yellow solid. ESI-Mass m/Z 239/241 (M−H).
(2) The above 5-bromo-3-chloro-2-thiophenecarboxylic acid was treated in a manner similar to Reference Example 94 to give 5-bromo-3-chloro-2-(4-ethylphenylmethyl) thiophene as colorless oil.

REFERENCE EXAMPLE 96

3-Bromo-1-(benzo[b]thiophen-3-ylmethyl)benzene

Thianaphthene-3-carboxaldehyde was treated in a manner similar to Reference Example 1 to give the target compound.

REFERENCE EXAMPLE 97

3-Bromo-1-(5-ethyl-2-furylmethyl)benzene

(1) 5-Ethyl-2-furaldehyde was treated in a manner similar to Reference Example 1-(1) to give 3-bromophenyl-5-ethyl-2-furylmethanol as oil. APCI-Mass m/Z 263/265 (M+H—H_2O).
(2) The above 3-bromophenyl-5-ethyl-2-furylmethanol was treated in a manner similar to Reference Example 9-(2) to give the target compound as oil.

REFERENCE EXAMPLE 98

3-Bromo-1-(benzo[b]furan-2-ylmethyl)benzene

2-Benzo[b]furancarboxaldehyde was treated in a manner similar to Reference Example 97 to give the target compound.

REFERENCE EXAMPLE 99

1-(Benzo[b]furan-2-ylmethyl)-5-bromo-2-chlorobenzene

Benzo[b]furan and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

REFERENCE EXAMPLE 100

1-(Benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene

(1) Benzothiazole and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-methylphenyl-(benzothiazol-2-yl)methanol as pale yellow crystals. APCI-Mass m/Z 334/336 (M+H).
(2) To a solution of the above 5-bromo-2-methylphenyl-(benzothiazol-2-yl)methanol (2.60 g) in dichloromethane (30 ml)-toluene (10 ml) was added manganese(IV) oxide (3.42 g), and the mixture was stirred at room temperature for 3 hours. Insoluble materials were filtered off, and the filtrate was evaporated under reduced pressure to give 5-bromo-2-methylphenyl benzothiazol-2-yl ketone (2.45 g) as colorless crystals. APCI-Mass m/Z 332/334 (M+H).
(3) The above 5-bromo-2-methylphenyl benzothiazol-2-yl ketone was treated in a manner similar to Reference Example 14-(1) to give 1-(benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene as oil. APCI-Mass m/Z 318/320 (M+H)

REFERENCE EXAMPLE 101

1-(Benzothiazol-2-ylmethyl)-5-bromo-2-chlorobenzene

Benzothiazole and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 100 to give the target compound. APCI-Mass m/Z 338/340 (M+H).

REFERENCE EXAMPLE 102

5-Bromo-2-chloro-1-(5-phenyl-2-thiazolylmethyl)benzene

(1) A solution of thiazole (10.0 g), iodobenzene (2.63 ml), tetrakis(triphenylphosphine)palladium (0) (1.36 g) and potassium acetate (3.46 g) in N,N-dimethylacetamide (100 ml) was stirred under heating at 100° C. overnight. The solvent was evaporated under reduced pressure, and added to the residue was ethyl acetate. The mixture was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-90:10) to give 5-phenylthiazole (1.50 g) as a pale yellow solid. APCI-Mass m/Z 162 (M+H).
(2) The above 5-phenylthiazole and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 100 to give 5-bromo-2-chloro-1-(5-phenyl-2-thiazolylmethyl)benzene as a yellow solid. APCI-Mass m/Z 364/366 (M+H).

REFERENCE EXAMPLE 103

3-(4-Ethylphenylmethyl)-2,4-pentanedione

A suspension of sodium iodide (15.0 g) in acetonitrile (100 ml) was cooled to 0° C. under argon atmosphere, and thereto were added dropwise chlorotrimethylsilane (12.7 ml), 2,4-pentanedione (2.05 ml) and 4-ethylbenzaldehide (2.68 g), successively. The reaction mixture was stirred at room temperature for 17 hours, and further stirred at 60° C. for 10 hours. The reaction mixture was cooled to room temperature and poured into an aqueous sodium thiosulfate solution. The mixture was extracted with diethyl ether, and the extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) to give 3-(4-ethylphenylmehyl)-2,4-pentanedione (2.72 g) as pale yellow oil. APCI-Mass m/Z 219 (M+H).

REFERENCE EXAMPLE 104

Tri-n-butyl(4-ethylphenyl)tin

To a solution of magnesium (896 mg) in tetrahydrofuran (20 ml) was added dibromoethan (0.1 ml), and the mixture was stirred at room temperature for 15 minutes. Thereto was added dropwise a solution of 1-bromo-4-ethylbenzene (5.7 g) in tetrahydrofuran (20 ml), and subsequently, the mixture was stirred at room temperature for one hour. The reaction mixture was cooled to −78° C., and thereto was added dropwise tributyltin chloride (9.49 g). The mixture was stirred at the same temperature for 30 minutes, and then at room temperature for one hour. To the reaction mixture were added 10% aqueous potassium fluoride solution and ethyl acetate, and the mixture was stirred at room temperature for 30 minutes. Insoluble materials were filtered off. The organic layer of the filtrate was washed with water and brine successively, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by alumina

column chromatography (hexane) to give the desired tri-n-butyl(4-ethylphenyl)tin (10.7 g) as colorless oil. EI-Mass m/Z 337 (M-Bu).

REFERENCE EXAMPLE 105

4-(4-Ethylphenylmethyl)pyrazole

(1) A mixed solution of 4-ethylbenzyl bromide (10.0 g), malononitrile (6.64 g), potassium carbonate (6.94 g) and tetra-n-butylammonium bromide (648 mg) in toluene (100 ml) was agitated at room temperature for 17 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate twice. The extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=6:1) to give 2-(4-ethylphenylmethyl)malononitrile (3.28 g) as a colorless solid.

(2) A solution of the above 2-(4-ethylphenylmethyl)malononitrile (1.30 g) and hydrazine hydrate (0.86 ml) in ethanol (35 ml) was heated under reflux for 4 hours. Hydrazine hydrate (0.43 ml) was further added thereto and the mixture was further heated under reflux for 4 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-diethyl ether to give 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (2.63 g) as pale pink powder. APCI-Mass m/Z 217 (M+H).

(3) The above 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (1.30 g) was added to 50% aqueous phosphoric acid solution (19 ml), and further added thereto was water (10 ml). The mixture was cooled to 0° C., and thereto was added dropwise an aqueous solution (4 ml) of sodium nitrite (912 mg). The mixture was stirred at the same temperature for 30 minutes, and further stirred at room temperature for 4 hours. The reaction mixture was cooled again to 0° C., 10% aqueous sodium hydroxide solution was added thereto to adjust pH of the reaction mixture to 7. The mixture was extracted with ethyl acetate, washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10) to give the desired 4-(4-ethylphenylmethyl)pyrazole (414 mg) as a pale brown semisolid. APCI-Mass m/Z 187 (M+H).

REFERENCE EXAMPLE 106

3-(4-Ethylphenylmethyl)-5-methyl-1H-pyrazole

(1) 4-Ethylphenylacetic acid (3.0 g) (see Japanese Unexamined Patent Publication 63-233975) was dissolved in dichloromethane (15 ml), and thereto were added oxalyl chloride (6.0 ml) and N,N-dimethylformamide (one drop). The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene to give a crude 4-ethylphenylacetyl chloride, which was used in the subsequent step without further purification.

(2) A suspension of magnesium chloride (1.74 g) in dichloromethane (30 ml) was cooled to 0° C., and thereto were added t-butyl acetoacetate (3.03 ml) and pyridine (2.96 ml), and successively was added a solution of the above 4-ethylphenylacetyl chloride in dichloromethane (30 ml). The mixture was stirred at the same temperature for 2.5 hours, and an aqueous citric acid solution was added thereto. The mixture was extracted with chloroform. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=15:1) to give t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate (4.75 g) as pale yellow oil. APCI-Mass m/Z 322 ($M+NH_4$)

(3) A solution of the above t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate in trifluoroacetic acid (60 ml) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate, and the mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (4.00 g) as yellow oil. APCI-Mass m/Z 205 (M+H).

(4) A solution of the above 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (3.98 g) and hydrazine hydrate (4.0 ml) in toluene (20 ml) was stirred under heating at 100° C. for 1.5 hours. The reaction mixture was cooled to room temperature, and washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:ethyl acetate=2:1) to give 3-(4-ethylphenylmethyl)-5-methyl-1H-pyrazole (3.12 g) as yellow oil. APCI-Mass m/Z 201 (M+H).

REFERENCE EXAMPLE 107

3-(4-Ethylphenylmethyl)-6-hydroxypyridine

(1) To a solution of 6-chloronicotinoyl chloride (10.0 g) and N,O-dimethylhydroxyamine hydrochloride (6.65 g) in dichloromethane (200 ml) was added dropwise triethylamine (17.2 g) at 0° C. Subsequently the mixture was stirred at room temperature overnight. The mixture was washed successively with water, 5% aqueous citric acid solution, water and brine, and then, dried over sodium sulfate. The solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-6-chloronicotinamide (11.73 g) as pale yellow oil. APCI-Mass m/Z 201/203 (M+H).

(2) A solution of the N-methoxy-N-methyl-6-chloronicotineamide (4.2 g) in tetrahydrofuran (40 ml) was cooled to 0° C., and thereto was added dropwise 4-ethylphenylmagnesium bromide (0.5 M tetrahydrofuran solution, 55 ml). The mixture was stirred at 0° C. for 4 hours, and then at the room temperature for 10 minutes. The reaction mixture was cooled again to 0° C., and added thereto was 10% aqueous hydrochloric acid solution. The mixture was extracted with ethyl acetate, and washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=20:1) to give 6-chloro-3-pyridyl 4-ethylphenyl ketone (3.68 g) as colorless crystals. APCI-Mass m/Z 246/248 (M+H).

(3) The above 6-chloro-3-pyridyl 4-ethylphenyl ketone (1.68 g) was dissolved in N-methyl-2-pyrrolidinone (20 ml), and thereto were added benzylalcohol (815 ml) and 60% sodium hydride (275 mg). The mixture was stirred at room temperature for 6 hours, and then at 90° C. for one hour. The reaction mixture was cooled to room temperature, and

water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-95:5) to give 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.68 g) as colorless oil. APCI-Mass m/Z 318 (M+H).

(4) The above 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (865 mg) was dissolved in ethylene glycol (8.5 ml), and thereto were added hydrazine hydrate (0.44 ml) and potassium hydroxide (550 mg). The mixture was stirred under heating at 190° C. for 8 hours. The reaction mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water three times, and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-0:100) to give the desired 3-(4-ethylphenylmethyl)-6-hydoroxypyridine (256 mg) as colorless powder. APCI-Mass m/Z 214 (M+H).

REFERENCE EXAMPLE 108

3-(4-Ethylphenylmethyl)-2-hydroxypyridine

(1) 2-Chloronicotinoyl chloride was treated in a manner similar to Reference Example 107-(1), (2) and (3) to give 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone as colorless oil. APCI-Mass m/Z 318 (M+H).

(2) The above 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.69 g) was dissolved in ethanol (15 ml), and thereto was added sodium borohydride (403 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed with water and successively with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give crude 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol as colorless oil, which was used in the subsequent step without further purification.

(3) The above 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol was dissolved in methanol (10 ml), and thereto were added concentrated hydrochloric acid (1.0 ml) and 10% palladium-carbon (500 mg). The mixture was stirred at room temperature for 15 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with water and successively with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-97:3) to give the desired 3-(4-ethylphenylmethyl)-2-hydoroxypyridine (307 mg) as a pale brown solid. APCI-Mass m/Z 214 (M+H).

REFERENCE EXAMPLE 109

3-(4-Ethylphenylmethyl)-1H-indole

(1) To a solution of indole (6.00 g) in methanol (60 ml) were added sodium hydroxide (2.25 g) and 4-ethylbenzaldehyde (7.56 g), and the mixture was stirred at room temperature for 3 days under argon atmosphere. Added thereto was water, and methanol was evaporated under reduced pressure. The residue was extracted with diethyl ether, and the extract was washed with water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-70:30) to give 4-ethylphenyl-(1H-indol-3-yl)methanol (2.10 g) as a colorless solid. APCI-Mass m/Z 234 (M+H—H_2O).

(2) The above 4-ethylphenyl-(1H-indol-3-yl)methanol was treated in a manner similar to Reference Example 1-(2) to give the desired 3-(4-ethylphenylmethyl)-1H-indole as colorless crystals. APCI-Mass m/Z 236 (M+H).

REFERENCE EXAMPLE 110

3-(4-Ethylphenylmethyl)-1H-indazole

(1) A mixture of zinc powder (712 mg) and dibromoethane (0.04 ml) in N,N-dimethylformamide (2.5 ml) were stirred under heating at 70° C. for 10 minutes under argon atmosphere. The reaction mixture was cooled to room temperature, and chlorotrimethylsilane (0.04 ml) was added thereto, and the mixture was stirred at room temperature for 30 minutes. To the activated zinc solution was added dropwise a solution of 4-ethylbenzyl bromide (1.74 g) in N,N-dimethylformamide (10 ml) at 0° C. over a period of 2 hours. Subsequently, the mixture was stirred at 0° C. for 2 hours, to prepare a solution of 4-ethylbenzylzinc bromide in N,N-dimethylformamide, which was used in the subsequent step without further purification.

(2) A solution of tris(dibenzylideneacetone)dipalladium (0) (167 mg) and tri(2-furyl)phosphine (135 mg) in tetrahydrofuran (20 ml) was stirred at room temperature for 5 minutes under argon atmosphere. Thereto were added 1-t-butoxycarbonyl-3-iodo-1H-indazole (2.0 g) and the above 4-ethylbenzylzinc bromide (N,N-dimethylformamide solution) at 0° C., and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into water, and the mixture was extracted with diethyl ether. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-92:8) to give 1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.37 g) as colorless oil. APCI-Mass m/Z 337 (M+H).

(3) The above 1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.35 g) was dissolved in methanol (15 ml), and added thereto was 28% sodium methoxide solution (methanol solution, 1.0 ml), and the mixture was stirred at room temperature for one hour. Added thereto was an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from hexane to give the desired 3-(4-ethylphenylmethyl)-1H-indazole (800 mg) as colorless crystals. APCI-Mass m/Z 237 (M+H).

REFERENCE EXAMPLE 111

5-Bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 4-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-trifluoromethylphenyl)thiophene as colorless crystals.

(2) The above 2-(4-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienyl-methyl)benzene as colorless crystals. APCI-Mass m/Z 425/427 (M+H+MeOH).

REFERENCE EXAMPLE 112

5-Bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 3-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-trifluoromethylphenyl)thiophene as colorless oil.

(2) The above 2-(3-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienyl-methyl)benzene as colorless oil.

REFERENCE EXAMPLE 113

2-(4-Ethylphenyl)thiophene

2-Bromothiophene and 4-ethylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

REFERENCE EXAMPLE 114

2-(4-Methylphenyl)thiophene

2-Bromothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

REFERENCE EXAMPLE 115

2-(2,3-Dihydro-5-benzo[b]furanyl)thiophene

(1) 5,7-Dibromo-2,3-dihydrobenzo[b]furan (see WO 02/070020) (3.0 g) in diethyl ether was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.09 ml). The mixture was stirred at the same temperature for 30 minutes, and poured into a saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2,3-dihydrobenzo[b]furan (2.0 g) as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2,3-dihydrobenzo[b]furan and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give the desired 2-(2,3-dihydro-5-benzo[b]furanyl)thiophene as pale yellow crystals. APCI-Mass m/Z 203 (M+H).

REFERENCE EXAMPLE 116

4-Bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (1.04 g) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.58 M hexane solution, 4.43 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 1-bromo-4-fluoronaphthalene (1.50 g) in tetrahydrofuran (12 ml) at −78° C. The mixture was stirred at the same temperature for one hour, and thereto was added dropwise a solution of 5-chloro-2-thiophenecarboxaldehyde (1.07 g) in tetrahydrofuran (11 ml) at −78° C. The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by an aminosilane-treated silica gel column chromatography (hexane:ethyl acetate=3:1) to give 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol (2.00 g) as pale yellow powder. APCI-Mass m/Z 353/355 (M+H—H_2O).

(2) The above 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol was treated in a manner similar to Reference Example 1-(2) to give the desired 4-bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene as a yellow solid.

REFERENCE EXAMPLE 117

5-Bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl)benzene

(1) 2,4-dimethylbenzoic acid (20.0 g) was suspended in chloroform (100 ml), and thereto were added oxalyl chloride (6.8 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol (200 ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give methyl 2,4-dimethylbenzoate as pale yellow oil, which was used in the subsequent step without further purification.

(2) To a mixture of the above methyl 2,4-dimethylbenzoate (19.75 g) and activated aluminum neutral oxide (120 g) was added dropwise bromine (9.25 ml) while stirring at room temperature. The mixture was stirred at room temperature for 8 hours, and diluted with diethyl ether (1000 ml). Insoluble materials were filtered off, and washed with diethyl ether (500 ml). The combined filtrate was washed successively with 10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol (40 ml) to give methyl 5-bromo-2,4-dimethylbenzoate (6.34 g) as colorless crystals. APCI-Mass m/Z 243/245 (M+H).

(3) The above methyl 5-bromo-2,4-dimethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2,4-dimethylbenzoic acid as colorless crystals. ESI-Mass m/Z 227/229 (M−H).

(4) The above 5-bromo-2,4-dimethylbenzoic acid and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 357/359 (M+H).

REFERENCE EXAMPLE 118

5-Bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethyl-benzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 117-(1) to give methyl 5-bromo-2-iodobenzoate as a brown solid.

(2) To a solution of the above methyl 5-bromo-2-iodobenzoate (4.65 g) in N-methyl-2-pyrrolydinone (20 ml) were added copper (I) bromide (235 mg) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.6 ml), and the mixture was stirred under heating at 120° C. for 1.5 hours. The reaction mixture was cooled, and added thereto were 10% aqueous hydrochloric acid solution and ethyl acetate. Insoluble materials were filtered off, and an organic layer of the filtrate was washed with water for 4 times, and subsequently washed with a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexan:ethyl acetate=80:1) to give methyl 5-bromo-2-trifluoromethylbenzoate (3.55 g) as colorless oil.

(3) The above methyl 5-bromo-2-trifluoromethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2-trifluoromethylbenzoic acid as pale brown crystals. ESI-Mass m/Z 267/269 (M−H).

(4) The above 5-bromo-2-trifluoromethylbenzoic acid and 2-phenylthiophene were treated in a manner similar to Reference Example 5-(1) to give 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone as pale yellow crystals. APCI-Mass m/Z 411/413 (M+H).

(5) To a mixed solution of the above 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone (670 mg) in methanol (20 ml)-tetrahydrofuran (10 ml) was added sodium borohydride (62 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in chloroform (10 ml)-acetonitrile (20 ml). Thereto was added triethylsilane (0.78 ml), and the mixture was cooled to 0° C. Thereto was added dropwise boron trifluoride.diethyl ether complex (0.52 ml). The mixture was stirred at room temperature for 45 minutes, and added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give the desired 5-bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethylbenzene (565 mg) as colorless oil.

REFERENCE EXAMPLE 119

5-Bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methyl-benzene

(1) 1-Bromo-3-ethylbenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethylphenyl)thiophene as a pale yellow liquid.

(2) The above 2-(3-ethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give 5-bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methyl-benzene as pale yellow oil. APCI-Mass m/Z 371/373 (M+H).

REFERENCE EXAMPLE 120

5-Bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl) benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol as colorless oil. APCI-Mass m/Z 360/362 (M+H).

(2) A solution of the above 5-bromo-2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol (1.59 g) in trifluoroacetic acid (40 ml) was cooled to 0° C., and thereto were added gradually sodium triacetoxyborohydride (4.68 g). The mixture was stirred at room temperature for one hour, and cooled again to 0° C. 10% aqueous sodium hydroxide solution was added thereto to basify the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give the desired 5-bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl)benzene (1.38 g) as a colorless solid. APCI-Mass m/Z 344/346 (M+H).

REFERENCE EXAMPLE 121

2-(5-Fluoro-2-thienyl)thiophene

2,2'-Bithiophene (7.40 g) in tetrahydrofuran (90 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise n-butyl lithium (1.59 M hexane solution, 28.0 ml). The mixture was stirred at 0° C. for one 30 minutes, and cooled again to −78° C. Added thereto was N-fluorobenzenesulfonimide (15.5 g), and the mixture was gradually warmed, and stirred at room temperature for 17 hours. The reaction mixture was poured into ice-cold water, and the solution was extracted with hexane twice, and the extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-fluoro-2-thienyl) thiophene (5.89 g) as colorless oil.

REFERENCE EXAMPLE 122

5-Bromo-2-methyl-1-(5-(3-pyridyl)-2-thienylmethyl) benzene

2-(3-Pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the target compound as colorless crystals. APCI-Mass m/Z 344/346 (M+H).

REFERENCE EXAMPLE 123

5-Bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) p-Bromoanisole and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-methoxyphenyl)thiophene as a pale yellow solid. APCI-Mass m/Z 191 (M+H).

(2) The above 2-(4-methoxyphenyl)thiophene and 4-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methyl-benzene as a pale yellow solid. APCI-Mass m/Z 373/375 (M+H).

REFERENCE EXAMPLE 124

5-bromo-2-methyl-1-(5-(1,2-Methylenedioxybenzen-4-yl)-2-thienylmethyl)benzene

4-Bromo-1,2-(methylenedioxy)benzene was treated in a manner similar to Reference Example 119 to give the target compound as colorless powder.

REFERENCE EXAMPLE 125

5-Bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl) benzene

(1) To a solution of 5-bromo-2-chlorobenzyl alcohol (10.66 g) in toluene (100 ml) solution were added thionyl chloride (10 ml), and pyridine (2 drops), and the mixture was stirred under heating at 100° C. overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, a 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride was dissolved in acetonitrile (100 ml), and the mixture was cooled to 0° C. Added thereto was tetraethylammonium cyanide (8.8 g), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetonitrile as a pale yellow solid, which was used in the subsequent step without further purification.

(3) The above 5-bromo-2-chlorophenylacetonitrile was added to water (90 ml)-sulfuric acid (75 ml), and the mixture was stirred under heating at 160° C. overnight. The mixture was further diluted with water, and cooled to 0° C. The solvent was removed by decant, and the residue was dissolved in diethyl ether. The solution was washed with water and brine, and extracted with 10% sodium hydroxide. To the extract was added concentrated hydrochloric acid to make the solution acidic. The precipitates were collected by filtration, and purified by silica gel column chromatography (chloroform) to give 5-bromo-2-chlorophenylacetic acid (6.67 g) as colorless crystals. ESI-Mass m/Z 247/249 (M−H).

(4) The above 5-bromo-2-chlorophenylacetic acid was treated in a manner similar to Reference Example 118-(4) and (5) to give the desired 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)benzene as a pale yellow solid. APCI-Mass m/Z 377/379 (M+H).

REFERENCE EXAMPLE 126

5-Bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl) 2-methylbenzene

(1) 2-Bromo-6-fluoropyridine and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(6-fluoro-2-pyridyl)thiophene as yellow oil. APCI-Mass m/Z 180 (M+H).

(2) The above 2-(6-fluoro-2-pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the desired 5-bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl)2-methyl-benzene as a colorless solid. APCI-Mass m/Z 362/364 (M+H).

REFERENCE EXAMPLE 127

5-Bromo-2-methyl-1-(5-trifluoromethyl-2-thienylmethyl)-benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the target compound as colorless oil.

REFERENCE EXAMPLE 128

5-Bromo-1-(5-(5-fluoro-2-thienyl)-2-thienylmethyl)-2-methyl benzene

5-Bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) and 2-(5-fluoro-2-thienyl)thiophene obtained in Reference Example 121 were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

REFERENCE EXAMPLE 129

3-Bromo-2-fluoro-6-methyl-1-(5-phenyl-2-thienylmethyl)-benzene

4-Bromo-3-fluorotoluene and 5-phenyl-2-thiophenecarboxaldehyde were treated in a manner similar to Reference Example 116 to give the target compound as pale blue powders. APCI-Mass m/Z 361/363 (M+H).

REFERENCE EXAMPLE 130

5-Bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl) benzene

(1) 5-Bromo-2-chlorophenylacetic acid (2.0 g) obtained in Reference Example 125-(3) was dissolved in dichloromethane (40 ml), and thereto were added oxalyl chloride (0.77 ml) and N,N-dimethylformamide (one drop) at 0° C. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetyl chloride, which was used in the subsequent step without further purification.

(2) A solution of potassium t-butoxide (1.35 g) in tetrahydrofuran (20 ml) was cooled to 0° C., and thereto was added methyl isocyanoacetate (1.33 ml). Then, a solution of the above 5-bromo-2-chlorophenylacetyl chloride in tetrahydrofuran (20 ml) was added thereto, and the mixture was stirred at 0° C. for 2 hours, and then at room temperature overnight. The mixture was cooled again to 0° C. 10%

aqueous citric acid solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)-benzene (1.12 g) as a yellow solid. APCI-Mass m/Z 330/332 (M+H).

(3) The above 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)-benzene (1.37 g) was heated under reflux in 6N aqueous hydrochloric acid solution (20 ml) overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol, and treated with carbon powder. The carbon powder was filtered off, and the filtrate was evaporated under reduced pressure to give crude 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene-hydro-chloride (1.73 g) as a pale brown solid, which was used in the subsequent step without further purification. APCI-Mass m/Z 262/264 (M+H).

(4) A mixed solution of the above 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene-hydro-chloride (1.70 g) in ethyl acetate (30 ml)-water (15 ml) was cooled to 0° C. Added thereto were benzoyl chloride (0.99 ml) and sodium hydrogen carbonate (2.39 g), and the mixture was stirred at the same temperature for 3 hours. The organic layer was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:ethyl acetate=95:5) to give 1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) as a colorless solid. APCI-Mass m/Z 366/368 (M+H).

(5) To a solution of the above 1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) in toluene (20 ml) was added Lawesson reagent (2.35 g), and the mixture was heated under reflux for 2 hours. The reaction mixture was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10) to give the desired 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene (512 mg) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

REFERENCE EXAMPLE 131

t-Butyl 5-bromo-2-chlorobenzoic acid

To a solution of 5-bromo-2-chlorobenzoic acid (11.75 g) in N,N-dimethylformamide (50 ml) was added 1,1'-carbonyldiimidazole (8.10 g), and the mixture was stirred under heating at 40° C. for one hour. Thereto were added t-butanol (7.40 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (7.60 g), and the mixture was further stirred under heating at 40° C. overnight. The mixture was diluted with diethyl ether, and washed successively with water (3 times), 2% aqueous hydrochloric acid solution (twice), a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give t-butyl 5-bromo-2-chlorobenzoate (12.53 g) as pale yellow oil.

REFERENCE EXAMPLE 132

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

(1) A solution of 5-bromo-2-chloro-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)benzene (2.70 g) obtained in Reference Example 46 in dichloromethane (27 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise boron tribromide (0.83 ml). The mixture was warmed to room temperature, and stirred for 30 minutes. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and subsequently, the reaction mixture was made acidic with a saturated aqueous citric acid solution. The mixture was extracted with chloroform, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from chloroform-hexane to give 5-bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene (2.01 g) as pale green crystals. ESI-Mass m/Z 351/353 (M−H).

(2) The above 5-bromo-2-chloro-1-(6-hydroxy-benzo[b]thiophen-2-ylmethyl)benzene (500 mg) was dissolved in N,N-dimethylformamide (5 ml), and thereto were added iodoethane (0.23 ml) and potassium carbonate (390 mg). The mixture was stirred at room temperature for 2 days. Added there to was water, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-80:20) to give the desired 5-bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene (492 mg) as pale pink oil. APCI-Mass m/Z 381/383 (M+H).

REFERENCE EXAMPLE 133

5-Bromo-2-chloro-3-(5-phenyl-2-thienylmethyl) thiophene

5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

REFERENCE EXAMPLE 134

6-Fluoro-2-pyridylboronic acid pinacol ester

A solution of 2-bromo-6-fluoropyridine (1.0 g) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (2.59 M hexane solution, 2.24 ml) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 45 minutes, and thereto was added dropwise a solution of triisopropoxyborane (1.28 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 2 hours, warmed, and further stirred at room temperature for one hour. Subsequently, a solution of pinacol (0.91 g) in tetrahydrofuran (10 ml) was added dropwise thereto, and stirred at room temperature for 20 minutes. Insoluble materials were filtered off. The filtrate was extracted with 2.5% sodium hydroxide, and the extract was cooled to 0° C., and was made weakly acidic with 2N aqueous hydrochloric acid solution. It was extracted with diethyl ether, washed with a small amount of brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was solidified with hexane

to give 6-fluoro-2-pyridylboronic acid pinacol ester (850 mg) as a colorless solid. APCI-Mass m/Z 224 (M+H).

REFERENCE EXAMPLE 135

5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl) benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-chlorobenzamide as a colorless solid. APCI-Mass m/Z 278/280 (M+H).
(2) The above N-methoxy-N-methyl-5-bromo-2-chlorobenzamide and 2,5-dibromopyridine were treated in a manner similar to Reference Example 31-(4) to give 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone as a pale yellow solid. APCI-Mass m/Z 374/376 (M+H).
(3) The above 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone and phenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone as yellow crystals. APCI-Mass m/Z 372/374 (M+H).
(4) The above 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene as colorless crystals. APCI-Mass m/Z 358/360 (M+H).

REFERENCE EXAMPLE 136

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b] thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene obtained in Reference Example 132-(1) and 2-iodopropane were treated in a manner similar to Reference Example 132-(2) to give the titled compound. APCI-Mass m/Z 395/397 (M+H).

REFERENCE EXAMPLE 137

4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl) naphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (4.13 ml) in tetrahydrofuran (40 ml) was cooled to −78° C. under argon atmosphere, and added dropwise thereto was n-butyl lithium (2.44 M hexane solution, 10.0 ml). The mixture was stirred at the same temperature for 30 minutes, and added dropwise thereto at −78° C. was a solution of 1-bromo-4-fluoronaphthalene (5.0 g) in tetrahydrofuran (20 ml). The mixture was stirred at the same temperature for 1 hour, and added dropwise thereto at −78° C. was N,N-dimethylformamide (5.16 ml). The mixture was stirred at the same temperature for 1 hour, and added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from diisopropyl ether and hexane to give 4-bromo-1-fluoro-2-naphthaldehyde (4.43 g) as pale yellow crystals. APCI-Mass m/Z 267/269 ($M+NH_4$).
(2) The above 4-bromo-1-fluoro-2-naphthaldehyde and 2-(2-pyridyl)thiophene were treated in a manner similar to Reference Example 120 to give the desired 4-bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl)naphthalene as colorless powder. APCI-Mass m/Z 398/400 (M+H).

REFERENCE EXAMPLE 138

5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene

(1) 5-Bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone (3.2 g) from Reference Example 135-(2) was dissolved in tetrahydrofuran (80 ml), and added thereto were triethylaluminium (1.0 M hexane solution, 9.9 ml), tetrakis(triphenylphosphine)palladium(0) (570 mg) and cerium(III) chloride (7.3 g), and the mixture was stirred at 30° C. for 1.5 hours. The reaction mixture was diluted with methanol, and the reaction solution was basified with a saturated aqueous sodium hydrogen carbonate solution. The insoluble materials were filtered off and, the filtrate was extracted with ethyl acetate and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=99:1-85:15) to give 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone (1.98 g) as a colorless solid. APCI-Mass m/Z 324/326 (M+H).
(2) The above 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene as a colorless oil. APCI-Mass m/Z 310/312 (M+H).

REFERENCE EXAMPLE 139

6-Ethylbenzo[b]thiophene

(1) 4-Bromo-2-flurobenzaldehyde and ethyl thioglycolate were treated in a manner similar to Reference Example 31-(1) to give 6-bromo-2-ethoxycarbonylbenzo[b] thiophene as a colorless solid.
(2) The above 6-bromo-2-ethoxycarbonylbenzo[b]thiophene was treated in a manner similar to Reference Example 138-(1) to give 6-ethyl-2-ethoxycarbonylbenzo[b] thiophene as colorless oil. APCI-Mass m/Z 235 (M+H).
(3) The above 6-ethyl-2-ethoxycarbonylbenzo[b]thiophene (1.26 g) was dissolved in tetrahydrofuran (4 ml) and methanol (8 ml), and added thereto was lithium hydroxide monohydrate (677 mg), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in water and the solution was made acidic with a 10% aqueous hydrochloric acid solution. The precipitates were collected by filtration and washed with water to give 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid (1.15 g) as colorless crystals. ESI-1-Mass m/Z 205 (M−H).
(4) The above 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid was tread in a manner similar to Reference Example 47-(2) to give the desired 6-ethylbenzo[b]thiophene as colorless oil.

REFERENCE EXAMPLE 140

5-Bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl) benzene

(1) 5-Bromo-2-chlorobenzyl alcohol (3.0 g) was dissolved in toluene (30 ml), and added thereto were thionyl chloride (2.35 ml) and pyridine (two drops), and the mixture was

heated under stirring at 100° C. for 2 hours. The mixture was cooled, washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride (3.34 g) as pale brown oil, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride (3.34 g) was dissolved in N,N-dimethylformamide (30 ml), and added thereto was potassium phthalimide (2.63 g), and the mixture was heated under stirring at 70° C. for 3 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from diisopropyl ether to give 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl)-henzene (3.33 g) as colorless crystals. APCI-Mass m/Z 350/352 (M+H).

(3) The above 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl)-benzene (4.3 g) was dissolved in acetic acid (43 ml), and added thereto was zinc powder (8.02 g), and the mixture was heated at reflux for 3 days. The mixture was cooled and diluted with chloroform and it was basified with an aqueous sodium hydroxide solution. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=6:1-4:1) to give the desired 5-bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl)benzene (1.39 g) as colorless powder. APCI-Mass m/Z 336/338 (M+H).

REFERENCE EXAMPLE 141

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl) benzene

(1) A solution of 1-phenyl-4-bromopyrazole (see M. A. Khan, et al., Can. J. Chem., (1963) 41 1540) (2.23 g) in diethyl ether (30 ml) wad cooled to −78° C. under argon atmosphere, and added dropwise thereto was n-butyl lithium (1.59 M hexane solution, 6.9 ml). The mixture was stirred at −20° C. to −10° C. for 5 hours, and added dropwise thereto at the same temperature was a solution of 5-bromo-2-chlorobenzaldehyde (2.19 g) obtained in Reference Example 16-(1) in diethyl ether (30 ml). The mixture was stirred at the same temperature for 30 minutes, and added thereto was tetrahydrofuran (30 ml), and the mixture was stirred at 0° C. for further 30 minutes. A saturated aqueous ammonium chloride solution was added thereto, and the mixture was extracted with ethylacetate. The extract was washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=83:17-80:20) to give 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol (831 mg) as yellow oil. APCI-Mass m/Z 363/365 (M+H).

(2) The above 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol was treated in a manner similar to Reference Example 120-(2) to give the desired 5-bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene as colorless powder. APCI-Mass m/Z 347/349 (M+H).

REFERENCE EXAMPLE 142

5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b] thiophen-2-yl-methyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-yl-methyl)benzene obtained in Reference Example 132-(1) and 1-bromopropane were treated in a manner similar to Reference Example 132-(2) to give the target compound. APCI-Mass m/Z 395/397 (M+H).

REFERENCE EXAMPLE 143

5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b] thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-yl-methyl)-benzene obtained in Reference Example 132-(1) and 1-bromo-2-fluoroethane were treated in a manner similar to Reference Example 132-(2) to give the target compound. APCI-Mass m/Z 399/401 (M+H).

REFERENCE EXAMPLE 144

5-Tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in WO 03/087104.

REFERENCE EXAMPLE 145

4-Tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in WO 03/087104.

REFERENCE EXAMPLE 146

Tri-n-butyl(6-methoxy-2-pyridyl)tin

The target compound was prepared according to a method described in P. Gros, et al., *Synthesis* (1999) 754.

REFERENCE EXAMPLE 147

5-Bromo-2-chloro-1-(5-ethoxybenzo[b]thiophen-2-ylmethyl)-benzene

(1) 5-Bromo-2-chloro-1-(5-methoxybenzo[b]thiophene-2-yl-methyl)benzene obtained in Reference Example 54 was treated in a manner similar to Reference Example 132-(1) to give 5-bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene. ESI-Mass m/Z 351/353 (M−H).

(2) The above 5-bromo-2-chloro-1-(5-hydroxy-benzo[b] thiophen-2-ylmethyl)benzene and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-Bromo-2-chloro-1-(5-ethoxybenzo[b] thiophene-2-ylmethyl)-benzene. APCI-Mass m/Z 382/380 (M+H).

REFERENCE EXAMPLE 148

5-Bromo-2-chloro-1-(5-(1-pyrazolyl)-2-thienylmethyl)benzene

1-(2-thienyl)pyrazole (see: Chemica Scripta (1979) 13, 157-161) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner

similar to Reference Example 7 to give the title compound as colorless solid. APCI-Mass m/z 353/355 (M+H).

REFERENCE EXAMPLE 149

5-Bromo-2-chloro-1-(tert-butyldiphenylsilyloxymethyl)-benzene

To a solution of 5-Bromo-2-chlorobenzylalcohol (5.15 g) in N,N-dimethylformamide (50 ml) was added diisopropylethylamine (19.8 ml) and tert-butyldiphenylchlorosilane (11.9 ml), and the mixture was stirred at room temperature for 2 days. Under ice-cooling, to the mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with successively with 0.4 M aqueous hydrochloric acid solution (twice), water, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by an aminosilane-treated silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(tert-butyldiphenylsiloxymethyl) benzene 77 (10.79 g) as colorless oil. APCI-Mass m/Z 476/478 ($M+NH_4$).

REFERENCE EXAMPLE 150

2-Fluoropyridin-4-boronic acid

The target compound was prepared according to a method described in *Tetrahedron* (2002) 58, 4369-4373.

REFERENCE EXAMPLE 151

3-Difluoromethoxybenzeneboronic acid

A solution of 3-(difluoromethoxy)benzene (3.0 g) and triisopropoxyborane (2.78 g) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (1.59 M hexane solution, 9.3 ml). The mixture was stirred at same temperature for 10 minutes, warmed, and further stirred at room temperature overnight. Thereto was added 3N aqueous hydrochloric acid solution (10 ml), and the mixture was stirred at room temperature for 5 minutes. The mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from hexane to give 3-difluoromethoxybenzene-boronic acid (1.6 g) as colorless crystals.

REFERENCE EXAMPLE 152

Tri-n-butyl(2-cyano-5-pyridyl)tin

5-Bromo-2-cyanopyridine was treated in a manner similar to the methods described in European Patent Publication No. 93-00867.

REFERENCE EXAMPLE 153

5-Bromo-2-chloro-1-(6-difluoromethoxybenzo[b]thiophen-2-yl-methyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-yl-methyl)-benzene (1.8 g) obtained in Reference Example 132-(1) was dissolved in dimethylformamide (15 ml), and added thereto were methyl 2-chloro-2,2-difluoroacetate (1.63 ml) and potassium carbonate (2.28 g), and the mixture was stirred at 100° C. for 1.5 hours under argon atmosphere. The reaction mixture was acidified with 2N aqueous HCl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(6-difluoromethoxybenzo[b]thiophen-2-yl-methyl)benzene (695 mg) as a colorless solid. GC-Mass m/Z 402/404 (M+).

REFERENCE EXAMPLE 154

5-Bromo-1-(6-difluoromethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

(1) 6-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give 5-Bromo -1-(6-methoxybenzo[b] thiophen-2-ylmethyl)-2-methyl-benzene. APCI-Mass m/Z 347/349 ($M+NH_4$).

(2) The above 5-bromo-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene was treated in a manner similar to Reference Example 132-(1) to give 5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-yl-methyl)-2-methylbenzene. ESI-Mass m/Z 331/333 (M−H).

(3) The above 5-bromo-1-(6-hydroxybenzo[b]thiophen-2-yl-methyl)-2-methylbenzene was treated in a manner similar to Reference Example 153 to give the desired 5-bromo-1-(6-difluoromethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene as colorless oil. GC-Mass m/Z 382/384 (M+).

REFERENCE EXAMPLE 155

(6-Cyanopyridin-2-yl)trimethyltin

2-Bromo-6-cyanopyridine (see Japanese Patent Publication 04-253974) (1.5 g) and hexamethylditin (2.69 g) were dissolved in dimethoxyethane (50 ml) and thereto was added tetrakis(triphenylphosphine)palladium(0) (972 mg). The mixture was refluxed for 5 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:1) to give (6-cyanopyridin-2-yl)trimethyltin (980 mg) as colorless oil. APCI-Mass m/Z 265/267/269 (M+H).

REFERENCE EXAMPLE 156

5-Bromo-2-methyl-1-(5-(1-pyrazolyl)-2-thienylmethyl)benzene

1-(2-thienyl)pyrazole (see Chemica Scripta (1979) 13, 157-161) and 5-bromo-2-methybenzaldehyde obtained in Reference Example 4 were used and treated in a manner similar to Reference Example 7 to give the title compound as colorless oil. APCI-Mass m/z 333/335 (M+H).

REFERENCE EXAMPLE 157

5-Bromo-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene

5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene obtained in Reference Example 154-(2) and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(6-ethoxy-

benzo[b]thiophene-2-ylmethyl)-2-methylbenzene as pale yellow wax. APCI-Mass m/Z 361/363 (M+H).

REFERENCE EXAMPLE 158

5-Bromo-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene

5-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give 5-bromo-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene as colorless wax.

REFERENCE EXAMPLE 159

5-Bromo-1-(5-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)-2-methylbenzene

(1) 5-Bromo-1-(5-methoxybenzo[b]thiophene-2-yl-methyl)-2-methylbenzene obtained in Reference Example 158 was treated in a manner similar to Reference Example 132-(1) to give 5-bromo-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene as colorless powder. ESI-Mass m/Z 331/333 (M−H).

(2) The above 5-bromo-1-(5-hydroxybenzo[b]thiophen-2-yl-methyl)-2-methylbenzene and 1-bromo-2-fluoroethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(5-(2-fluoroethyloxy)-benzo[b]thiophene-2-ylmethyl)-2-methylbenzene.

REFERENCE EXAMPLE 160

5-Bromo-1-(5-ethoxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene

5-Bromo-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene obtained in Reference Example 159-(1) and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(5-ethoxybenzo[b]thiophene-2-ylmethyl)-2-methylbenzene as colorless powder.

REFERENCE EXAMPLE 161

5-Bromo-2-chloro-1-(5-(2-fluoroethyloxy)benzo[b] thiophene-2 ylmethyl)benzene

5-Bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene obtained in Reference Example 147-(1) and 1-bromo-2-fluoroethane were treated in a manner similar to Example 132-(2) to give the target compound.

REFERENCE EXAMPLE 162

5-Bromo-1-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)2-methylbenzene

5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methyl-benzene obtained in Reference Example 154-(2) and 1-bromo-2-fluoroethane were treated in a manner similar to Example 132-(2) to give the target compound as colorless wax. APCI-Mass m/Z 379/381 (M+H).

REFERENCE EXAMPLE 163

4-(Difluoromethoxy)phenylboronic acid

A solution of (4-bromophenoxy)difluoromethane (3 g) and triisopropyl borate (3.42 ml) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (1.59M hexane solution, 3.42 ml). The mixture was stirred at room temperature overnight. Added thereto was 6N aqueous hydrochloric acid at 0° C., and the mixture was extracted with ethyl acetate. The extract was washed with brine. and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was triturated with cold hexane to give 4-(difluoromethoxy)phenylboronic acid (1.88 g) as colorless solid.

REFERENCE EXAMPLE 164

Tri-n-butyl(3-methyl-5-isooxazolyl)tin

The target compound was prepared according to a method described in Bioorg. & Med. Chem. Lett. (2003) 13, 4117-4120.

REFERENCE EXAMPLE 165

5-Bromo-2-chloro-1-(2-trifluoromethyl-5-pyridylmethyl)-benzene

(1) A solution of 5-Bromo-2-trifluoromethylpyridine (5.3 g) (see Eur. J. Org. Chem. (2003) 1159-1168) in tetrahydrofuran (70 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise isopropylmagnesium chloride (1 mol/l tetrahydrofuran solution, 23.45 ml). The reaction mixture was stirred at the same temperature for 2 hours, and thereto was added dropwise a solution of 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) (5.15 g) in tetrahydrofuran (20 ml). The mixture was stirred at the same temperature for 60 minutes, and thereto was added a saturated ammonium chloride solution, and the reaction mixture was warmed to room temperature. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-85:15) to give (5-Bromo-2-chloro)phenyl-(2-trifluoromethyl-5-pyridyl)methanol (4.56 g) as a pale brown syrup. APCI-Mass m/Z 366/368 (M+H).

(2) The above (5-Bromo-2-chloro)phenyl-(2-trifluoromethyl-5-pyridyl)methanol (4.55 g) was dissolved in dichloromethane (50 ml) and toluene (50 ml), and added thereto was manganese (IV) oxide (5.39 g), and the mixture was stirred at room temperature overnight. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-92:8) to give (5-Bromo-2-chloro)phenyl(2-trifluoromethyl-5-pyridyl) ketone (2.64 g) as a pale yellow syrup. APCI-Mass m/Z 364/366 (M+H).

(3) The above (5-Bromo-2-chloro)phenyl (2-trifluoromethyl-5-pyridyl) ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-Bromo-2-chloro-1-(2-trifluoromethyl-5-pyridylmethyl)-benzene. APCI-Mass m/Z 350/352 (M+H).

REFERENCE EXAMPLE 166

4-Methyl-2-tributylstannanylthiazole

A solution of n-butyl lithium (2.71 M hexane solution, 3.9 ml) in tetrahydrofuran (10 ml) was cooled to −78° C. under

argon atmosphere, and thereto was added dropwise a solution of 4-methylthiazole (1.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at same temperature for one hour and thereto was added dropwise a solution of tri-n-butyltin chloride (3.6 g) in tetrahydrofuran (10 ml). The mixture was stirred at same temperature for 30 minutes, warmed, and further stirred at room temperature overnight. Thereto was added water, and the mixture was extracted with diethyl ether. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by alumina column chromatography (hexane) to give the title compound (1.76 g) as oil. APCI-Mass m/z 386/388 (M+H).

REFERENCE EXAMPLE 167

2-Fluoropyridine-3-boronic acid

The target compound was prepared according to a method described in Tetrahedron (2002) 58, 3323-3328.

REFERENCE EXAMPLE 168

4-Bromo-2-(5-chloro-2-thienylmethyl)-1-methoxynaphthalene

2,4-Dibromo-1-methoxynaphthalene (see *Org. Lett.* (2003) 5, 831) and 5-chloro-2-thiophenecarboxaldehyde were treated in a manner similar to Reference Example 1 to give 4-Bromo-2-(5-chloro-2-thienylmethyl)-1-methoxynaphthalene.

REFERENCE EXAMPLE 169

2-(2-(6-Chloro)pyridine)-4,4,5,5-tetramethyl-1,3-dioxa-borolane

The target compound was prepared according to a method described in *Tetrahedron* (2003) 59, 10043-10049.

REFERENCE EXAMPLE 170

2-Methyl-4-tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in Tetrahedron (2003), 9979-9984.

REFERENCE EXAMPLE 171

2-(4-(2-Methyl)pyridine)-4,4,5,5-tetramethyl-1,3-dioxaborolane

The target compound was prepared according to a method described in United States Patent Publication No. 2003-024914.

REFERENCE EXAMPLE 172

1-(β-D-glucopyranosyl)-5-chloroindole

5-Chloro-2,3-dihydro-(1H)-indole was treated in a manner similar to the methods described in Eur. J. Med. Chem. (2004) 39, 453-458 to give the title compound. APCI-Mass m/z 314/316 (M+H).

REFERENCE EXAMPLE 173

5-Bromo-2-chloro-1-(5-(5-fluorothiazol-2-yl)-2-thienylmethyl)benzene

(1) 2-Bromothiazole (15.0 g) and 2-thiopheneboronic acid (14.0 g) were dissolved in dimethoxyethane (150 ml). To the mixture was added bis(triphenyl)phosphine palladium (II) dichloride (3.2 g) and 2M sodium carbonate (137 ml), and the mixture was refluxed under argon atmosphere for 2 hours. The mixture was cooled to room temperature, and the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was collected, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=96:4) to give 2-(2-thienyl)thiazole (9.87 g) as oil. APCI-Mass m/z 168 (M+H).

(2) The above compound (3.17 g) was treated in a manner similar to Reference Example 121 to give 5-fluoro-2-(2-thienyl)-thiazole (1.58 g) as oil. APCI-Mass m/z 186 (M+H).

(3) The above compound (1.58 g) was dissolved in chloroform (16 ml), cooled to 0° C., and thereto was added dropwise a solution of bromine (1.43 g) in chloroform (15 ml). The mixture was stirred at the same temperature for one hour, warmed, and further stirred at room temperature for one hour. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform. The extract was washed with 10% aqueous sodium thiosulfate solution, brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=97:3) to give 2-(5-bromo-2-thienyl)-5-fluorothiazole (1.81 g) as a pale yellow solid.

(4) The above compound (300 mg) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-chloro-1-(5-(5-fluorothiazol-2-yl)-2-thienylmethyl)benzene (199 mg) as a pale yellow powder.

REFERENCE EXAMPLE 174

1-(β-D-glucopyranosyl)-4-chloroindole

(1) 4-Chloroindole (3.15 g) was dissolved in trifluoroacetic acid (32 ml), thereto was added triethylsilane (8.3 ml) and the mixture was heated at 50° C. with stirring for 30 minutes. The resultant mixture was cooled to room temperature, and trifluoroacetic acid was evaporated under reduced pressure. To the residue was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate twice. The organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-80:20) to give 4-chloro-2,3-dihydro-(1H)-indole (2.89 g) as colorless oil. APCI-Mass m/z 154/156 (M+H).

(2) The above 4-chloro-2,3-dihydro-(1H)-indole was treated in a manner similar to described in Eur. J. Med. Chem. (2004) 39, 453-458 to give the title compound. APCI-Mass m/z 314/316 (M+H).

REFERENCE EXAMPLE 175

1-(β-D-glucopyranosyl)-6-chloroindole

6-Chloroindole was treated in a manner similar to Reference Example 174 to give the title compound. APCI-Mass m/z 314/316 (M+H).

Pharmacological Experiment

1. Assay for SGLT2 Inhibition

Test Compounds:

Compounds described in the above examples were used for the SGLT2 inhibition assay.

Method:

CHOK1 cells expressing human SGLT2 were seeded in 24-well plates at a density of 400,000 cells/well in F-12 nutrient mixture (Ham's F-12) containing 10% fetal bovine serum, 400 μg/ml Geneticin, 50 units/ml sodium penicillin G (Gibco-BRL) and 50 μg/ml streptomycin sulfate. After 2 days of culture at 37° C. in a humidified atmosphere containing 5% CO_2, cells were washed once with the assay buffer (137 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 50 mM Hepes, and 20 mM Tris, pH 7.4) and incubated with 250 μl of the buffer containing test compounds for 10 min at 37° C. Test compounds were dissolved in DMSO. The final concentration of DMSO was 0.5%. The transport reaction was initiated by addition of 50 μl [^{14}C]-methyl-α-D-glucopyranoside (^{14}C-AMG) solution (final concentration, 0.5 mM). After incubation for 2 hours at 37° C., the uptake was stopped by aspiration of the incubation mixture, the cells were washed three times with ice-cold PBS. Then, cells were solubilized with 0.3 N NaOH and aliquots were taken for determination of radioactivity by a liquid scintillation counter. Nonspecific AMG uptake was defined as that which occurred in the presence of 100 μM of phlorizin, a specific inhibitor of sodium-dependent glucose cotransporter. Specific uptake was normalized for the protein concentrations measured by the method of Bradford. The 50% inhibitory concentration (IC_{50}) values were calculated from dose-response curves by least square method.

Results:

Results are shown in the following table:

Test Compounds (Example No.)	IC50 (nM)
69	7.9
70	7.0
71	6.6
72	4.6
78	1.7
79	9.0
80	6.8
83	1.3
84	2.2
86	2.8
87	3.4
88	2.6
89	3.0
90	2.0
120	3.4
122	8.2
123	1.4
127	1.3
130	2.4
140	5.9
142	5.6
144	4.1
145	4.0
146	2.2
148	2.8
151	2.5
155	1.7
156	1.1
168	2.3
169	3.6
170	3.5
173	8.0
176	7.7
177	6.7
178	5.1
179	9.8
183	9.5
185	5.6
186	5.4
187	4.3
188	1.6
189	2.4
190	3.1
191	7.7
192	7.4
193	0.9
194	2.6
197	2.0
201	8.2
202	8.7
204	1.4
207	0.6
208	2.4
209	3.9
210	1.0
211	1.2
212	2.6
213	5.6
214	1.5
215	4.3
216	3.3
217	3.6
218	2.4
219	6.7
221	5.5
222	1.8
223	3.1
224	5.9
225	1.5
226	1.2
227	3.2
228	3.6
229	2.7
230	4.0
231	3.5
232	4.0
233	2.9
234	2.4
235	2.6
236	4.4
237	2.8
238	1.6
240	1.2
241	1.0
242	4.6
244	1.2
246	6.4
247	2.5
248	5.1
249	4.3
250	4.2
251	3.6
252	1.4
253	1.6
254	1.7
255	6.5
256	3.1
257	3.3
260	2.3
264	1.5
265	3.4
266	3.2
267	1.5
268	2.5

2. Urinary Glucose Excretion Test in Rats

Test Compounds:

Compounds described in the above examples were used for the urinary glucose excretion test in rats.

Methods:

6-week-old male Sprague-Dawley (SD) rats were housed in individual metabolic cages with free access to food and water from 2 days prior to the experiment. On the morning of the experiment, rats were administered vehicle (0.2% carboxymethyl cellulose solution containing 0.2% Tween80) or test compounds (30 mg/kg) by oral gavage at a volume of 10 ml/kg. Then, urine of the rat was collected for 24 hours, and the urine volume was measured. Subsequently, the glucose concentration in urine was quantified using the enzymatic assay kit and the daily amount of glucose excreted in urine per individual was calculated.

Results:

Urinary glucose amount ranges are depicted by A and B. These ranges are as follows: A≧2000 mg; 2000 mg>B≧1000 mg.

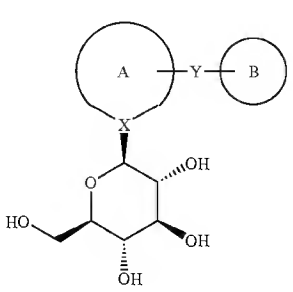
Test compounds (Example No.)	Urinary glucose
22	A
25	B
69	B
70	A
81	B
83	A
84	A
88	B
89	B
120	A
123	A
127	A
133	B
140	B
142	A
144	B
146	A
148	B
151	B
155	A
156	A
168	A
169	B
170	B
177	A
178	B
189	B
194	A
195	B
204	A
207	A
208	A
209	B
210	B
214	B
216	A
217	B
221	B
223	A
226	B
227	B
228	B
229	B
230	A
231	B
232	B
233	B
235	A
236	B
237	B
238	A
247	A

-continued

Test compounds (Example No.)	Urinary glucose
248	B
251	A
252	B

What is claimed is:

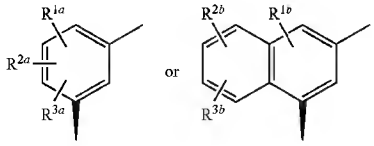
1. A compound of Formula (I):



(I)

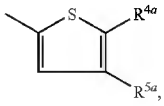
wherein

Ring A is



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



wherein R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, or a mono- or di-alkylamino group; or a hererocyclyl group substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, or a haloalkoxy group, where the hererocyclyl group is a thienyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl

group, a pyrazonyl group, a thiazonyl group, a quinolyl group, or a tetrazolyl group; R^{5a} is a hydrogen atom;

X is a carbon atom; and

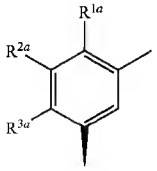
Y is $-(CH_2)_n-$ (wherein n is 1 or 2);

or a pharmaceutically acceptable salt thereof.

2. The compound, or a pharmaceutically acceptable salt thereof according to claim **1**, wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;

R^{4a} is a phenyl group substituted by halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

3. The compound, or a pharmaceutically acceptable salt thereof according to claim **2**, wherein Ring A is

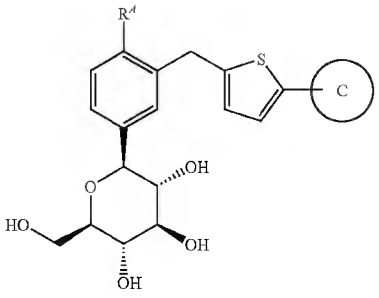


wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms;

R^{4a} is a phenyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, and Y is $-CH_2-$.

4. The compound, or a pharmaceutically acceptable salt thereof according to claim **3**, wherein R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

5. A compound represented by the following formula:



wherein R^A is a halogen atom, or a lower alkyl group; and

Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group; where the heterocyclyl group is a thienyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyrazolyl group, a thiazolyl group, a quinolyl group, or tetrazonyl group;

or a pharmaceutically acceptable salt thereof.

6. The compound, or a pharmaceutically acceptable salt thereof, according to claim **5**, wherein Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

7. The compound, or a pharmaceutically acceptable salt thereof, according to claim **6**, wherein Ring C is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

8. The compound, or a pharmaceutically acceptable salt thereof, according to claim **5**, wherein Ring C is a phenyl group substituted by a halogen atom or a cyano group, or a pyridyl group substituted by a halogen atom.

9. The compound, according to claim **1**, wherein the compound is selected from the group consisting of:

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethylyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[(5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethyl-phenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene; and

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene;

or a pharmaceutically acceptable salt thereof.

10. 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

11. 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

12. 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

13. 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

14. 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

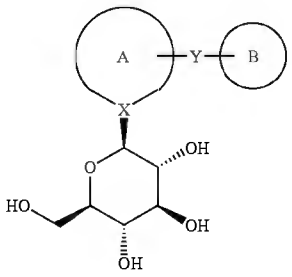
15. 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

16. 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition, which comprises the compound as set forth in claim **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

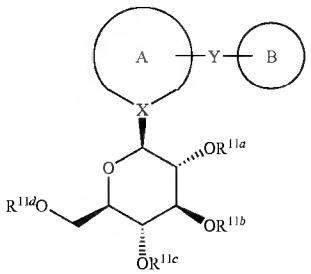
18. A process for preparing a compound of formula I:

(I)



wherein Ring A, Ring B, X and Y are as defined in claim **1**, which comprises deprotecting a compound of formula II:

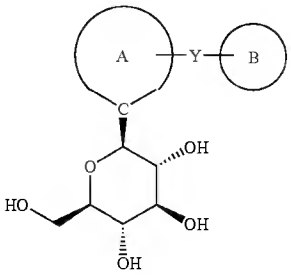
(II)



wherein Ring A, Ring B and Y are defined in claim **1** R^{11a} is a hydrogen atom or a protecting group for a hydroxy group and R^{11b}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group.

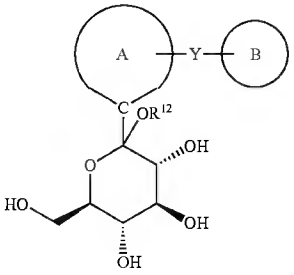
19. A process for preparing a compound of formula I-a:

(I-a)



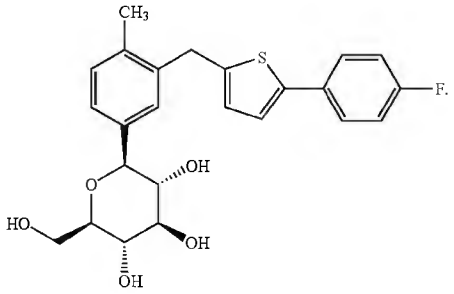
wherein Ring A, Ring B and Y are as defined in claim **1**, which comprises reducing a compound of formula III:

(III)



wherein Ring A, Ring B and Y are as defined in claim **1**, and R^{12} is a lower alkyl group.

20. A compound having the following structure:

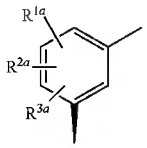


21. A pharmaceutical composition which comprises the compound of claim **20** and a pharmaceutically acceptable carrier or diluent.

22. 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene or a pharmaceutically acceptable salt thereof.

23. 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethyl-phenyl)-2-thienylmethyl]benzene or a pharmaceutically acceptable salt thereof.

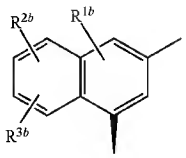
24. The compound, or a pharmaceutically acceptable salt thereof according to claim **1**, wherein Ring A is



wherein R^{1a} is a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and R^{2a} and R^{3a} are hydrogen.

25. The compound, or a pharmaceutically acceptable salt thereof according to claim **24**, wherein R^{1a} is a halogen atom or an alkyl group, and R^{2a} and R^{3a} are hydrogen.

26. The compound, or a pharmaceutically acceptable salt thereof according to claim **1**, wherein Ring A is



wherein R^{1b}, R^{2b}, and R^{3b} are as defined in claim **1**.

* * * * *

US008222219B2

(12) **United States Patent**
Nomura et al.

(10) **Patent No.: US 8,222,219 B2**
(45) **Date of Patent: Jul. 17, 2012**

(54) **GLUCOPYRANOSIDE COMPOUND**

(75) Inventors: **Sumihiro Nomura**, Kawaguchi (JP); **Eiji Kawanishi**, Kitamoto (JP); **Kiichiro Ueta**, Wako (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/174,814**

(22) Filed: **Jul. 1, 2011**

(65) **Prior Publication Data**

US 2012/0058941 A1 Mar. 8, 2012

Related U.S. Application Data

(60) Division of application No. 13/005,757, filed on Jan. 13, 2011, which is a division of application No. 11/045,446, filed on Jan. 31, 2005, now Pat. No. 7,943,788, which is a continuation-in-part of application No. PCT/JP2004/011312, filed on Jul. 30, 2004.

(60) Provisional application No. 60/491,534, filed on Aug. 1, 2003.

(51) **Int. Cl.**
A01N 43/04 (2006.01)
A61K 31/70 (2006.01)

(52) **U.S. Cl.** **514/23**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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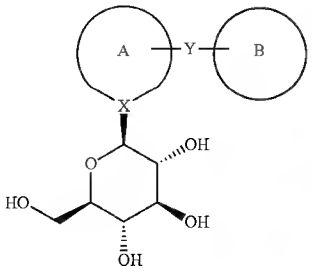
(57) **ABSTRACT**

A compound of the formula:

(I)



wherein Ring A and Ring B are: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring or an optionally substituted unsaturated fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, and Ring B are independently an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring; X is a carbon atom or a nitrogen atom; Y is $—(CH_2)_n—$ (n is 1 or 2); or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

25 Claims, No Drawings

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GLUCOPYRANOSIDE COMPOUND

TECHNICAL FIELD

This application is a Divisional of U.S. application Ser. No. 13/005,757, filed Jan. 13, 2011, which is a Divisional of U.S. application Ser. No. 11/045,446, filed Jan. 31, 2005, which issued as U.S. Pat. No. 7,943,788 B2 on May 17, 2011. U.S. application Ser. No. 11/045,446 is a Continuation-In-Part of PCT International Application No. PCT/JP2004/011312 filed on Jul. 30, 2004, which designated the United States and on which priority is claimed under 35 U.S.C. §120, which claims priority of Provisional Application No. 60/491,534 filed on Aug. 1, 2003. The entire contents of each of the above applications are hereby incorporated by reference.

BACKGROUND ART

Diet therapy and exercise therapy are essential in the treatment of diabetes mellitus. When these therapies do not sufficiently control the conditions of patients, insulin or an oral antidiabetic agent is additionally used for the treatment of diabetes. At the present, there have been used as an antidiabetic agent biguanide compounds, sulfonylurea compounds, insulin resistance improving agents and α-glucosidase inhibitors. However, these antidiabetic agents have various side effects. For example, biguanide compounds cause lactic acidosis, sulfonylurea compounds cause significant hypoglycemia, insulin resistance improving agents cause edema and heart failure, and α-glucosidase inhibitors cause abdominal bloating and diarrhea. Under such circumstances, it has been desired to develop novel drugs for treatment of diabetes mellitus having no such side effects.

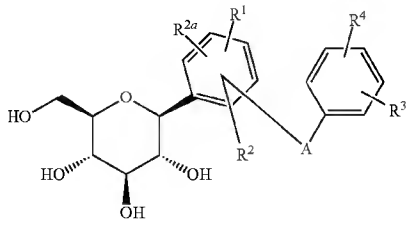
Recently, it has been reported that hyperglycemia participates in the onset and progressive impairment of diabetes mellitus, i.e., glucose toxicity theory. Namely, chronic hyperglycemia leads to decrease of insulin secretion and further to decrease of insulin sensitivity, and as a result, the blood glucose concentration is increased so that diabetes mellitus is self-exacerbated [cf., Diabetologia, vol. 28, p. 119 (1985); Diabetes Care, vol. 13, p. 610 (1990), etc.]. Therefore, by treating hyperglycemia, the aforementioned self-exacerbating cycle is interrupted so that the prophylaxis or treatment of diabetes mellitus is made possible.

As one of the methods for treating hyperglycemia, it is considered to excrete an excess amount of glucose directly into urine so that the blood glucose concentration is normalized. For example, by inhibiting sodium-dependent glucose transporter being present at the proximal convoluted tubule of kidney, the re-absorption of glucose at the kidney is inhibited, by which the excretion of glucose into urine is promoted so that the blood glucose level is decreased. In fact, it is confirmed that by continuous subcutaneous administration of phlorizin having SGLT inhibitory activity to diabetic animal models, hyperglycemia is normalized and the blood glucose level thereof can be kept normal for a long time so that the insulin secretion and insulin resistance are improved [cf., Journal of Clinical Investigation, vol. 79, p. 1510 (1987); ibid., vol. 80, p. 1037 (1987); ibid., vol. 87, p. 561 (1991), etc.].

In addition, by treating diabetic animal models with SGLT inhibitory agents for along time, insulin secretion response and insulin sensitivity of the animals are improved without incurring any adverse affects on the kidney or imbalance in blood levels of electrolytes, and as a result, the onset and progress of diabetic nephropathy and diabetic neuropathy are prevented [cf., Journal of Medicinal Chemistry, vol. 42, p. 5311 (1999); British Journal of Pharmacology, vol. 132, p. 578 (2001), Ueta, Ishihara, Matsumoto, Oku, Nawano, Fujita, Saito, Arakawa, Life Sci., in press (2005), etc.].

From the above, SGLT inhibitors may be expected to improve insulin secretion and insulin resistance by decreasing the blood glucose level in diabetic patients and further prevent the onset and progress of diabetes mellitus and diabetic complications.

WO 01/27128 discloses an aryl C-glycoside compound having the following structure.

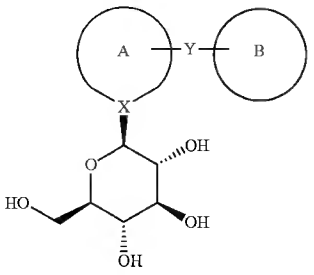


This compound is disclosed to be useful in the prophylaxis or treatment of diabetes mellitus, etc., as an SGLT inhibitor.

DISCLOSURE OF INVENTION

The present invention relates to a compound of the following formula I, or a pharmaceutically acceptable salt thereof, or a prodrug thereof:

(I)



wherein Ring A and Ring B are one of the followings: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring wherein Y is linked to the heterocyclic ring of the fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, wherein the sugar moiety X-(sugar) and the moiety —Y-(Ring B) are both on the same heterocyclic ring of the fused heterobicyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring;

X is a carbon atom or a nitrogen atom; and

Y is —$(CH_2)_n$— (wherein n is 1 or 2).

The compound of the formula I exhibits an inhibitory activity against sodium-dependent glucose transporter being

present in the intestine and the kidney of mammalian species, and is useful in the treatment of diabetes mellitus or diabetic complications such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, obesity, and delayed wound healing.

BEST MODE FOR CARRYING OUT THE INVENTION

Hereinafter, the present compound (I) is illustrated in more detail.

The definitions for each term used in the description of the present invention are listed below.

The term "halogen atom" or "halo" means chlorine, bromine, fluorine and iodine, and chlorine and fluorine are preferable.

The term "alkyl group" means a straight or branched saturated monovalent hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkyl group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkyl group having 1 to 4 carbon atoms is more preferable. Examples thereof are methyl group, ethyl group, propyl group, isopropyl group, butyl group, t-butyl group, isobutyl group, pentyl group, hexyl group, isohexyl group, heptyl group, 4,4-dimethylpentyl group, octyl group, 2,2,4-trimethylpentyl group, nonyl group, decyl group, and various branched chain isomers thereof. Further, the alkyl group may optionally and independently be substituted by 1 to 4 substituents as listed below, if necessary.

The term "alkylene group" or "alkylene" means a straight or branched divalent saturated hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkylene group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkylene group having 1 to 4 carbon atoms is more preferable. Examples thereof are methylene group, ethylene group, propylene group, trimethylene group, etc. If necessary, the alkylene group may optionally be substituted in the same manner as the above-mentioned "alkyl group".

Where alkylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The term "alkenyl group" means a straight or branched monovalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. Preferable alkenyl group is a straight chain or branched chain alkenyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkenyl group having 2 to 4 carbon atoms is more preferable. Examples thereof are vinyl group, 2-propenyl group, 3-butenyl group, 2-butenyl group, 4-pentenyl group, 3-pentenyl group, 2-hexenyl group, 3-hexenyl group, 2-heptenyl group, 3-heptenyl group, 4-heptenyl group, 3-octenyl group, 3-nonenyl group, 4-decenyl group, 3-undecenyl group, 4-dodecenyl group, 4,8,12-tetradecatrienyl group, etc. The alkenyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "alkenylene group" means a straight or branched divalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. The straight chain or branched chain alkenylene group having 2 to 6 carbon atoms is preferable, and the straight chain or branched chain alkenylene group having 2 to 4 carbon atoms is more preferable. Examples thereof are vinylene group, propenylene group, butadienylene group, etc. If necessary, the alkylene group may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary.

Where alkenylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle (e.g., a fused benzene ring) together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The term "alkynyl group" means a straight or branched monovalent hydrocarbon chain having at least one triple bond. The preferable alkynyl group is a straight chain or branched chain alkynyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkynyl group having 2 to 4 carbon atoms is more preferable. Examples thereof are 2-propynyl group, 3-butynyl group, 2-butynyl group, 4-pentynyl group, 3-pentynyl group, 2-hexynyl group, 3-hexynyl group, 2-heptynyl group, 3-heptynyl group, 4-heptynyl group, 3-octynyl group, 3-nonynyl group, 4-decynyl group, 3-undecynyl group, 4-dodecynyl group, etc. The alkynyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "cycloalkyl group" means a monocyclic or bicyclic monovalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms is more preferable. Examples thereof are a monocyclic alkyl group and a bicyclic alkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, cyclodecyl group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. The cycloalkyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the condensed unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkylidene group" means a monocyclic or bicyclic divalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 6 carbon atoms is preferable. Examples thereof are a monocyclic alkylidene group and a bicyclic alkylidene group such as cyclopropylidene group, cyclobutylidene group, cyclopentylidene group, cyclohexylidene group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkylidene group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkenyl group" means a monocyclic or bicyclic monovalent unsaturated hydrocarbon ring having 4 to 12 carbon atoms and having at least one double bond. The preferable cycloalkenyl group is a monocyclic unsaturated hydrocarbon group having 4 to 7 carbon atoms. Examples thereof are monocyclic alkenyl groups such as cyclopentenyl group, cyclopentadienyl group, cyclohexenyl group, etc. These groups may optionally and independently be substi-

tuted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkenyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkynyl group" means a monocyclic or bicyclic unsaturated hydrocarbon ring having 6 to 12 carbon atoms, and having at least one triple bond. The preferable cycloalkynyl group is a monocyclic unsaturated hydrocarbon group having 6 to 8 carbon atoms. Examples thereof are monocyclic alkynyl groups such as cyclooctynyl group, cyclodecynyl group. These groups may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkynyl group may optionally and independently be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "aryl group" means a monocyclic or bicyclic monovalent aromatic hydrocarbon group having 6 to 10 carbon atoms. Examples thereof are phenyl group, naphthyl group (including 1-naphthyl group and 2-naphthyl group). These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the aryl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "unsaturated monocyclic heterocyclic ring" means an unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the preferable one is a 4- to 7-membered saturated or unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof are pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, 4,5-dihydrooxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole, etc. Among them, pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, oxazole, and thiazole can be preferably used. The "unsaturated monocyclic heterocyclic ring" may optionally and independently be substituted by 1-4 substituents as mentioned below, if necessary.

The term "unsaturated fused heterobicyclic ring" means hydrocarbon ring comprised of a saturated or a unsaturated hydrocarbon ring condensed with the above mentioned unsaturated monocyclic heterocyclic ring where said saturated hydrocarbon ring and said unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO, or SO_2 within the ring, if necessary. The "unsaturated fused heterobicyclic ring" includes, for example, benzothiophene, indole, tetrahydrobenzothiophene, benzofuran, isoquinoline, thienothiophene, thienopyridine, quinoline, indoline, isoindoline, benzothiazole, benzoxazole, indazole, dihydroisoquinoline, etc. Further, the "heterocyclic ring" also includes possible N- or S-oxides thereof.

The term "heterocyclyl" means a monovalent group of the above-mentioned unsaturated monocyclic heterocyclic ring or unsaturated fused heterobicyclic ring and a monovalent group of the saturated version of the above-mentioned unsaturated monocyclic heterocyclic or unsaturated fused heterobicyclic ring. If necessary, the heterocyclyl may optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "alkanoyl group" means a formyl group and ones formed by binding an "alkyl group" to a carbonyl group.

The term "alkoxy group" means ones formed by binding an "alkyl group" to an oxygen atom.

The substituent for the above each group includes, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group. Each group as mentioned above may optionally be substituted by these substituents.

Further, the terms such as a haloalkyl group, a halo-lower alkyl group, a haloalkoxy group, a halo-lower alkoxy group, a halophenyl group, or a haloheterocyclyl group mean an alkyl group, a lower alkyl group, an alkoxy group, a lower alkoxy group, a phenyl group or a heterocyclyl group (hereinafter, referred to as an alkyl group, etc.) being substituted by one or more halogen atoms, respectively. Preferable ones are an alkyl group, etc. being substituted by 1 to 7 halogen atoms, and more preferable ones are an alkyl group, etc. being substituted by 1 to 5 halogen atoms. Similarly, the terms such as a hydroxyalkyl group, a hydroxy-lower alkyl group, a

hydroxyalkoxy group, a hydroxy-lower alkoxy group and a hydroxyphenyl group mean an alkyl group, etc., being substituted by one or more hydroxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 hydroxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 hydroxy groups. Further, the terms such as an alkoxyalkyl group, a lower alkoxyalkyl group, an alkoxy-lower alkyl group, a lower alkoxy-lower alkyl group, an alkoxyalkoxy group, a lower alkoxyalkoxy group, an alkoxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, an alkoxyphenyl group, and a lower alkoxyphenyl group means an alkyl group, etc., being substituted by one or more alkoxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 alkoxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 alkoxy groups.

The terms "arylakyl" and "arylalkoxy" as used alone or as part of another group refer to alkyl and alkoxy groups as described above having an aryl substituent.

The term "lower" used in the definitions for the formulae in the present specification means a straight or branched carbon chain having 1 to 6 carbon atoms, unless defined otherwise. More preferably, it means a straight or branched carbon chain having 1 to 4 carbon atoms.

The term "prodrug" means an ester or carbonate, which is formed by reacting one or more hydroxy groups of the compound of the formula I with an acylating agent substituted by an alkyl, an alkoxy or an aryl by a conventional method to produce acetate, pivalate, methylcarbonate, benzoate, etc. Further, the prodrug includes also an ester or amide, which is similarly formed by reacting one or more hydroxy groups of the compound of the formula I with an α-amino acid or a β-amino acid, etc. using a condensing agent by a conventional method.

The pharmaceutically acceptable salt of the compound of the formula I includes, for example, a salt with an alkali metal such as lithium, sodium, potassium, etc.; a salt with an alkaline earth metal such as calcium, magnesium, etc.; a salt with zinc or aluminum; a salt with an organic base such as ammoniun, choline, diethanolamine, lysine, ethylenediamine, t-butylamine, t-octylamine, tris(hydroxymethyl)aminomethane, N-methyl glucosamine, triethanolamine and dehydroabietylamine; a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; or a salt with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, etc.; or a salt with an acidic amino acid such as aspartic acid, glutamic acid, etc.

The compound of the present invention also includes a mixture of stereoisomers, or each pure or substantially pure isomer. For example, the present compound may optionally have one or more asymmetric centers at a carbon atom containing any one of substituents. Therefore, the compound of the formula I may exist in the form of enantiomer or diastereomer, or a mixture thereof. When the present compound (I) contains a double bond, the present compound may exist in the form of geometric isomerism (cis-compound, trans-compound), and when the present compound (I) contains an unsaturated bond such as carbonyl, then the present compound may exist in the form of a tautomer, and the present compound also includes these isomers or a mixture thereof. The starting compound in the form of a racemic mixture, enantiomer or diastereomer may be used in the processes for preparing the present compound. When the present compound is obtained in the form of a diastereomer or enantiomer, they can be separated by a conventional method such as chromatography or fractional crystallization.

In addition, the present compound (I) includes an intramolecular salt, hydrate, solvate or polymorphism thereof.

Examples of the optionally substituted unsaturated monocyclic heterocyclic ring of the present invention include an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxyl group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group wherein each substituent may optionally be further substituted by these substituents.

Examples of the optionally substituted unsaturated fused heterobicyclic ring of the present invention include an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidene-methyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenyl-carbonyl group, a cycloalkynyl-carbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxy-carbonyl group, a cycloalkyloxycarbo-

nyl group, a cycloalkenyloxy-carbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cyclo-alkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclyl-carbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoyl-amino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkyl-sulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cyclo-alkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group, wherein each substituent may optionally be further substituted by these substituents.

Examples of the optionally substituted benzene ring of the present invention include a benzene ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, a heterocyclylsulfonyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group wherein each substituent may optionally be further substituted by these substituents. Moreover, examples of the optionally substituted benzene ring include a benzene ring substituted with an alkylene group to form an annelated carbocycle together with the carbon atoms to which they are attached, and also includes a benzene ring substituted with an alkenylene group to form an annelated carbocycle such as a fused benzene ring together with the carbon atoms to which they are attached.

Preferable examples of the optionally substituted unsaturated monocyclic heterocyclic ring include an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

Preferable examples of the optionally substituted unsaturated fused heterobicyclic ring include an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

Preferable examples of the optionally substituted benzene ring include a benzene ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group.

In another preferable embodiment of the present invention, the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring

which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, phenylsulfonyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, a mono- or di-alkylamino group, a carboxyl group, an alkoxycarbonyl group, a phenyl group, an alkyleneoxy group, an alkylenedioxy group, an oxo group, a carbamoyl group, and a mono- or di-alkylcarbamoyl group.

In a preferable embodiment, the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, an alkoxycarbonyl group, a carbamoyl group and a mono- or di-alkylcarbamoyl group.

In another preferable embodiment,

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

(2) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl

group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group; or

(3) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group;

wherein each of the above-mentioned substituents on Ring A and Ring B may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, an alkoxycarbonyl group, a carbamoyl group and a mono- or di-alkylcarbamoyl group.

In a more preferable embodiment of the present invention, Ring A and Ring B are

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group;

(2) Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a phenyl group, or a lower alkenylene group, and Ring B is (a) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, or a carbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group or a carbamoyl group; (b) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or

(3) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may

optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group.

In another more preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which is substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a phenyl group, and a lower alkenylene group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxy phenyl group, a lower alkylenedioxyphenyl group, a lower alkyleneoxy phenyl group, a mono- or di-lower alkylaminophenyl group, a carbamoyl phenyl group, a mono- or di-lower alkylcarbamoylphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, a lower alkoxyheterocyclyl group, a mono- or di-lower alkylaminoheterocycyclyl group, a carbamoylheterocyclyl group, and a mono- or di-lower alkylcarbamoyl group.

In another more preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is a benzene ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, and a lower alkoxyheterocyclyl group.

Further, in another preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, and a lower alkoxyheterocyclyl group.

In a more preferable embodiment of the present invention, X is a carbon atom and Y is —CH_2—.

Further, in another preferable embodiment, Ring A and Ring B are

(1) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, a phenyl group, and a lower alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, or a carbamoyl group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group or a carbamoyl group; and an oxo group,

(2) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group, and

Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-

lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a lower alkylene group,

(3) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group;

(4) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and a lower alkylene group, or

(5) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group.

In another preferable embodiment of the present invention, Y is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group, or a phenyl group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom. a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and an oxo group.

In another more preferable embodiment of the present invention, Y is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a substituent selected from a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and a lower alkylene group.

Preferable examples of unsaturated monocyclic heterocyclic ring include a 5- or 6-membered unsaturated heterocyclic ring containing 1 or 2 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are furan, thiophene, oxazole, isoxazole, triazole, tetrazole, pyrazole, pyridine, pyrimidine, pyrazine, dihydroisoxazole. dihydropyridine. and triazole. Preferable unsaturated fused heterobicyclic ring includes a 9- or 10-membered unsaturated fused heterocyclic ring containing 1 to 4 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are indoline, isoindoline, benzothiazole, benzoxazole, indole, indazole, quinoline, isoquinoline, benzothiophene, benzofuran, thienothiophene, and dihydroisoquinoline.

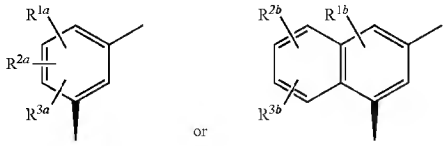
In a more preferred embodiment of the present invention, Ring A is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a phenyl group, and Ring B is a heterocyclic ring selected from the group consisting of thiophene, furan, benzofuran, benzothiophene, and benzothiazole, wherein the heterocyclic ring may optionally be substituted by a substituent selected from the following group: a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a lower alkylphenyl group, a lower alkoxyphenyl group, a thienyl group, a halothienyl group, a pyridyl group, a halopyridyl group, and a thiazolyl group.

In yet another preferred embodiment, Y is —CH_2—, Ring A is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring selected from the group consisting of thiophene, dihydroisoquinoline, dihydroisoxazole, triazole. pyrazole, dihydropyridine, dihydroindole, indole, indazole, pyridine, pyrimidine, pyrazine, quinoline, and a isoindoline, wherein the heterocyclic ring may optionally

substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

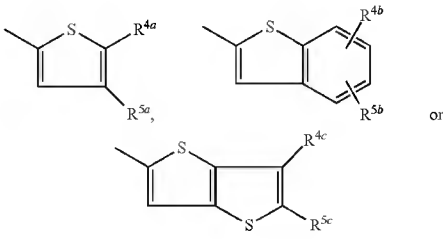
In a further preferred embodiment of the present invention, Ring A is a benzene ring which is substituted by a halogen atom or a lower alkyl group, and Ring B is thienyl group which is substituted by phenyl group or a heterocyclyl group in which said phenyl group and heterocyclyl group is substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

Further, in another aspect of the present invention, preferable examples of the compound of the formula I include a compound wherein Ring A is



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



wherein R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, a mono- or di-alkylamino group, a carbamoyl group, or a mono- or di-alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, a carbamoyl group, or a mono- or di-alkylcarbamoyl group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form an alkylene group; and

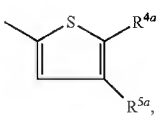
R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group or a haloalkoxy group.

More preferred is a compound wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;

R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group; and

R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

Further preferred is a compound in which Ring B is

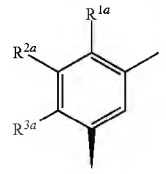


wherein R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a

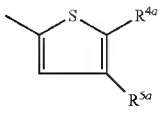
mono- or di-lower alkylamino group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, and R^{5a} is a hydrogen atom, or

R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group.

Further more preferred is a compound in which Ring A is



wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is

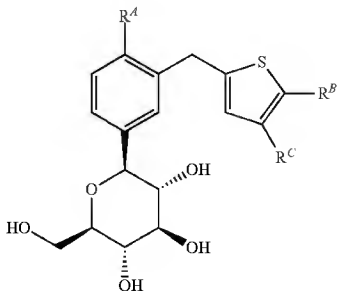


wherein R^{4a} is a phenyl group optionally substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, and R^{5a} is a hydrogen atom, and Y is $—CH_2—$.

In more preferable embodiment, R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

In another preferable embodiment of the present invention, a preferable compound can be represented by the following formula IA:

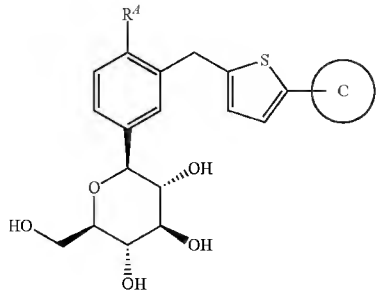
(IA)



wherein R^A is a halogen atom, a lower alkyl group or a lower alkoxy group; R^B is a phenyl group optionally substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; and R^C is hydrogen atom; or R^B and R^C taken together are a fused benzene ring which may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group.

In a preferable embodiment, R^A is a halogen atom or a lower alkyl group, R^C is hydrogen atom, and R^B is phenyl group substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group. The chemical structure of such compounds are represented by the following formula (IA'):

(IA')



wherein R^A is a halogen atom, or a lower alkyl group, Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group.

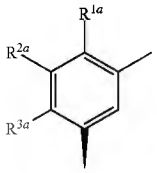
In a more preferable embodiment, Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

Among them, a compound in which Ring C is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group is preferred.

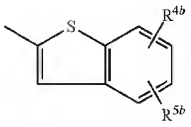
A preferred heterocyclyl group includes a 5- or 6-membered heterocyclyl group containing 1 or 2 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom, or a 9- or 10-membered heterocyclyl group containing 1 to 4 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. Specifically, a thienyl group, a pyridyl group, a pyrimidyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, a tetrazolyl group and an oxazolyl group are preferred.

In a further preferable embodiment, Ring C is a phenyl group substituted by a halogen atom or a cyano group, or a pyridyl group substituted by a halogen atom.

In another preferable embodiment of the present invention, preferred is a compound in which Ring A is



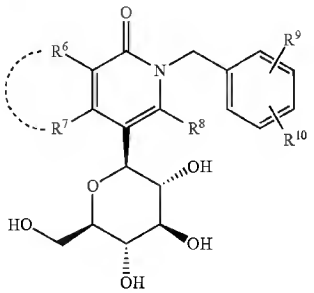
wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is



wherein R^{4b} and R^{5b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

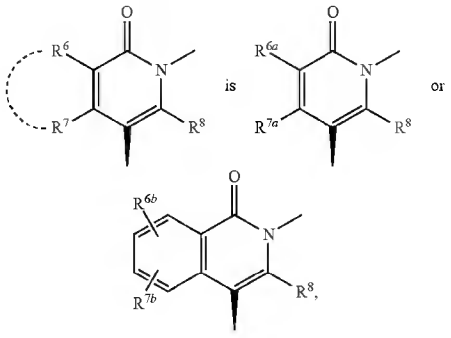
In another aspect of the present invention, preferable examples of the compound I include a compound represented by the following formula IB:

(IB)



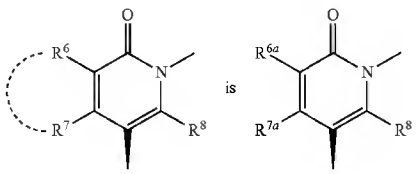
wherein R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group; and

a group represented by:

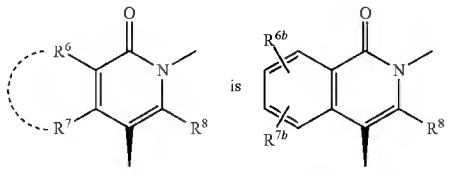


wherein R^{6a} and R^{7a} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group and R^{6b} and R^{7b} are each independently a hydrogen atom, a halogen atom, an alkyl group, a haloalkyl group, or an alkoxy group.

Among the compounds represented by the formula IB, more preferred is a compound in which R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a cycloalkoxy group, a halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, and a group represented by:



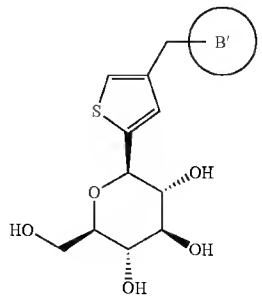
wherein R^{6a}, R^{7a} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a cycloalkoxy group, a halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, or a group represented by:



wherein R^{6b} and R^{7b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group.

In another aspect of the present invention, preferable examples of the compound I include a compound represented by the following formula IC:

(IC)



wherein Ring B' is an optionally substituted benzene ring, an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring.

Preferable examples of Ring B' include a benzene ring and a heterocyclic ring, both of which may have a substituent(s) selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a lower alkanoyl group; a mono- or di-lower alkylamino group; a lower alkoxycarbonyl group; a carbamoyl group; a mono- or di-lower alkylcarbamoyl group; a phenyl group optionally substituted by a substituent(s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; a heterocyclyl group optionally substituted by a substituent(s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; an alkylene group; and an oxo group.

More preferable examples of Ring B' include a benzene ring which may be substituted by a substituent selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom.

Preferred compound of the present invention may be selected from the following group:

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b]thiophen-2-ylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(5-thiazolyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-(5-phenyl-2-thienylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-β-D-glucopyranosyl)-4-methyl-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethylphenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene;

the pharmaceutically acceptable salt thereof; and the prodrug thereof.

Particularly Preferred compounds of the present invention include:

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof; and

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

The compound (I) of the present invention exhibits an excellent inhibitory activity against sodium-dependent glucose transporter, and an excellent blood glucose lowering effect. Therefore, the compound of the present invention is useful for treating or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension. In particular, the compound of the present invention is useful in the treatment or the prophylaxis of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy) or obesity, or is useful in the treatment of postprandial hyperglycemia.

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparation for oral administration includes, for example, solid preparation such as tablets, granules, capsules, powders, etc., or solution preparations, suspension preparations, or emulsion preparations, etc. Suitable pharmaceutical preparation for parenteral administration includes, for example, suppositories; injection preparations and intravenous drip preparations using distilled water for injection, physiological saline solution or aqueous glucose solution; or inhalant preparations.

The dosage of the present compound (I) or a pharmaceutically acceptable salt thereof may vary according to the administration routes, ages, body weight, conditions of a patient, or kinds and severity of a disease to be treated, and it is usually in the range of about 0.1 to 50 mg/kg/day, preferably in the range of about 0.1 to 30 mg/kg/day.

The compound of the formula I may be used, if necessary, in combination with one or more of other antidiabetic agents, one or more agents for treating diabetic complications, and/or one or more agents for treatment of other diseases. The present compound and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The other antidiabetic agents include, for example, antidiabetic or antihyperglycemic agents including insulin, insulin secretagogues, or insulin sensitizers, or other antidiabetic agents having an action mechanism different from SGLT inhibition, and 1, 2, 3 or 4 of these other antidiabetic agents may preferably be used. Concrete examples thereof are biguanide compounds, sulfonylurea compounds, α-glucosidase inhibitors, PPARγ agonists (e.g., thiazolidinedione compounds), PPARα/γ dual agonists, dipeptidyl peptidase IV (DPP4) inhibitors, mitiglinide compounds, and/or nateglinide compounds, and insulin, glucagon-like peptide-1 (GLP-1), PTP1B inhibitors, glycogen phosphorylase inhibitors, RXR modulators, and/or glucose 6-phosphatase inhibitors.

The agents for treatment of other diseases include, for example, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an anti-atherosclerotic agent and/or a hypolipidemic agent.

The SGLT inhibitors of the formula I may be used in combination with agents for treatment of diabetic complications, if necessary. These agents include, for example, PKC inhibitors and/or ACE inhibitors.

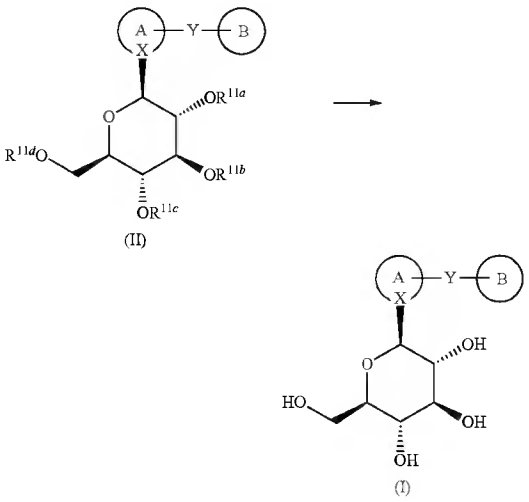
The dosage of those agents may vary according to ages, body weight, and conditions of patients, and administration routes, dosage forms, etc.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, dogs, etc., for example, in the dosage form of tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The present compound of the formula I may be prepared by the following Processes.

Process 1

The compound of the formula I may be prepared by a method as shown in the following scheme:



wherein R^{11a} is a hydrogen atom or a protecting group for a hydroxy group, and R^{11b}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group, and other symbols are as defined above.

The compound of the formula I may be prepared by deprotecting the compound of the formula II.

In the compound of the formula II, the protecting group for hydroxy group may be any conventional protecting groups, and a benzyl group, an acetyl group, and an alkylsily group such as a trimethylsilyl group may be used. Further, the protecting group for hydroxy group may form acetal or silylacetal together with adjacent hydroxy groups. Examples of such protecting group include an alkylidene group such as an isopropylidene group, a sec-butylidene group, etc., a benzylidene group, or a dialkylsilylene group such as di-tert-butylsilylene group, etc., which can be formed, for example, by combining R^{11c} and R^{11d} at the terminal thereof.

The deprotection can be carried out according to the kinds of protecting group to be removed, for example, by conventional processes such as reduction, hydrolysis, acid treatment, fluoride treatment, etc.

For example, when a benzyl group is to be removed, the deprotection can be carried out by (1) catalytic reduction using a palladium catalyst (e.g., palladium-carbon, palladium

hydroxide) under hydrogen atmosphere in a suitable solvent (e.g., methanol, ethanol, ethyl acetate); (2) treatment with an dealkylating agent such as boron tribromide, boron trichloride, boron trichloride•dimethylsulfide complex, or iodotrimethylsilane in a suitable solvent (e.g., dichloromethane); or (3) treatment with a lower alkylthiol such as ethanethiol in the presence of a Lewis acid (e.g., boron trifluoride•diethyl ether complex) in a suitable solvent (e.g., dichloromethane).

When a protecting group is removed by hydrolysis, the hydrolysis can be carried out by treating the compound of formula II with a base (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, sodium ethoxide, etc.) in a suitable solvent (e.g., tetrahydrofuran, dioxane, methanol, ethanol, water, etc.).

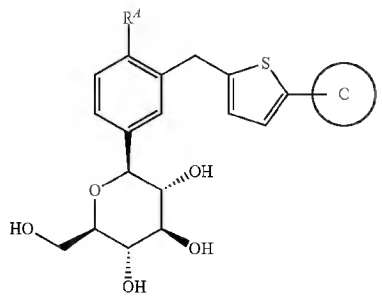
Acid treatment can be carried out by treating the compound of formula II with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

In case of the fluoride treatment, it can be carried out by treating the compound of formula II with a fluoride (e.g., hydrogen fluoride, hydrogen fluoride-pyridine, tetrabutylammonium fluoride. etc.) in a suitable solvent (e.g., acetic acid, a lower alcohol (methanol, ethanol, etc.), acetonitrile, tetrahydrofuran, etc.).

The deprotection reaction can be preferably carried out under cooling or with heating, for example, at a temperature of from 0° C. to 50° C., more preferably at a temperature of from 0° C. to room temperature.

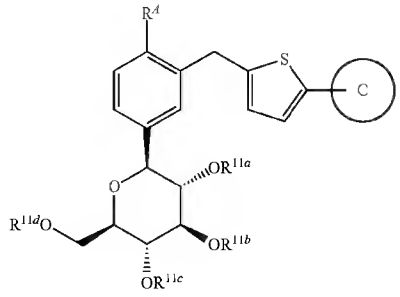
Accordingly, a compound of formula (IA'):

(IA')



wherein the symbols are the same as defined above, can be prepared by deprotecting a compound of formula (II-A):

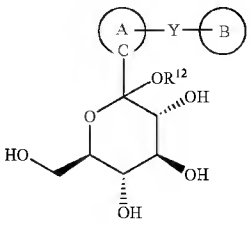
(II-A)



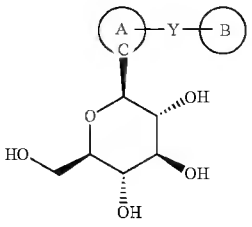
wherein the symbols are the same as defined above, as described above.

Process 2

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(III)



(I-a)

wherein R^{12} is a lower alkyl group, and other symbols are as defined above.

The compound of the formula I-a may be prepared by reducing the compound of the formula III.

The reduction can be carried out by treatment with a silane reagent, in the presence of an acid, in a suitable solvent or in the absence of a solvent.

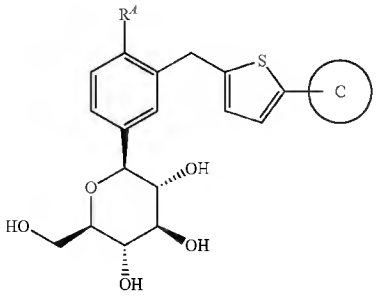
As the acid, for example, a Lewis acid such as boron trifluoride•diethyl ether complex, titanium tetrachloride, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc., may preferably be used.

As the silane reagent, for example, a trialkylsilane such as triethylsilane, triisopropylsilane, etc. may preferably be used.

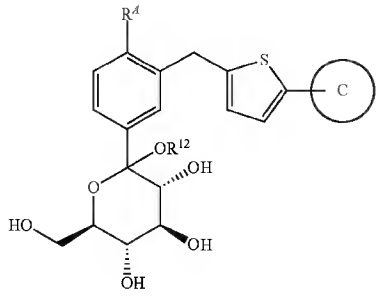
As the solvent, any kinds of solvent may be used as long as it does not affect the reaction, and for example, acetonitrile, dichloromethane, or an acetonitrile/dichloromethane mixture may preferably be used.

Accordingly, the compound of the formula (IA'):

(IA')



wherein the symbols are the same as defined above, can be prepared by reducing a compound of formula (III-A):

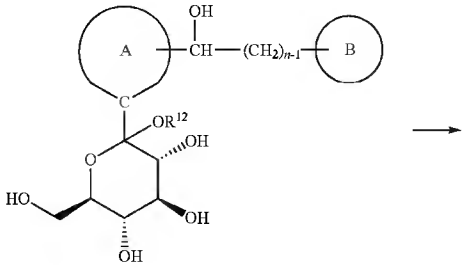


(III-A)

wherein the symbols are the same as defined above, as described above.

Process 3

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(IV)

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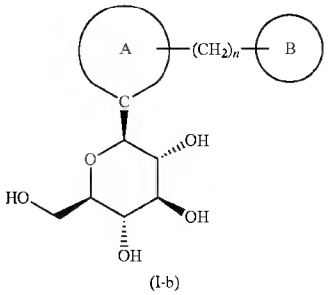


(I-b)

wherein the symbols are as defined above.

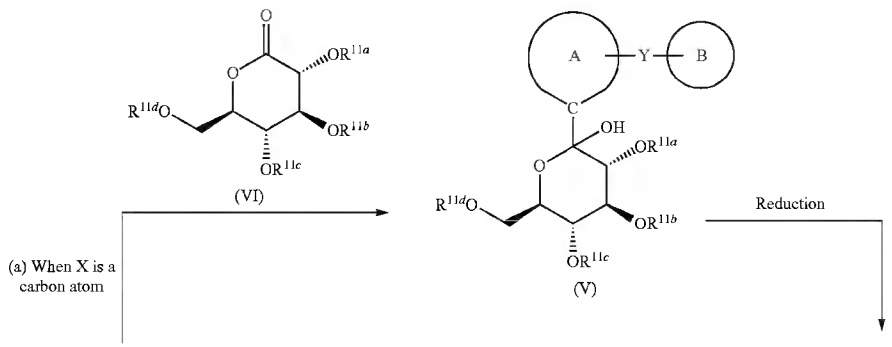
Namely, the compound of the formula I-b may be prepared by reducing the compound of the formula IV.

The reduction can be carried out in a manner similar to Process 2. In other words, it can be carried out by treatment with a silane reagent (e.g., triethylsilane, etc.), in the presence of a Lewis acid (e.g., boron trifluoride•diethyl ether complex, etc.), in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.).

The compound of the present invention thus obtained may be isolated and purified by a conventional method well known in the organic synthetic chemistry such as recrystallization, column chromatography, etc.

The starting compound represented by the formula (II), (III) or (IV) may be prepared by either one of the following steps (a)-(l).

Steps (a) and (b):



(a) When X is a carbon atom

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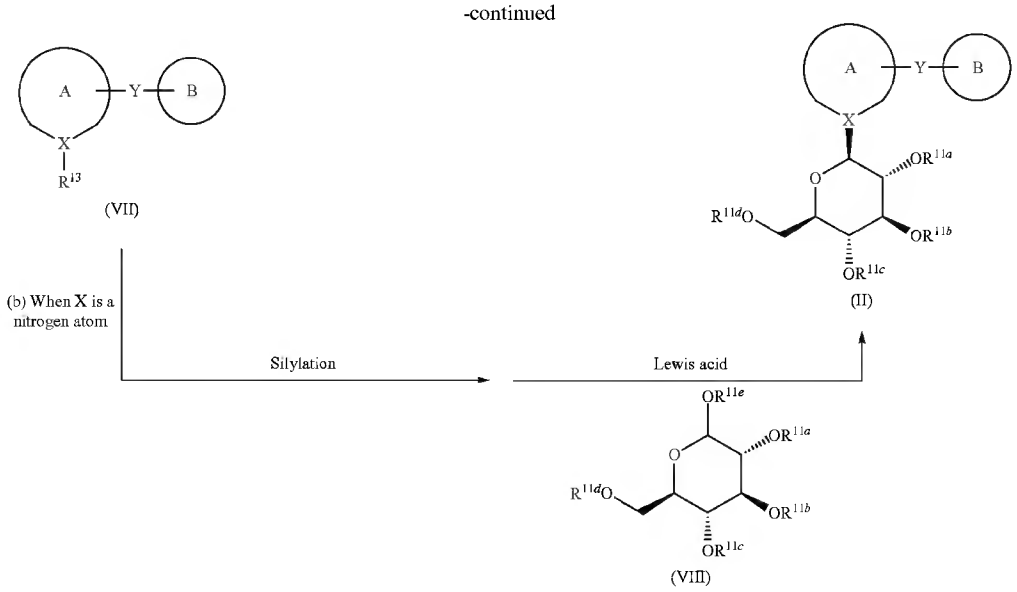


In the above scheme, R^{13} is (1) a bromine atom or an iodine atom when X is a carbon atom; or (2) a hydrogen atom when X is a nitrogen atom, R^{11e} is a protecting group for hydroxy group, and the other symbols are as defined above.

Step (a):

Among the compounds of the formula II, the compound wherein X is a carbon atom may be prepared by coupling the compound of the formula VII with the compound of the formula VI to give the compound of formula V, followed by reduction of the compound of the formula V.

The coupling reaction can be carried out by lithiating the compound of the formula VII, followed by reacting the resultant with the compound of the formula VI.

In particular, the compound of the formula VII can be treated with an alkyllithium, followed by reacting the resultant with the compound of the formula VI. As the alkyllithium, methyl lithium, n-butyl lithium, t-butyl lithium, etc. are preferably used. The solvent may be any solvent which does not disturb the reaction, and ethers such as tetrahydrofuran, diethyl ether, etc.. are preferably used. This reaction can be carried out from under cooling (e.g., at −78° C.) to room temperature.

The reduction can be carried out in a manner similar to Process 2. Namely, it can be carried out by treating the compound of formula V with a silane reagent (e.g., triethylsilane, etc.) in the presence of a Lewis acid (e.g., boron trifluoride•diethyl ether complex, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.).

Step (b)

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by silylating the compound of the formula VII in a solvent, followed by reacting the resultant with the compound of the formula VIII (e.g., an α- or β-D-glucose pentaacetate, etc.) in the presence of a Lewis acid.

The silylation reaction can be carried out by treating the compound of formula VII with a silylating agent in a solvent. The silylating agent includes, for example, N,O-bis(trimethylsilyl)acetamide, 1,1,1,3,3,3-hexamethyldisilazane, etc.

The solvent may be, for example, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, etc., ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, etc., acetonitrile, etc.

This reaction is preferably carried out under cooling or with heating, for example, at a temperature of from 0° C. to 60° C., preferably at a temperature of from room temperature to 60° C.

The reaction with the compound of the formula VIII can be carried out in a solvent in the presence of a Lewis acid.

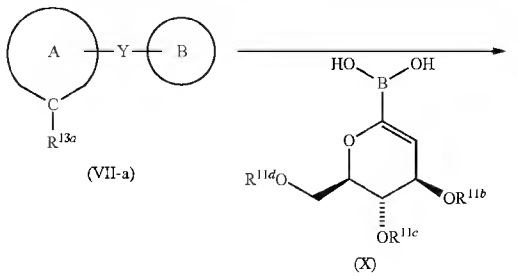
The Lewis acid includes, for example, trimethylsilyl trifluoromethanesulfonate, titanium tetrachloride, tin tetrachloride, boron trifluoride•diethyl ether complex.

The solvent may be, for example, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, etc., acetonitrile, etc.

This reaction can be carried out under cooling or with heating, for example, at a temperature of from 0° C. to 100° C., preferably at a temperature of from room temperature to 60° C.

Step (c):

Among the compounds of the formula II, the compound wherein X is a carbon atom and R^{11a} is a hydrogen atom may be prepared by a method as shown in the following scheme:



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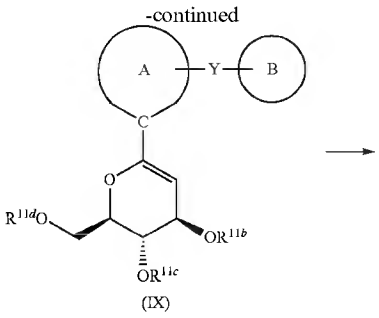
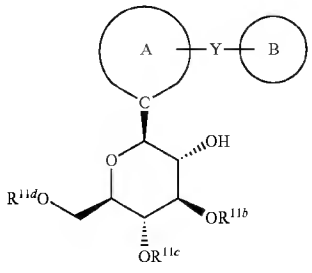


(IX)

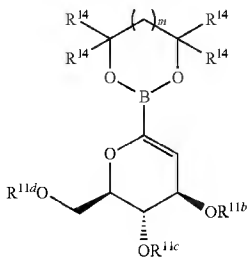


(II-a)

wherein R^{13a} is a bromine atom or an iodine atom, and the other symbols are as defined above.

Namely, the compounds of the formula II-a may be prepared by coupling the compound of the formula VII-a with the compound of the formula X or an ester thereof to give the compound of the formula IX, followed by hydrating the compound of the formula IX.

The ester of the compound of the formula X includes, for example, a lower alkyl ester thereof, and a compound represented by the formula XI:



(XI)

wherein R^{14} is a lower alkyl group, m is 0 or 1, and the other symbols are as defined above.

The coupling reaction of the compound of the formula VII-a with the compound of the formula X or an ester thereof can be carried out in the presence of a base and a palladium catalyst in a suitable solvent.

The base includes an inorganic base such as an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), potassium fluoride, potassium phosphate, etc., and an organic base such as a tri-lower alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), a cyclic tertiary amine (e.g., 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo [4.3.0]-nona-5-ene, 1,8-diazabicyclo[5.4.0]undeca-7-ene, etc.).

The palladium catalyst may be a conventional catalyst such as tetrakis(triphenyl)phosphinepalladium(0), palladium(II) acetate, palladium(II) chloride, bis(triphenyl)phosphine palladium(II) chloride, palladium(II) chloride•1,1-bis(diphenylphosphino)ferrocene complex, etc.

The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., amide solvents such as N,N-dimethylformamide, 1,3-dimethyl-2-imidazolidinone, etc., aromatic hydrocarbons such as toluene, xylene, etc., dimethylsulfoxide, water, and if desired, a mixture of two or more of these solvents.

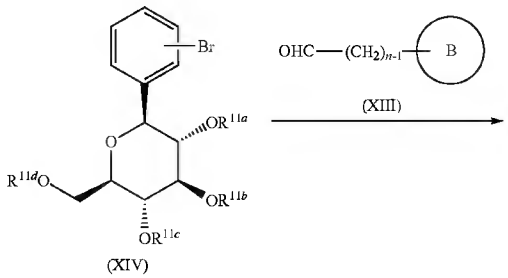
This reaction is preferably carried out with heating, for example, at a temperature of from 50° C. to a boiling point of the reaction mixture, and more preferably at a temperature of from 50° C. to 100° C.

The hydration reaction of the compound of the formula IX can be carried out, for example, by hydroboration, more specifically, by reacting with diborane, borane•tetrahydrofuran complex, or 9-borabicyclononane, etc. in a suitable solvent, followed by treating with hydrogen peroxide solution in the presence of a base (e.g., an alkali metal hydroxide such as sodium hydroxide, etc.), or by treating with an oxidizing reagent such as sodium perborate, and oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) in a suitable solvent.

The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., water, and if desired, a mixture of two or more of these solvents. This reaction can be carried out at a temperature of a broad range such as under cooling or with heating, and preferably carried out at a temperature of from −10° C. to a boiling point of the reaction mixture.

Step (d):

Among the compound of the formula II, the compound wherein Ring A is a benzene ring may be prepared in a method as shown in the following scheme:



(XIV)

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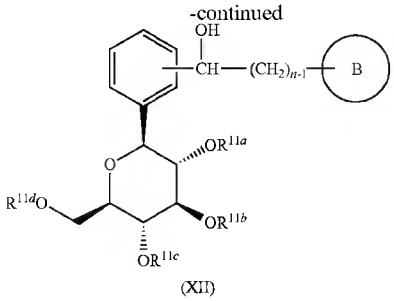
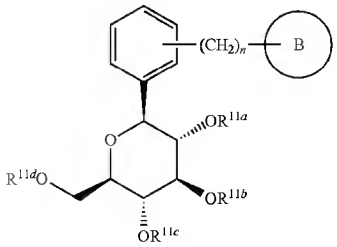


(XII)



(II-b)

wherein the symbols are as defined above.

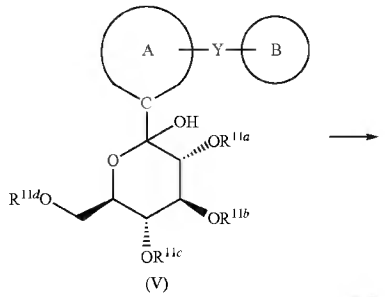
Namely, the compounds of the formula II-b may be prepared by coupling the compound of the formula XIV with the compound of the formula XIII, to give the compound of the formula XII, followed by reduction of the compound of the formula XII.

The coupling reaction can be carried out in a manner similar to Step (a). Namely, it can be carried out by lithiating the compound of formula XIV with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound (XIII).

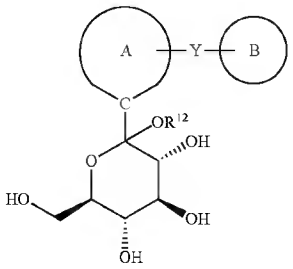
The reduction reaction can be carried out by (1) treatment with a silane reagent (e.g., trialkyl silane such as triethyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at −30° C. to 60° C., in the presence of a Lewis acid such as boron trifluoride•diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane, or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., and a Lewis acid such as aluminum chloride, etc.).

Step (e):

The compound of the formula III may be prepared by a method as shown in the following scheme:



(V)



(III)

wherein the symbols are as defined above.

Namely, the compound of the formula III may be prepared by deprotecting the compound of the formula V which is a synthetic intermediate of Step (a), followed by treating the resultant compound with an acid in an alcohol solvent.

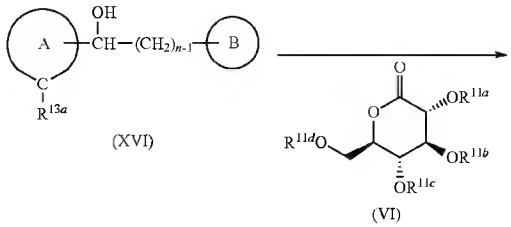
The deprotection reaction can be carried out in a manner similar to Process 1. Namely, it can be carried out by subjecting the compound V to an acid treatment, reduction, or a fluoride treatment, etc.

Following the deprotection reaction, the resultant compound is treated with an acid in a suitable alcohol. The acid includes, for example, an inorganic acid such as hydrochloric acid, nitric acid, sulfuric acid, etc., an organic acid such as p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc. The alcohol includes a conventional alkyl alcohol which does not disturb the reaction, for example, methanol, ethanol, n-propanol, i-propanol, n-butanol, etc.

Additionally, the deprotection reaction and acid treatment may be carried out in the same step, depending on the kind of the protecting group.

Step (f):

The compound of the formula IV may be prepared by a method as shown in the following scheme:



(XVI)

(VI)

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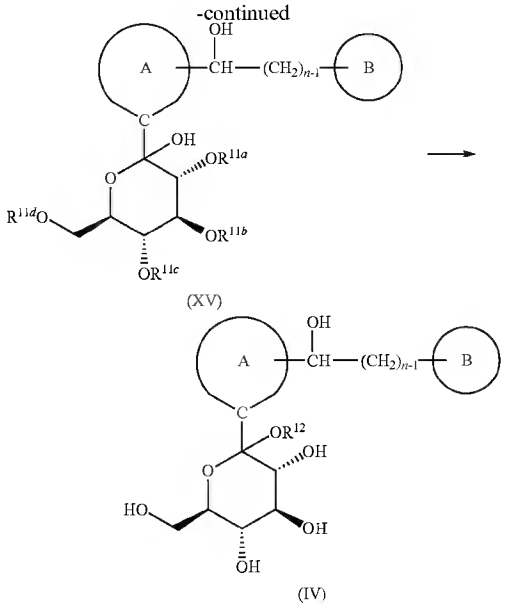


(XV)

(IV)

wherein the symbols are as defined as above.

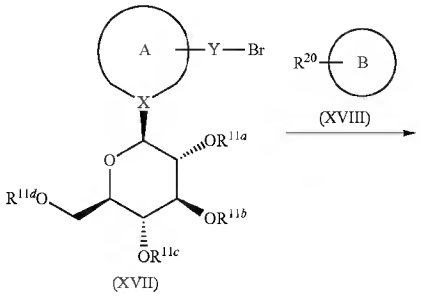
First, the compound of the formula XVI is coupled with the compound of the formula VI to give the compound of the formula XV. Then, after protecting groups are removed from the compound of the formula XV, the resultant is treated with an acid in an alcohol to give the compound of the formula IV.

The coupling reaction can be carried out in a manner similar to Step (a). Namely, the compound XVI is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc,) in a suitable solvent (e.g., diethyl ether. tetrahydrofuran, etc.), followed by reacting the resultant with the compound VI.

The removal of protecting groups and the acid treatment are carried out in a manner similar to Step (e). Namely, it can be carried out by subjecting the compound XV to reduction, acid treatment or fluoride treatment, depending on the kind of the protecting group to be removed, followed by treating the resultant with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

Step (g):

The compound of the formula II may be prepared by a method as shown in the following scheme:



(XVII)

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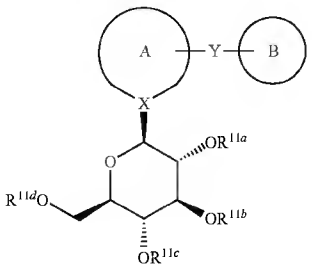


(II)

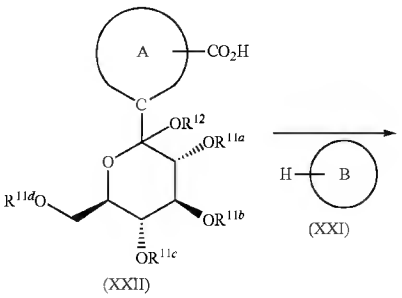
wherein R^{20} is a trialkylstannyl group, or a dihydroxyboryl group or an ester thereof, and the other symbols are as defined above. Examples of esters of dihydroxyboryl group include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol.

Namely, the compound of the formula II may be prepared by coupling the compound XVII with the compound XVIII in a suitable solvent, in the presence of a palladium catalyst, and in the presence or in the absence of a base.

The coupling reaction can be carried out in a manner similar to Step (c).

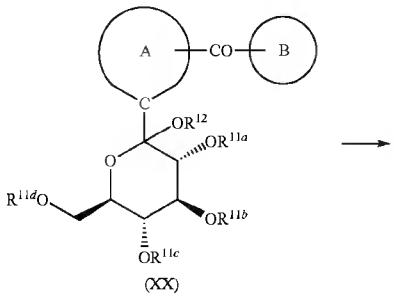
Step (h):

Among the compound of the formula II, the compound wherein n is 1 and X is a carbon atom may be prepared in a method as shown in the following scheme:



(XXII)

(XXI)



(XX)

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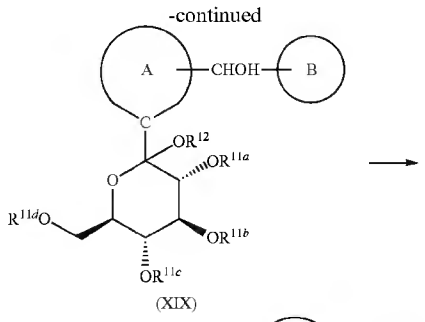
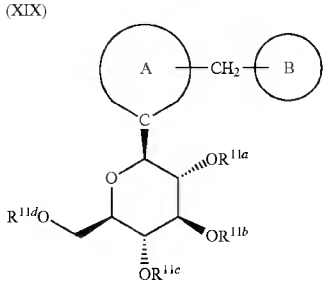


(XIX)



(II)

wherein the symbols are as defined above.

Namely, the compound of the formula II may be prepared by the following steps: (1) treating the compound of the formula XXII with a halogenating agent in a suitable solvent or in the absence of a solvent, followed by condensation of the resultant with the compound of the formula XXI in the presence of a Lewis acid to give the compound of formula XX, (2) reducing the compound of formula XX, and (3) further reducing the compound of formula XIX.

The halogenating agent includes a conventional halogenating agent such as thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.

The solvent may be any solvent which does not disturb the reaction, and for example, dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc. may be mentioned.

Further, in the present reaction, the reaction suitably proceeds by adding a catalyst such as dimethylformamide, etc.

The condensation reaction of the compound (XXII) and the compound (XXI) can be carried out according to a conventional method as known as Friedel-Crafts reaction, in the presence of a Lewis acid and in a suitable solvent.

The Lewis acid includes aluminum chloride, boron trifluoride•diethyl ether complex, tin(IV) chloride, titanium tetrachloride, etc. which are conventionally used in Friedel-Crafts reaction.

The solvent includes halogenated hydrocarbons such as dichloromethane, carbon tetrachloride, dichloroethane, etc.

The reduction of the compound of formula XX can be carried out by treating the compound (XX) with borohydrides (e.g., sodium borohydride, sodium triacetoxyborohydride, etc.) in a suitable solvent (e.g., tetrahydrofuran, etc.).

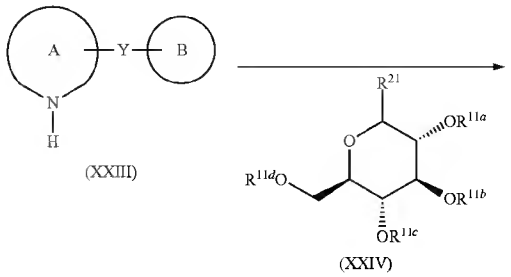
The present reaction can be carried out under cooling or with heating, for example, at a temperature of from −30° C. to 60° C.

The subsequent reduction reaction can be carried out by treating the compound of formula XIX with a silane reagent (e.g., trialkyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride•diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

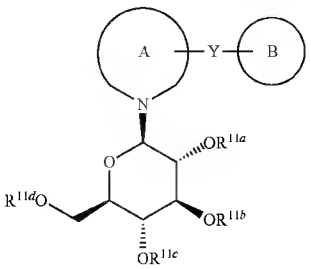
The present reaction can be carried out under cooling or with heating, for example, at a temperature of from −30° C. to 60° C.

Step (i):

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by a method as shown in the following scheme:



(XXIII) (XXIV)



(II-d)

wherein R^{21} is a leaving group, and the other symbols are as defined above.

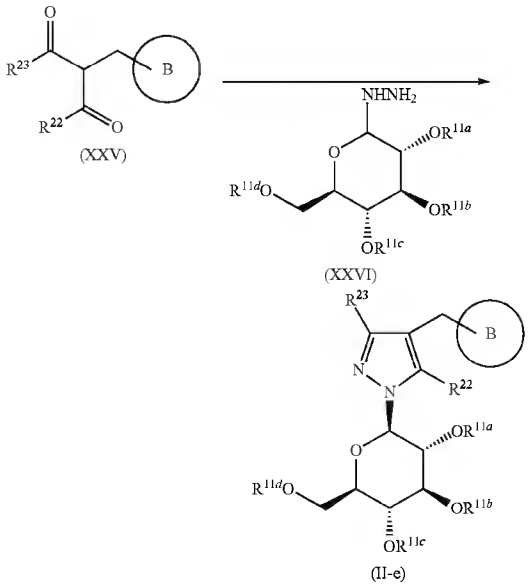
Examples of the leaving group include a halogen atom such as chlorine atom and bromine atom.

Namely, the compound of the formula II-d may be prepared by condensation of the compound of the formula XXIII with the compound of the formula XXIV.

The condensation reaction can be carried out in a suitable solvent such as acetonitrile, etc., in the presence of a base (e.g., an alkali metal hydroxide, such as potassium hydroxide, etc.).

Step (j):

Among the compound of the formula II, the compound wherein Ring A is a pyrazole substituted by a lower alkyl group, X is a nitrogen atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:

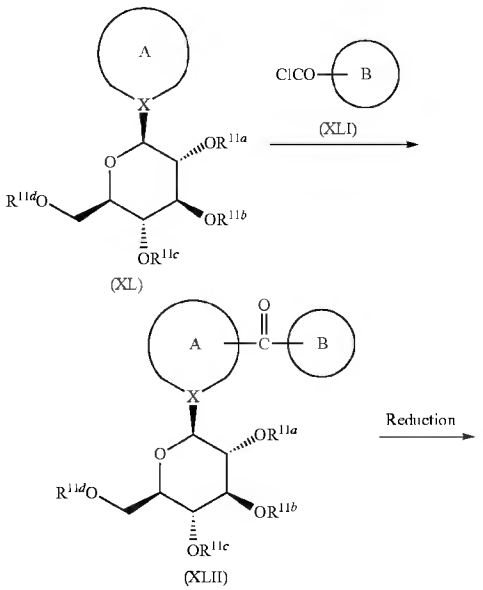


wherein R^{22} and R^{23} are each independently a lower alkyl group, and the other symbols are as defined above.

Namely, the compound II-e may be prepared by condensation of the compound of the formula XXV with the compound of the formula XXVI in a suitable solvent (e.g., ethers such as tetrahydrofuran, etc., an aromatic hydrocarbons such as toluene, etc.).

Step (k):

Among the compounds represented by formula (II), a compound wherein Y is $—CH_2—$ group can be prepared by a method as shown in the following scheme:



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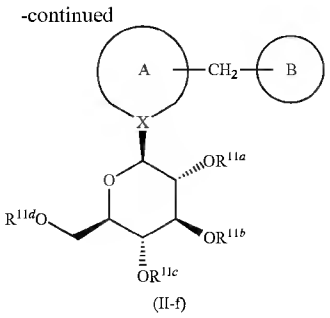


wherein the symbols are the same as defined above.

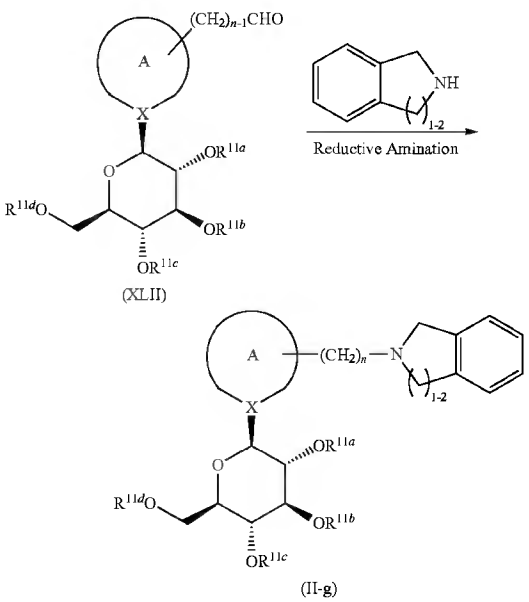
The compound (II-f) can be prepared by condensing a compound of formula (XL) with a compound of formula (XLI), and reducing a compound of formula (XLII).

The condensation reaction can be carried out in a similar manner as described in Step (h). Namely, the condensation reaction can be carried out in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, dichloroethane, etc.) in the presence of a Lewis acid (e.g., aluminum chloride, zinc chloride, titanium tetrachloride, etc.).

The reduction reaction can be carried out in a similar manner as described in Step (h).

Step (l)

Among the compounds represented by the formula (II), a compound wherein Ring B is an isoindolinyl or dihydroisoquinolinyl group can be prepared by a method as shown in the following scheme:



wherein the symbols are the same as defined above.

A compound of formula (II-g) can be prepared by reductive amination of a compound of formula (XLIII) with isoindoline or dihydroisoquinoline. Reductive amination can be carried out in a suitable solvent (e.g., tetrahydrofuran, acetic acid, dichloroethane, etc.) in the presence of a reducing agent such

as borohydrides (e.g., sodium borohydride, sodium triacetoxyborohydride) and aluminum hydrides (e.g., lithium aluminum hydride).

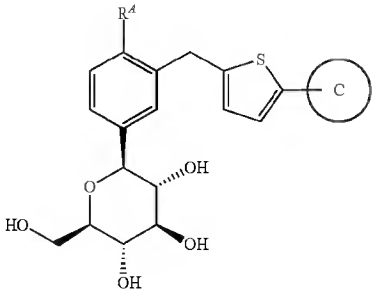
Further, the compound of the present invention may be converted to each other within the objective compounds of the present invention. Such conversion reaction may be carried out according to a conventional method, depending on the kind of the objective substituents. It may be preferable that functional groups in the compound would be protected before the conversion. The protective groups for the functional groups can be selected from conventional ones which can be removed by usual methods.

For example, a compound having as a substituent of Ring B an aryl group such as phenyl group or a heterocyclyl group may be prepared by coupling the compound in which substituents of the Ring B is a halogen atom such as a bromine atom, with a suitable phenylboronic acid, phenyltin, heterocyclylboronic acid, or heterocyclyltin.

The coupling reaction may be carried out in a manner similar to Step (c) or Step (g), or in a method as described in the following Examples.

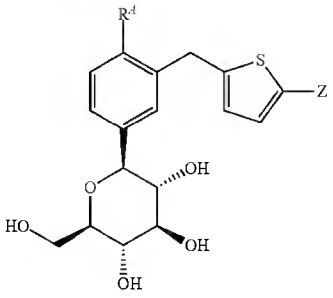
Accordingly, the compound of formula (IA'):

(IA')



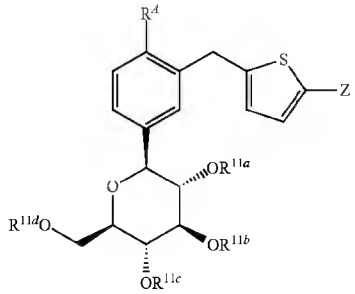
wherein the symbols are the same as defined above, can be prepared by (1) protecting a compound of formula (I-c):

(I-c)



wherein Z is a halogen atom such as chlorine, bromine and iodine atom and R^A is the same as defined above, to afford a compound of formula (II-h):

(II-h)

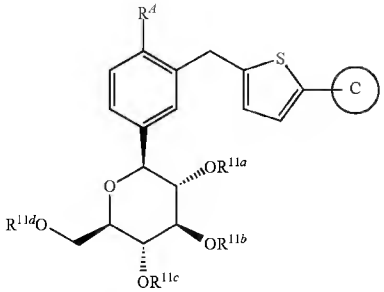


wherein the symbols are the same as defined above, (2) coupling the compound (II-h) with a compound of formula (XLIV):

(XLIV)

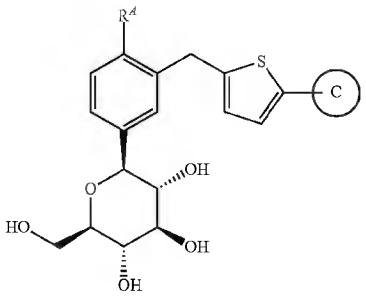
wherein R^X is B $(OH)_2$ or an ester thereof, or Sn (lower alkyl)$_3$, and Ring C is the same as defined above, to afford a compound of formula (II-A):

(II-A)



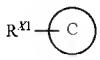
wherein the symbols are the same as defined above, and (3) removing the protecting groups. Examples of esters of $B(OH)_2$ include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol. Protection of hydroxyl groups can be carried out by conventional methods. Coupling reaction and deprotection can be carried out as described in Step (c) or (g) and Process 1, respectively.

Additionally, the compound of formula (IA'):



(IA')

wherein the symbols are the same as defined above, can be prepared by (1) converting Z group of a compound of formula (II-h) to $B(OH)_2$ or an ester thereof, (2) coupling said compound with a compound of formula (XLV):



(XLV)

wherein R^{X1} is a halogen atom such as chlorine, bromine and iodine atom and Ring C is the same as defined above, and (3) removing the protecting groups.

Examples of esters of $B(OH)_2$ include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol.

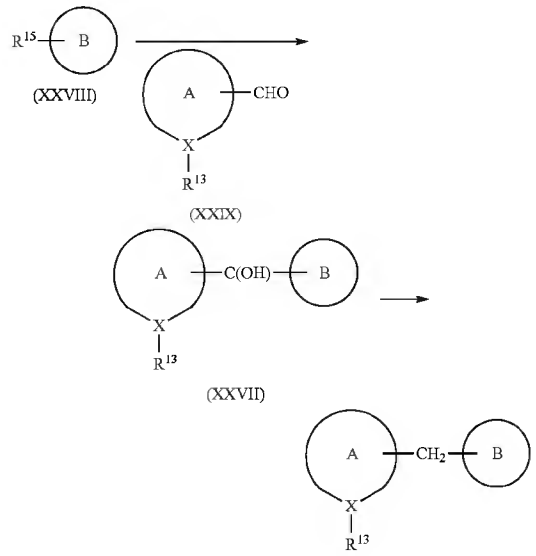
Conversion of a halogen atom to $B(OH)_2$ or an ester thereof can be carried out in a conventional method. For example, conversion of a halogen atom to $B(OH)_2$ can be carried out by treating the compound (II-h) with an alkyl lithium such as tert-butyl lithium in a suitable solvent (e.g., tetrahydrofuran), reacting the resulting compound with a tri-alkoxyborane in a suitable solvent (e.g., tetrahydrofuran), and hydrolyzing the resulting compound with an acid (such as acetic acid). And conversion of a halogen atom to an ester of $B(OH)_2$ can be carried out by treating the compound (II-h) with an alkyl lithium (such as tert-butyl lithium) in a suitable solvent (e.g., tetrahydrofuran), reacting the resulting compound with a tri-alkoxyborane in a suitable solvent (e.g., tetrahydrofuran), and reacting the resulting compound with an appropriate alcohol in a suitable solvent (e.g., tetrahydrofuran) or without solvent. Coupling reaction and deprotection can be carried out as described in Step (c) or (g) and Process 1, respectively.

In the present compound, the compound wherein heteroatom is oxidized (e.g., S-oxide, S,S-oxide, or N-oxide compounds) may be prepared by oxidizing a corresponding S-form or N-form.

The oxidation reaction can be carried out by a conventional method, for example, by treatment with an oxidizing agent (e.g., peracids such as hydrogen peroxide, m-chloroperbenzoic acid, peracetic acid, etc.) in a suitable solvent (e.g., halogenated hydrocarbons such as dichloromethane. etc.).

The starting compounds of the respective steps described above may be prepared by the methods as disclosed in Reference Examples or a process as mentioned below.

(1) Among the compounds of the formula VII, the compound wherein Y is —CH_2— may be prepared by a method as shown in the following scheme:



(XXVIII)

(XXIX)

(XXVII)

(VII-b)

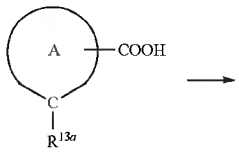
wherein R^{15} is a hydrogen atom or a halogen atom, and the other symbols are as defined above.

Namely, the compound of the formula VII-b may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXIX to give the compound of the formula XXVII, followed by reducing the obtained compound of the formula XXVII.

The coupling reaction of the present step may be carried out in a manner similar to Step (a). Namely, the compound of the formula XXVIII is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound of the formula XXIX.

The reduction reaction may be carried out in a manner similar to Step (d), more specifically, by (1) treatment with a silane reagent such as triethylsilane, etc., in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at −30° C. to 60° C., in the presence of a Lewis acid such as boron trifluoride•diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane, or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., a Lewis acid such as aluminum chloride, etc.).

(2) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:



(XXXIII)

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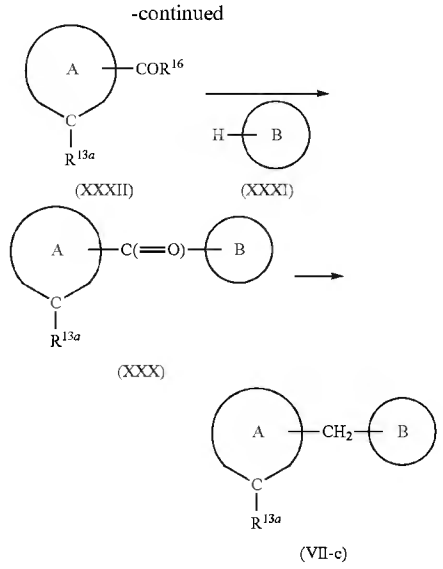


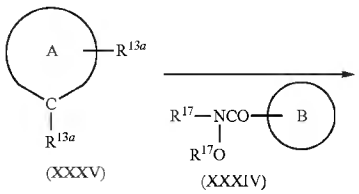
wherein R^{16} is a halogen atom, and the other symbols are as defined above.

The present process may be carried out in a manner similar to Step (h) as mentioned above.

Namely, the compound of the formula VII-c may be prepared by treating the compound of the formula XXXIII with a halogenating reagent (e.g., thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.) in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc.) or in the absence of a solvent, to give the compound of the formula XXXII, subsequently by condensing this compound with the compound of the formula XXXI in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, dichloroethane, etc.) in the presence of a Lewis acid (e.g., aluminum chloride, zinc chloride, titanium tetrachloride, etc.), to give the compound of the formula XXX, and further by reducing the obtained compound.

The reduction reaction can be carried out by treating with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride•diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

(3) Among the compounds of the formula VII, the compound wherein X is a carbon atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:



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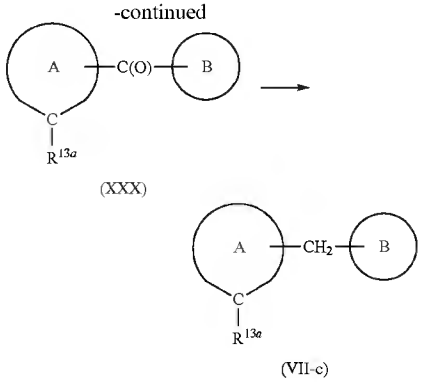


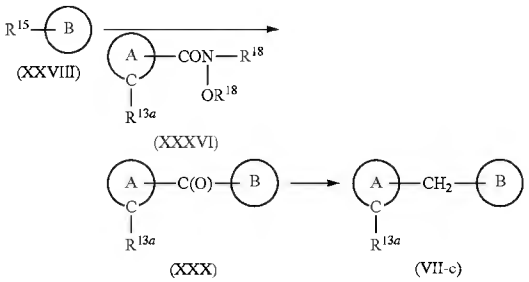
wherein R^{17} is a lower alkyl group, and the other symbols are as defined above.

The compound of the formula VII-c may be prepared by coupling the compound of the formula XXXV with the compound of the formula XXXIV to give the compound of the formula XXX, and subsequently by reducing the obtained compound.

The coupling reaction may be carried out in a manner similar to Step (a). Namely, the compound of the formula (XXV) is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the resultant with the compound (XXIV).

The reduction reaction may be carried out in a manner similar to Step (a). Namely, it can be carried out by treating the compound of formula XXX with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., boron trifluoride•diethyl ether complex, etc).

(4) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:



wherein R^{18} is a lower alkyl group, and the other symbols are as defined above.

Namely, the compound of the formula VII-c may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXXVI to give the compound of the formula XXX, and subsequently by reducing the compound.

The present process may be carried out in a manner similar to Step (3). Namely, the compound of the formula (XXVIII) is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the

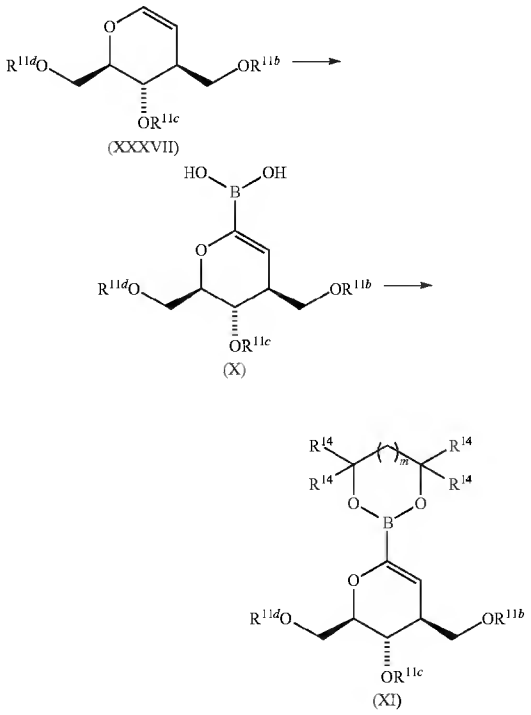
resultant with the compound (XXXVI) to give the compound of the formula (XXX). Subsequently, the compound of the formula XXX is treated with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.) in the presence of an acid (e.g., boron trifluoride•diethyl ether complex, etc), to give the compound of the formula (VII-c).

The compound of the formula XIV wherein Ring A is a benzene ring is disclosed in WO 01/27128 pamphlet.

The compound of the formula VI is disclosed in WO 01/27128 or Benhaddu, S. Czernecki et al., Carbohydr. Res., vol. 260, p. 243-250, 1994.

The compound of the formula VIII may be prepared from D-(+)-glucono-1,5-lactone according to the method disclosed in U.S. Pat. No. 6,515,117.

The compound of the formula X and the compound of the formula XI may be prepared by the following Reaction Scheme:



wherein the symbols are as defined above.

First, the compound of the formula XXXVII is lithiated with t-butyl lithium in a suitable solvent (e.g., tetrahydrofuran, etc.) under cooling (e.g., −78° C.), followed by reacting with trimethyl borate to give the compound of the formula X.

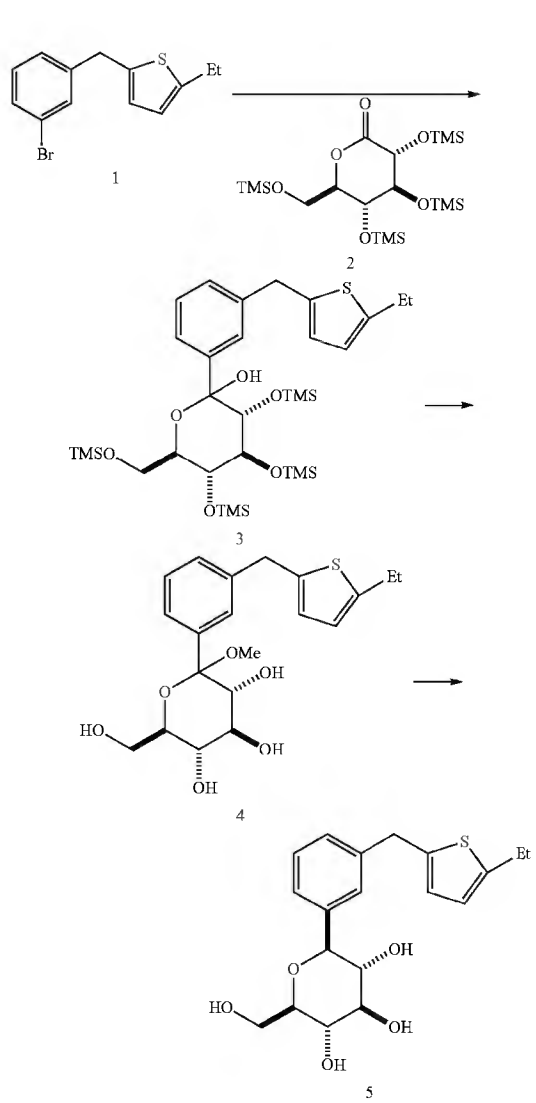
Then, the compound of the formula X is reacted with a 1,2-diol (e.g., pinacol, etc.) or 1,3-diol (e.g., 2,4-dimethyl-2,4-pentanediol, etc.) to give the compound of the formula XI.

The other starting compounds are commercially available or are described in WO 01/27128 or WO 2004/080990, or may easily be prepared by a standard method well known to an ordinary skilled person in this field.

Hereinafter, the present invention will be illustrated by Examples and Reference Examples, but the present invention should not be construed to be limited thereto.

Example 1

1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienylmethyl) benzene



In the above scheme, Me is a methyl group, Et is an ethyl group, TMSO and OTMS are a trimethylsilyloxy group.

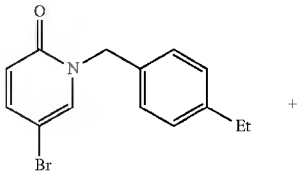
(1) 3-Bromo-(5-ethyl-2-thienylmethyl)benzene 1 (211 mg) was dissolved in tetrahydrofuran (2 ml)-toluene (4 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.29 ml), and the mixture was stirred at the same temperature for 30 minutes. Then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (233 mg) in toluene (5 ml) was

added dropwise, and the mixture was further stirred at the same temperature for one hour to give a lactol compound 3. Without isolating this compound, a solution of methanesulfonic acid (0.1 ml) in methanol (5 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give a methyl ether compound 4 (136 mg) of the lactol. APCI-Mass m/Z 412 ($M+NH_4$).

(2) A solution of the above methyl ether compound 4 (100 mg) in dichloromethane (5 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triisopropylsilane (0.16 ml), and boron trifluoride•diethyl ether complex (0.10 ml). The mixture was stirred at the same temperature for 10 minutes, and warmed. The mixture was stirred at 0° C. for 1 hour and 20 minutes, and then further stirred at room temperature for 2 hours. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienylmethyl)benzene 5 (59 mg). APCI-Mass m/Z 382 ($M+NH_4$).

Example 2

5-(β-D-glucopyranosyl)-1-(4-ethylphenylmethyl)-1H-pyridin-2-one



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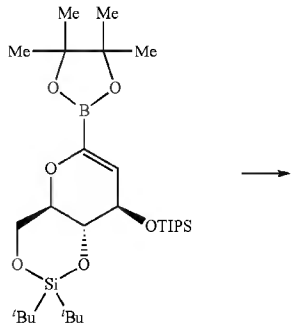

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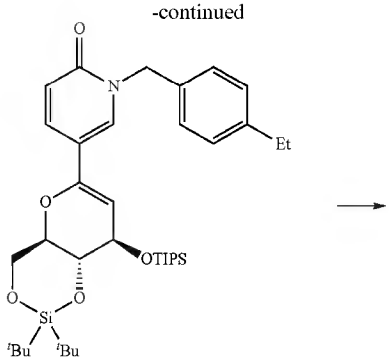

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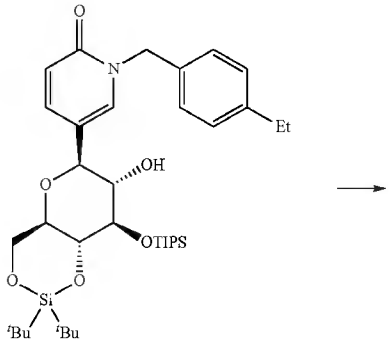

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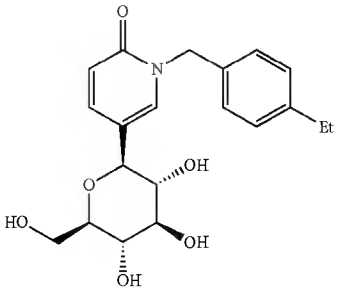

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In the above scheme, tBu is a tert-butyl group, OTIPS is a triisopropylsilyloxy group, and the other symbols are as defined above.

(1) 5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one 6 (293 mg) and boronic acid ester of glucal 7 (1.0 g) were dissolved in dimethoxyethane (5 ml). To the mixture were added bis(triphenyl)phosphine palladium(II)dichloride (35 mg) and 2M sodium carbonate (2.5 ml), and the mixture was heated with stirring under reflux under argon atmosphere for 5 hours. The mixture was cooled to room temperature, and the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-70:30) to give glucal derivative 8 (276 mg) as colorless powder. APCI-Mass m/Z 654 (M+H).

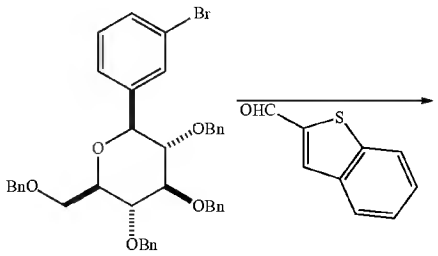
(2) A solution of glucal derivative 8 (260 mg) in tetrahydrofuran (5 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise a solution of

borane•tetrahydrofuran complex (1.13 M tetrahydrofuran solution, 1.06 ml), and the reaction solution was stirred at the same temperature overnight. A mixture of an aqueous hydrogen peroxide solution (31%, 5.0 ml) and 3N aqueous sodium hydroxide solution (5.0 ml) was added to the reaction solution, and the mixture was warmed to room temperature, and stirred for 30 minutes. To the mixture was added 20% aqueous sodium thiosulfate solution (30 ml), and the mixture was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=96:4-66:34) to give C-glucoside compound 9 (59 mg) as colorless powder. APCI-Mass m/Z 672 (M+H).

(3) The above C-glucoside compound 9 (55 mg) was dissolved in tetrahydrofuran (2 ml), and thereto was added tetrabutyl ammonium fluoride (1.0 M tetrahydrofuran solution, 0.41 ml). The mixture was heated with stirring under reflux for 3 hours under argon atmosphere, and the reaction solution was cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-88:12) to give the desired 5-(β-D-glucopyranosyl)-1-(4-ethylphenylmethyl)-1H-pyridin-2-one 10 (10 mg) as colorless powder. APCI-Mass m/Z 376 (M+H).

Example 3

1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)benzene



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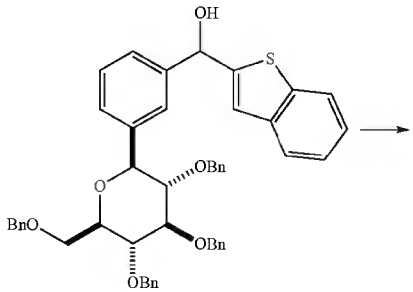

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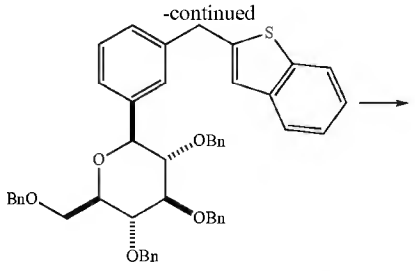

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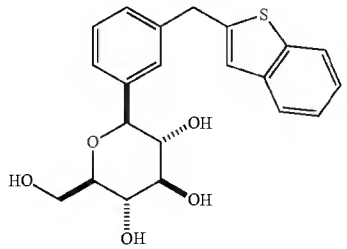


14

In the above scheme, Bn is a benzyl group.

(1) β-m-Bromophenyl-tetra-O-benzyl-C-glucoside 11 (see WO 01/27128) (1.00 g) was dissolved in diethyl ether (60 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise t-butyl lithium (1.49 M pentane solution, 0.99 ml), and the mixture was stirred at the same temperature for 10 minutes. Then, a solution of 2-formylbenzo[b]thiophene (286 mg) in diethyl ether (2 ml) was added dropwise, and the mixture was further stirred at the same temperature for 30 minutes. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was warmed to room temperature. The mixture was extracted with diethyl ether, the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-50:50) to give an alcohol compound 12 (835 mg). APCI-Mass m/Z 780 ($M+NH_4$).

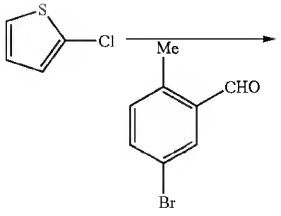
(2) A solution of the above alcohol compound 12 (820 mg) in dichloromethane (15 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (0.52 ml), and boron trifluoride•diethyl ether complex (0.20 ml). The reaction mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=94:6-75:25) to give the compound 13 (703 mg). APCI-Mass m/Z 764 ($M+NH_4$).

(3) A solution of the above compound 13 (690 mg) in dichloromethane (20 ml) was cooled to 0° C., and iodotrimethylsilane (0.66 ml) was added thereto and the mixture was stirred at room temperature for one hour. Addition of iodotrimethylsilane and stirring at room temperature were repeated in the same manner for 3 times. Total amount of the iodotrimethylsilane was summed up to 2.64 ml. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with diethyl ether twice, and washed with an aqueous sodium thiosulfate solution. The extract was dried over

magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-89:11) to give the desired 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen2-ylmethyl)benzene 14 (180 mg). APCI-Mass m/Z 404 ($M+NH_4$).

Example 4

1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene



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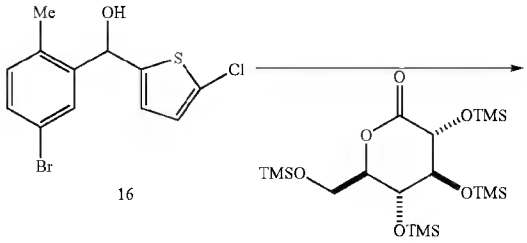
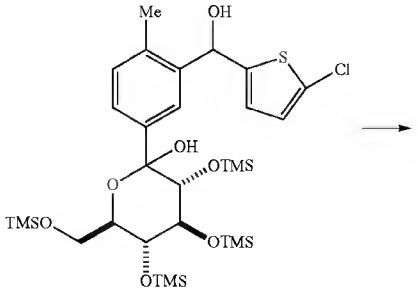


16

2



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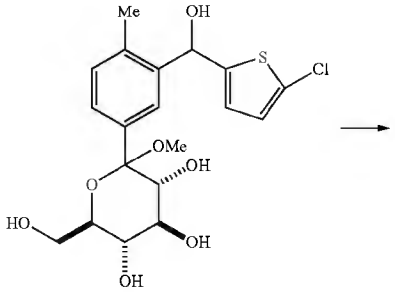

18

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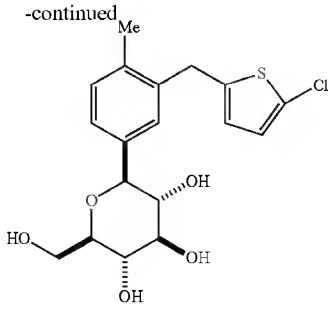


19

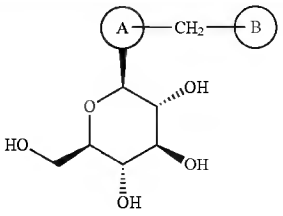
In the above scheme, the symbols are as defined above.

(1) A solution of 2-chlorothiophene (447 mg) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 2.61 ml). The mixture was stirred at the same temperature for one hour, and added dropwise thereto was a solution of 5-bromo-2-methylbenzaldehyde 15 (750 mg) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for 30 minutes to give a compound 16. Toluene (30 ml) was added, and further added dropwise thereto was n-butyl lithium (1.59 M hexane solution, 2.37 ml). The mixture was further stirred at the same temperature for 30 minutes, and a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (1.76 g) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for one and a half hours to give a lactol compound 17. Subsequently, a solution of methanesulfonic acid (1.22 ml) in methanol (25 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give a crude methyl ether compound 18, which was used in the subsequent step without further purification.

(2) A solution of the above crude methyl ether compound 18 in dichloromethane (25 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (3.01 ml), and boron trifluoride•diethyl ether complex (2.39 ml). The reaction mixture was warmed to 0° C., and stirred at the same temperature for 3 hours. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-92:8) to give the desired 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 19 (183 mg). APCI-Mass m/Z 402/404 ($M+NH_4$).

In a manner similar to the method disclosed in any of the above Examples 1 to 4, the compounds shown in Table 1 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out.

TABLE 1



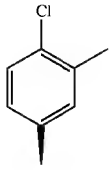
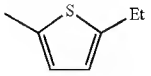
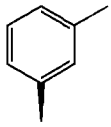
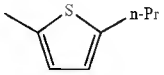
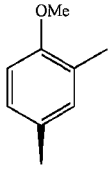
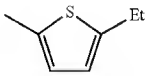
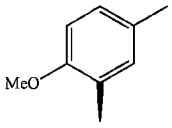
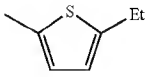
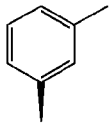
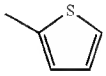
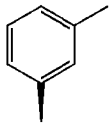
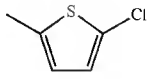
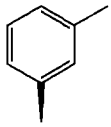
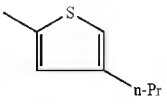
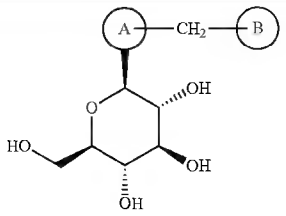
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
5			1	416/418 ($M + NH_4$)
6			1	396 ($M + NH_4$)
7			1	412 ($M + NH_4$)
8			1	412 ($M + NH_4$)
9			3	354 ($M + NH_4$)
10			3	388/390 ($M + NH_4$)
11			1	396 ($M + NH_4$)

TABLE 1-continued



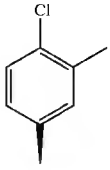
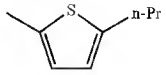
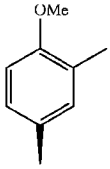
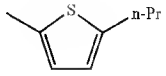
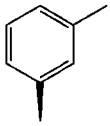
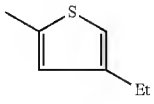
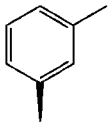
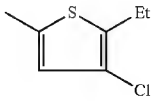
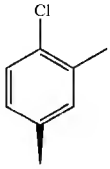
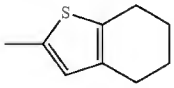
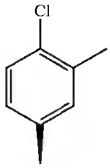
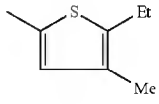
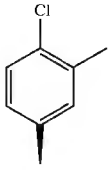
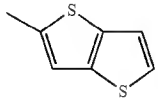
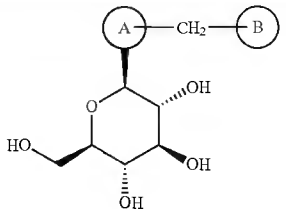
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
12			1	430/432 ($M + NH_4$)
13			1	426 ($M + NH_4$)
14			1	382 ($M + NH_4$)
15			1	416/418 ($M + NH_4$)
16			1	442/444 ($M + NH_4$)
17			1	430/432 ($M + NH_4$)
18			2	444/446 ($M + NH_4$)

TABLE 1-continued



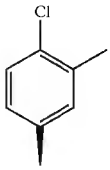
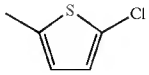
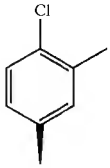
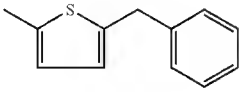
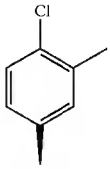
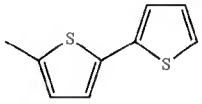
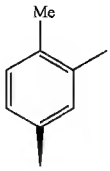
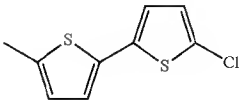
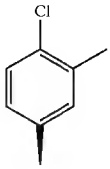
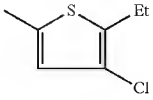
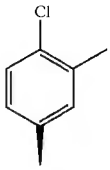
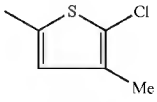
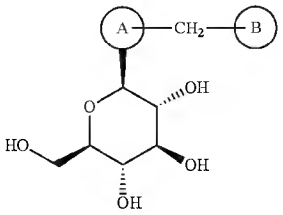
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
19			1	422/424 ($M + NH_4$)
20			1	478/480 ($M + NH_4$)
21			2	470/472 ($M + NH_4$)
22			1	484/486 ($M + NH_4$)
23			1	450/452 ($M + NH_4$)
24			4	436/438 ($M + NH_4$)

TABLE 1-continued



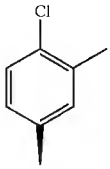
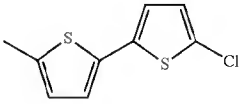
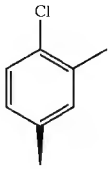
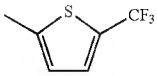
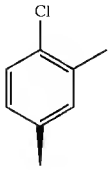
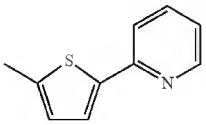
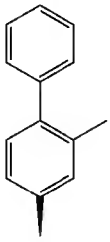
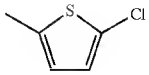
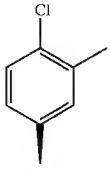
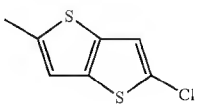
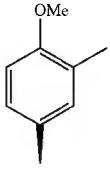
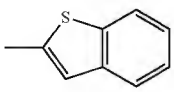
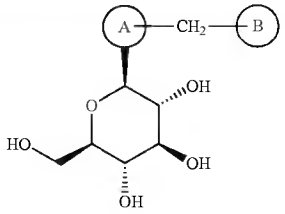
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
25			1	504/506 ($M + NH_4$)
26			2	456/458 ($M + NH_4$)
27			1	448/450 ($M + NH_4$)
28			1	464/466 ($M + NH_4$)
29			4	478/480 ($M + NH_4$)
30			1	434 ($M + NH_4$)

TABLE 1-continued



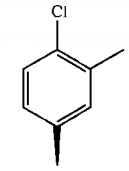
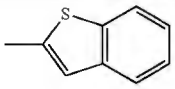
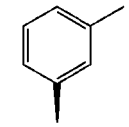
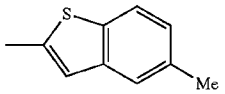
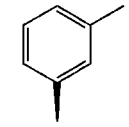
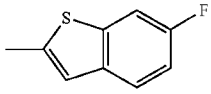
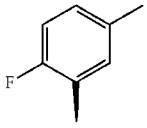
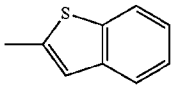
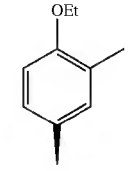
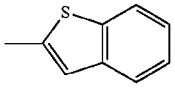
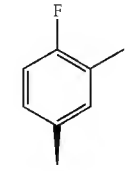
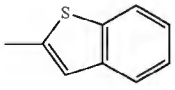
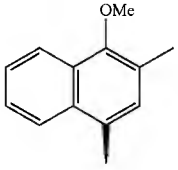
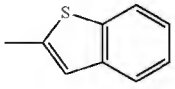
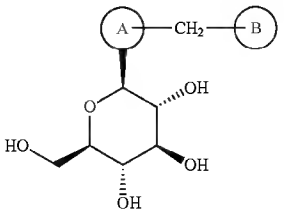
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
31			1	438/440 ($M + NH_4$)
32			1	418 ($M + NH_4$)
33			1	422 ($M + NH_4$)
34			1	422 ($M + NH_4$)
35			1	448 ($M + NH_4$)
36			1	422 ($M + NH_4$)
37			1	484 ($M + NH_4$)

TABLE 1-continued



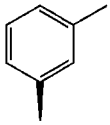
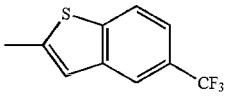
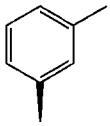
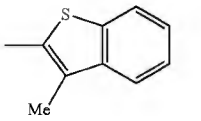
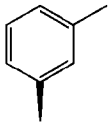
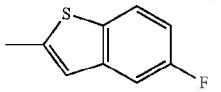
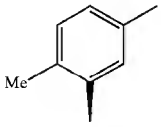
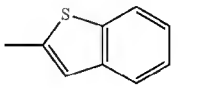
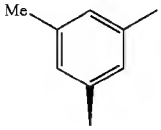
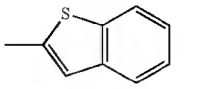
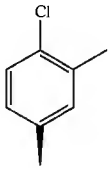
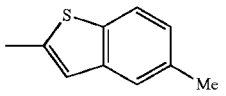
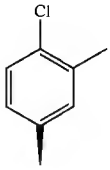
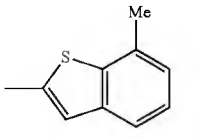
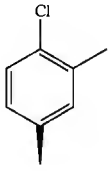
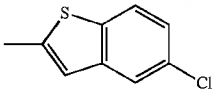
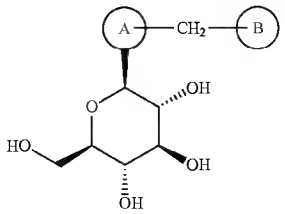
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
38			1	472 ($M + NH_4$)
39			1	418 ($M + NH_4$)
40			1	422 ($M + NH_4$)
41			2	418 ($M + NH_4$)
42			1	418 ($M + NH_4$)
43			1	452/454 ($M + NH_4$)
44			1	452/454 ($M + NH_4$)
45			1	472/474 ($M + NH_4$)

TABLE 1-continued



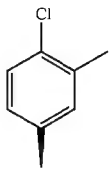
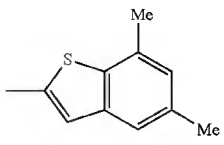
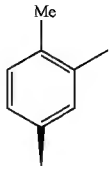
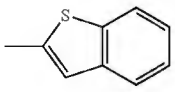
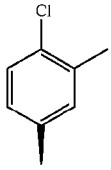
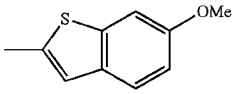
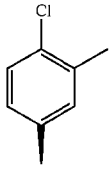
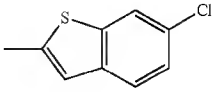
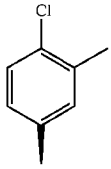
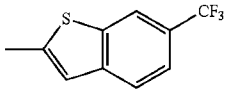
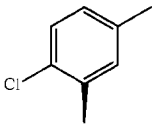
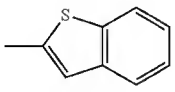
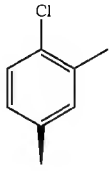
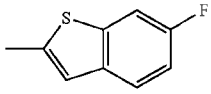
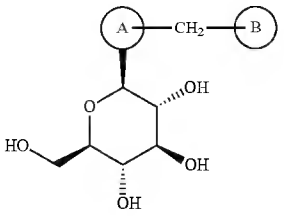
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
46			1	466/468 ($M + NH_4$)
47			1	418 ($M + NH_4$)
48			1	468/470 ($M + NH_4$)
49			1	472/474 ($M + NH_4$)
50			2	506/508 ($M + NH_4$)
51			2	438/440 ($M + NH_4$)
52			2	456/458 ($M + NH_4$)

TABLE 1-continued



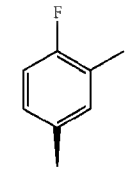
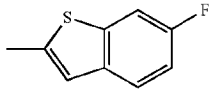
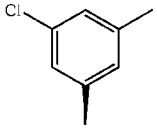
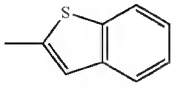
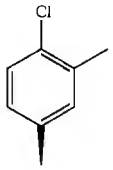
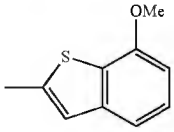
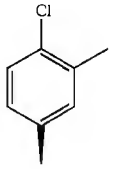
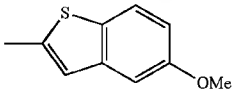
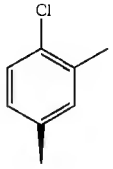
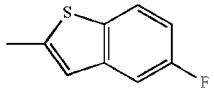
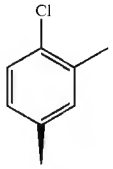
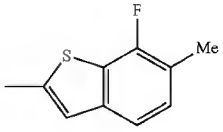
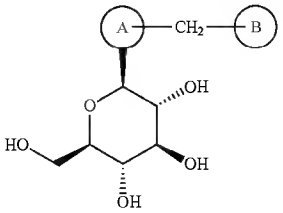
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
53			2	440 (M + NH_4)
54			2	438/440 (M + NH_4)
55			1	468/470 (M + NH_4)
56			1	468/470 (M + NH_4)
57			2	456/458 (M + NH_4)
58			1	470/472 (M + NH_4)

TABLE 1-continued



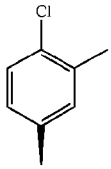
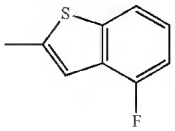
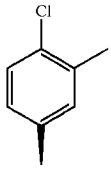
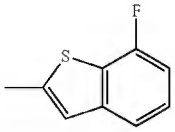
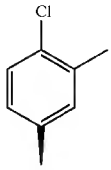
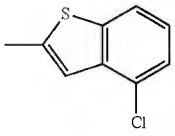
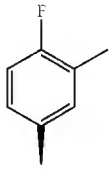
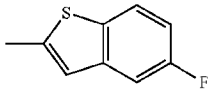
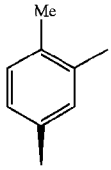
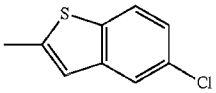
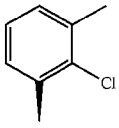
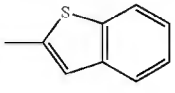
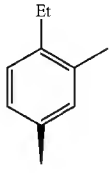
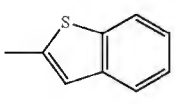
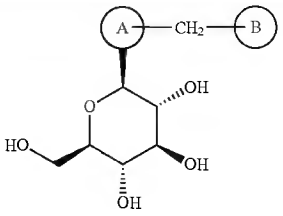
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
59			2	456/458 ($M + NH_4$)
60			2	456/458 ($M + NH_4$)
61			2	472/474 ($M + NH_4$)
62			2	440 ($M + NH_4$)
63			4	452/454 ($M + NH_4$)
64			2	438/440 ($M + NH_4$)
65			1	432 ($M + NH_4$)

TABLE 1-continued



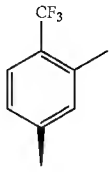
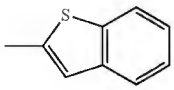
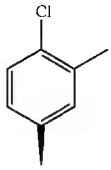
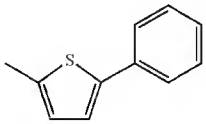
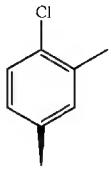
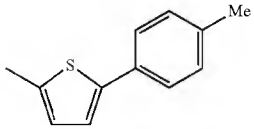
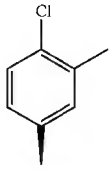
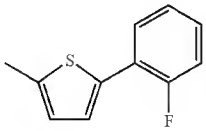
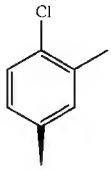
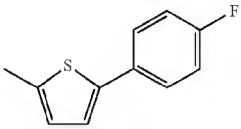
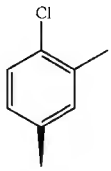
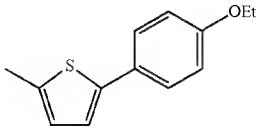
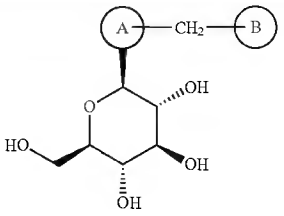
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
66			2	472 ($M + NH_4$)
67			1	464/466 ($M + NH_4$)
68			1	478/480 ($M + NH_4$)
69			1	482/484 ($M + NH_4$)
70			1	482/484 ($M + NH_4$)
71			1	508/510 ($M + NH_4$)

TABLE 1-continued



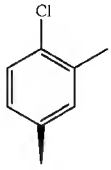
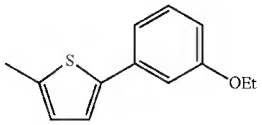
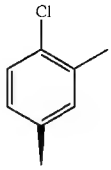
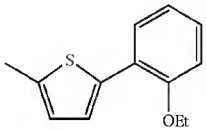
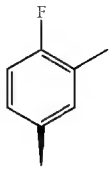
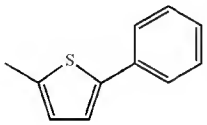
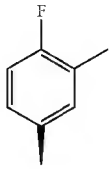
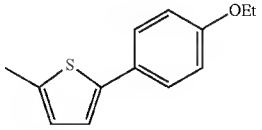
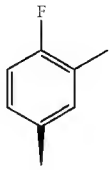
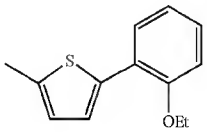
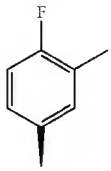
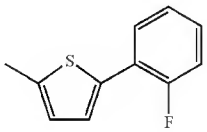
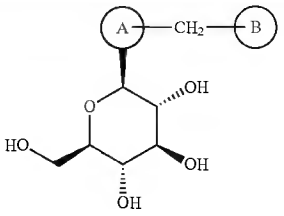
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
72			1	508/510 ($M + NH_4$)
73			1	508/510 ($M + NH_4$)
74			1	448 ($M + NH_4$)
75			1	492 ($M + NH_4$)
76			1	492 ($M + NH_4$)
77			1	466 ($M + NH_4$)

TABLE 1-continued



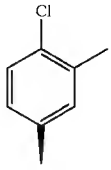
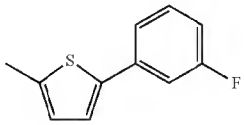
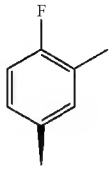
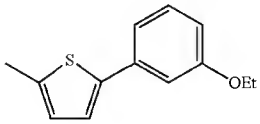
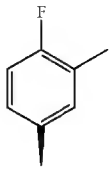
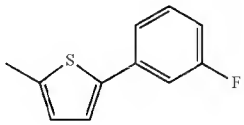
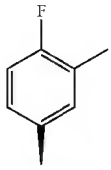
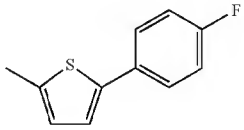
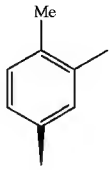
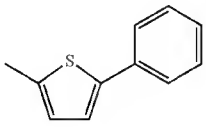
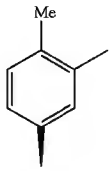
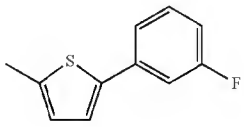
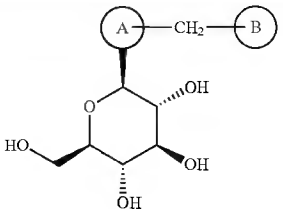
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
78			1	482/484 ($M + NH_4$)
79			1	492 ($M + NH_4$)
80			1	466 ($M + NH_4$)
81			1	466 ($M + NH_4$)
82			1	444 ($M + NH_4$)
83			1	462 ($M + NH_4$)

TABLE 1-continued



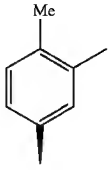
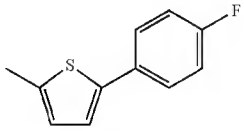
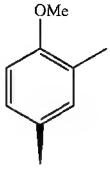
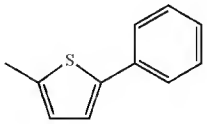
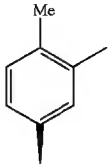
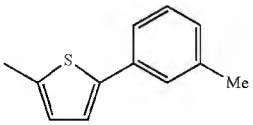
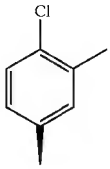
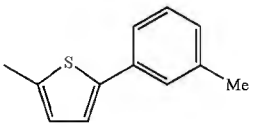
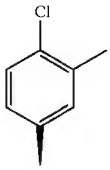
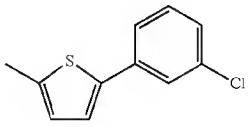
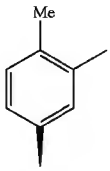
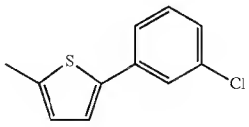
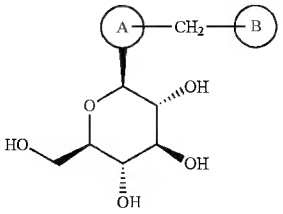
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
84			1	462 ($M + NH_4$)
85			2	460 ($M + NH_4$)
86			1	458 ($M + NH_4$)
87			1	478/480 ($M + NH_4$)
88			1	498/500 ($M + NH_4$)
89			1	478/480 ($M + NH_4$)

TABLE 1-continued



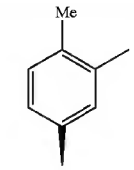
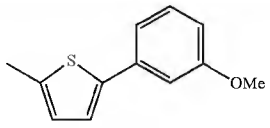
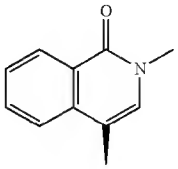
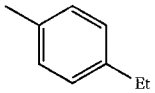
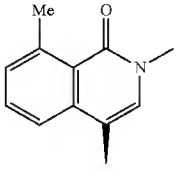
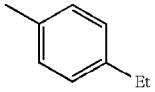
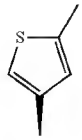
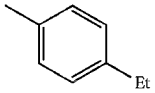
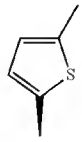
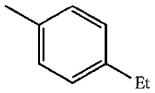
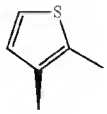
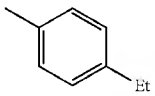
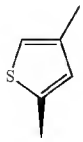
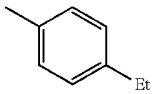
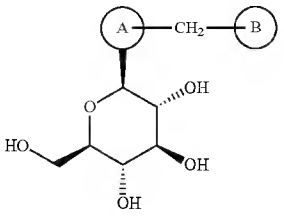
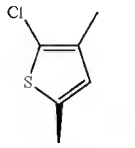
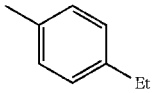
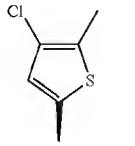
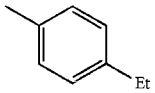
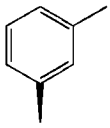
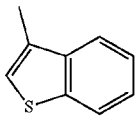
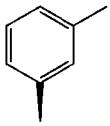
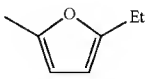
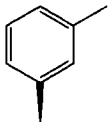
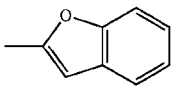
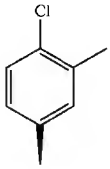
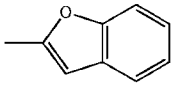
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
90			1	474 (M + NH_4)
91			2	426 (M + H)
92			2	440 (M + H)
93			2	382 (M + NH_4)
94			2	382 (M + NH_4)
95			2	382 (M + NH_4)
96			2	382 (M + NH_4)

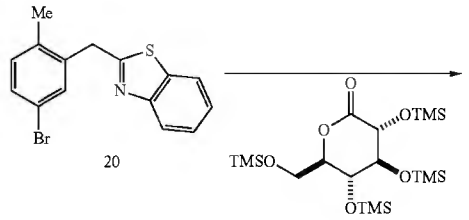
TABLE 1-continued



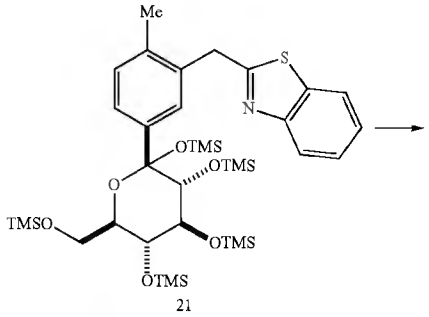
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
97			2	416/418 (M + NH_4)
98			2	416/418 (M + NH_4)
99			1	404 (M + NH_4)
100			1	366 (M + NH_4)
101			1	388 (M + NH_4)
102			1	422/424 (M + NH_4)

Example 103

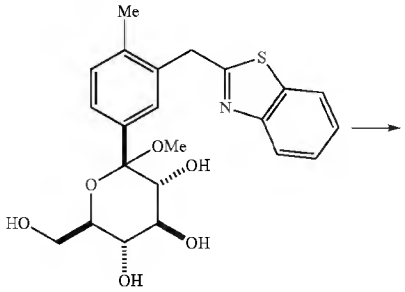
1-(β-D-glucopyranosyl)-3-(benzothiazol-2-ylm-ethyl)-4-methylbenzene



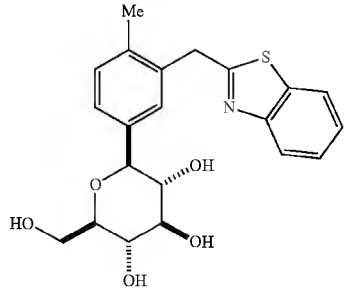
20 2



21



22



23

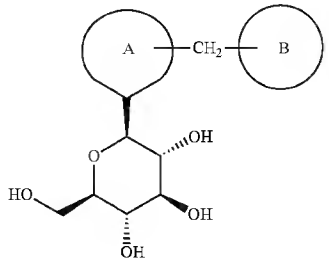
In the above scheme, the symbols are as defined above.

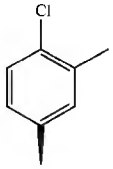
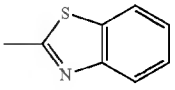
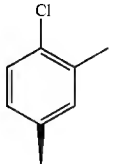
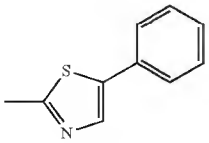
(1) 1-(benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene 20 (495 mg) was dissolved in tetrahydrofuran (5 ml)-toluene (10 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.67 ml), and successively was added dropwise t-butyl lithium (2.44 M pentane solution, 1.57 ml). The mixture was stirred at the same temperature for 10 minutes, and then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (2.17 g) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for 15 minutes to give a lactol compound 21. Without isolating this compound, a solution of methanesulfonic acid (1.5 ml) in methanol (25 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give a methyl ether compound 22, which was used in the subsequent step without further purification.

(2) A solution of the above methyl ether compound 22 in dichloromethane (20 ml)-acetonitrile (10 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (1.24 ml), and boron trifluoride diethyl ether complex (0.99 ml). The mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-85:15) to give 1-(β-D-glucopyranosyl)-3-(benzothiazol-2-ylmethyl)-4-methylbenzene 23 (200 mg) as colorless powder. APCI-Mass m/Z 402 (M+H).

In a manner similar to Examples 103, the compounds shown in Table 2 below were prepared from corresponding starting materials.

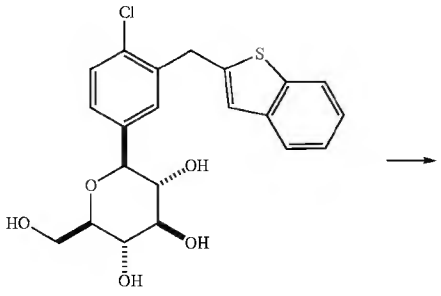
TABLE 2



Examples	Ring A	Ring B	APCI-Mass (m/Z)
104			422/424 (M + H)
105			480/482 ($M + NH_4$)

Example 106

1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxybenzo[b] thiophen-2-ylmethyl)benzene



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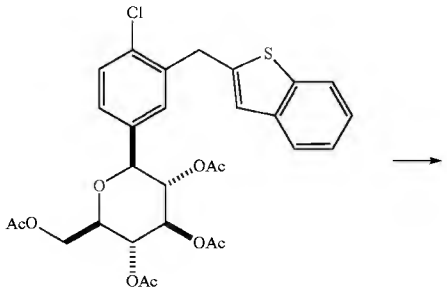
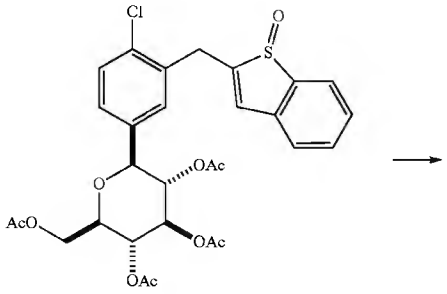
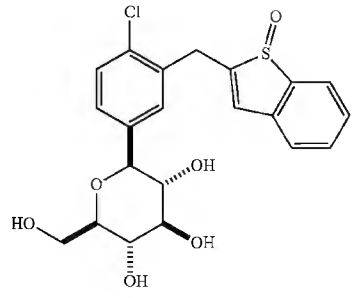


25



26



27

In the above scheme, AcO and OAc are an acetyloxy group. (1) The compound 24 (9.61 g) obtained in Example 31 was dissolved in chloroform (100 ml), and to the mixture were added acetic anhydride (21.6 ml), pyridine (18.5 ml), and 4-dimethylaminopyridine (128 mg), and the mixture was

stirred at room temperature for 3.5 days. Then, Chloroform was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (200 ml). The solution was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over magnesium sulfate, and treated with activated carbon. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol to give a tetraacetate compound 25 (6.14 g). APCI-Mass m/Z 606/608 ($M+NH_4$).

(2) The above tetraacetate compound 25 (1.00 g) was dissolved in dichloromethane (20 ml), and under ice-cooling, m-chloroperbenzoic acid (439 mg) was added thereto, and the mixture was stirred a room temperature overnight. m-Chloroperbenzoic acid was further added thereto, and the mixture was stirred again at room temperature overnight. The reaction mixture was washed successively with 10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution, and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1-1:2) to give a sulfoxide compound 26 (295 mg). APCI-Mass m/Z 622/624 ($M+NH_4$).

(3) The above sulfoxide compound 26 (293 mg) was dissolved in a mixture of methanol (10 ml)-tetrahydrofuran (5 ml), and sodium methoxide (28% methanol solution, 2 drops) was added thereto, and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give 1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxybenzo[b] thiophen-2-yl methyl)benzene as pale yellow powder. APCI-Mass m/Z 454/456 ($M+NH_4$).

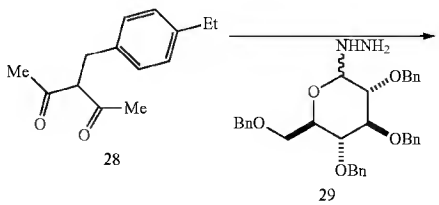
Example 107

1-(β-D-glucopyranosyl)-4-chloro-3-(1,1-dioxybenzo[b]thiophen-2-ylmethyl)benzene

The target compound was prepared in a manner similar to Example 106. APCI-Mass m/Z 470/472 ($M+NH_4$).

Example 108

3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-pyrazole



28 29

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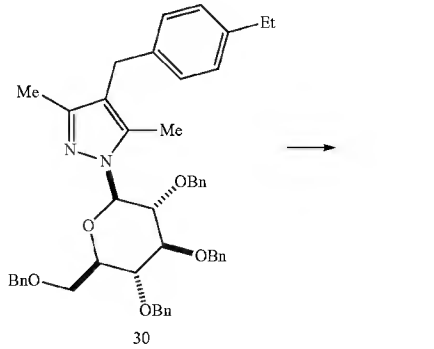
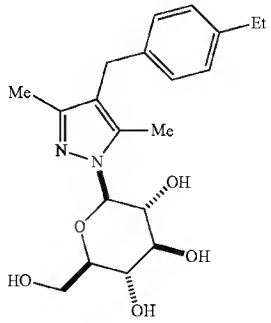


30



31

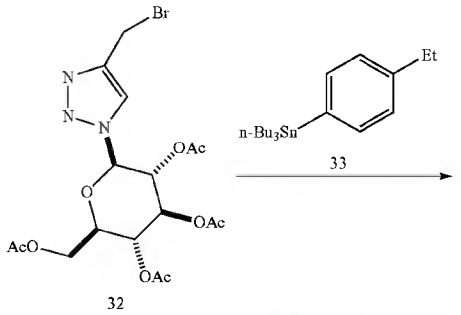
In the above scheme, the symbols are as defined above.

(1) 3-(4-ethylphenylmethyl)-2,4-pentanedione 28 (700 mg) and 2,3,4,6-tetra-O-benzyl-α,β-D-glucosehydrazone 29 (1.70 g) (See Schmidt, R. R. et al., *Liebigs Ann. Chem.* 1981, 2309) were dissolved in tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 18 hours under argon atmosphere. The solvent was evaporated under reduced pressure, and the residue was dissolved in toluene (20 ml), and the mixture was heated with stirring under reflux for 2 hours. The mixture was left alone until it was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=90:10-65:35) to give 3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)pyrazole 30 (299 mg) as a pale yellow semisolid. APCI-Mass m/Z 737 (M+H).

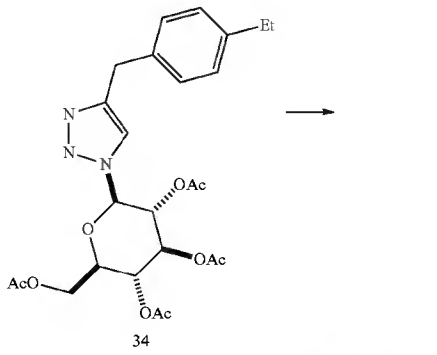
(2) The above tetrabenzyl compound 30 (294 mg) was dissolved in a mixture of ethanol (5 ml) and tetrahydrofuran (4 ml), and added thereto was palladium hydroxide (100 mg), and the mixture was stirred at room temperature for 16 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was crystallized from diethyl ether to give the desired 3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole 31 (118 mg) as colorless powder. APCI-Mass m/Z 377 (M+H).

Example 109

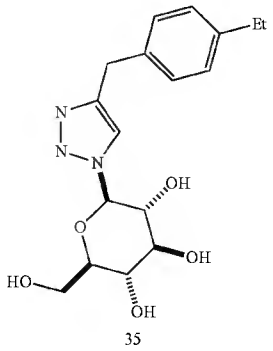
4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-1,2,3-triazole



32



34



35

In the above scheme, n-Bu is n-butyl group, and other symbols are as defined above.

(1) A solution of 4-(bromomethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,3-triazole 32 (500 mg) (See Federico G. H. et al., *J. Med. Chem.* (1979) 29, 496), tri-n-butyl(4-ethylphenyl)tin 33 (604 mg) and tetrakis(triphenylphosphine)palladium (0) (59 mg) in tetrahydrofuran (10 ml) was stirred under heating at 70° C. for 12 hours under argon atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and then, an aqueous potassium fluoride solution was added thereto and the mixture was stirred at room temperature for one hour. Insoluble materials were filtered off, and the filtrate was washed with

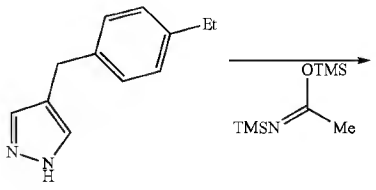
water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,3-triazole 34 (90 mg) as a colorless solid. APCI-Mass m/Z 518 (M+H).

(2) From the above tetraacetate compound 34, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)1,2,3-triazole 35 was prepared in a manner similar to Example 106-(3) as a colorless solid.

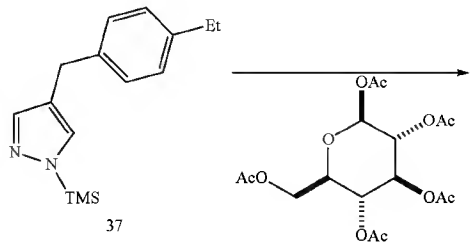
APCI-Mass m/Z 350 (M+H).

Example 110

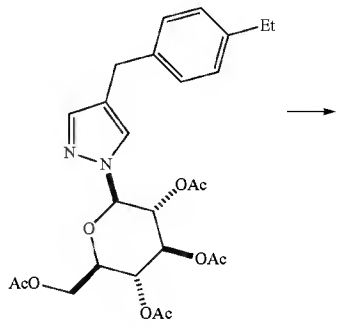
4-(4-Ethylphenylmethyl)-1-(β-D-glucopyranosyl) pyrazole



36



37 38



39

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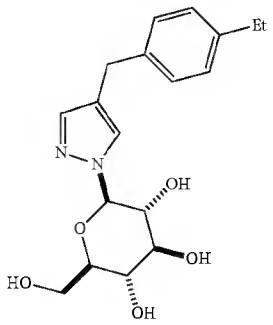


40

In the above scheme, TMS is a trimethylsilyl group, and other symbols are as defined above.

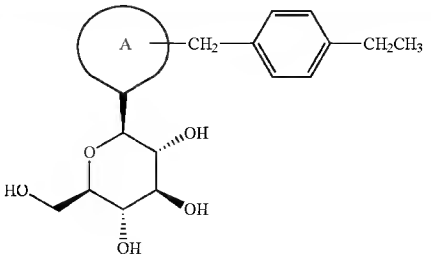
(1) To a solution of 4-(4-ethylphenylmethyl)pyrazole 36 (495 mg) in acetonitrile (2.0 ml) was added N,O-bis(trimethylsilyl)acetamide (1.05 ml), and the mixture was stirred under heating at 60° C. for 2.5 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure to give crude 4-(4-ethylphenylmethyl)-1-trimethylsilylpyrazole 37, which was used in the subsequent reaction without further purification.

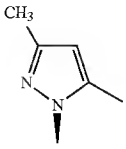
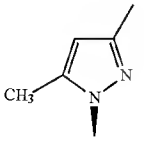
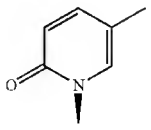
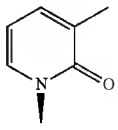
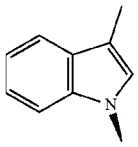
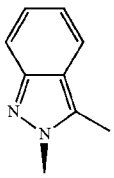
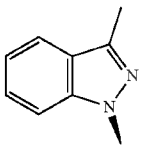
(2) The above N-silyl compound 37 was dissolved in dichloroethane (7.0 ml), and added thereto were molecular sieve 4A powder (500 mg), 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose 38 (1.04 g) and trimethylsilyl trifluoromethanesulfonate (0.51 ml). The mixture was stirred under heating at heating at 80° C. for 3 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and insoluble materials were filtered off. Subsequently, the filtrate was poured into a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with dichloromethane, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20-50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) pyrazole 39 (610 mg) as a colorless semisolid. APCI-Mass m/Z 517 (M+H).

(3) From the above tetraacetate compound 39, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole 40 was prepared in a manner similar to Example 106-(3) as colorless oil. APCI-Mass m/Z 349 (M+H).

In a manner similar to Example 110, the compounds shown in Table 3 below were prepared from corresponding starting materials.

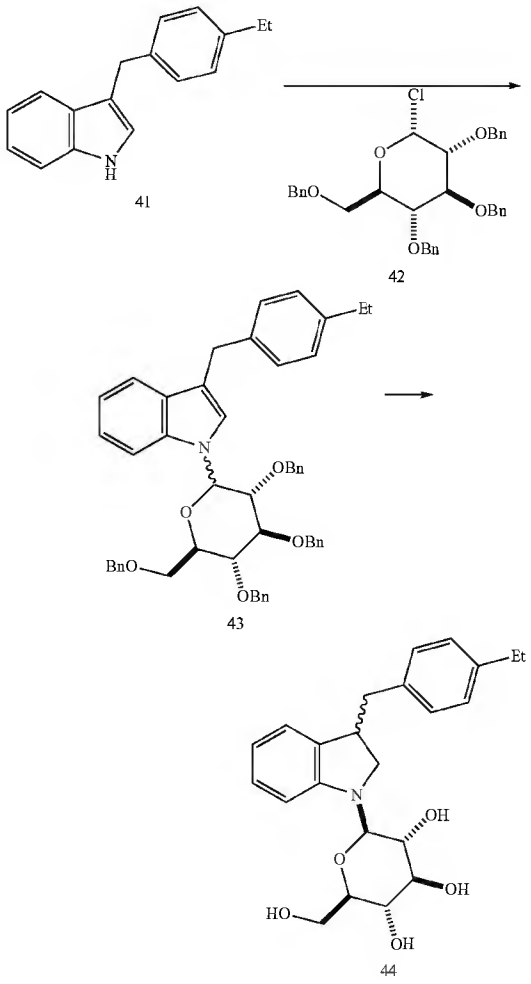
TABLE 3



Examples	Ring A	APCI-Mass (m/Z)
111		363 (M + H)
112		363 (M + H)
113		376 (M + H)
114		393 (M + NH_4)
115		415 (M + NH_4)
116		399 (M + H)
117		399 (M + H)

Example 118

3-RS-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-2,3-dihydroindole



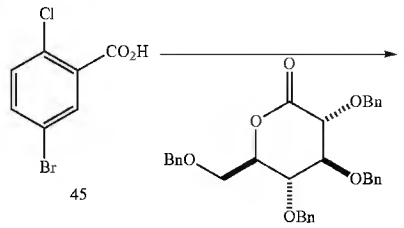
In the above scheme, the symbols are as defined above.

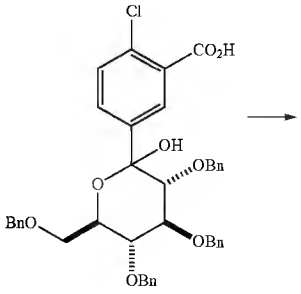
(1) To a suspension of potassium hydroxide power (953 mg) and sodium sulfate (6.0 g) in acetonitrile (50 ml) was added 3-(4-ethylphenylmethy)-1H-indole 41 (500 mg), and the mixture was stirred at room temperature for one hour under argon atmosphere. To the reaction mixture was added a solution of benzylchloro-α-D-glucose 42 (3.0 g) (see Cicchillo R. M. et al., *Carbohydrate Research* (2000) 328, 431) in acetonitrile (20 ml), and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 2N aqueous hydrochloric acid solution, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give 3-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-αβ-D-glucopyranosyl)-1H-indole 43 (1.04 g) as a pale yellow syrup. APCI-Mass m/Z 758 (M+H).

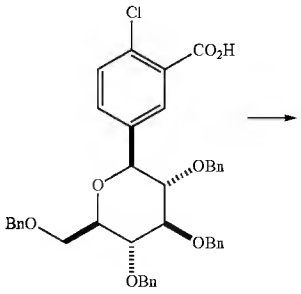
(3) From the above tetrabenzyl compound 43, the desired 3-RS-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-2,3-dihydroindole 44 was prepared in a manner similar to Example 108-(2) as pale pink powder. APCI-Mass m/Z 400 (M+H).

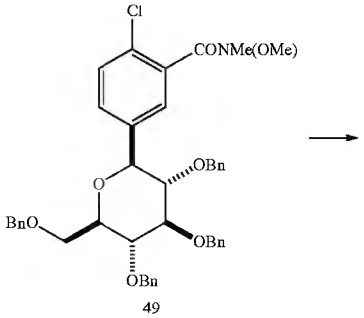
Example 119

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene









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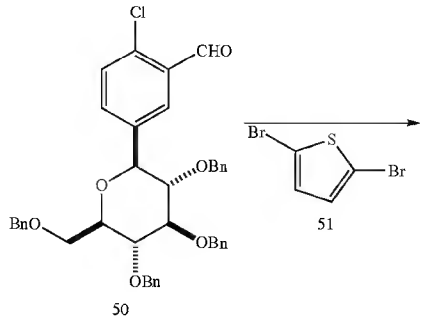

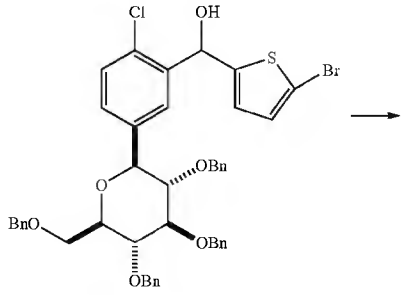

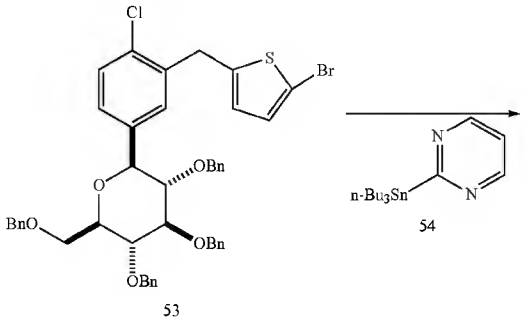

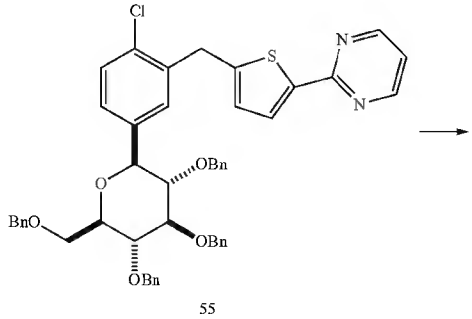

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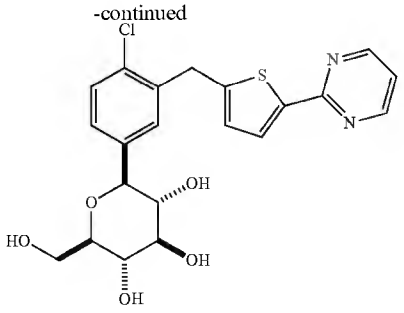


56

In the above scheme, the symbols are as defined above.

(1) To a solution of 5-bromo-2-chlorobenzoic acid 45 (1.22 g) in a mixture of tetrahydrofuran (20 ml)-toluene (20 ml) was added dropwise n-butyl lithium (2.44 M hexane solution, 4.26 ml) at −78° C. under argon atmosphere. The mixture was stirred at −78° C. for 30 minutes, and added dropwise thereto was a solution of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone 46 (2.16 g) in toluene (10 ml), and the mixture was further stirred at the same temperature for 2 hours. To the mixture was added a saturated aqueous ammonium chloride solution, and the mixture was warmed to room temperature. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude compound 47 as oil, which was used in the subsequent step without further purification.

(2) The above crude compound 47 was dissolved in dichloromethane (30 ml), and thereto were added dropwise triisopropylsilane (2.46 ml) and boron trifluoride•diethyl ether complex (1.52 ml) at −78° C. Subsequently, the mixture was stirred at 0° C. for one hour, and added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was further stirred for 20 minutes. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=100:1-50:1) to give a compound 48 (1.41 g) as oil.

(3) The compound 48 (1.41 g) was dissolved in dichloromethane (10 ml), and added thereto was oxalyl chloride (2 ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The compound was dissolved in chloroform (10 ml), and added dropwise to a solution of N,O-dimethylhydroxyamine hydrochloride (390 mg) and triethyl amine (1.12 ml) in chloroform (10 ml) at 0° C. The mixture was stirred at room temperature overnight, and the reaction mixture was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel

column chromatography (hexane:ethyl acetate=4:1-2:1) to give a compound 49 (784 mg) as pale yellow oil. APCI-Mass m/Z 739/741 ($M+NH_4$).

(4) The compound 49 (1.22 g) was dissolved in tetrahydrofuran (20 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise diisobutylaluminum hydride (1.0 M toluene solution, 4.2 ml), and the mixture was stirred at the same temperature for 3 hours. Added thereto was 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) to give a compound 50 (771 mg) as pale yellow oil. APCI-Mass m/Z 680/682 ($M+NH_4$).

(5) 2,5-dibromothiophene 51 (1.31 g) was dissolved in tetrahydrofuran (30 ml) and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.59 M hexane solution, 2.01 ml), and the mixture was stirred at the same temperature for 30 minutes. Added dropwise thereto was a solution of the above compound 50 (2.40 g) in tetrahydrofuran (15 ml), and the mixture was stirred at −78° C. for 2 hours. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate and washed with brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-4:1) to give a compound 52 (2.62 mg) as pale brown oil. APCI-Mass m/Z 842/844 ($M+NH_4$).

(6) The compound 52 was treated in a manner similar to Example 3-(2) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 as a pale yellow solid. APCI-Mass m/Z 826/828 ($M+NH_4$).

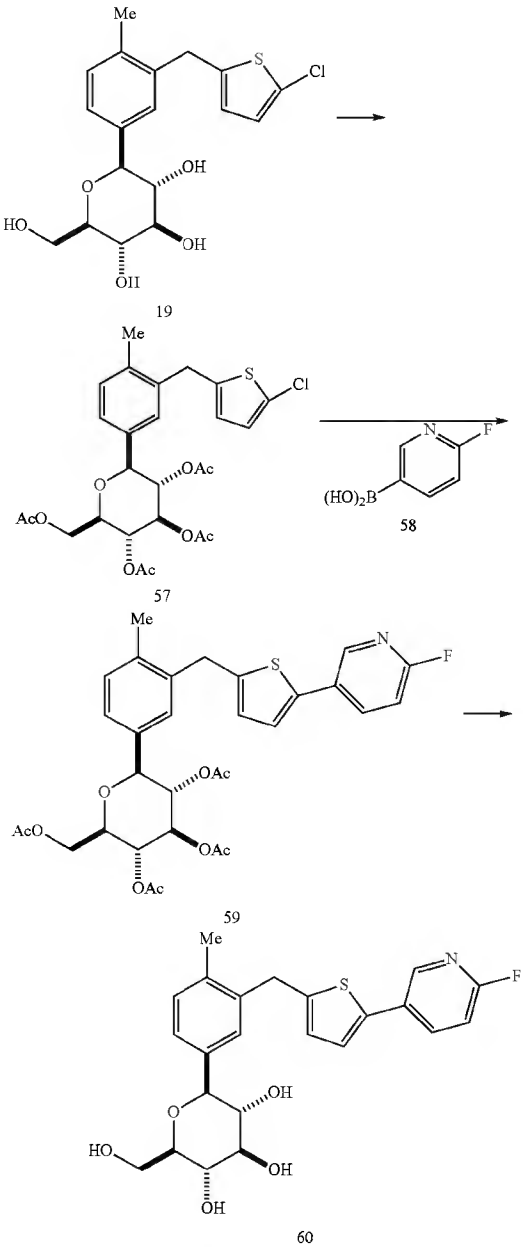
(7) A mixed solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 (200 mg), tri-n-butyl(2-pyrimidinyl)tin 54 (137 mg) and bis(triphenylphosphine)palladium(II)dichloride (9 mg) in N-methyl-2-pyrrolidinone (5 ml) was stirred at 100° C. four 7 hours under argon atmosphere. The mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and subsequently with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-2:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 55 (93 mg) as pale brown oil. APCI-Mass m/Z 826/828 ($M+NH_4$).

(8) To a solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 55 (90 mg) in ethanethiol (1.5 ml) was added boron trifluoride•ether complex (0.42 ml) at 0° C., and the mixture was stirred at room temperature overnight. The mixture was cooled again to 0° C., and added thereto were a saturated aqueous sodium hydrogen carbonate solution and an aqueous sodium thiosulfate solution. The mixture was extracted with ethyl acetate and tetrahydrofuran, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1-9:1) to give the desired 1-(β-D-glucopyranosyl)-4-

chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 56 (27 mg) as pale yellow powder. APCI-Mass m/Z 449/451 (M+H).

Example 120

1-(β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene



In the above scheme, the symbols are as defined as above.

(1) The compound 19 obtained in Example 4 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 as colorless crystals. APCI-Mass m/Z 570/572 ($M+NH_4$).

(2) A solution of the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (200 mg), 6-fluoropyridine-3-boronic acid 58 (117 mg), tri-tert-butylphosphine•tetrafluoroboric acid adduct (24 mg), potassium fluoride (80 mg) and tris(dibenzylideneacetone) dipalladium (0) (27 mg) in tetrahydrofuran (8 ml) was stirred at room temperature for 2 days under argon atmosphere. Added thereto was a saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-70:30) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59 (44 mg) as colorless crystals. APCI-Mass m/Z 631 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59 (39 mg) was dissolved in 1,4-dioxane (4 ml)-tetrahydrofuran (4 ml), and added thereto was 2N sodium hydroxide (2 ml). The mixture was stirred at room temperature for one hour. The mixture was made acidic by addition of an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and then dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the desired 1-(β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 60 (34 mg) as colorless powder. APCI-Mass m/Z 463 ($M+NH_4$).

Example 121

1-(β-D-glucopyranosyl)-4-chloro-3-(2-(5-phenyl-2-thienyl)ethyl)benzene

The target compound was obtained in a manner similar to Example 1, from 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)-ethyl)benzene. APCI-Mass m/Z 478/480 ($M+NH_4$).

Example 122

1-(β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120 (1) and 3-dimethylaminophenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 638 (M+H).

(2) the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 470 (M+H).

Example 123

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chloroben-

zene 53 (1.24 g) obtained in Example 119-(6), 3-cyanophenylboronic acid (270 ml), bis(triphenylphosphine)palladium (II)dichloride (54 mg) and 2M aqueous sodium carbonate solution (2.3 ml) in 1,2-dimethoxyethane (12 ml) was heated under reflux for 4 hours. The mixture was diluted with ethyl acetate and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:1-5:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene (1.12 g) as colorless oil. APCI-Mass m/Z 849/851 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 3-(3) to give the target compound as colorless powder. APCI-Mass m/Z 489/491 ($M+NH_4$).

Example 124

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (600 mg) obtained in Example 120-(1), tri-n-butyl(5-pyrimidinyl)tin (600 mg), tri-tert-butylphosphine•tetrafluoroboric acid adduct (116 mg), cesium fluoride (414 mg), and tris(dibenzylideneacetone) dipalladium (0) (91 mg) in 1,4-dioxane (18 ml) was heated under reflux at 100° C. for 3 hours under argon atmosphere. Insoluble materials were filtered off, and the filtrate was diluted with ethyl acetate and washed with brine. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-40:60) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene (266 mg) as colorless crystals. APCI-Mass m/Z 597 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 106-(3) to give the target compound as colorless powder. APCI-Mass m/Z 429 (M+H).

Example 125

1-(β-D-glucopyranosyl)-4-chloro-3-(2-phenyl-5-thiazolyl-methylbenzene

The target compound was prepared in a manner similar to Example 1, starting from 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene. APCI-Mass m/Z 448/450 (M+H).

Example 126

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-pyridyl)-2-thienylmethyl)benzene

(1) 1-(β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene obtained in Example 19 was used and treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 590/592 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene and tri-n-butyl(3-pyridyl)tin were used and treated in a manner similar to Example 124 to give the target compound as colorless powder. APCI-Mass m/Z 448/450 (M+H).

Example 127

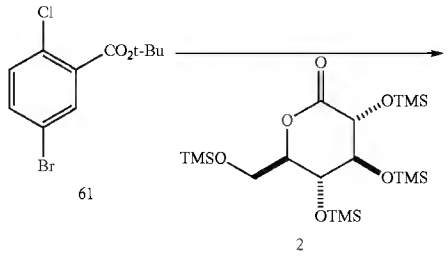
1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120-(1) and 3-cyanophenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-cyano phenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 637 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-methylbenzene was used and treated in a manner similar to Example 106-(3) to give the target compound as colorless powder. APCI-Mass m/Z 469 ($M+NH_4$).

Example 128

1-(β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene



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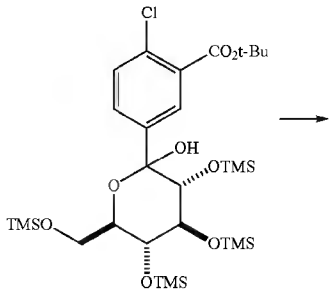

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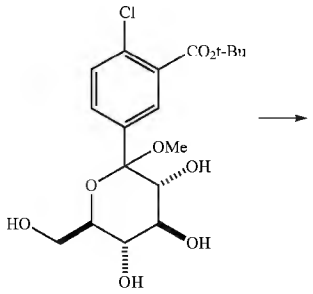

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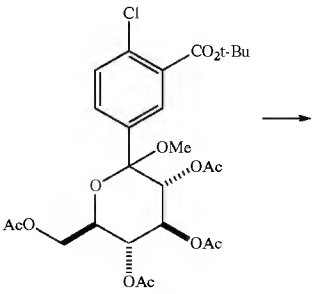

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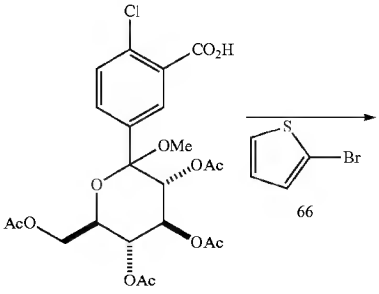

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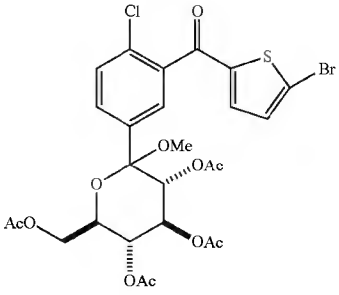

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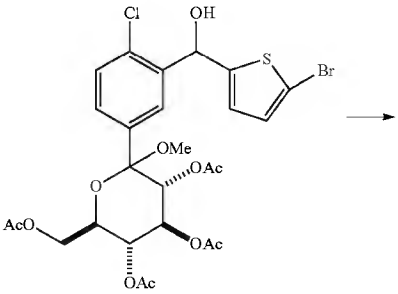

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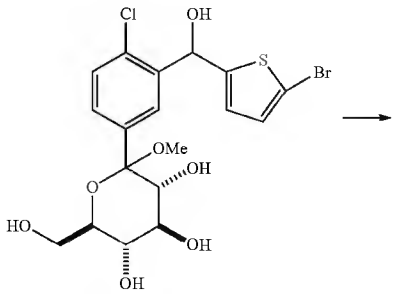

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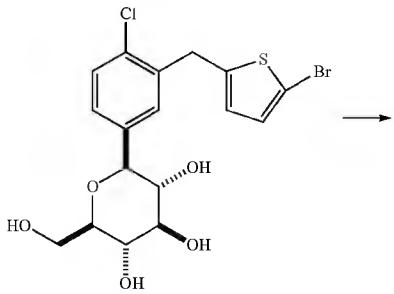

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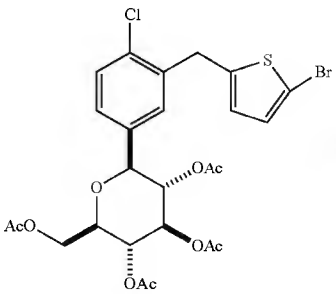

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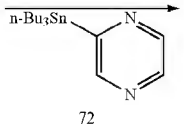

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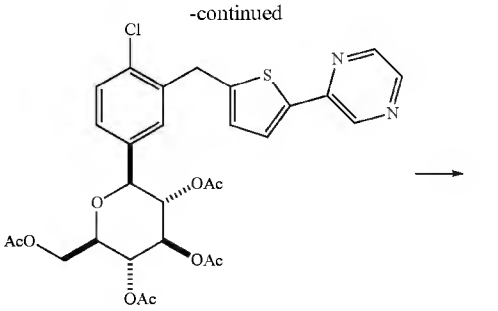

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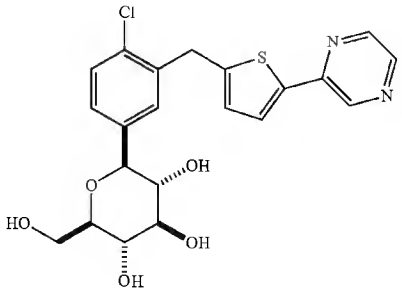


74

In the above scheme, the symbols are as defined above.

(1) A solution of mesityl bromide (4.74 g) in tetrahydrofuran (100 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise t-butyl lithium (1.43 M pentane solution, 33 ml). The mixture was stirred at −30 to −20° C. for one hour, and then, a mixed solution of t-butyl 5-bromo-2-chlorobenzoate 61 (4.94 g) and 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (11.10 g) in tetrahydrofuran (70 ml) was added dropwise thereto at −78° C. The mixture was stirred at the same temperature for one hour to give a compound 62. Without isolating this compound, a solution of methanesulfonic acid (3.75 ml) in methanol (50 ml) was added to the reaction solution, and the mixture was stirred at room temperature for 18 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution at 0° C., and the mixture was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give a methyl ether compound 63 (4.55 g) of the lactol as pale yellow powder. APCI-Mass m/Z 422/424 ($M+NH_4$).

(2) The compound 63 was treated in a manner similar to Example 106-(1) to give the compound 64. APCI-Mass m/Z 590/592 ($M+NH_4$).

(3) A solution of the above compound 64 (7.10 g) in formic acid (50 ml) was stirred at 50° C. for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene, twice, to give a compound 65 as colorless powder. Without further purification, this compound was dissolved in dichloromethane (50 ml). Added thereto were oxalyl chloride (1.3 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was dissolved in dichloroethane (50 ml), without further purification. To the solution was added 2-bromothiophene 66 (2.63 g) and the mixture was cooled to 0° C. Added gradually thereto was aluminum chloride (8.26 g), and subsequently, the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-cold water, and the mixture was extracted with ethyl acetate. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1-5:1) to give a compound 67 (7.01 g) as pale yellowish powder. APCI-Mass m/Z 678/680 ($M+NH_4$).

(4) The above ketone compound 67 (7.01 g) was dissolved in ethanol (50 ml), and thereto was added sodium borohydride (401 mg), and the mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with successively with water, 2N aqueous hydrochloride acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a compound 68 as pale yellow powder, which was dissolved in methanol (50 ml) without further purification. To the solution, sodium methoxide (28% methanol solution, 5 drops) was added, and then the mixture was stirred at room temperature for 2.5 hours. The solvent was evaporated under reduced pressure to give a deacetylated compound 69 as pale yellow powder. Without further purification, it was dissolved in dichloromethane (170 ml)-acetonitrile (70 ml), and added thereto was triethylsilane (10.2 ml), and the mixture was cooled to 0° C. Added dropwise thereto was boron trifluoride•diethyl ether complex (8.1 ml), and the mixture was stirred at room temperature for 5 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 70 as pale brown powder. Without further purification, this was dissolved in dichloromethane (30 ml), and added thereto were acetic anhydride (10.0 ml), pyridine (8.57 ml) and 4-dimethylaminopyridine (258 mg), and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate, and the solution was washed successively with water, 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The solution was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (3.17 g) as colorless crystals. APCI-Mass m/Z 634/636 ($M+NH_4$).

(5) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (600 mg) was dissolved in 1,4-dioxane (11 ml). Added thereto were tri-n-butyl(pyrazinyl)tin 72 (720 mg), tetrakis(triphenylphosphine)palladium (0) (206 mg) and copper (I) iodide (51 mg), and the mixture was stirred under heating at 100° C. for 1.5 hours, under irradiation by a microwave (500 W). The mixture was diluted with ethyl acetate, the insoluble materials were filtered off, and the filtrate was washed with water. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-30:70), and crystallized from hexane-diethyl ether to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopy-

ranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 (263 mg) as pale yellow crystals. APCI-Mass m/Z 617/619 (M+H).

(6) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 was used and treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienyl methyl)benzene 74 as colorless powder. APCI-Mass m/Z 449/451 (M+H).

Example 129

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)-benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482/484 ($M+NH_4$).

Example 130

1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120-(1) and 3-formylphenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 640 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) 3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene (100 mg) was dissolved in dichloromethane (2 ml), and added thereto was (diethylamino) sulfur trifluoride (0.30 ml). The mixture was stirred at room temperature overnight. Water was added to the mixture and the mixture was extracted with chloroform. The extract was washed with brine and dried over magnesium sulfate, and then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-1:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methyl benzene (82 mg). APCI-Mass m/Z 662 ($M+NH_4$).

(3) The above obtained 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienyl methyl)-4-methylbenzene was used and treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

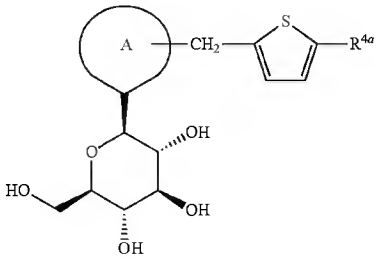
Example 131

1-(β-D-glucopyranosyl)-4-chloro-3-(6-phenyl-3-pyridylmethyl)benzene

5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 442/444 (M+H).

In a manner similar to the method disclosed in any of the above Examples, the compounds shown in Table 4 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out in the similar manner.

TABLE 4



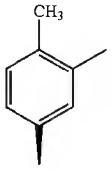
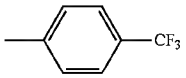
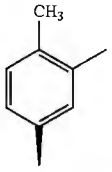
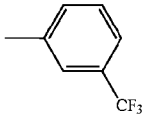
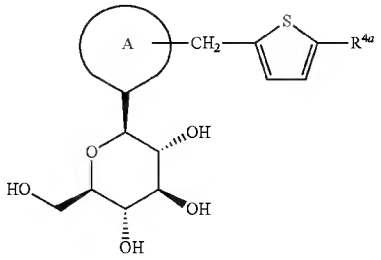
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
132			1	512 ($M + NH_4$)
133			1	512 ($M + NH_4$)

TABLE 4-continued



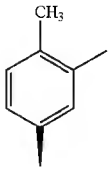
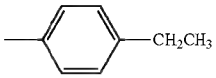
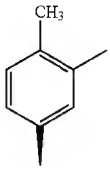
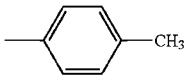
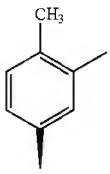
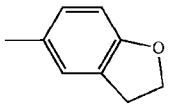
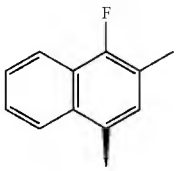
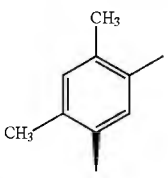
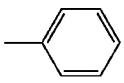
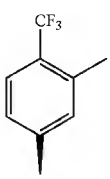
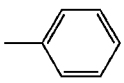
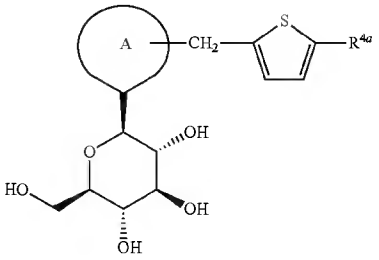
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
134			4	472 ($M + NH_4$)
135			4	458 ($M + NH_4$)
136			4	486 ($M + NH_4$)
137		Cl	1	456/458 ($M + NH_4$)
138			2	458 ($M + NH_4$)
139			2	498 ($M + NH_4$)

TABLE 4-continued



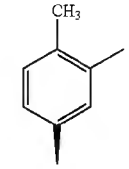
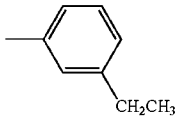
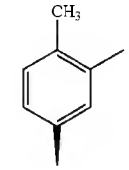
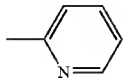
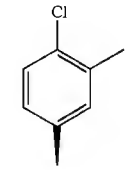
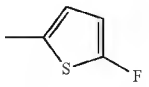
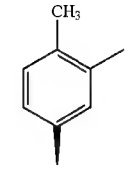
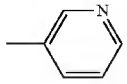
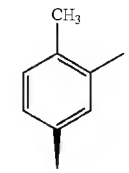
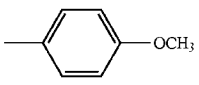
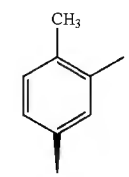
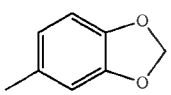
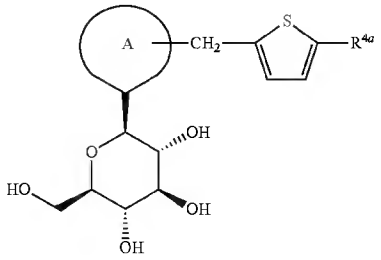
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
140			1	472 (M + NH_4)
141			1	428 (M + H)
142			4	488/490 (M + NH_4)
143			1	428 (M + H)
144			1	474 (M + NH_4)
145			1	488 (M + NH_4)

TABLE 4-continued



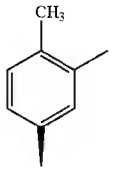
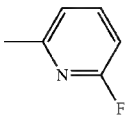
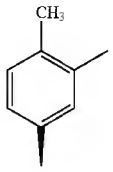
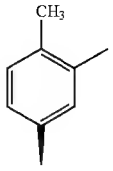
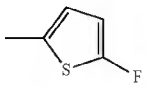
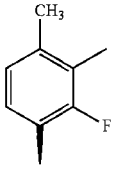
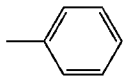
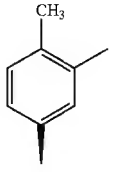
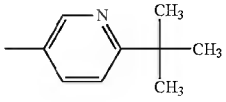
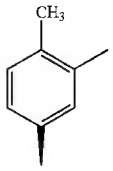
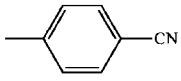
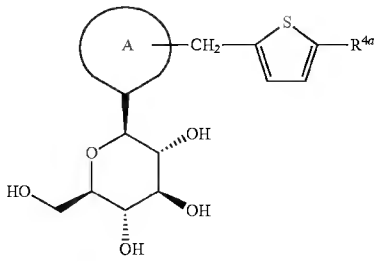
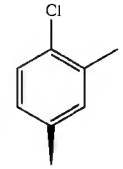
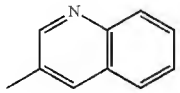
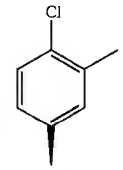
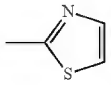
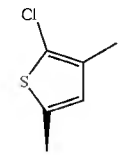
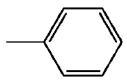
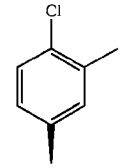
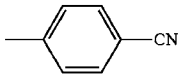
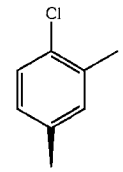
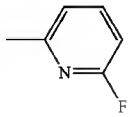
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
146			1	463 ($M + NH_4$)
147		CF_3	1	436 ($M + NH_4$)
148			1	468 ($M + NH_4$)
149			1	462 ($M + NH_4$)
150			103	484 ($M + H$)
151			124	469 ($M + NH_4$)

TABLE 4-continued



Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
152			122	498/500 (M + H)
153			128	454/456 (M + H)
154			2	470/472 (M + NH_4)
155			122	489/491 (M + NH_4)
156			122	466/468 (M + H)

Example 157

1-(β-D-glucopyranosyl)-4-chloro-3-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 (M+NH_4).

Example 158

1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (12.0 g) obtained in Example 120-(1) was dissolved in tetrahydrofuran (120 ml) and methanol (360 ml), and added thereto were triethylamine (24.2 ml) and 10% palladium carbon catalyst (wet, 3.6 g), and the mixture was stirred at room temperature for 18 hours under hydrogen atmosphere under normal pres-

sure. The insoluble materials were filtered off, washed with tetrahydrofuran, and the filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform, washed successively with a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution and water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene (7.79 g) as colorless crystals. APCI-Mass m/Z 536 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl3-(2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 368 ($M+NH_4$).

Example 159

1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene (11.08 g) obtained in Example 158-(1) was dissolved in chloroform (100 ml), and added dropwise thereto at 0° C. was a solution of bromine (3.71 g) in chloroform (13 ml). The mixture was stirred at 0° C. for 1.5 hours, and then, at room temperature for 1 hour, and the mixture was poured into a 10% aqueous sodium thiosulfate solution and a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20-67:33) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (7.13 g) as a colorless solid. APCI-Mass m/Z 614/616 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 446/448 ($M+NH_4$).

Example 160

1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 3-bromobenzadlehyde was treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 430 ($M+NH_4$).

Example 161

1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (500 mg) obtained in Example 159-(1) was dissolved in N,N-dimethylacetamide (10 ml), and added thereto were zinc cyanide (98 mg), tris(dibenzylideneacetone)dipalladium(0) (77 mg), 1,1'-bis(diphenylphosphino)ferrocene (47 mg) and zinc power (14 mg). The mixture was heated under stirring at 120° C. overnight. The reaction solution was cooled, diluted with ethyl acetate and water, and the insoluble materials were filtered off. The organic layer of the filtrate was washed twice with water and successively washed with brine. After drying the same over sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-50:50) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene (207 mg) as colorless crystals. APCI-Mass m/Z 561 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 393 ($M+NH_4$).

Example 162

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(2-pyridyl)-2-thienylmethyl)naphthalene

4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl) naphthalene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482 (M+H).

Example 163

1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 466/468 ($M+NH_4$).

Example 164

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and tri-n-butyl (2-pyrimidinyl) tin 54 were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 429 (M+H).

Example 165

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-thiazolyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and tri-n-butyl(2-thiazolyl)tin were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 434 (M+H).

Example 166

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethyl-3-pyridylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 394/396 (M+H).

Example 167

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b] thiophen-2-ylmethyl)benzene

6-Ethylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 466/468 (M+H).

Example 168

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (500 mg) obtained in Example 128-(4) was dissolved in 1,2-dimethoxyethane (15 ml), and added thereto were 6-fluoropyridine-3-boronic acid 58 (228 mg), tetrakis(triphenylphosphine)palladium(0) (94 mg) and cesium fluoride (738 mg). The mixture was heated under reflux for 30 minutes. The reaction solution was poured into a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-60:40) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene (454 mg) as a colorless solid. APCI-Mass m/Z 634/636 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl) benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 483 ($M+NH_4$), 466 (M+H).

Example 169

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-3-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 6-methoxypyridine-3-boronic acid were treated in a manner similar to Example 168 to give the target compound. APCI-Mass m/Z 478/480 (M+H).

Example 170

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-2-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl(6-methoxy-2-pyridyl)tin (see Gros, Philippe; Fort, Yves. Synthesis (1999), 754-756) were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 478/480 (M+H).

Example 171

1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxo-2-isoindolinylmethyl)benzene

5-Bromo-2-chloro-1-(1-oxo-2-isoindolynilmethyl)benzene was treated in a manner similar to Example 2 to give the target compound. APCI-Mass m/Z 437/439 ($M+NH_4$).

Example 172

1-(β-D-glucopyranosyl)-4-chloro-3-(1-phenyl-4-pyrazolylmethyl)benzene

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 431/433 (M+H).

Example 173

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl (6-ethoxy-2-pyridyl) tin (see WO 00/74681) were treated in a manner similar to Example 128-(5) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl) benzene as colorless crystals. APCI-Mass m/Z 660/662 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl) benzene (245 mg) was dissolved in tetrahydrofuran (5 ml), added thereto was a solution of sodium hydride (oil, 9 mg) in ethanol (5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene (145 mg) as colorless powder. APCI-Mass m/Z 492/494 (M+H).

Example 174

1-(β-D-glucopyranosyl)-4-chloro-3-(6-n-propyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b]thiophen-2-yl methyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 ($M+NH_4$).

Example 175

1-(β-D-glucopyranosyl)-4-chloro-3-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b] thiophen-2-yl methylbenzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 500/502 ($M+NH_4$).

Example 176

1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene from Example

159-(1) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-formylphenyl)-2-thienylmethyl)-4-methylbenzene as a colorless solid. APCI-Mass m/Z 640 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-formylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 130-(2) to give the desired 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless crystals. APCI-Mass m/Z 662 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

Example 177

1-(β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and 3,4-difluorophenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless crystals. APCI-Mass m/Z 648 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 480 ($M+NH_4$).

Example 178

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 3-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 130-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 682/684 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 514/516 ($M+NH_4$).

Example 179

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 130-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 682/684 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl) benzene was treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 514/516 ($M+NH_4$).

Example 180

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethyl-3-fluorophenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and 3-fluoro-4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl)benzene as colorless foam. APCI-Mass m/Z 678/680 ($M+NH_4$).

(2) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl) benzene was treated in a manner similar to Example 178-(2) and

(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethyl-3-fluorophenyl)-2-thienylmethyl)benzene as a colorless foam. APCI-Mass m/Z 532/534 ($M+NH_4$).

Example 181

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and (2-benzyloxymethyl-2H-tetrazol-5-yl) tri-n-butyltin (see *Tetrahedron Lett.* (2000) 2805) were treated in a manner similar to Example 128-(5) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-benzyloxymethyl-2H-tetrazol-5-yl)-2-thienylmethyl)-4-chlorobenzene as colorless solid. APCI-Mass m/Z 727/729 (M+H).

(2) A mixture of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-benzyloxymethyl-2H-tetrazol-5-yl)-2-thienylmethyl)-4-chlorobenzene (247 mg), 6M aqueous hydrochloric acid solution (2 ml) and methanol (20 ml) was refluxed overnight. The solvent was evaporated under reduced pressure and the residue was triturated with diethyl ether to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tet-

razol-5-yl)-2-thienylmethyl)benzene (172 mg) as colorless powder. ESI-Mass m/Z 437/439 (M−H).

Example 182

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methyl-2H-tetrazol-5-yl)-2-thienylmethyl)benzene

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2-thienylmethyl)benzene (140 mg) obtained in Example 181 was dissolved in dimethylformamide (5 ml) and added thereto were methyl iodide (100 μl) and potassium carbonate (220 mg). The mixture was stirred at room temperature overnight. The reaction solution was poured into water and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methyl-2H-tetrazol-5-yl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 470/472 ($M+NH_4$).

Example 183

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene

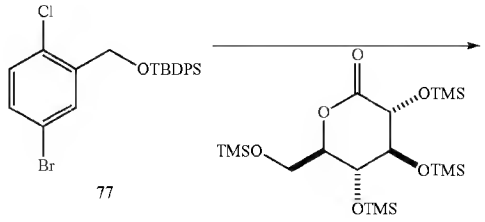
(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl) benzene (272 mg) obtained in Example 180-(1) was dissolved in N-methyl-2-pyrrolidone (10 ml) and added thereto was hydroxylamine hydrochloride (34 mg). The mixture was heated under stirring at 117° C. overnight. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=3:1-2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxyimino-3-fluorophenyl)-2-thienylmethyl)benzene (177 mg) as colorless caramel. APCI-Mass m/Z 693/695 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxyimino-3-fluorophenyl)-2-thienylmethyl)benzene (175 mg) was dissolved in chloroform (5 ml) and added thereto was 1,1'-carbonyldiimidazole (46 mg). The mixture was stirred at room temperature overnight. 1,1'-Carbonyldiimidazole (92 mg) was further added thereto, and the mixture was stirred at 40° C. for 6 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was separated and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene (158 mg) as colorless caramel. APCI-Mass m/Z 675/677 ($M+NH_4$).

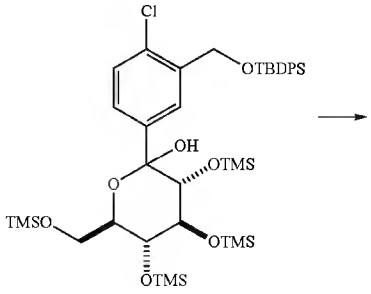
(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 507/509 ($M+NH_4$).

Example 184

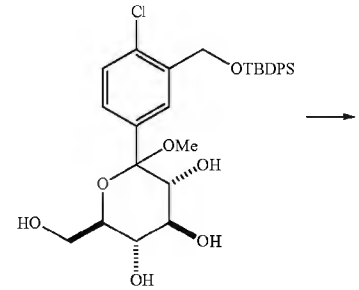
1-(β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene



77 2



78



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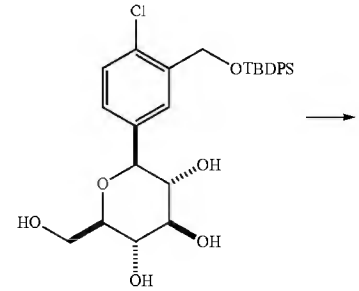

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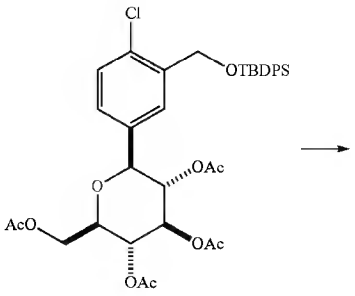
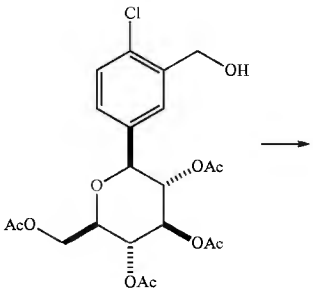
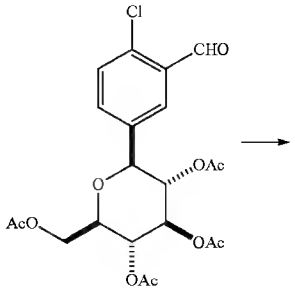


81



82



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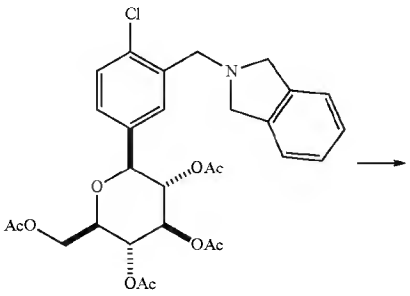

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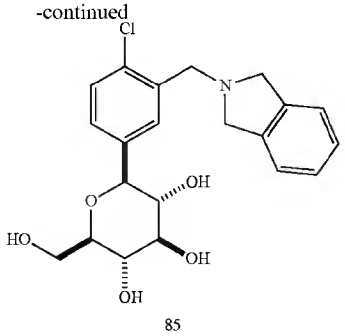


85

(In the above scheme, OTBDPS is a tert-butyldiphenylsilyloxy group, and the other symbols are the same as defined above.)

(1) A mixed solution of 5-bromo-2-chloro-1-(tert-butyldiphenylsilyloxymethyl)benzene 77 (10.83 g) and 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (13.2 g) in tetrahydrofuran (400 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise tert-butyl lithium (1.60 M pentane solution, 30.9 ml), and the mixture was stirred at the same temperature for 30 minutes to give a compound 78. Without isolating this compound, a solution of methanesulfonic acid (6.12 ml) in methanol (200 ml) was added to the reaction solution, and the reaction mixture was warmed to room temperature, and stirred at the same temperature for 15 hours. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=93:7) to give a methyl ether compound 79 (9.71 g) as colorless powder. APCI-Mass m/Z 590/592 ($M+NH_4$).

(2) A solution of the above methyl ether compound 79 (3.46 g) in dichloromethane (70 ml) was cooled to 0° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (2.89 ml) and boron trifluoride•diethyl ether complex (2.28 ml). The mixture was stirred at the same temperature for 1 hour. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-94:4) to give 1-(β-D-glucopyranosyl)-4-chloro-3-(tert-butyldiphenylsilyloxymethyl)benzene 80 (2.52 g) as colorless powder. APCI-Mass m/Z 560/562 ($M+NH_4$).

(3) The above compound 80 (4.12 g) was treated in a manner similar to Example 106-(1) to give the compound 81 (5.44 g). APCI-Mass m/Z 728/730 ($M+NH_4$).

(4) A mixed solution of the above compound 81 (5.44 g), acetic acid (1.29 ml) in tetrahydrofuran (60 ml) was cooled to 0° C. under argon atmosphere, and thereto was added tetrabutyl ammonium fluoride (1.0 M tetrahydrofuran solution, 8.43 ml). The mixture was stirred at the same temperature for 30 minutes, and then further stirred at room temperature for 15 hours. The mixture was diluted with ethyl acetate and washed successively with 0.4 M aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the

solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=4:1-1:1) to give the compound 82 (2.97 g) as a colorless solid. APCI-Mass m/Z 490/492 ($M+NH_4$).

(5) A solution of the above compound 82 (1.60 g) in dichloromethane (50 ml) was cooled to 0° C. under argon atmosphere, and thereto was added Dess-Martin periodinane (1.58 g). The mixture was warmed to room temperature and stirred at the same temperature for 3 hours. The mixture was diluted with ethyl acetate, and insoluble materials were filtered off. The filtrate was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1-1:1) to give 5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-chloro benzaldehyde 83 (1.35 g) as colorless crystals. APCI-Mass m/Z 488/490 ($M+NH_4$).

(6) To a mixed solution of the above 5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-chlorobenzaldehyde 83 (325 mg), 2,3-dihydro-1H-isoindole (98 mg), acetic acid (82 mg) in 1,2-dichloroethane (5 ml) was added sodium triacetoxyborohydride (219 mg). The mixture was stirred at room temperature for 3 hours, and cooled to 0° C. A saturated aqueous sodium hydrogen carbonate solution was added thereto to basify the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:0-1:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 84 (234 mg) as a colorless solid. APCI-Mass m/Z 574/576 (M+H).

(7) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 84 was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 85 as colorless powder. APCI-Mass m/Z 406/408 (M+H).

Example 185

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(3-cyano-4-fluorophenyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and 4-fluoro-3-formylphenylboronic acid were used and treated in a manner similar to Example 177-(1) and Example 183 to give the title compound as colorless powder. APCI-Mass m/z 487 ($M+NH_4$).

Example 186

1-(β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (597 mg) obtained in Example 159-(1) was dissolved in N-methyl-2-pyrrolidone (10 ml) and added thereto were tri-n-butyl(2-cyano-5-pyridyl)tin (590 mg), dichlorobis(triphenylphosphine)palladium(II) (70 mg) and copper(I) iodide (19 mg). The mixture was heated under stirring at 100° C. for 4 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (351 mg) as colorless powder. APCI-Mass m/Z 621 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (62 mg) was dissolved in a mixture of tert-butanol (3 ml)tetrahydrofuran (3 ml) and added thereto was sodium tert-butoxide (48 mg). The mixture was stirred at room temperature for 3.5 hours. Sodium tert-butoxide (19 mg) was further added thereto, and the mixture was stirred at room temperature for 1 hour. To the mixture was added a saturated aqueous ammonium chloride solution at 0° C., and the mixture was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(2cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (23 mg) as colorless powder. APCI-Mass m/Z 470 ($M+NH_4$).

Example 187

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) was treated in a manner similar to Example 186-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl) benzene as colorless powder. APCI-Mass m/Z 641/643 (M+H).

(2) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 186-(2) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 490/492 ($M+NH_4$).

Example 188

1-(β-D-glucopyranosyl)-3-(5-(2-carbamoyl-5-pyridyl)-2-thienylmethyl)-4-chlorobenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene obtained in Example 187-(1) was treated in a manner similar to Example 106-(3) to give the mixture of 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene and 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene. This mixture was dissolved in methanol, and sodium methoxide (28% methanol solution, 1 drop) was added thereto, and the mixture was stirred at 60° C. for 6 hours. The reaction solution was cooled and the solvent was evaporated under reduced pressure to give pure 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene. APCI-Mass m/Z 505/507 (M+H).

(2) The above 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene was suspended in tetrahydrofuran, and sodium hydride (60% mineral oil suspension, 2 equivalent) was added thereto, and the mixture was stirred under reflux for 3 hours. The reaction

solution was cooled and to the mixture was added a saturated aqueous ammonium chloride solution at 0° C., and the mixture was extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1-5:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(2-carbamoyl-5-pyridyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow powder. APCI-Mass m/Z 491/493 (M+H).

Example 189

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene

(1) 5-bromo-2-fluorobenzaldehyde and 2-chlorothiophene were used and treated in a manner similar to Example 4 and Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 574/576 ($M+NH_4$). mp 130-131° C.

(2) The above compound was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 540 ($M+NH_4$). mp 119-121° C.

(3) The above compound was treated in a manner similar to Example 159-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 618/620 ($M+NH_4$). mp 127-129° C.

(4) The above compound and 3-cyanophenylboronic acid were used and treated in a manner similar to Example 168 to give the title compound as colorless powder. APCI-Mass m/z 473 ($M+NH_4$).

Example 190

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(2-thiazolyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluorobenzene obtained in Example 189-(3) and tri-n-butyl(2-thiazolyl)tin were used and treated in a manner similar to Example 128 to give the title compound as colorless crystals. APCI-Mass m/z 438 ($M+NH_4$). mp 161.5-162° C.

Example 191

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-ethoxycarbonylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and 4-cyanophenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl) benzene as colorless powder. APCI-Mass m/Z 657/659 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (128 mg) was suspended in ethanol (2 ml) and added thereto was a concentrated hydrochloric acid aqueous solution (1 ml). The mixture was heated reflux for 8.5 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-ethoxycarbonylphenyl)-2-thienylmethyl)benzene (39 mg) as pale yellow foam. APCI-Mass m/Z 536/538 ($M+NH_4$).

Example 192

1-(β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (128 mg) obtained in Example 191-(1) was dissolved in acetic acid (2 ml) and added thereto was a concentrated hydrochloric acid aqueous solution (2 ml). The mixture was refluxed for 6.5 hours. To the mixture was added a 10% aqueous sodium hydroxide solution at 0° C., and the mixture was washed with ethyl acetate. The aqueous layer was acidified by adding concentrated hydrochloric acid, and extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by washing with a mixture of ethyl acetate and diethyl ether to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (49 mg) as pale brown powder. ESI-Mass m/Z 489/491 (M−H).

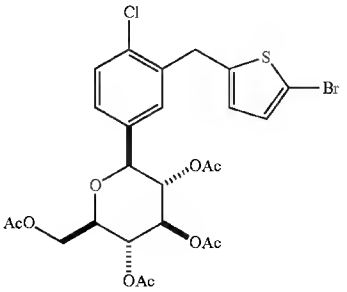
Example 193

1-(β-D-glucopyranosyl)-3-(5-(4-carbamoylphenyl)-2-thienylmethyl)-4-chlorobenzene

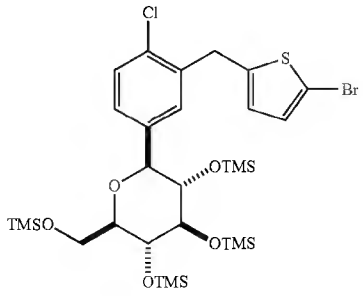
1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (282 mg) obtained in Example 191-(1) was suspended in ethanol (5 ml) and added thereto was a 6N aqueous sodium hydroxide solution (0.37 ml). The mixture was stirred at room temperature for 10 minutes. To the mixture was added a 30% aqueous hydrogen peroxide solution (0.2 ml), and the mixture was stirred at room temperature for 1.5 hours and at 45° C. for 3 hours. To the mixture was added water (20 ml) and the mixture was cooled. The powder was collected by filtration and washed with diethyl ether and dried to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-carbamoylphenyl)-2-thienylmethyl)-4-chlorobenzene (176 mg) as colorless powder. APCI-Mass m/Z 507/509 ($M+NH_4$).

Example 194

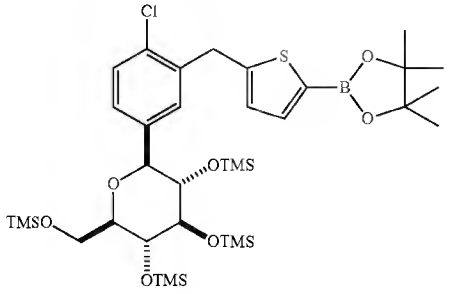
1-(β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene



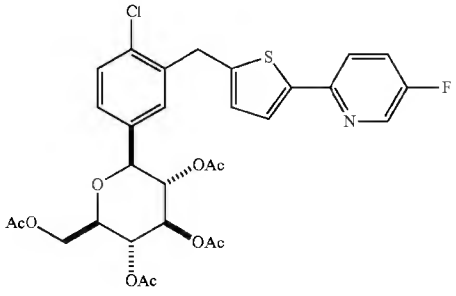
71



86



87



88

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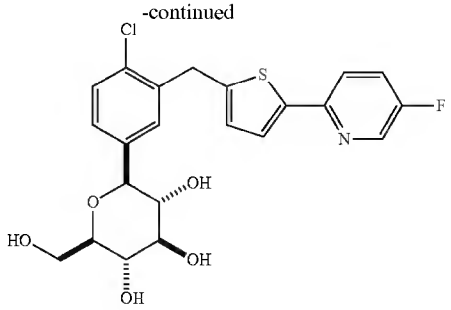


89

In the above scheme, the symbols are defined as above.

(1) The 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (750 mg) obtained in Example 128-(4) was dissolved in a mixture of methanol (8 ml)-tetrahydrofuran (8 ml), and sodium methoxide (28% methanol solution, 1 drop) was added thereto, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 ml), and thereto were added pyridine (0.69 ml) and 4-dimethylaminopyridine (15 mg). The mixture was cooled to 0° C., and thereto was added trimethylsilyl trifluoromethanesulfonate (1.54 ml). The mixture was stirred at room temperature for 3 days. To the mixture was added water, and the mixture was extracted with diethyl ether. The extract was washed with successively with water, a saturated aqueous ammonium chloride solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the compound 86 (900 mg) as colorless oil.

(2) A mixed solution of the above compound 86 (900 mg), triisopropoxyborane (252 mg) in tetrahydrofuran (22 ml) was cooled to −78° C. under argon atmosphere. Thereto was added dropwise tert-butyl lithium (1.46 M pentane solution, 0.9 ml), and the mixture was stirred at the same temperature for 1 hour. The mixture was warmed to room temperature, and thereto was added pinacol (2.24 g). The mixture was stirred at the same temperature overnight. The mixture was diluted with ethyl acetate, and washed successively with water and brine. The solvent was evaporated under reduced pressure to give the compound 87, which was used in the subsequent reaction without further purification.

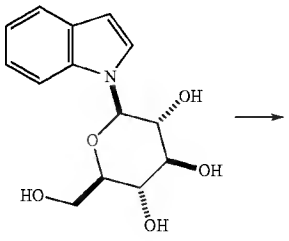
(3) The whole amount of the above compound 87 was dissolved in dimethoxyethane (20 ml), and thereto were added 2-bromo-5-fluoropyridine (460 mg), tetrakis(triphenylphosphine)palladium(0) (150 mg) and cesium fluoride (1.4 g). The mixture was stirred at 80° C. for 3 hours. The mixture was cooled to room temperature, acidified with 2 M aqueous hydrochloric acid solution, and stirred at the same temperature overnight. Under ice-cooling, the reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was passed through silica gel column chromatography (chloroform:methanol=100:0-88:12) to give crude oil, which was dissolved in dichloromethane (20 ml). To the mixture were added acetic anhydride (0.71 ml), pyridine (0.61 ml), and 4-dimethylaminopyridine (13 mg), and the mixture was stirred at room temperature for 1 hour. Then, dichloromethane was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was

washed successively with 2 M aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:0-3:2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene 88 (218 mg) as a colorless solid. APCI-Mass m/Z 634/636 (M+H).

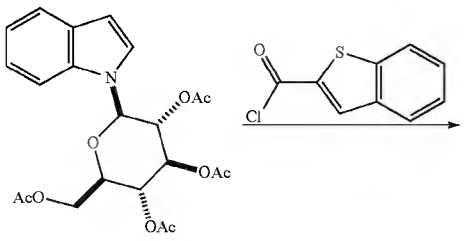
(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl) benzene 88 was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene 89 as a colorless solid. APCI-Mass m/Z 466/468 (M+H).

Example 195

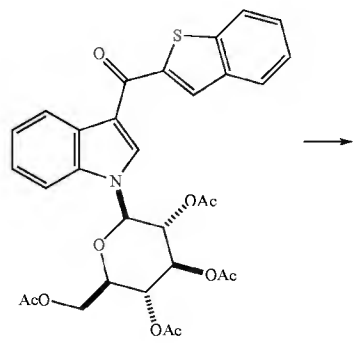
1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)indole



90

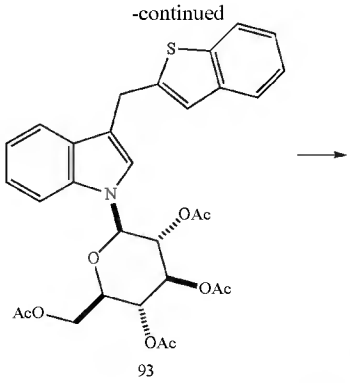


91



92

-continued



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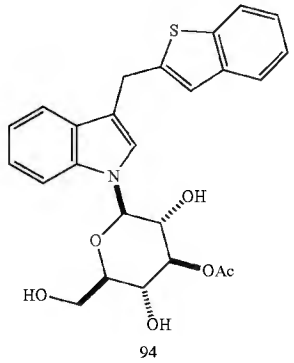


94

In the above scheme, the symbols are defined as above.

(1) 1-(β-D-glucopyranosyl)indole 90 (see *Eur. J. Med. Chem.* (2004) 39, 453-458) was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indole 91 as colorless crystals. APCI-Mass m/Z 465 ($M+NH_4$).

(2) Benzo[b]thiophene-2-carboxylic acid (598 mg) was suspended in dichloromethane (10 ml). Added thereto were oxalyl chloride (0.39 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was dissolved in dichloroethane (30 ml). To the solution was added 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indole 91 (1 g) obtained above, and the mixture was cooled to 0° C. Added gradually thereto was aluminum chloride (2.09 g), and subsequently, the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-cold water, and the mixture was extracted with chloroform. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-5:4) to give Benzo[b]thiophen-2-yl (1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-indol-3-yl) ketone 92 (570 mg) as colorless crystals. APCI-Mass m/Z 608 (M+H).

(3) The above Benzo[b]thiophen-2-yl (1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-indol-3-yl) ketone 92 (440 mg) was dissolved in tetrahydrofuran (6 ml) and ethanol (3 ml). To the solution was added sodium borohydride (137 mg), and the mixture was stirred at room temperature for 60 minutes. The reaction mixture was quenched with cold aqueous HCl solution (0.5 N), and extracted with ethyl acetate. The extract was

washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The resultant residue was dissolved in dichloromethane (8 ml) and acetonitrile (4 ml), and the mixture was cooled to 0° C. under argon atmosphere. To the mixture were added triethylsilane (0.58 ml) and boron trifluoride•diethyl ether complex (0.46 ml). After 30 minutes, the mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the organic layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The resultant residue was dissolved in chloroform (20 ml), and to the mixture were added acetic anhydride (0.16 ml), triethylamine (0.2 ml), and 4-dimethylaminopyridine (15 mg), and the mixture was stirred at room temperature for 30 minutes. Then, the solution was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (hexane:ethyl acetate=8:2-6:4) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(benzo-[b]thiophen-2-ylmethyl)indole 93 (290 mg). APCI-Mass m/Z 611 ($M+NH_4$).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)indole 93 (336 mg) was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)indole 94 (208 mg) as a colorless powder. APCI-Mass m/Z 443 ($M+NH_4$).

Example 196

1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-fluoronaphthalene

(1) The 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene obtained in Example 137 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 624/626 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 590 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-fluoronaphthalene was treated in a manner similar to Example 159-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 668/670 ($M+NH_4$).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluoronaphthalene and 3-cyanophenylboronic acid were treated in a manner similar to Example 168 to give 1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 523 ($M+NH_4$).

Example 197

1-(β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and 4-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)aniline were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow powder. APCI-Mass m/Z 630/632 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow foam. APCI-Mass m/Z 479/481 ($M+NH_4$).

Example 198

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)benzene

(1) 1-(β-D-Glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (637 mg) obtained in Example 192 was dissolved in a mixture of dichloromethane (10 ml)-tetrahydrofuran (5 ml) and added thereto were acetic anhydride (1.22 ml), pyridine (1.05 ml) and 4-dimethylaminopyridine (32 mg). The mixture was stirred at room temperature overnight. The solvents were evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 2N hydrochloric acid aqueous solution and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:1-50:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (687 mg) as pale yellow powder. ESI-Mass m/Z 657/659 (M−H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (198 mg) was dissolved in dichloromethane (5 ml) and added thereto were oxalyl chloride (1 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature for 3.5 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was suspended in tetrahydrofuran (4 ml), without further purification. To the suspension was added a 2.0 M solution of methylamine in tetrahydrofuran (1.5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)-benzene (218 mg) as pale yellow powder. APCI-Mass m/Z 689/691 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)-benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 521/523 ($M+NH_4$).

Example 199

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene (126 mg) obtained in Example 197-(1) was dissolved in dichloromethane (3 ml) and added thereto were methanesulfonyl

chloride (48 mg) and pyridine (48 mg). The mixture was stirred at room temperature for 3.5 hours. To the mixture was added 2N hydrochloric acid aqueous solution at 0° C. and extracted with ethyl acetate. The organic layer was washed with water, aqueous sodium hydrogen carbonate solution and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1-1:2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene (154 mg) as yellow caramel. ESI-Mass m/Z 706/708 (M−H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene as yellow foam. ESI-Mass m/Z 538/540 (M−H).

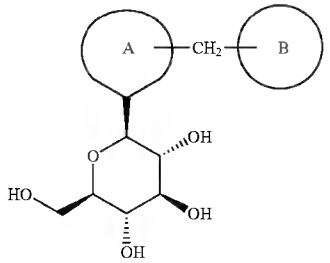
Example 200

1-(β-D-glucopyranosyl)-3-(5-(4-acetylaminophenyl)-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene (126 mg) obtained in Example 197-(1) was treated in a manner similar to Example 106-(1) and (3) to give the target compound as colorless powder. APCI-Mass m/Z 521/523 ($M+NH_4$).

The compounds shown in Table 5 below were prepared in a manner similar to one of the above Examples from the corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out.

TABLE 5



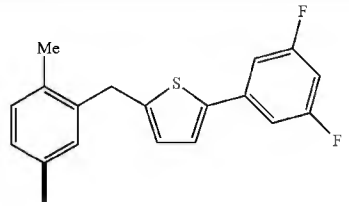
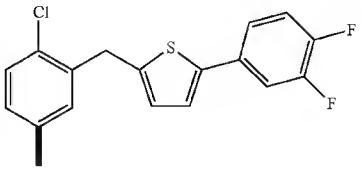
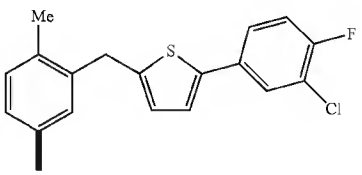
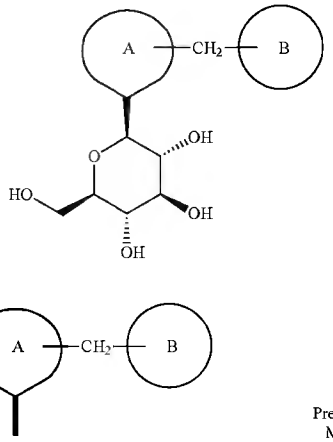
Examples		Preparation Method	APCI-Mass (m/Z)
201		177	480 ($M + NH_4$)
202		168	500/502 ($M + NH_4$)
203		177	496/498 ($M + NH_4$)

TABLE 5-continued



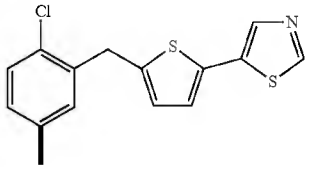
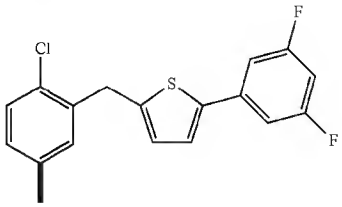
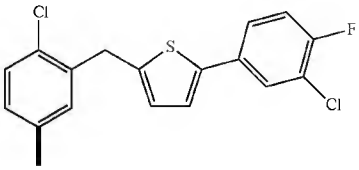
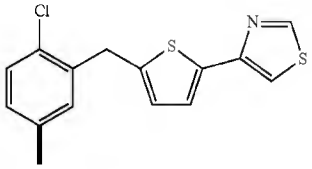
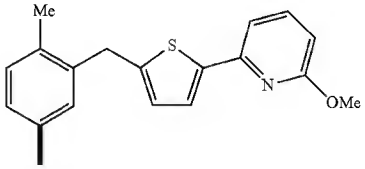
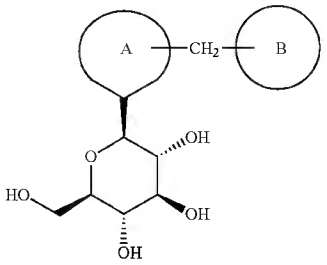
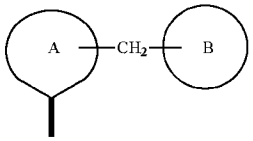
Examples		Preparation Method	APCI-Mass (m/Z)
204		128	454/456 (M + H)
205		168	500/502 (M + NH_4)
206		168	516/518 (M + NH_4)
207		128	454/456 (M + H)
208		164	458 (M + H)

TABLE 5-continued





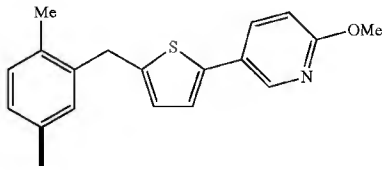
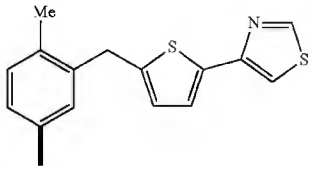
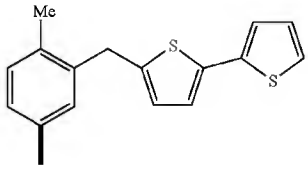
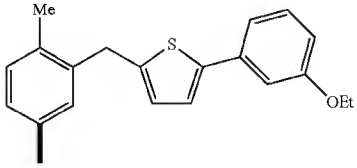
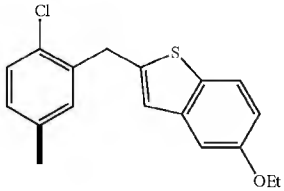
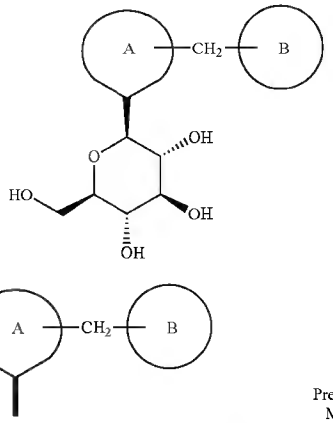
Examples		Preparation Method	APCI-Mass (m/Z)
209		177	458 (M + H)
210		164	434 (M + H)
211		177	450 ($M + NH_4$)
212		177	488 ($M + NH_4$)
213		1	482/484 ($M + NH_4$)

TABLE 5-continued



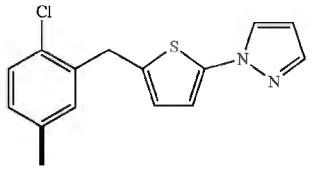
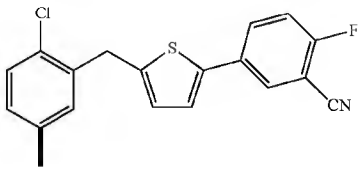
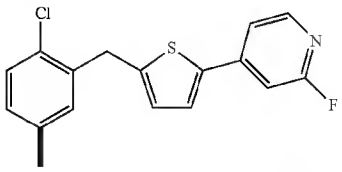
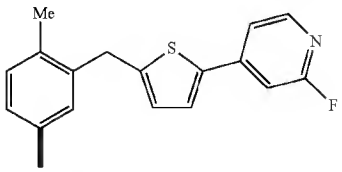
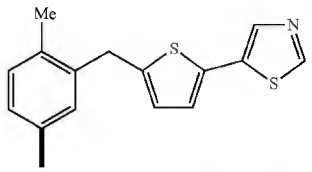
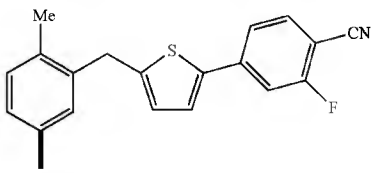
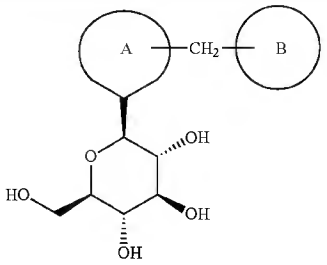
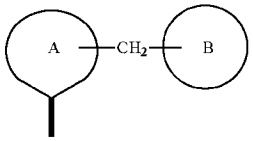
Examples		Preparation Method	APCI-Mass (m/Z)
214		2	437/439 (M + H)
215		183	507/509 (M + NH_4)
216		168	466/468 (M + H)
217		177	446 (M + H)
218		164	434 (M + H)
219		185	487 (M + NH_4)

TABLE 5-continued





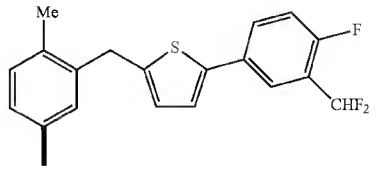
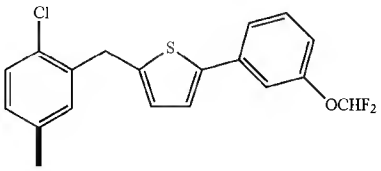
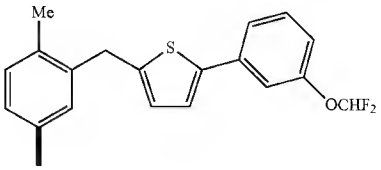
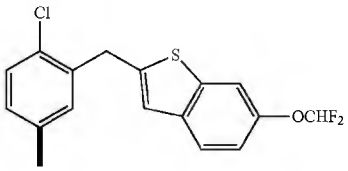
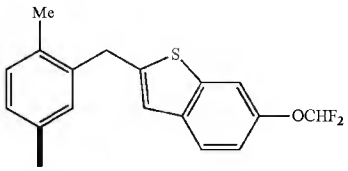
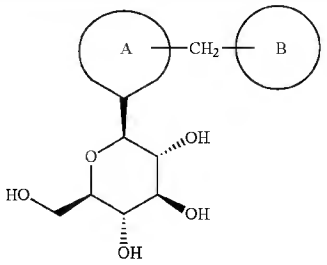
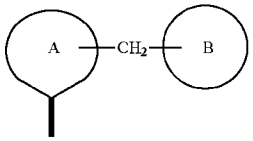
Examples		Preparation Method	APCI-Mass (m/Z)
220		176	512 (M + NH_4)
221		168	530/532 (M + NH_4)
222		177	510 (M + NH_4)
223		2	504/506 (M + NH_4)
224		2	484 (M + NH_4)

TABLE 5-continued





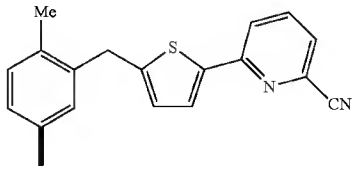
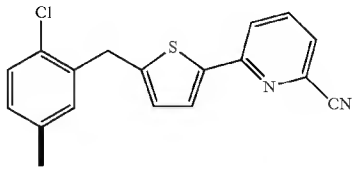
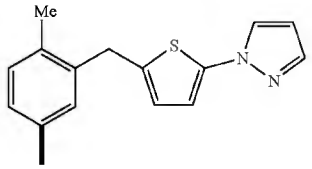
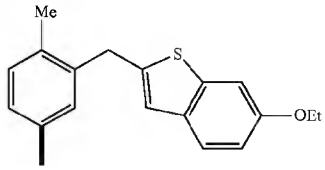
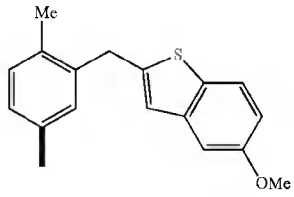
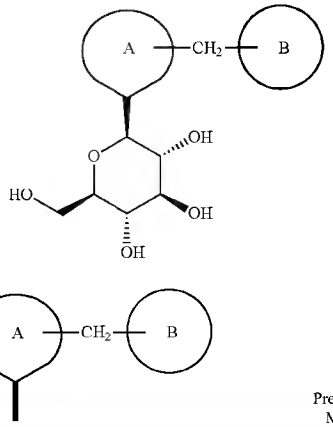
Examples		Preparation Method	APCI-Mass (m/Z)
225		186	470 (M + NH_4)
226		187	490/492 (M + NH_4)
227		2	417 (M + H)
228		1	462 (M + NH_4)
229		1	448 (M + NH_4)

TABLE 5-continued



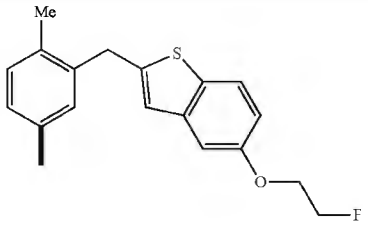
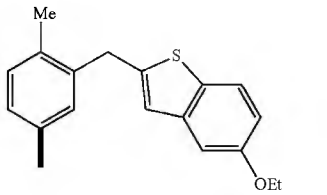
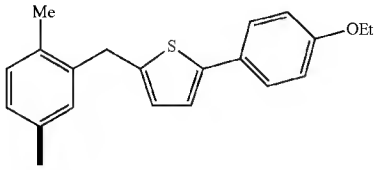
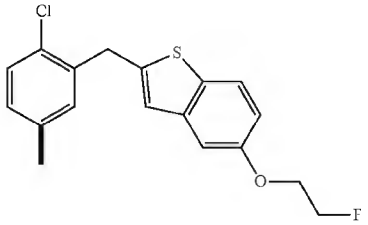
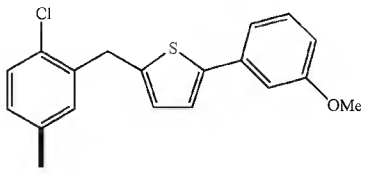
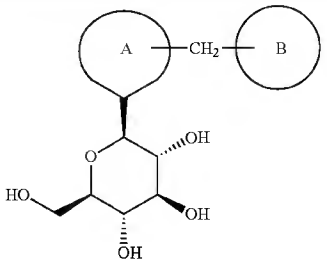
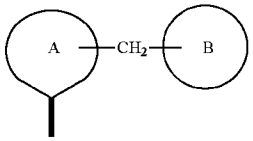
Examples		Preparation Method	APCI-Mass (m/Z)
230		1	480 ($M + NH_4$)
231		1	462 ($M + NH_4$)
232		177	488 ($M + NH_4$)
233		1	500/502 ($M + NH_4$)
234		168	494/496 ($M + NH_4$)

TABLE 5-continued





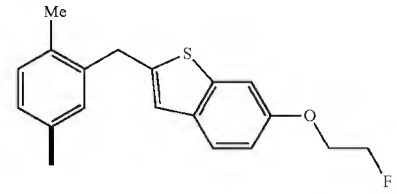
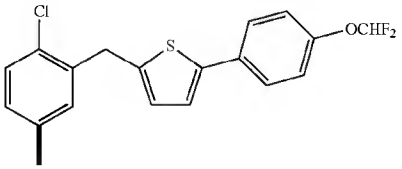
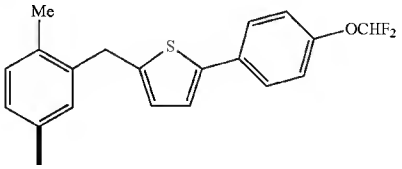
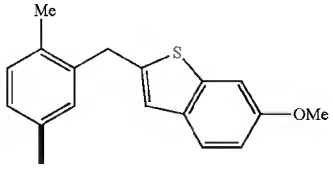
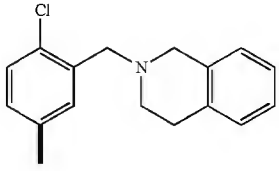
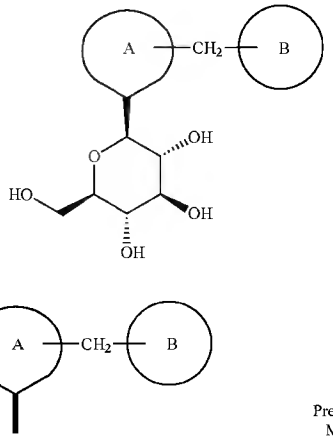
Examples		Preparation Method	APCI-Mass (m/Z)
235		1	480 (M + NH_4)
236		168	530/532 (M + NH_4)
237		177	510 (M + NH_4)
238		1	448 (M + NH_4)
239		184	420/422 (M + H)

TABLE 5-continued



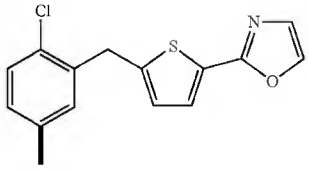
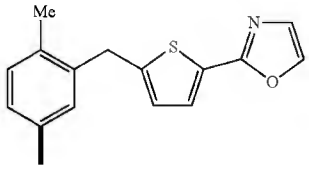
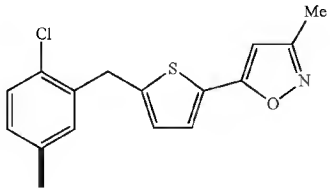
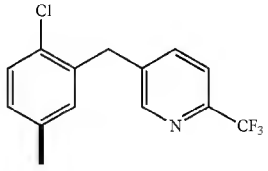
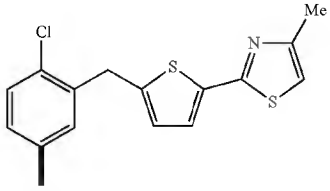
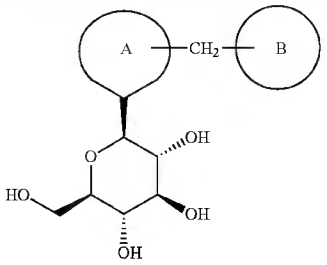
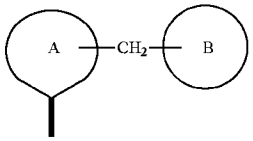
Examples		Preparation Method	APCI-Mass (m/Z)
240		128	438/440 (M + H)
241		164	418 (M + H)
242		128	469/471 (M + NH_4)
243		1	434/436 (M + H)
244		128	468/470 (M + H)

TABLE 5-continued





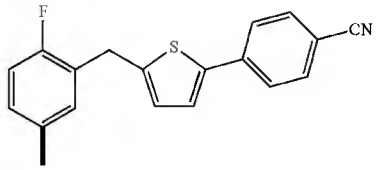
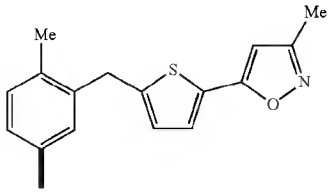
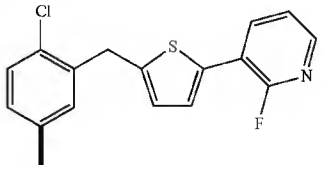
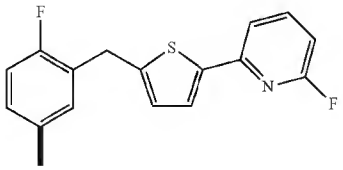
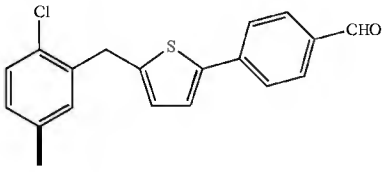
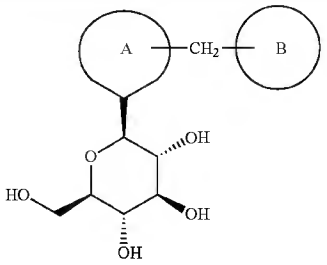
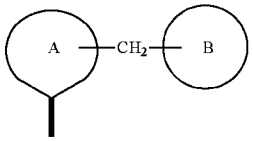
Examples		Preparation Method	APCI-Mass (m/Z)
245		189	473 ($M + NH_4$)
246		164	449 ($M + NH_4$)
247		168	483/485 ($M + NH_4$)
248		189	467 ($M + NH_4$)
249		168	492/494 ($M + NH_4$)

TABLE 5-continued





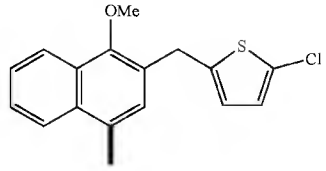
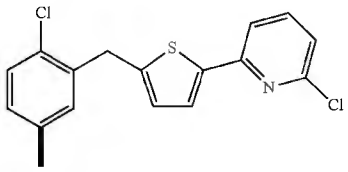
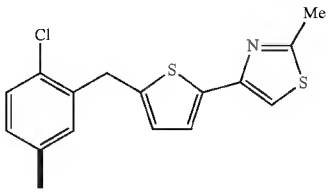
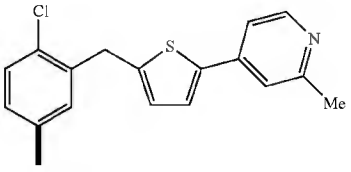
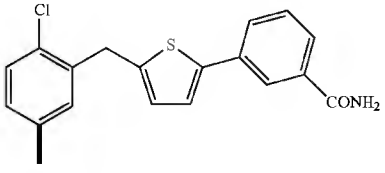
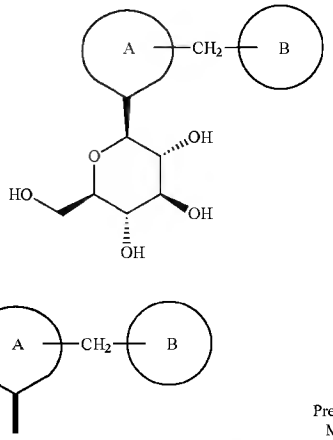
Examples		Preparation Method	APCI-Mass (m/Z)
250		1	468/470 (M + NH_4)
251		168	499/501 (M + NH_4)
252		128	468/470 (M + H)
253		168	462/464 (M + H)
254		193	507/509 (M + NH_4)

TABLE 5-continued



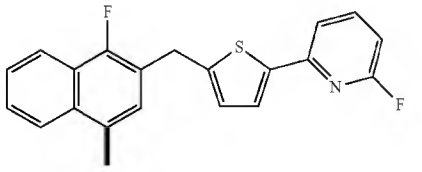
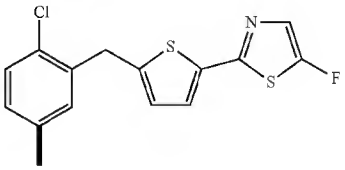
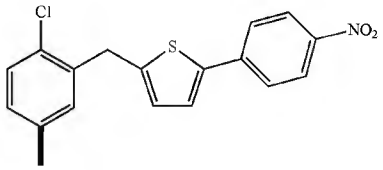
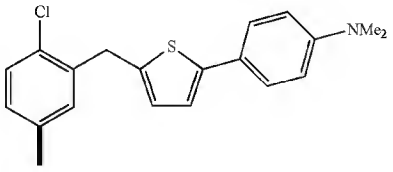
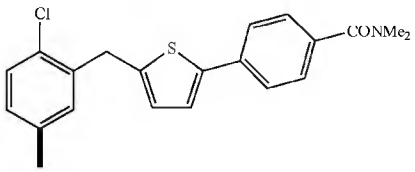
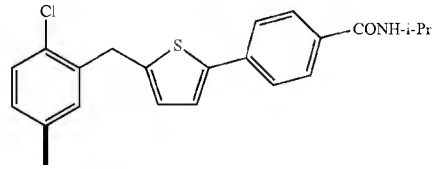
Examples		Preparation Method	APCI-Mass (m/Z)
255		196	517 (M + NH_4)
256		1	472/474 (M + H)
257		168	509/511 (M + NH_4)
258		168	490/492 (M + H)
259		198	535/537 (M + NH_4)

TABLE 5-continued

Examples		Preparation Method	APCI-Mass (m/Z)
260		198	549/551 (M + NH_4)

The compounds shown in Table 6 below were prepared in a manner similar to Example 195 from the corresponding starting materials.

TABLE 6

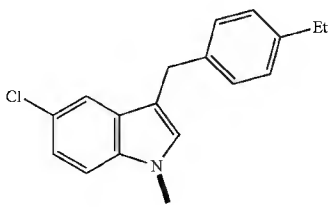
Exam-ples		APCI-Mass (m/Z)
261		449/451 (M + NH_4)

TABLE 6-continued

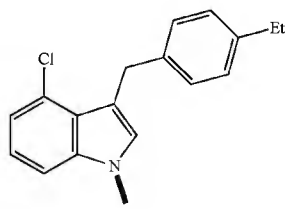
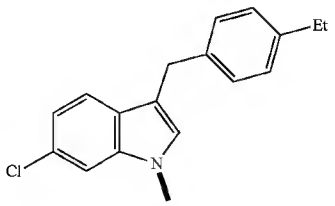
Exam-ples		APCI-Mass (m/Z)
262		432/434 (M + H)

TABLE 6-continued

Examples		APCI-Mass (m/Z)
263		449/451 ($M + NH_4$)

Example 264

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxymethylphenyl)-2-thienylmethyl)benzene

1-(β-D-Glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene (84 mg) obtained in Example 249 was dissolved in a mixture of ethanol (2 ml)-tetrahydrofuran (2 ml) and added thereto was sodium borohydride (7 mg). The mixture was stirred at room temperature for 1 hour. The mixture was quenched by 2N hydrochloric acid aqueous solution (3 drops) at 0° C., and the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxymethylphenyl)-2-thienylmethyl)benzene (82 mg) as colorless foam. APCI-Mass m/Z 494/496 ($M+NH_4$).

Example 265

1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)-4-methoxynaphthalene

(1) 1-(β-D-Glucopyranosyl)-3-(5-chloro-2-thienyl methyl)-4-methoxynaphthalene obtained in Example 250 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 636/638 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methoxynaphthalene was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 602 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-methoxynaphthalene was treated in a manner similar to Example 159-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 680/682 ($M+NH_4$).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxynaphthalene and phenylboronic acid were treated in a manner similar to Example 168 to give the desired 1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 510 ($M+NH_4$).

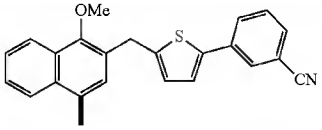
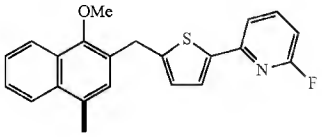
Example 266

1-β-D-glucopyranosyl)-3-(5-(2-pyrimidinyl)-2-thienylmethyl)-4-methoxynaphthalene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxylnaphthalene obtained in Example 265-(3) and 2-tributylstannylpyrimidine were treated in a manner similar to Example 128-(5) and (6) to give 1-(β-D-glucopyranosyl)-3-(5-(2-pyrimidinyl)-2-thienylmethyl)-4-methoxylnaphthalene. APCI-Mass m/Z 495 (M+H).

The compounds shown in Table 7 below were prepared in a manner similar to Example 265 from the corresponding starting materials.

TABLE 7

Examples		APCI-Mass (m/Z)
267		535 ($M + NH_4$)
268		529 ($M + NH_4$)

Reference Example 1

3-Bromo-1-(5-ethyl-2-thienylmethyl)benzene

(1) A solution of 1,3-dibromobenzene (3.7 g) in tetrahydrofuran (25 ml) was cooled to −78° C. under argon atmosphere,

and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.55 ml). The reaction mixture was stirred at the same temperature for 10 minutes, and thereto was added dropwise a solution of 5-ethyl-2-thiophenecarboxaldehyde (2.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated ammonium chloride solution, and the reaction mixture was warmed to room temperature. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=97:3-85:15) to give 3-bromophenyl-5-ethyl-2-thienylmethanol (2.97 g) as a pale yellow syrup. APCI-Mass m/Z 279/281 (M+H—H_2O).

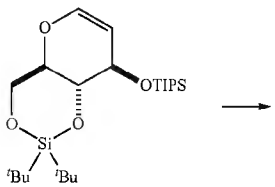
(2) The above 3-bromophenyl-5-ethyl-2-thienylmethanol (2.90 g) was dissolved in dichloromethane (38 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture were added triethylsilane (6.18 ml) and boron trifluoride•diethyl ether complex (2.45 ml), and the mixture was gradually warmed to room temperature over a period of one hour. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the dichloromethane layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give the desired 3-bromo-(5-ethyl-2-thienylmethyl)benzene (2.57 g) as a colorless syrup. APCI-Mass m/Z 281/283 (M+H).

Reference Example 2

5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one

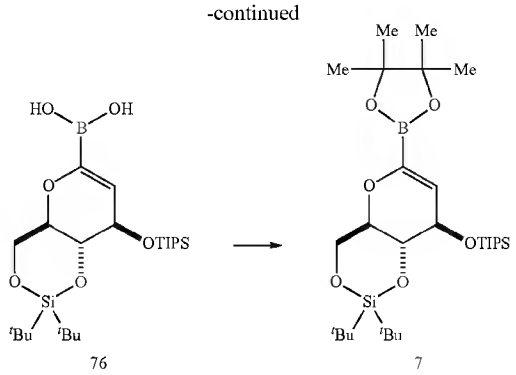
5-Bromo-1H-pyridin-2-one (1.04 g) and 4-ethylbenzyl bromide (1.43 g) were dissolved in N,N-dimethylformamide (15 ml), and thereto was added potassium carbonate (1.66 g). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and washed successively with water and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1-3:1) to give 5-bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one (1.58 g) as colorless crystals. APCI-Mass m/Z 292/294 (M+H).

Reference Example 3



75

-continued



76 7

In the above scheme, the symbols are as defined above.

(1) A solution of silylated glucal 75 (see Parker et al., Org. Lett. 2000, 2, 497-499) (7.00 g) in tetrahydrofuran (70 ml) was cooled to −78° C. under argon atmosphere. Thereto was added dropwise t-butyl lithium (1.45 M pentane solution, 49.0 ml) over a period of 10 minutes. The mixture was stirred at the same temperature for 15 minutes, and then warmed to room temperature, and further stirred for 30 minutes. The mixture was cooled again to −78° C., and thereto was added trimethyl borate (8.90 ml) in one portion. After 15 minutes, the reaction solution was warmed to room temperature over a period of one hour, and thereto was added water (100 ml) at 0° C. The mixture was stirred for 30 minutes, and extracted twice with diethyl ether. The extract was washed with water, and then washed with brine. The resultant was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give the compound 76, which was used in the subsequent reaction without further purification.

(2) The whole amount of the above compound 76 was dissolved in toluene (65 ml), and thereto was added pinacol (2.24 g). The mixture was stirred at room temperature under argon atmosphere for 17 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, and the extract was washed with brine, dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the compound 7 (10.4 g) as a yellow semisolid, which was used in the subsequent reaction without further purification. APCI-Mass m/Z 569 (M+H).

Reference Example 4

5-Bromo-2-methylbenzaldehyde

(1) Methyl 5-bromo-2-methylbenzoate (see Japanese Unexamined Patent Publication No. 9-263549) (16.12 g) was dissolved in methanol (100 ml), and thereto was added 10% aqueous sodium hydroxide solution (50 ml). The mixture was stirred at 50° C. for 40 minutes. Under ice-cooling, the mixture was adjusted to pH 1 by addition of 10% aqueous hydrochloric acid solution, and diluted with water. Precipitated powder was collected by filtration, and dried to give 5-bromo-2-methylbenzoic acid (14.1 g). ESI-Mass m/Z 213/215 (M−H).

(2) The above 5-bromo-2-methylbenzoic acid (10.0 g) was suspended in dichloromethane (100 ml), and thereto were added oxalyl chloride (8.1 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-methylbenzoyl chloride. This benzoyl chlo-

ride was dissolved in dichloromethane (200 ml), and thereto was added N,O-dimethylhydroxylamine hydrochloride (12.3 g). To the mixture was added dropwise triethylamine (20 ml) at 0° C., and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate, and washed successively with water, 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.25 g) as oil. APCI-Mass m/Z 258/260 (M+H).

(3) A solution of the above N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.2 g) in tetrahydrofuran (100 ml) was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise diisobutyl aluminum hydride (1.0 M toluene solution, 75 ml), and the mixture was stirred at the same temperature for one hour. 10% aqueous hydrochloric acid solution (50 ml) was added thereto, and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate twice, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was solidified to give 5-bromo-2-methylbenzaldehyde (8.73 g). APCI-Mass m/Z 213/215 (M+H+MeOH—H_2O).

Reference Example 5

5-Bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene

(1) 5-Bromo-2-chlorobenzoic acid (5.00 g) was suspended in dichloromethane (10 ml), and thereto were added oxalyl chloride (2.2 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 6 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzoyl chloride. This compound and 2-ethylthiophene (2.38 g) were dissolved in dichloromethane (20 ml), and thereto was added aluminum chloride (3.11 g) at 0° C. The mixture was stirred at the same temperature for one hour. The reaction mixture was poured into a cold 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:1) to give 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) as an oil. APCI-Mass m/Z 329/331 (M+H).

(2) A solution of the above 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) in dichloromethane (50 ml)-acetonitrile (50 ml) was cooled under ice-cooling, and thereto were added dropwise triethylsilane (7.69 ml) and boron trifluoride•diethyl ether complex (6.1 ml). Subsequently, the mixture was stirred at room temperature for 3.5 hours, and was cooled again under ice-cooling. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene (4.52 g) as a colorless liquid.

Reference Example 6

3-Bromo-1-(5-n-propyl-2-thienylmethyl)benzene

3-Bromobenzoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 7

5-Bromo-(5-ethyl-2-thienylmethyl)-2-methoxybenzene

(1) A solution of 2-ethylthiophene (3.00 g) in tetrahydrofuran (36 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.56 M hexane solution, 17.1 ml). The mixture was stirred at the same temperature for 30 minutes, and cooled to −78° C., and thereto was added dropwise a suspension of 5-bromo-2-methoxybenzaldehyde (5.74 g) in tetrahydrofuran (60 ml). The mixture was stirred at the same temperature for 2 hours, warmed to 0° C., and thereto was added a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol (5.99 g) as a pale yellow syrup. APCI-Mass m/Z 309/311 (M+H—H_2O).

(2) The above 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol was treated in a manner similar to Reference Example 1-(2) to give 5-bromo-(5-ethyl-2-thienylmethyl)-2-methoxybenzene as oil. APCI-Mass m/Z 311/313 (M+H).

Reference Example 8

3-Bromo-1-(5-ethyl-2-thienylmethyl)-4-methoxybenzene

2-Ethylthiophene and 3-bromo-4-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 9

3-Bromo-1-(4-n-propyl-2-thienylmethyl)benzene

(1) 3-n-Propylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 7-(1) to give 3-bromophenyl-4-n-propyl-2-thienyl methanol. APCI-Mass m/Z 293/295 (M+H—H_2O).

(2) A solution of the above 3-bromophenyl-4-n-propyl-2-thienyl methanol (2.4 g) in acetonitrile (10 ml) was added dropwise to a mixed solution of chlorotrimethylsilane (4.54 ml) and sodium iodide (5.36 g) in acetonitrile (10 ml) at 0° C., over a period of 2 hours. The mixture was further stirred at room temperature for 5 minutes, and cooled again to 0° C. An aqueous solution (10 ml) of sodium hydroxide (1.0 g) was added thereto, and the mixture was stirred at 0° C. for 0.5 hours. The mixture was extracted with ethyl acetate, washed successively with an aqueous sodium thiosulfate solution, water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-1-(4-n-propyl-2-thienyl)benzene (1.97 g) as colorless oil.

Reference Example 10

5-Bromo-2-chloro-1-(5-n-propyl-2-thienylmethyl) benzene

5-Bromo-2-chlorobenozoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 11

5-Bromo-2-methoxy-1-(5-n-propyl-2-thienylmethyl) benzene

2-n-Propylthiophene and 5-bromo-2-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 325/327 (M+H).

Reference Example 12

3-Bromo-1-(4-ethyl-2-thienylmethyl)benzene

3-Ethylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 281/283 (M+H).

Reference Example 13

3-Bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene

(1) To a solution of 5-ethyl-2-thiophenecarboxaldehyde (6.0 g) in N,N-dimethylformamide (60 ml) was added N-chlorosuccinimide (8.57 g), and the mixture was stirred at room temperature for 2 hours, and subsequently stirred under heating at 60° C. for 2 hours. N-chlorosuccinimide (4.00 g) was further added thereto, and the mixture was further stirred under heating at 60° C. for 2 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=33:1) to give 4-chloro-5-ethyl-2-thiophenecarboxaldehyde (3.1 g) as colorless oil.
(2) The above 4-chloro-5-ethyl-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 1 to give 3-bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene as yellow oil. APCI-Mass m/Z 347/349 (M+H+MeOH).

Reference Example 14

5-Bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b] thiophen-2-ylmethyl)benzene

(1) To a solution of 4-keto-4,5,6,7-tetrahydrothianaphthene (9.83 g) in ethylene glycol (100 ml) were added hydrazine hydrate (10.4 ml) and potassium hydroxide (13.0 g), and the mixture was stirred under argon atmosphere at 190° C. for 4 hours. The reaction mixture was cooled to room temperature, and poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 4,5,6,7-tetrahydrothianaphthene (2.75 g) as colorless oil.
(2) The above 4,5,6,7-tetrahydrothianaphthene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylmethyl)benzene as a colorless solid. APCI-Mass m/Z 341/343 (M+H).

Reference Example 15

5-Bromo-2-chloro-1-(5-ethyl-4-methyl-2-thienylmethyl)benzene

(3) 2-Acetyl-3-methylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 329/331 (M+H).

Reference Example 16

5-Bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl) benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chlorobenzaldehyde. APCI-Mass m/Z 233/235 (M+H+MeOH—H_2O).
(2) The above 5-bromo-2-chlorobenzaldehyde and thieno[3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans* 1 1997, 3465-3470) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 343/345 (M+H).

Reference Example 17

5-Bromo-2-chloro-1-(5-chloro-2-thienylmethyl)benzene

2-Chlorothiophene was treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 18

5-Bromo-2-chloro-1-(5-phenylmethyl-2-thienylmethyl)benzene

2-Benzoylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 377/379 (M+H).

Reference Example 19

5-Bromo-2-chloro-1-(5-(2-thienyl)-2-thienylmethyl) benzene

2,2'-Bithiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

Reference Example 20

5-Bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methylbenzene

(1) To a solution of 2-bromo-5-chlorothiophene (4.11 g), thiophene-2-boronic acid (4.00 g), tetrakis(triphenylphosphine)palladium (0) (1.20 g) and 2M aqueous sodium carbonate solution (31.3 ml) in dimethoxyethane (100 ml) was

heated under reflux under argon atmosphere for 2.5 hours. The reaction mixture was cooled, and extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-chloro-2-thienyl)thiophene (3.37 g) as pale yellow oil.

(2) The above 2-(5-chloro-2-thienyl)thiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were used and treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methylbenzene as a colorless solid. APCI-Mass m/Z 383/385 (M+H).

Reference Example 21

5-Bromo-2-chloro-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene

2-Acetyl-3-chlorothiophene (see Japanese Unexamined Patent Publication No. 2000-34230) was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

Reference Example 22

5-Chloro-4-methylthiophene

The target compound was prepared according to a method described in Japanese Unexamined Patent Publication No. 10-324632.

Reference Example 23

5-Bromo-2-chloro-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)benzene

2-(5-Chloro-2-thienyl)thiophene and 5-bromo-2-chlorobenzoic acid were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 24

5-Bromo-2-chloro-1-(5-trifluoromethyl-2-thienylmethyl)benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 25

5-Bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl) benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol as colorless powder. APCI-Mass m/Z 380/382 (M+H).

(2) A solution of the above 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol (3.52 g) in trifluoroacetic acid (45 ml) was added to a solution of sodium borohydride (1.75 g) in trifluoroacetic acid (45 ml), and the mixture was stirred at room temperature for 4 hours. Trifluoroacetic acid was evaporated under reduced pressure. The residue was basified with an aqueous potassium hydroxide solution, and extracted with diethyl ether. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-4:1) to give 5-bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl)benzene (2.42 g) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 26

5-Bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) and 2-chlorothiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene as colorless oil.

(2) To a solution of the above 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene (1.0 g) in dimethoxyethane (10 ml) were added phenylboronic acid (310 mg), bis(triphenylphosphine)palladium(II)dichloride (85 mg) and 2M aqueous sodium carbonate solution (3.8 ml), and the mixture was stirred at 50° C. overnight. Added thereto was a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene (683 mg) as oil.

Reference Example 27

2-Chlorothieno[3,2-b]thiophene

(1) A solution of thieno[3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans* 1 1997, 3465-3470) (1.27 g) in tetrahydrofuran (30 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 5.70 ml). The mixture was stirred at 0° C. for 30 minutes, and cooled again to −78° C. Added thereto was a solution of hexachloroethane (2.14 g) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for one hour, and warmed to 0° C. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give 2-Chlorothieno[3,2-b]thiophene (1.19 g) as a solid.

Reference Example 28

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methoxybenzene

Thianaphthene was treated in a manner similar to Reference Example 7 to give the target compound. ESI-Mass m/Z 331/333 (M−H).

Reference Example 29

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-chlorobenzene

Thianaphthene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 30

3-Bromo-1-(5-methylbenzo[b]thiophen-2-ylmethyl) benzene

5-Methylbenzo[b]thiophene and 3-bromobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 31

3-Bromo-1-(6-fluorobenzo[b]thiophen-2-ylmethyl) benzene

(1) To a solution of 2,4-difluorobenzaldehyde (5.0 g) in dimethylsulfoxide (100 ml) were added methyl thioglycolate (3.45 ml) and triethylamine (10 ml), and the mixture was stirred at 80° C. overnight. The reaction mixture was poured into ice-cold water. The mixture was extracted with ethyl acetate, washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:1) to give 6-fluoro-2-methoxycarbonylbenzo[b]thiophene (1.32 g) as colorless powder. GC-EI-Mass m/Z 210 (M).

(2) The above 6-fluoro-2-methoxycarbonylbenzo[b] thiophene was treated in a manner similar to Reference Example 4-(1) to give 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid as colorless powder. ESI-Mass m/Z 195 (M−H).

(3) The above 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 4-(2) to give 6-fluoro-2-(N-methoxy-N-methylcarbamoyl)benzo[b] thiophene as colorless powder. APCI-Mass m/Z 240 (M+H).

(4) A solution of 1,3-dibromobenzene (493 mg) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 0.86 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of the above 6-fluoro-2-(N-methoxy-N-methylcarbamoyl)benzo[b]thiophene (500 mg) in tetrahydrofuran (3 ml). The mixture was warmed to room temperature, and added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-85:15) to give 3-bromophenyl 6-fluorobenzo [b]thiophen-2-yl ketone (479 mg) as a pale yellow solid. APCI-Mass m/Z 335/337 ($M+NH_4$).

(5) The above 3-bromophenyl 6-fluorobenzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 3-bromo-1-(6-fluorobenzo[b] thiophen-2-ylmethyl)benzene as a colorless solid.

Reference Example 32

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-fluorobenzene

Thianaphthene and 3-bromo-4-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 33

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethoxybenzene

Thianaphthene and 5-bromo-2-ethoxybenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 34

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-fluorobenzene

Thianaphthene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 35

2-(Benzo[b]thiophen-2-ylmethyl)-4-bromo-1-methoxynaphthalene

2,4-Dibromo-1-methoxynaphthalene (see J. Clayden, et al. *Org. Lett.*, 5, (2003) 831) and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 36

3-Bromo-1-(5-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

5-Trifluoromethylbenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 31-(3), (4), and (5) to give the target compound.

Reference Example 37

3-Bromo-1-(3-methylbenzo[b]thiophen-2-ylmethyl) benzene

3-Methylbenzo[b]thiophene-2-carboxaldehyde was treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 38

3-Bromo-1-(5-fluorobenzo[b]thiophen-2-ylmethyl) benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 31 to give the target compound.

Reference Example 39

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene

(1) 3-Bromo-4-methylbenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 3-bromo-4-methylbenzaldehyde as colorless crystals. APCI-Mass m/Z 213/215 (M+H+MeOH).

(2) The above 3-bromo-4-methylbenzaldehyde and thianaphthene were treated in a manner similar to Reference Example

7 to give (Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene as a colorless solid.

Reference Example 40

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-methylbenzene

3,5-Dibromotoluene and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 41

5-Bromo-2-chloro-1-(5-methylbenzo[b]thiophen-2-ylmethyl)benzene

5-Methylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 42

5-Bromo-2-chloro-1-(7-methylbenzo[b]thiophen-2-ylmethyl)benzene

7-Methylbenzo[b]thiophene (see Tilak, B. D. *Tetrahedron* 9 (1960) 76-95) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 43

5-Bromo-2-chloro-1-(5-chlorobenzo[b]thiophen-2-ylmethyl)benzene

5-Chlorobenzo[b]thiophene (see Tilak, B. D. *Tetrahedron* 9 (1960) 76-95) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 44

5-Bromo-2-chloro-1-(5,7-dimethylbenzo[b]thiophen-2-ylmethyl)benzene

5,7-Dimethylbenzo[b]thiophene (see Yoshimura, Y. et al., *J. Med. Chem.* 43 (2000) 2929-2937) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 45

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene

(1) A solution of thianaphthene (543 mg) in diethyl ether (20 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 1.74 ml). The reaction mixture was stirred at the same temperature for 3 hours. The reaction mixture was added dropwise to a solution of N-methoxy-N-methyl-5-bromo-2-methylbenzamide (1.15 g) obtained in Reference Example 4-(2) in diethyl ether (10 ml) cooled to −78° C. The mixture was warmed to room temperature and stirred for one hour. Added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-95:5) to give 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone (995 mg) as a pale yellow syrup. APCI-Mass m/Z 331/333 (M+H).
(2) The above 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 1-(benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene as colorless oil.

Reference Example 46

5-Bromo-2-chloro-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)benzene

6-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 47

5-Bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)benzene

(1) 4-Chloro-2-fluorobenzaldehyde was treated in a manner similar to Reference Example 31-(1) and (2) to give 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid as colorless crystals. ESI-Mass m/Z 211/213 (M−H).
(2) A solution of the above 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid (3.0 g) and copper powder (1.2 g) in quinoline (20 ml) was stirred at 210° C. for 40 minutes. The mixture was cooled to room temperature and diluted with diethyl ether, and insoluble materials were filtered off. The filtrate was washed successively with 10% aqueous hydrochloric acid solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 6-chlorobenzo[b]thiophene (1.79 g) as colorless crystals.
(3) The above 6-chlorobenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give 5-bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)benzene as colorless crystals.

Reference Example 48

5-Bromo-2-chloro-1-(6-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

2-Fluoro-4-trifluoromethylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 49

1-Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-chlorobenzene

3-Bromo-4-chlorobenzoic acid was treated in a manner similar to Reference Example 39 to give the target compound.

Reference Example 50

5-Bromo-2-chloro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,4-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 51

5-Bromo-2-fluoro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)benzene

6-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 50 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 52

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-chlorobenzene

1-Chloro-3,5-dibromobenzene and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 53

5-Bromo-2-chloro-1-(7-methoxybenzo[b]thiophen-2-ylmethyl)benzene

7-Methoxybenzo[b]thiophene (see WO 02/094262) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

Reference Example 54

5-Bromo-2-chloro-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)benzene

5-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

Reference Example 55

5-Bromo-2-chloro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 56

5-Bromo-2-chloro-1-(7-fluoro-6-methylbenzo[b]thiophen-2-ylmethyl)benzene

2,3-Difluoro-4-methylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

Reference Example 57

5-Bromo-2-chloro-1-(4-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2.6-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 58

5-Bromo-2-chloro-1-(7-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,3-difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 59

5-Bromo-2-chloro-1-(4-chlorobenzo[b]thiophen-2-ylmethyl)benzene

2-Chloro-6-fluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 60

5-Bromo-2-fluoro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)benzene

5-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 55 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 61

3-Bromo-2-chloro-1-(benzo[b]thiophen-2-ylmethyl)benzene

(1) 3-Bromo-2-chlorobenzoic acid (see Frederic Gohier et al., *J. Org. Chem.* (2003) 68 2030-2033.) was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-3-bromo-2-chlorobenzamide as oil. APCI-Mass m/Z 278/280/282 (M+H).

(2) The above N-methoxy-N-methyl-3-bromo-2-chlorobenzamide was treated in a manner similar to Reference Example 45 to give 3-bromo-2-chloro-1-(benzo[b]thiophen-2-ylmethyl)benzene as a colorless solid.

Reference Example 62

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethylbenzene

(1) To a solution of 2-ethylbenzoic acid (10.0 g) in dichloromethane (50 ml) were added oxalyl chloride (7.0 ml) and N,N-dimethylformamide (3 drops) and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The acid chloride was dissolved in methanol (60 ml) and the mixture was stirred at room temperature for 3 hours, and then, the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to

give methyl 2-ethylbenzoate, which was used in the subsequent step without further purification.

(2) The above methyl 2-ethylbenzoate was mixed with molecular sieve 13× (powder, 70 g), and while stirring the mixture, bromine (5.2 ml) was added dropwise thereto at 80° C. The mixture was further stirred at the same temperature for 1.5 hours. The mixture was cooled to room temperature, and added thereto were potassium carbonate (7.4 g), water (70 ml) and methanol (350 ml), and the mixture was stirred for 8 hours. Insoluble materials were filtered off, and suspended in a mixed solution of methanol (500 ml)—water (500 ml), and the mixture was stirred at room temperature overnight. Insoluble materials were filtered off and the filtrate was combined with the previously obtained filtrate, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was distilled under reduced pressure, to give methyl 5-bromo-2-ethylbenzoate (2.44 g). APCI-Mass m/Z 260/262 ($M+NH_4$).

(3) The above methyl 5-bromo-2-ethylbenzoate was treated in a manner similar to Reference Example 4-(1) and (2) to give N-methoxy-N-methyl-5-bromo-2-ethylbenzamide as colorless oil. APCI-Mass m/Z 272/274 (M+H).

(4) The above N-methoxy-N-methyl-5-bromo-2-ethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give 1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethylbenzene as oil.

Reference Example 63

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-trifluoromethylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-iodobenzamide as a pale yellow solid. APCI-Mass m/Z 370/372 (M+H).

(2) To a solution of the above N-methoxy-N-methyl-5-bromo-2-iodobenzamide (2.67 g) in N-methyl-2-pyrrolidinone (12 ml) were added copper (I) bromide (124 mg) and methyl fluorosulfonyl(difluoro)acetate (1.34 ml), and the mixture was stirred under heating for 1.5 hours. The reaction mixture was cooled to room temperature, and then, a diluted aqueous ammonia was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide (1.59 g) as colorless oil. APCI-Mass m/Z 312/314 (M+H).

(3) The above N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give 1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-trifluoromethylbenzene as a colorless solid. ESI-Mass m/Z 369/371 (M−H).

Reference Example 64

5-Bromo-2-chloro-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 363/365 (M+H).

Reference Example 65

5-Bromo-2-chloro-1-(5-(4-methylphenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(4-methylphenyl)thiophene as colorless crystals. APCI-Mass m/Z 175 (M+H).

(2) The above 2-(4-methylphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-methylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 377/379 (M+H).

Reference Example 66

5-Bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)benzene

(1) 2-Fluorobromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-fluorophenyl)thiophene as a colorless liquid.

(2) The above 2-(2-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 381/383 (M+H).

Reference Example 67

5-Bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 4-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(4-fluorophenyl)thiophene as colorless powder.

(2) The above 2-(4-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)benzene as colorless powder.

Reference Example 68

5-Bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)benzene

(1) 2-Bromothiophene and 4-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-ethoxyphenyl)thiophene as a colorless solid. APCI-Mass m/Z 205 (M+H).

(2) The above 2-(4-ethoxyphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 407/409 (M+H).

Reference Example 69

5-Bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)benzene

(1) 2-Bromothiophene and 3-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethoxyphenyl)thiophene as colorless oil. APCI-Mass m/Z 205 (M+H).

(2) The above 2-(3-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to

give 5-bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H).

Reference Example 70

5-Bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 2-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-ethoxyphenyl)thiophene as a pale yellow solid.
(2) The above 2-(2-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H).

Reference Example 71

5-Bromo-2-fluoro-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

Reference Example 72

5-Bromo-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(4-Ethoxyphenyl)thiophene obtained in Reference Example 68-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 73

5-Bromo-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(2-Ethoxyphenyl)thiophene obtained in Reference Example 70-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 74

5-Bromo-2-fluoro-1-(5-(2-fluorophenyl)-2-thienylmethyl)benzene

2-(2-Fluorophenyl)thiophene obtained in Reference Example 66-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 365/367 (M+H).

Reference Example 75

5-Bromo-2-chloro-1-(5-(3-fluorophenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 3-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-fluorophenyl)thiophene as oil.
(2) The above 2-(3-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give the target compound as powder.

Reference Example 76

5-Bromo-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(3-Ethoxyphenyl)thiophene obtained in Reference Example 69-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 77

5-Bromo-2-fluoro-1-(5-(3-fluorophenyl)-2-thienylmethyl)benzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 78

5-Bromo-2-fluoro-1-(5-(4-fluorophenyl)-2-thienylmethyl)benzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 79

5-Bromo-2-methyl-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 343/345 (M+H).

Reference Example 80

5-Bromo-1-(5-(3-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 81

5-Bromo-1-(5-(4-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-methylbenzoic acid obtained

in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 82

5-Bromo-2-methoxy-1-(5-phenyl-2-thienylmethyl) benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 359/361 (M+H).

Reference Example 83

5-Bromo-2-methyl-1-(5-(3-methylphenyl)-2-thienyl-methyl)benzene

(1) 2-Bromothiophene and 3-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methylphenyl)thiophene as colorless oil.
(2) The above 2-(3-methylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 357/359 (M+H).

Reference Example 84

5-Bromo-2-chloro-1-(5-(3-methylphenyl)-2-thienyl-methyl)benzene

2-(3-Methylphenyl)thiophene obtained in Reference Example 83-(1) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 377/379/381 (M+H).

Reference Example 85

5-Bromo-2-chloro-1-(5-(3-chlorophenyl)-2-thienyl-methyl)benzene

(1) 2-Bromothiophene and 3-chlorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-chlorophenyl)thiophene as colorless oil.
(2) The above 2-(3-chlorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give the target compound as colorless oil.

Reference Example 86

5-Bromo-1-(5-(3-chlorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Chlorophenyl)thiophene obtained in Reference Example 85-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound as colorless oil.

Reference Example 87

5-Bromo-1-(5-(3-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) 3-Methoxybromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methoxyphenyl)thiophene as a yellow liquid. APCI-Mass m/Z 191 (M+H).
(2) The above 2-(3-methoxyphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound as yellow oil. APCI-Mass m/Z 373/375 (M+H).

Reference Example 88

4-Bromo-2-(4-ethylphenylmethyl)-2H-isoquinolin-1-one

4-Bromo-2H-isoquinolin-1-one (see EP0355750) was treated in a manner similar to Reference Example 2 to give the target compound. APCI-Mass m/Z 342/344 (M+H).

Reference Example 89

4-Bromo-2-(4-ethylphenylmethyl)-8-methyl-2H-isoquinolin-1one

(1) To a solution of 8-methyl-2H-isoquiolin-1-one (1.15 g) in dichloromethane (20 ml) was added dropwise a solution of bromine (1.26 g) in dichloromethane (4 ml) at room temperature. The mixture was stirred at the same temperature for one hour. and the solvent was evaporated under reduced pressure. The residue was crystallized from ether to give 4-bromo-8-methyl-2H-isoquinolin-1-one (1.86 g) as colorless crystals. APCI-Mass m/Z 238/240 (M+H).
(2) The above 4-bromo-8-methyl-2H-isoquinolin-1-one was treated in a manner similar to Reference Example 2 to give the target compound as colorless crystals. APCI-Mass m/Z 356/358M+H).

Reference Example 90

4-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) A solution of 4-bromo-2-thiophenecarboxaldehyde (4.78 g) in tetrahydrofuran (40 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise 4-ethylphenyl-magnesium bromide (0.5 M tetrahydrofuran solution, 50 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate—97:3-84:16) to give 4-bromo-2-thienyl-4-ethylphenylmethanol (5.37 g) as colorless oil. APCI-Mass m/Z 279/281 (M+H—H_2O).
(2) The above 4-bromo-2-thienyl-4-ethylphenylmethanol was treated in a manner similar to Reference Example 1-(2) to give the target compound as colorless oil.

Reference Example 91

5-Bromo-2-(4-ethylphenylmethyl)thiophene

5-Bromo-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound. ESI-Mass m/Z 279/281 (M−H).

Reference Example 92

3-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) 2,3-Dibromothiophene and 4-ethylbenzaldehyde were treated in a manner similar to Reference Example 1-(1) to

give 3-bromo-2-thienyl-4-ethylphenylmethanol as yellow oil. APCI-Mass m/Z 279/281 (M+H—H_2O).

(2) A solution of the above 3-bromo-2-thienyl-4-ethylphenylmethanol (12.4 g) in diethyl ether (10 ml) was added dropwise into a suspension of lithium aluminum hydride (2.6 g) and aluminum chloride (9.0 g) in diethyl ether (35 ml) at 0° C. Subsequently, the mixture was stirred at room temperature overnight, and then poured onto ice. The mixture was extracted with diethyl ether, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-2-(4-ethylphenylmethyl)thiophene (8.77 g) as colorless oil. APCI-Mass m/Z 279/281 (M+H).

Reference Example 93

5-Bromo-3-(4-ethylphenylmethyl)thiophene

5-Bromo-3-thiophenecarboxaldehyde (see Amishiro, N. et al., *Chem. Pharm. Bull.* 47 (1999) 1393-1403.) was treated in a manner similar to Reference Example 90 to give the target compound.

Reference Example 94

5-Bromo-2-chloro-3-(4-ethylphenylmethyl)thiophene

(1) 5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chloro-3-thiophenecarboxaldehyde as pale yellow oil. APCI-Mass m/Z 239/241/243 (M+H+MeOH—H_2O).

(2) The above 5-bromo-2-chloro-3-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound as colorless oil.

Reference Example 95

5-Bromo-3-chloro-2-(4-ethylphenylmethyl)thiophene

(1) A solution of diisopropylamine (6.8 ml) in tetrahydrofuran (75 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 30.5 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 3-chloro-2-thiophenecarboxylic acid (3.92 g) in tetrahydrofuran (40 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise 1,2-dibromo-1,1,2,2-tetrafluoroethane (6.0 ml). The mixture was stirred at the same temperature for one hour, and then, warmed to room temperature. The mixture was poured into a diluted aqueous hydrochloric acid solution, and the solution was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was crystallized from a mixed solvent of diisopropyl ether and hexane to give 5-bromo-3-chloro-2-thiophenecarboxylic acid (3.79 g) as a yellow solid. ESI-Mass m/Z 239/241 (M−H).

(2) The above 5-bromo-3-chloro-2-thiophenecarboxylic acid was treated in a manner similar to Reference Example 94 to give 5-bromo-3-chloro-2-(4-ethylphenylmethyl)thiophene as colorless oil.

Reference Example 96

3-Bromo-1-(benzo[b]thiophen-3-ylmethyl)benzene

Thianaphthene-3-carboxaldehyde was treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 97

3-Bromo-1-(5-ethyl-2-furylmethyl)benzene

(1) 5-Ethyl-2-furaldehyde was treated in a manner similar to Reference Example 1-(1) to give 3-bromophenyl-5-ethyl-2-furylmethanol as oil. APCI-Mass m/Z 263/265 (M+H—H_2O).

(2) The above 3-bromophenyl-5-ethyl-2-furylmethanol was treated in a manner similar to Reference Example 9-(2) to give the target compound as oil.

Reference Example 98

3-Bromo-1-(benzo[b]furan-2-ylmethyl)benzene

2-Benzo[b]furancarboxaldehyde was treated in a manner similar to Reference Example 97 to give the target compound.

Reference Example 99

1-(Benzo[b]furan-2-ylmethyl)-5-bromo-2-chlorobenzene

Benzo[b]furan and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 100

1-(Benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene

(1) Benzothiazole and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-methylphenyl-(benzothiazol-2-yl)methanol as pale yellow crystals. APCI-Mass m/Z 334/336 (M+H).

(2) To a solution of the above 5-bromo-2-methylphenyl-(benzothiazol-2-yl)methanol (2.60 g) in dichloromethane (30 ml)-toluene (10 ml) was added manganese (IV) oxide (3.42 g), and the mixture was stirred at room temperature for 3 hours. Insoluble materials were filtered off, and the filtrate was evaporated under reduced pressure to give 5-bromo-2-methylphenyl benzothiazol-2-yl ketone (2.45 g) as colorless crystals. APCI-Mass m/Z 332/334 (M+H).

(3) The above 5-bromo-2-methylphenyl benzothiazol-2-yl ketone was treated in a manner similar to Reference Example 14-(1) to give 1-(benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene as oil. APCI-Mass m/Z 318/320 (M+H).

Reference Example 101

1-(Benzothiazol-2-ylmethyl)-5-bromo-2-chlorobenzene

Benzothiazole and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a man-

ner similar to Reference Example 100 to give the target compound. APCI-Mass m/Z 338/340 (M+H).

Reference Example 102

5-Bromo-2-chloro-1-(5-phenyl-2-thiazolylmethyl) benzene

(1) A solution of thiazole (10.0 g), iodobenzene (2.63 ml), tetrakis(triphenylphosphine)palladium (0) (1.36 g) and potassium acetate (3.46 g) in N,N-dimethylacetamide (100 ml) was stirred under heating at 100° C. overnight. The solvent was evaporated under reduced pressure, and added to the residue was ethyl acetate. The mixture was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-90:10) to give 5-phenylthiazole (1.50 g) as a pale yellow solid. APCI-Mass m/Z 162 (M+H).
(2) The above 5-phenylthiazole and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 100 to give 5-bromo-2-chloro-1-(5-phenyl-2-thiazolylmethyl)benzene as a yellow solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 103

3-(4-Ethylphenylmethyl)-2,4-pentanedione

A suspension of sodium iodide (15.0 g) in acetonitrile (100 ml) was cooled to 0° C. under argon atmosphere, and thereto were added dropwise chlorotrimethylsilane (12.7 ml), 2,4-pentanedione (2.05 ml) and 4-ethylbenzaldehide (2.68 g), successively. The reaction mixture was stirred at room temperature for 17 hours, and further stirred at 60° C. for 10 hours. The reaction mixture was cooled to room temperature and poured into an aqueous sodium thiosulfate solution. The mixture was extracted with diethyl ether, and the extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) to give 3-(4-ethylphenylmethyl)-2,4-pentanedione (2.72 g) as pale yellow oil. APCI-Mass m/Z 219 (M+H).

Reference Example 104

Tri-n-butyl(4-ethylphenyl)tin

To a solution of magnesium (896 mg) in tetrahydrofuran (20 ml) was added dibromoethane (0.1 ml), and the mixture was stirred at room temperature for 15 minutes. Thereto was added dropwise a solution of 1-bromo-4-ethylbenzene (5.7 g) in tetrahydrofuran (20 ml), and subsequently, the mixture was stirred at room temperature for one hour. The reaction mixture was cooled to −78° C., and thereto was added dropwise tributyltin chloride (9.49 g). The mixture was stirred at the same temperature for 30 minutes, and then at room temperature for one hour. To the reaction mixture were added 10% aqueous potassium fluoride solution and ethyl acetate, and the mixture was stirred at room temperature for 30 minutes. Insoluble materials were filtered off. The organic layer of the filtrate was washed with water and brine successively, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by alumina column chromatography (hexane) to give the desired tri-n-butyl(4-ethylphenyl)tin (10.7 g) as colorless oil. EI-Mass m/Z 337 (M-Bu).

Reference Example 105

4-(4-Ethylphenylmethyl)pyrazole

(1) A mixed solution of 4-ethylbenzyl bromide (10.0 g), malononitrile (6.64 g), potassium carbonate (6.94 g) and tetra-n-butylammonium bromide (648 mg) in toluene (100 ml) was agitated at room temperature for 17 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate twice. The extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=6:1) to give 2-(4-ethylphenylmethyl)malononitrile (3.28 g) as a colorless solid.
(2) A solution of the above 2-(4-ethylphenylmethyl) malononitrile (1.30 g) and hydrazine hydrate (0.86 ml) in ethanol (35 ml) was heated under reflux for 4 hours. Hydrazine hydrate (0.43 ml) was further added thereto and the mixture was further heated under reflux for 4 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-diethyl ether to give 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (2.63 g) as pale pink powder. APCI-Mass m/Z 217 (M+H).
(3) The above 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (1.30 g) was added to 50% aqueous phosphoric acid solution (19 ml), and further added thereto was water (10 ml). The mixture was cooled to 0° C., and thereto was added dropwise an aqueous solution (4 ml) of sodium nitrite (912 mg). The mixture was stirred at the same temperature for 30 minutes, and further stirred at room temperature for 4 hours. The reaction mixture was cooled again to 0° C., 10% aqueous sodium hydroxide solution was added thereto to adjust pH of the reaction mixture to 7. The mixture was extracted with ethyl acetate, washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10) to give the desired 4-(4-ethylphenylmethyl)pyrazole (414 mg) as a pale brown semisolid. APCI-Mass m/Z 187 (M+H).

Reference Example 106

3-(4-Ethylphenylmethyl)-5-methyl-1H-pyrazole

(1) 4-Ethylphenylacetic acid (3.0 g) (see Japanese Unexamined Patent Publication 63-233975) was dissolved in dichloromethane (15 ml), and thereto were added oxalyl chloride (6.0 ml) and N,N-dimethylformamide (one drop). The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene to give a crude 4-ethylphenylacetyl chloride, which was used in the subsequent step without further purification.
(2) A suspension of magnesium chloride (1.74 g) in dichloromethane (30 ml) was cooled to 0° C., and thereto were added t-butyl acetoacetate (3.03 ml) and pyridine (2.96 ml), and successively was added a solution of the above 4-ethylphenylacetyl chloride in dichloromethane (30 ml). The mixture was stirred at the same temperature for 2.5 hours, and an aqueous citric acid solution was added thereto. The mix-

ture was extracted with chloroform. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=15:1) to give t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate (4.75 g) as pale yellow oil. APCI-Mass m/Z 322 ($M+NH_4$).

(3) A solution of the above t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate in trifluoroacetic acid (60 ml) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate, and the mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (4.00 g) as yellow oil. APCI-Mass m/Z 205 (M+H).

(4) A solution of the above 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (3.98 g) and hydrazine hydrate (4.0 ml) in toluene (20 ml) was stirred under heating at 100° C. for 1.5 hours. The reaction mixture was cooled to room temperature, and washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:ethyl acetate=2:1) to give 3-(4-ethylphenylmethyl)-5-methyl-1H-pyrazole (3.12 g) as yellow oil. APCI-Mass m/Z 201 (M+H).

Reference Example 107

3-(4-Ethylphenylmethyl)-6-hydroxypyridine

(1) To a solution of 6-chloronicotinoyl chloride (10.0 g) and N,O-dimethylhydroxyamine hydrochloride (6.65 g) in dichloromethane (200 ml) was added dropwise triethylamine (17.2 g) at 0° C. Subsequently the mixture was stirred at room temperature overnight. The mixture was washed successively with water, 5% aqueous citric acid solution, water and brine, and then, dried over sodium sulfate. The solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-6-chloronicotinamide (11.73 g) as pale yellow oil. APCI-Mass m/Z 201/203 (M+H).

(2) A solution of the N-methoxy-N-methyl-6-chloronicotineamide (4.2 g) in tetrahydrofuran (40 ml) was cooled to 0° C., and thereto was added dropwise 4-ethylphenylmagnesium bromide (0.5 M tetrahydrofuran solution, 55 ml). The mixture was stirred at 0° C. for 4 hours, and then at the room temperature for 10 minutes. The reaction mixture was cooled again to 0° C., and added thereto was 10% aqueous hydrochloric acid solution. The mixture was extracted with ethyl acetate, and washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=20:1) to give 6-chloro-3-pyridyl 4-ethylphenyl ketone (3.68 g) as colorless crystals. APCI-Mass m/Z 246/248 (M+H).

(3) The above 6-chloro-3-pyridyl 4-ethylphenyl ketone (1.68 g) was dissolved in N-methyl-2-pyrrolidinone (20 ml), and thereto were added benzylalcohol (815 ml) and 60% sodium hydride (275 mg). The mixture was stirred at room temperature for 6 hours, and then at 90° C. for one hour. The reaction mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-95:5) to give 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.68 g) as colorless oil. APCI-Mass m/Z 318 (M+H).

(4) The above 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (865 mg) was dissolved in ethylene glycol (8.5 ml), and thereto were added hydrazine hydrate (0.44 ml) and potassium hydroxide (550 mg). The mixture was stirred under heating at 190° C. for 8 hours. The reaction mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water three times, and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-0:100) to give the desired 3-(4-ethylphenylmethyl)-6-hydroroxypyridine (256 mg) as colorless powder. APCI-Mass m/Z 214 (M+H).

Reference Example 108

3-(4-Ethylphenylmethyl)-2-hydroxypyridine

(1) 2-Chloronicotinoyl chloride was treated in a manner similar to Reference Example 107-(1), (2) and (3) to give 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone as colorless oil. APCI-Mass m/Z 318 (M+H).

(2) The above 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.69 g) was dissolved in ethanol (15 ml), and thereto was added sodium borohydride (403 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed with water and successively with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give crude 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol as colorless oil, which was used in the subsequent step without further purification.

(3) The above 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol was dissolved in methanol (10 ml), and thereto were added concentrated hydrochloric acid (1.0 ml) and 10% palladium-carbon (500 mg). The mixture was stirred at room temperature for 15 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with water and successively with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-97:3) to give the desired 3-(4-ethylphenylmethyl)-2-hydroroxypyridine (307 mg) as a pale brown solid. APCI-Mass m/Z 214 (M+H).

Reference Example 109

3-(4-Ethylphenylmethyl)-1H-indole

(1) To a solution of indole (6.00 g) in methanol (60 ml) were added sodium hydroxide (2.25 g) and 4-ethylbenzaldehyde (7.56 g), and the mixture was stirred at room temperature for 3 days under argon atmosphere. Added thereto was water, and methanol was evaporated under reduced pressure. The residue was extracted with diethyl ether, and the extract was washed with water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hex-

ane:ethyl acetate=98:2-70:30) to give 4-ethylphenyl-(1H-indol-3-yl)methanol (2.10 g) as a colorless solid. APCI-Mass m/Z 234 (M+H—H_2O).

(2) The above 4-ethylphenyl-(1H-indol-3-yl)methanol was treated in a manner similar to Reference Example 1-(2) to give the desired 3-(4-ethylphenylmethyl)-1H-indole as colorless crystals. APCI-Mass m/Z 236 (M+H).

Reference Example 110

3-(4-Ethylphenylmethyl)-1H-indazole

(1) A mixture of zinc powder (712 mg) and dibromoethane (0.04 ml) in N,N-dimethylformamide (2.5 ml) were stirred under heating at 70° C. for 10 minutes under argon atmosphere. The reaction mixture was cooled to room temperature, and chlorotrimethylsilane (0.04 ml) was added thereto, and the mixture was stirred at room temperature for 30 minutes. To the activated zinc solution was added dropwise a solution of 4-ethylbenzyl bromide (1.74 g) in N,N-dimethylformamide (10 ml) at 0° C. over a period of 2 hours. Subsequently, the mixture was stirred at 0° C. for 2 hours, to prepare a solution of 4-ethylbenzylzinc bromide in N,N-dimethylformamide, which was used in the subsequent step without further purification.

(2) A solution of tris(dibenzylideneacetone)dipalladium (0) (167 mg) and tri(2-furyl)phosphine (135 mg) in tetrahydrofuran (20 ml) was stirred at room temperature for 5 minutes under argon atmosphere. Thereto were added 1-t-butoxycarbonyl-3-iodo-1H-indazole (2.0 g) and the above 4-ethylbenzylzinc bromide (N,N-dimethylformamide solution) at 0° C., and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into water, and the mixture was extracted with diethyl ether. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-92:8) to give 1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.37 g) as colorless oil. APCI-Mass m/Z 337 (M+H).

(3) The above 1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.35 g) was dissolved in methanol (15 ml), and added thereto was 28% sodium methoxide solution (methanol solution, 1.0 ml), and the mixture was stirred at room temperature for one hour. Added thereto was an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from hexane to give the desired 3-(4-ethylphenylmethyl)-1H-indazole (800 mg) as colorless crystals. APCI-Mass m/Z 237 (M+H).

Reference Example 111

5-Bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 4-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-trifluoromethylphenyl)thiophene as colorless crystals.

(2) The above 2-(4-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienylmethyl) benzene as colorless crystals. APCI-Mass m/Z 425/427 (M+H+MeOH).

Reference Example 112

5-Bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 3-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-trifluoromethylphenyl)thiophene as colorless oil.

(2) The above 2-(3-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desire 5-bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienylmethyl)benzene as colorless oil.

Reference Example 113

2-(4-Ethylphenyl)thiophene

2-Bromothiophene and 4-ethylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

Reference Example 114

2-(4-Methylphenyl)thiophene

2-Bromothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

Reference Example 115

2-(2,3-Dihydro-5-benzo[b]furanyl)thiophene

(1) 5,7-Dibromo-2,3-dihydrobenzo[b]furan (see WO 02/070020) (3.0 g) in diethyl ether was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.09 ml). The mixture was stirred at the same temperature for 30 minutes, and poured into a saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2,3-dihydrobenzo[b]furan (2.0 g) as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2,3-dihydrobenzo[b]furan and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give the desired 2-(2,3-dihydro-5-benzo[b]furanyl)thiophene as pale yellow crystals. APCI-Mass m/Z 203 (M+H).

Reference Example 116

4-Bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (1.04 g) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.58 M hexane solution, 4.43 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 1-bromo-4-fluoronaphthalene (1.50 g) in tetrahydrofuran (12 ml) at −78° C. The mix-

ture was stirred at the same temperature for one hour, and thereto was added dropwise a solution of 5-chloro-2-thiophenecarboxaldehyde (1.07 g) in tetrahydrofuran (11 ml) at −78° C. The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by an aminosilane-treated silica gel column chromatography (hexane:ethyl acetate=3:1) to give 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol (2.00 g) as pale yellow powder. APCI-Mass m/Z 353/355 (M+H—H_2O).

(2) The above 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol was treated in a manner similar to Reference Example 1-(2) to give the desired 4-bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene as a yellow solid.

Reference Example 117

5-Bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl) benzene

(1) 2,4-dimethylbenzoic acid (20.0 g) was suspended in chloroform (100 ml), and thereto were added oxalyl chloride (6.8 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol (200 ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give methyl 2,4-dimethylbenzoate as pale yellow oil, which was used in the subsequent step without further purification.

(2) To a mixture of the above methyl 2,4-dimethylbenzoate (19.75 g) and activated aluminum neutral oxide (120 g) was added dropwise bromine (9.25 ml) while stirring at room temperature. The mixture was stirred at room temperature for 8 hours, and diluted with diethyl ether (1000 ml). Insoluble materials were filtered off, and washed with diethyl ether (500 ml). The combined filtrate was washed successively with 10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol (40 ml) to give methyl 5-bromo-2,4-dimethylbenzoate (6.34 g) as colorless crystals. APCI-Mass m/Z 243/245 (M+H).

(3) The above methyl 5-bromo-2,4-dimethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2,4-dimethylbenzoic acid as colorless crystals. ESI-Mass m/Z 227/229 (M−H)

(4) The above 5-bromo-2,4-dimethylbenzoic acid and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 357/359 (M+H).

Reference Example 118

5-Bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 117-(1) to give methyl 5-bromo-2-iodobenzoate as a brown solid.

(2) To a solution of the above methyl 5-bromo-2-iodobenzoate (4.65 g) in N-methyl-2-pyrrolydinone (20 ml) were added copper (I) bromide (235 mg) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.6 ml), and the mixture was stirred under heating at 120° C. for 1.5 hours. The reaction mixture was cooled, and added thereto were 10% aqueous hydrochloric acid solution and ethyl acetate. Insoluble materials were filtered off, and an organic layer of the filtrate was washed with water for 4 times, and subsequently washed with a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexan: ethyl acetate=80:1) to give methyl 5-bromo-2-trifluoromethylbenzoate (3.55 g) as colorless oil.

(3) The above methyl 5-bromo-2-trifluoromethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2-trifluoromethylbenzoic acid as pale brown crystals. ESI-Mass m/Z 267/269 (M−H).

(4) The above 5-bromo-2-trifluoromethylbenzoic acid and 2-phenylthiophene were treated in a manner similar to Reference Example 5-(1) to give 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone as pale yellow crystals. APCI-Mass m/Z 411/413 (M+H).

(5) To a mixed solution of the above 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone (670 mg) in methanol (20 ml)-tetrahydrofuran (10 ml) was added sodium borohydride (62 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in chloroform (10 ml)acetonitrile (20 ml). Thereto was added triethylsilane (0.78 ml), and the mixture was cooled to 0° C. Thereto was added dropwise boron trifluoride•diethyl ether complex (0.52 ml). The mixture was stirred at room temperature for 45 minutes, and added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give the desired 5-bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethylbenzene (565 mg) as colorless oil.

Reference Example 119

5-Bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methylbenzene

(1) 1-Bromo-3-ethylbenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethylphenyl)thiophene as a pale yellow liquid.

(2) The above 2-(3-ethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give 5-bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methylbenzene as pale yellow oil. APCI-Mass m/Z 371/373 (M+H).

Reference Example 120

5-Bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl) benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-

2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol as colorless oil. APCI-Mass m/Z 360/362 (M+H).

(2) A solution of the above 5-bromo-2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol (1.59 g) in trifluoroacetic acid (40 ml) was cooled to 0° C., and thereto were added gradually sodium triacetoxyborohydride (4.68 g). The mixture was stirred at room temperature for one hour, and cooled again to 0° C. 10% aqueous sodium hydroxide solution was added thereto to basify the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give the desired 5-bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl)benzene (1.38 g) as a colorless solid. APCI-Mass m/Z 344/346 (M+H).

Reference Example 121

2-(5-Fluoro-2-thienyl)thiophene

2,2'-Bithiophene (7.40 g) in tetrahydrofuran (90 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise n-butyl lithium (1.59 M hexane solution, 28.0 ml). The mixture was stirred at 0° C. for one 30 minutes, and cooled again to −78° C. Added thereto was N-fluorobenzenesulfonimide (15.5 g), and the mixture was gradually warmed, and stirred at room temperature for 17 hours. The reaction mixture was poured into ice-cold water, and the solution was extracted with hexane twice, and the extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-fluoro-2-thienyl) thiophene (5.89 g) as colorless oil.

Reference Example 122

5-Bromo-2-methyl-1-(5-(3-pyridyl)-2-thienylmethyl) benzene

2-(3-Pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the target compound as colorless crystals. APCI-Mass m/Z 344/346 (M+H).

Reference Example 123

5-Bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) p-Bromoanisole and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-methoxyphenyl)thiophene as a pale yellow solid. APCI-Mass m/Z 191 (M+H).

(2) The above 2-(4-methoxyphenyl)thiophene and 4-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene as a pale yellow solid. APCI-Mass m/Z 373/375 (M+H).

Reference Example 124

5-bromo-2-methyl-1-(5-(1,2-Methylenedioxybenzen-4-yl)-2-thienylmethyl)benzene

4-Bromo-1,2-(methylenedioxy)benzene was treated in a manner similar to Reference Example 119 to give the target compound as colorless powder.

Reference Example 125

5-Bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl) benzene

(1) To a solution of 5-bromo-2-chlorobenzyl alcohol (10.66 g) in toluene (100 ml) solution were added thionyl chloride (10 ml), and pyridine (2 drops), and the mixture was stirred under heating at 100° C. overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, a 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride was dissolved in acetonitrile (100 ml), and the mixture was cooled to 0° C. Added thereto was tetraethylammonium cyanide (8.8 g), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetonitrile as a pale yellow solid, which was used in the subsequent step without further purification.

(3) The above 5-bromo-2-chlorophenylacetonitrile was added to water (90 ml)-sulfuric acid (75 ml), and the mixture was stirred under heating at 160° C. overnight. The mixture was further diluted with water, and cooled to 0° C. The solvent was removed by decant, and the residue was dissolved in diethyl ether. The solution was washed with water and brine, and extracted with 10% sodium hydroxide. To the extract was added concentrated hydrochloric acid to make the solution acidic. The precipitates were collected by filtration, and purified by silica gel column chromatography (chloroform) to give 5-bromo-2-chlorophenylacetic acid (6.67 g) as colorless crystals. ESI-Mass m/Z 247/249 (M−H).

(4) The above 5-bromo-2-chlorophenylacetic acid was treated in a manner similar to Reference Example 118-(4) and (5) to give the desired 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)benzene as a pale yellow solid. APCI-Mass m/Z 377/379 (M+H).

Reference Example 126

5-Bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl)-2-methylbenzene

(1) 2-Bromo-6-fluoropyridine and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(6-fluoro-2-pyridyl)thiophene as yellow oil. APCI-Mass m/Z 180 (M+H).

(2) The above 2-(6-fluoro-2-pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the desired 5-bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl)-2-methylbenzene as a colorless solid. APCI-Mass m/Z 362/364 (M+H).

Reference Example 127

5-Bromo-2-methyl-1-(5-trifluoromethyl-2-thienylmethyl)benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-methyl-

benzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the target compound as colorless oil.

Reference Example 128

5-Bromo-1-(5-(5-fluoro-2-thienyl)-2-thienylmethyl)-2-methylbenzene

5-Bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) and 2-(5-fluoro-2-thienyl)thiophene obtained in Reference Example 121 were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

Reference Example 129

3-Bromo-2-fluoro-6-methyl-1-(5-phenyl-2-thienylmethyl)benzene

4-Bromo-3-fluorotoluene and 5-phenyl-2-thiophenecarboxaldehyde were treated in a manner similar to Reference Example 116 to give the target compound as pale blue powders. APCI-Mass m/Z 361/363 (M+H).

Reference Example 130

5-Bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene

(1) 5-Bromo-2-chlorophenylacetic acid (2.0 g) obtained in Reference Example 125-(3) was dissolved in dichloromethane (40 ml), and thereto were added oxalyl chloride (0.77 ml) and N,N-dimethylformamide (one drop) at 0° C. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetyl chloride, which was used in the subsequent step without further purification.

(2) A solution of potassium t-butoxide (1.35 g) in tetrahydrofuran (20 ml) was cooled to 0° C., and thereto was added methyl isocyanoacetate (1.33 ml). Then, a solution of the above 5-bromo-2-chlorophenylacetyl chloride in tetrahydrofuran (20 ml) was added thereto, and the mixture was stirred at 0° C. for 2 hours, and then at room temperature overnight. The mixture was cooled again to 0° C. 10% aqueous citric acid solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)benzene (1.12 g) as a yellow solid. APCI-Mass m/Z 330/332 (M+H).

(3) The above 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)benzene (1.37 g) was heated under reflux in 6N aqueous hydrochloric acid solution (20 ml) overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol, and treated with carbon powder. The carbon powder was filtered off, and the filtrate was evaporated under reduced pressure to give crude 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene•hydrochloride (1.73 g) as a pale brown solid, which was used in the subsequent step without further purification. APCI-Mass m/Z 262/264 (M+H).

(4) A mixed solution of the above 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene•hydrochloride (1.70 g) in ethyl acetate (30 ml)-water (15 ml) was cooled to 0° C. Added thereto were benzoyl chloride (0.99 ml) and sodium hydrogen carbonate (2.39 g), and the mixture was stirred at the same temperature for 3 hours. The organic layer was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:ethyl acetate=95:5) to give 1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) as a colorless solid. APCI-Mass m/Z 366/368 (M+H).

(5) To a solution of the above 1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) in toluene (20 ml) was added Lawesson reagent (2.35 g), and the mixture was heated under reflux for 2 hours. The reaction mixture was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10) to give the desired 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene (512 mg) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 131

t-Butyl 5-bromo-2-chlorobenzoic Acid

To a solution of 5-bromo-2-chlorobenzoic acid (11.75 g) in N,N-dimethylformamide (50 ml) was added 1.1'-carbonyldiimidazole (8.10 g), and the mixture was stirred under heating at 40° C. for one hour. Thereto were added t-butanol (7.40 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (7.60 g), and the mixture was further stirred under heating at 40° C. overnight. The mixture was diluted with diethyl ether, and washed successively with water (3 times), 2% aqueous hydrochloric acid solution (twice), a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give t-butyl 5-bromo-2-chlorobenzoate (12.53 g) as pale yellow oil.

Reference Example 132

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

(1) A solution of 5-bromo-2-chloro-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)benzene (2.70 g) obtained in Reference Example 46 in dichloromethane (27 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise boron tribromide (0.83 ml). The mixture was warmed to room temperature, and stirred for 30 minutes. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and subsequently, the reaction mixture was made acidic with a saturated aqueous citric acid solution. The mixture was extracted with chloroform, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from chloroform-hexane to give 5-bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene (2.01 g) as pale green crystals. ESI-Mass m/Z 351/353 (M−H).

(2) The above 5-bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene (500 mg) was dissolved in N,N-dimethylformamide (5 ml), and thereto were added iodoethane (0.23 ml) and potassium carbonate (390 mg). The mixture was stirred at room temperature for 2 days. Added thereto was water, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica

gel column chromatography (hexane:ethyl acetate=98:2-80:20) to give the desired 5-bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene (492 mg) as pale pink oil. APCI-Mass m/Z 381/383 (M+H).

Reference Example 133

5-Bromo-2-chloro-3-(5-phenyl-2-thienylmethyl) thiophene

5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

Reference Example 134

6-Fluoro-2-pyridylboronic Acid Pinacol Ester

A solution of 2-bromo-6-fluoropyridine (1.0 g) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (2.59 M hexane solution, 2.24 ml) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 45 minutes, and thereto was added dropwise a solution of triisopropoxyborane (1.28 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 2 hours, warmed, and further stirred at room temperature for one hour. Subsequently, a solution of pinacol (0.91 g) in tetrahydrofuran (10 ml) was added dropwise thereto, and stirred at room temperature for 20 minutes. Insoluble materials were filtered off. The filtrate was extracted with 2.5% sodium hydroxide, and the extract was cooled to 0° C., and was made weakly acidic with 2N aqueous hydrochloric acid solution. It was extracted with diethyl ether, washed with a small amount of brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was solidified with hexane to give 6-fluoro-2-pyridylboronic acid pinacol ester (850 mg) as a colorless solid. APCI-Mass m/Z 224 (M+H).

Reference Example 135

5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl) benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-chlorobenzamide as a colorless solid. APCI-Mass m/Z 278/280 (M+H).
(2) The above N-methoxy-N-methyl-5-bromo-2-chlorobenzamide and 2,5-dibromopyridine were treated in a manner similar to Reference Example 31-(4) to give 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone as a pale yellow solid. APCI-Mass m/Z 374/376 (M+H).
(3) The above 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone and phenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone as yellow crystals. APCI-Mass m/Z 372/374 (M+H).
(4) The above 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene as colorless crystals. APCI-Mass m/Z 358/360 (M+H).

Reference Example 136

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b] thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 132-(1) and 2-iodopropane were treated in a manner similar to Reference Example 132-(2) to give the titled compound. APCI-Mass m/Z 395/397 (M+H).

Reference Example 137

4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl) naphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (4.13 ml) in tetrahydrofuran (40 ml) was cooled to −78° C. under argon atmosphere, and added dropwise thereto was n-butyl lithium (2.44 M hexane solution, 10.0 ml). The mixture was stirred at the same temperature for 30 minutes, and added dropwise thereto at −78° C. was a solution of 1-bromo-4-fluoronaphthalene (5.0 g) in tetrahydrofuran (20 ml). The mixture was stirred at the same temperature for 1 hour, and added dropwise thereto at −78° C. was N,N-dimethylformamide (5.16 ml). The mixture was stirred at the same temperature for 1 hour, and added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from diisopropyl ether and hexane to give 4-bromo-1-fluoro-2-naphthaldehyde (4.43 g) as pale yellow crystals. APCI-Mass m/Z 267/269 ($M+NH_4$).
(2) The above 4-bromo-1-fluoro-2-naphthaldehyde and 2-(2-pyridyl)thiophene were treated in a manner similar to Reference Example 120 to give the desired 4-bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl)naphthalene as colorless powder. APCI-Mass m/Z 398/400 (M+H).

Reference Example 138

5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene

(1) 5-Bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone (3.2 g) from Reference Example 135-(2) was dissolved in tetrahydrofuran (80 ml), and added thereto were triethylaluminium (1.0 M hexane solution, 9.9 ml), tetrakis(triphenylphosphine) palladium(0) (570 mg) and cerium(III) chloride (7.3 g), and the mixture was stirred at 30° C. for 1.5 hours. The reaction mixture was diluted with methanol, and the reaction solution was basified with a saturated aqueous sodium hydrogen carbonate solution. The insoluble materials were filtered off and, the filtrate was extracted with ethyl acetate and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=99:1-85:15) to give 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone (1.98 g) as a colorless solid. APCI-Mass m/Z 324/326 (M+H).
(2) The above 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene as a colorless oil. APCI-Mass m/Z 310/312 (M+H).

Reference Example 139

6-Ethylbenzo[b]thiophene

(1) 4-Bromo-2-fluorobenzaldehyde and ethyl thioglycolate were treated in a manner similar to Reference Example 31-(1) to give 6-bromo-2-ethoxycarbonylbenzo[b]thiophene as a colorless solid.

(2) The above 6-bromo-2-ethoxycarbonylbenzo[b]thiophene was treated in a manner similar to Reference Example 138-(1) to give 6-ethyl-2-ethoxycarbonylbenzo[b]thiophene as colorless oil. APCI-Mass m/Z 235 (M+H).

(3) The above 6-ethyl-2-ethoxycarbonylbenzo[b]thiophene (1.26 g) was dissolved in tetrahydrofuran (4 ml) and methanol (8 ml), and added thereto was lithium hydroxide monohydrate (677 mg), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in water and the solution was made acidic with a 10% aqueous hydrochloric acid solution. The precipitates were collected by filtration and washed with water to give 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid (1.15 g) as colorless crystals. ESI-1-Mass m/Z 205 (M−H).

(4) The above 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid was tread in a manner similar to Reference Example 47-(2) to give the desired 6-ethylbenzo[b]thiophene as colorless oil.

Reference Example 140

5-Bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl) benzene

(1) 5-Bromo-2-chlorobenzyl alcohol (3.0 g) was dissolved in toluene (30 ml), and added thereto were thionyl chloride (2.35 ml) and pyridine (two drops), and the mixture was heated under stirring at 100° C. for 2 hours. The mixture was cooled, washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride (3.34 g) as pale brown oil, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride (3.34 g) was dissolved in N,N-dimethylformamide (30 ml), and added thereto was potassium phthalimide (2.63 g), and the mixture was heated under stirring at 70° C. for 3 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from diisopropyl ether to give 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl)benzene (3.33 g) as colorless crystals. APCI-Mass m/Z 350/352 (M+H).

(3) The above 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl) benzene (4.3 g) was dissolved in acetic acid (43 ml), and added thereto was zinc powder (8.02 g), and the mixture was heated at reflux for 3 days. The mixture was cooled and diluted with chloroform and it was basified with an aqueous sodium hydroxide solution. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=6:1-4:1) to give the desired 5-bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl) benzene (1.39 g) as colorless powder. APCI-Mass m/Z 336/338 (M+H).

Reference Example 141

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl) benzene

(1) A solution of 1-phenyl-4-bromopyrazole (see M.A. Khan, et al., Can. J. Chem., (1963) 41 1540) (2.23 g) in diethyl ether (30 ml) wad cooled to −78° C. under argon atmosphere, and added dropwise thereto was n-butyl lithium (1.59 M hexane solution, 6.9 ml). The mixture was stirred at −20° C. to −10° C. for 5 hours, and added dropwise thereto at the same temperature was a solution of 5-bromo-2-chlorobenzaldehyde (2.19 g) obtained in Reference Example 16-(1) in diethyl ether (30 ml). The mixture was stirred at the same temperature for 30 minutes, and added thereto was tetrahydrofuran (30 ml), and the mixture was stirred at 0° C. for further 30 minutes. A saturated aqueous ammonium chloride solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=83:17-80:20) to give 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol (831 mg) as yellow oil. APCI-Mass m/Z 363/365 (M+H).

(2) The above 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol was treated in a manner similar to Reference Example 120-(2) to give the desired 5-bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene as colorless powder. APCI-Mass m/Z 347/349 (M+H).

Reference Example 142

5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b] thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 132-(1) and 1-bromopropane were treated in a manner similar to Reference Example 132-(2) to give the target compound. APCI-Mass m/Z 395/397 (M+H).

Reference Example 143

5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b] thiophen-2-yl methyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 132-(1) and 1-bromo-2-fluoroethane were treated in a manner similar to Reference Example 132-(2) to give the target compound. APCI-Mass m/Z 399/401 (M+H).

Reference Example 144

5-Tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in WO 03/087104.

Reference Example 145

4-Tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in WO 03/087104.

Reference Example 146

Tri-n-butyl(6-methoxy-2-pyridyl)tin

The target compound was prepared according to a method described in P. Gros, et al., *Synthesis* (1999) 754.

Reference Example 147

5-Bromo-2-chloro-1-(5-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

(1) 5-Bromo-2-chloro-1-(5-methoxybenzo[b]thiophene-2-ylmethyl)benzene obtained in Reference Example 54 was treated in a manner similar to Reference Example 132-(1) to give 5-bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)benzene. ESI-Mass m/Z 351/353 (M−H).
(2) The above 5-bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)benzene and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-Bromo-2-chloro-1-(5-ethoxybenzo[b]thiophene-2-ylmethyl)-benzene. APCI-Mass m/Z 382/380 (M+H).

Reference Example 148

5-Bromo-2-chloro-1-(5-(1-pyrazolyl)-2-thienylmethyl)benzene

1-(2-thienyl)pyrazole (see: Chemica Scripta (1979) 13, 157-161) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 7 to give the title compound as colorless solid. APCI-Mass m/z 353/355 (M+H).

Reference Example 149

5-Bromo-2-chloro-1-(tert-butyldiphenylsilyloxymethyl)benzene

To a solution of 5-Bromo-2-chlorobenzylalcohol (5.15 g) in N,N-dimethylformamide (50 ml) was added diisopropylethylamine (19.8 ml) and tert-butyldiphenylchlorosilane (11.9 ml), and the mixture was stirred at room temperature for 2 days. Under ice-cooling, to the mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with successively with 0.4 M aqueous hydrochloric acid solution (twice), water, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by an aminosilane-treated silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(tert-butyldiphenylsiloxymethyl) benzene 77 (10.79 g) as colorless oil. APCI-Mass m/Z 476/478 ($M+NH_4$).

Reference Example 150

2-Fluoropyridin-4-boronic acid

The target compound was prepared according to a method described in *Tetrahedron* (2002) 58, 4369-4373.

Reference Example 151

3-Difluoromethoxybenzeneboronic acid

A solution of 3-(difluoromethoxy)benzene (3.0 g) and triisopropoxyborane (2.78 g) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (1.59 M hexane solution, 9.3 ml). The mixture was stirred at same temperature for 10 minutes, warmed, and further stirred at room temperature overnight. Thereto was added 3N aqueous hydrochloric acid solution (10 ml), and the mixture was stirred at room temperature for 5 minutes. The mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from hexane to give 3-difluoromethoxybenzeneboronic acid (1.6 g) as colorless crystals.

Reference Example 152

Tri-n-butyl(2-cyano-5-pyridyl)tin

5-Bromo-2-cyanopyridine was treated in a manner similar to the methods described in European Patent Publication No. 93-00867.

Reference Example 153

5-Bromo-2-chloro-1-(6-difluoromethoxybenzo[b]thiophen-2-yl-methylbenzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene (1.8 g) obtained in Reference Example 132-(1) was dissolved in dimethylformamide (15 ml), and added thereto were methyl 2-chloro-2,2-difluoroacetate (1.63 ml) and potassium carbonate (2.28 g), and the mixture was stirred at 100° C. for 1.5 hours under argon atmosphere. The reaction mixture was acidified with 2N aqueous HCl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(6-difluoromethoxybenzo[b]thiophen-2-yl methyl) benzene (695 mg) as a colorless solid. GC-Mass m/Z 402/404 (M+).

Reference Example 154

5-Bromo-1-(6-difluoromethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

(1) 6-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give 5-Bromo-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene. APCI-Mass m/Z 347/349 ($M+NH_4$).
(2) The above 5-bromo-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene was treated in a manner similar to Reference Example 132-(1) to give 5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene. ESI-Mass m/Z 331/333 (M−H).
(3) The above 5-bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene was treated in a manner similar to Reference Example 153 to give the desired 5-bromo-1-(6-difluoromethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene as colorless oil. GC-Mass m/Z 382/384 (M+).

Reference Example 155

(6-Cyanopyridin-2-yl)trimethyltin

2-Bromo-6-cyanopyridine (see Japanese Patent Publication 04-253974) (1.5 g) and hexamethylditin (2.69 g) were

dissolved in dimethoxyethane (50 ml) and thereto was added tetrakis(triphenylphosphine)palladium(0) (972 mg). The mixture was refluxed for 5 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:1) to give (6-cyanopyridin-2-yl)trimethyltin (980 mg) as colorless oil. APCI-Mass m/Z 265/267/269 (M+H).

Reference Example 156

5-Bromo-2-methyl-1-(5-(1-pyrazolyl)-2-thienylmethyl)benzene

1-(2-thienyl)pyrazole (see Chemica Scripta (1979) 13, 157-161) and 5-bromo-2-methybenzaldehyde obtained in Reference Example 4 were used and treated in a manner similar to Reference Example 7 to give the title compound as colorless oil. APCI-Mass m/z 333/335 (M+H).

Reference Example 157

5-Bromo-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene obtained in Reference Example 154-(2) and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(6-ethoxybenzo[b]thiophene-2-ylmethyl)-2-methylbenzene as pale yellow wax. APCI-Mass m/Z 361/363 (M+H).

Reference Example 158

5-Bromo-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give 5-bromo-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-2-methyl benzene as colorless wax.

Reference Example 159

5-Bromo-1-(5-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)-2-methylbenzene

(1) 5-Bromo-1-(5-methoxybenzo[b]thiophene-2-yl methyl)-2-methylbenzene obtained in Reference Example 158 was treated in a manner similar to Reference Example 132-(1) to give 5-bromo-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene as colorless powder. ESI-Mass m/Z 331/333 (M−H).
(2) The above 5-bromo-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene and 1-bromo-2-fluoroethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(5-(2-fluoroethyloxy)benzo[b]thiophene-2-ylmethyl)-2-methylbenzene.

Reference Example 160

5-Bromo-1-(5-ethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Bromo-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene obtained in Reference Example 159-(1) and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(5-ethoxybenzo[b]thiophene-2-ylmethyl)-2-methylbenzene as colorless powder.

Reference Example 161

5-Bromo-2-chloro-1-(5-(2-fluoroethyloxy)benzo[b]thiophene-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 147-(1) and 1-bromo-2-fluoroethane were treated in a manner similar to Example 132-(2) to give the target compound.

Reference Example 162

5-Bromo-1-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene obtained in Reference Example 154-(2) and 1-bromo-2-fluoroethane were treated in a manner similar to Example 132-(2) to give the target compound as colorless wax. APCI-Mass m/Z 379/381 (M+H).

Reference Example 163

4-(Difluoromethoxy)phenylboronic Acid

A solution of (4-bromophenoxy)difluoromethane (3 g) and triisopropyl borate (3.42 ml) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (1.59 M hexane solution, 3.42 ml). The mixture was stirred at room temperature overnight. Added thereto was 6N aqueous hydrochloric acid at 0° C., and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was triturated with cold hexane to give 4-(difluoromethoxy)phenylboronic acid (1.88 g) as colorless solid.

Reference Example 164

Tri-n-butyl(3-methyl-5-isooxazolyl)tin

The target compound was prepared according to a method described in Bioorg. & Med. Chem. Lett. (2003) 13, 4117-4120.

Reference Example 165

5-Bromo-2-chloro-1-(2-trifluoromethyl-5-pyridylmethyl)benzene

(1) A solution of 5-Bromo-2-trifluoromethylpyridine (5.3 g) (see Eur. J. Org. Chem. (2003) 1159-1168) in tetrahydrofuran (70 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise isopropylmagnesium chloride (1 mol/l tetrahydrofuran solution, 23.45 ml). The reaction mixture was stirred at the same temperature for 2 hours, and thereto was added dropwise a solution of 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) (5.15 g) in tetrahydrofuran (20 ml). The mixture was stirred at the same temperature for 60 minutes, and thereto was added a saturated ammonium chloride solution, and the reaction mixture was warmed to room temperature. The mixture was

extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-85:15) to give (5-Bromo-2-chloro)phenyl-(2-trifluoromethyl-5-pyridyl)methanol (4.56 g) as a pale brown syrup. APCI-Mass m/Z 366/368 (M+H).

(2) The above (5-Bromo-2-chloro)phenyl-(2-trifluoromethyl-5-pyridyl)methanol (4.55 g) was dissolved in dichloromethane (50 ml) and toluene (50 ml), and added thereto was manganese (IV) oxide (5.39 g), and the mixture was stirred at room temperature overnight. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-92:8) to give (5-Bromo-2-chloro)phenyl (2-trifluoromethyl-5-pyridyl) ketone (2.64 g) as a pale yellow syrup. APCI-Mass m/Z 364/366 (M+H).

(3) The above (5-Bromo-2-chloro)phenyl (2-trifluoromethyl-5-pyridyl) ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-Bromo-2-chloro-1-(2-trifluoromethyl-5-pyridylmethyl)benzene. APCI-Mass m/Z 350/352 (M+H).

Reference Example 166

4-Methyl-2-tributylstannanylthiazole

A solution of n-butyl lithium (2.71 M hexane solution, 3.9 ml) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise a solution of 4-methylthiazole (1.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at same temperature for one hour and thereto was added dropwise a solution of tri-n-butyltin chloride (3.6 g) in tetrahydrofuran (10 ml). The mixture was stirred at same temperature for 30 minutes, warmed, and further stirred at room temperature overnight. Thereto was added water, and the mixture was extracted with diethyl ether. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by alumina column chromatography (hexane) to give the title compound (1.76 g) as oil. APCI-Mass m/z 386/388 (M+H)

Reference Example 167

2-Fluoropyridine-3-boronic Acid

The target compound was prepared according to a method described in Tetrahedron (2002) 58, 3323-3328.

Reference Example 168

4-Bromo-2-(5-chloro-2-thienylmethyl)-1-methoxynaphthalene

2,4-Dibromo-1-methoxynaphthalene (see *Org. Lett.* (2003) 5, 831) and 5-chloro-2-thiophenecarboxaldehyde were treated in a manner similar to Reference Example 1 to give 4-Bromo-2-(5-chloro-2-thienylmethyl)-1-methoxynaphthalene.

Reference Example 169

2-(2-(6-Chloro)pyridine)-4,4,5,5-tetramethyl-1,3-dioxaborolane

The target compound was prepared according to a method described in *Tetrahedron* (2003) 59, 10043-10049.

Reference Example 170

2-Methyl-4-tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in *Tetrahedron* (2003), 9979-9984.

Reference Example 171

2-(4-(2-Methyl)pyridine)-4,4,5,5-tetramethyl-1,3-dioxaborolane

The target compound was prepared according to a method described in United States Patent Publication No. 2003-024914.

Reference Example 172

1-(β-D-glucopyranosyl)-5-chloroindole

5-Chloro-2,3-dihydro-(1H)-indole was treated in a manner similar to the methods described in Eur. J. Med. Chem. (2004) 39, 453-458 to give the title compound. APCI-Mass m/z 314/316 (M+H)

Reference Example 173

5-Bromo-2-chloro-1-(5-(5-fluorothiazol-2-yl)-2-thienylmethyl)benzene

(1) 2-Bromothiazole (15.0 g) and 2-thiopheneboronic acid (14.0 g) were dissolved in dimethoxyethane (150 ml). To the mixture was added bis(triphenyl)phosphine palladium(II)dichloride (3.2 g) and 2M sodium carbonate (137 ml), and the mixture was refluxed under argon atmosphere for 2 hours. The mixture was cooled to room temperature, and the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was collected, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=96:4) to give 2-(2-thienyl) thiazole (9.87 g) as oil. APCI-Mass m/z 168 (M+H)

(2) The above compound (3.17 g) was treated in a manner similar to Reference Example 121 to give 5-fluoro-2-(2-thienyl)thiazole (1.58 g) as oil. APCI-Mass m/z 186 (M+H)

(3) The above compound (1.58 g) was dissolved in chloroform (16 ml), cooled to 0° C., and thereto was added dropwise a solution of bromine (1.43 g) in chloroform (15 ml). The mixture was stirred at the same temperature for one hour, warmed, and further stirred at room temperature for one hour. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform. The extract was washed with 10% aqueous sodium thiosulfate solution, brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=97:3) to give 2-(5-bromo-2-thienyl)-5-fluorothiazole (1.81 g) as a pale yellow solid.

(4) The above compound (300 mg) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 7

to give the desired 5-bromo-2-chloro-1-(5-(5-fluorothiazol-2-yl)-2-thienylmethyl)benzene (199 mg) as a pale yellow powder.

Reference Example 174

1-(β-D-glucopyranosyl)-4-chloroindole

(1) 4-Chloroindole (3.15 g) was dissolved in trifluoroacetic acid (32 ml), thereto was added triethylsilane (8.3 ml) and the mixture was heated at 50° C. with stirring for 30 minutes. The resultant mixture was cooled to room temperature, and trifluoroacetic acid was evaporated under reduced pressure. To the residue was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate twice. The organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-80:20) to give 4-chloro-2,3-dihydro-(1H)-indole (2.89 g) as colorless oil. APCI-Mass m/z 154/156 (M+H)

(2) The above 4-chloro-2,3-dihydro-(1H)-indole was treated in a manner similar to described in Eur. J. Med. Chem. (2004) 39, 453-458 to give the title compound. APCI-Mass m/z 314/316 (M+H)

Reference Example 175

1-(β-D-glucopyranosyl)-6-chloroindole

6-Chloroindole was treated in a manner similar to Reference Example 174 to give the title compound. APCI-Mass m/z 314/316 (M+H).

Pharmacological Experiment

1. Assay for SGLT2 Inhibition

Test Compounds:

Compounds described in the above examples were used for the SGLT2 inhibition assay.

Method:

CHOK1 cells expressing human SGLT2 were seeded in 24-well plates at a density of 400,000 cells/well in F-12 nutrient mixture (Ham's F-12) containing 10% fetal bovine serum, 400 μg/ml Geneticin, 50 units/ml sodium penicillin G (Gibco-BRL) and 50 μg/ml streptomycin sulfate. After 2 days of culture at 37° C. in a humidified atmosphere containing 5% CO_2, cells were washed once with the assay buffer (137 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 50 mM Hepes, and 20 mM Tris, pH 7.4) and incubated with 250 μl of the buffer containing test compounds for 10 min at 37° C. Test compounds were dissolved in DMSO. The final concentration of DMSO was 0.5%. The transport reaction was initiated by addition of 50 μl [^{14}C]-methyl-α-D-glucopyranoside (^{14}C-AMG) solution (final concentration, 0.5 mM). After incubation for 2 hours at 37° C., the uptake was stopped by aspiration of the incubation mixture, the cells were washed three times with ice-cold PBS. Then, cells were solubilized with 0.3 N NaOH and aliquots were taken for determination of radioactivity by a liquid scintillation counter. Nonspecific AMG uptake was defined as that which occurred in the presence of 100 μM of phlorizin, a specific inhibitor of sodium-dependent glucose cotransporter. Specific uptake was normalized for the protein concentrations measured by the method of Bradford. The 50% inhibitory concentration (IC_{50}) values were calculated from dose-response curves by least square method.

Results:

Results are shown in the following table:

Test Compounds (Example No.)	IC50 (nM)
69	7.9
70	7.0
71	6.6
72	4.6
78	1.7
79	9.0
80	6.8
83	1.3
84	2.2
86	2.8
87	3.4
88	2.6
89	3.0
90	2.0
120	3.4
122	8.2
123	1.4
127	1.3
130	2.4
140	5.9
142	5.6
144	4.1
145	4.0
146	2.2
148	2.8
151	2.5
155	1.7
156	1.1
168	2.3
169	3.6
170	3.5
173	8.0
176	7.7
177	6.7
178	5.1
179	9.8
183	9.5
185	5.6
186	5.4
187	4.3
188	1.6
189	2.4
190	3.1
191	7.7
192	7.4
193	0.9
194	2.6
197	2.0
201	8.2
202	8.7
204	1.4
207	0.6
208	2.4
209	3.9
210	1.0
211	1.2
212	2.6
213	5.6
214	1.5
215	4.3
216	3.3
217	3.6
218	2.4
219	6.7
221	5.5
222	1.8
223	3.1
224	5.9
225	1.5
226	1.2
227	3.2
228	3.6
229	2.7

-continued

Test Compounds (Example No.)	IC50 (nM)
230	4.0
231	3.5
232	4.0
233	2.9
234	2.4
235	2.6
236	4.4
237	2.8
238	1.6
240	1.2
241	1.0
242	4.6
244	1.2
246	6.4
247	2.5
248	5.1
249	4.3
250	4.2
251	3.6
252	1.4
253	1.6
254	1.7
255	6.5
256	3.1
257	3.3
260	2.3
264	1.5
265	3.4
266	3.2
267	1.5
268	2.5

2. Urinary Glucose Excretion Test in Rats

Test Compounds:

Compounds described in the above examples were used for the urinary glucose excretion test in rats.

Methods:

6-week-old male Sprague-Dawley (SD) rats were housed in individual metabolic cages with free access to food and water from 2 days prior to the experiment. On the morning of the experiment, rats were administered vehicle (0.2% carboxymethyl cellulose solution containing 0.2% Tween80) or test compounds (30 mg/kg) by oral gavage at a volume of 10 ml/kg. Then, urine of the rat was collected for 24 hours, and the urine volume was measured. Subsequently, the glucose concentration in urine was quantified using the enzymatic assay kit and the daily amount of glucose excreted in urine per individual was calculated.

Results:

Urinary glucose amount ranges are depicted by A and B. These ranges are as follows: A≧2000 mg; 2000 mg>B≧1000 mg.

Test compounds (Example No.)	Urinary glucose
22	A
25	B
69	B
70	A
81	B
83	A
84	A
88	B
89	B
120	A
123	A
127	A

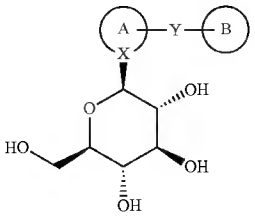
-continued

Test compounds (Example No.)	Urinary glucose
133	B
140	B
142	A
144	B
146	A
148	B
151	B
155	A
156	A
168	A
169	B
170	B
177	A
178	B
189	B
194	A
195	B
204	A
207	A
208	A
209	B
210	B
214	B
216	A
217	B
221	B
223	A
226	B
227	B
228	B
229	B
230	A
231	B
232	B
233	B
235	A
236	B
237	B
238	A
247	A
248	B
251	A
252	B

What is claimed is:

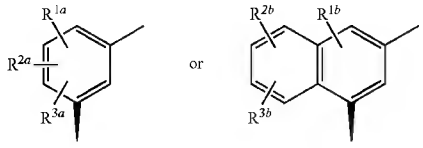
1. A method for treating or delaying the progression or onset of a disease selected from diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, and hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound of Formula (I):

(I)



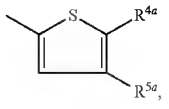
wherein

Ring A is



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



wherein R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, a mono- or di-alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, or a haloalkoxy group, where the heterocyclyl group is a thienyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, or a tetrazolyl group; R^{5a} is a hydrogen atom;

X is a carbon atom; and

Y is $—(CH_2)_n—$ (wherein n is 1 or 2);

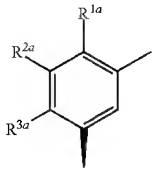
or a pharmaceutically acceptable salt thereof.

2. The method according to claim **1**, wherein

R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b} and R^{3b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;

R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

3. The method according to claim **2**, wherein Ring A is



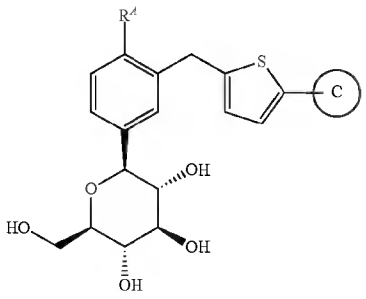
wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms;

R^{4a} is a phenyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group;

or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, and Y is $—CH_2—$.

4. The method according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

5. The method according to claim **1**, wherein the compound is represented by the following formula:



wherein R^A is a halogen atom, or a lower alkyl group; and

Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group. a methylenedioxy group, an ethyleneoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group; where the heterocyclyl group is a thienyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, or a tetrazolyl group;

or a pharmaceutically acceptable salt thereof.

6. The method according to claim **5**, wherein Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom. a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

7. The method according to claim 5, wherein Ring C is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

8. The method according to claim 5, wherein Ring C is a phenyl group substituted by a halogen atom or a cyano group, or a pyridyl group substituted by a halogen atom.

9. The method according to claim 1, wherein the compound is selected from the group consisting of:

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethylphenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene; and

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene;

or a pharmaceutically acceptable salt thereof.

10. The method according to claim 1, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

11. The method according to claim 1, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

12. The method according to claim 1, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

13. The method according to claim 4, wherein R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

14. The method according to claim 1, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

15. The method according to claim 1, wherein the compound is 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

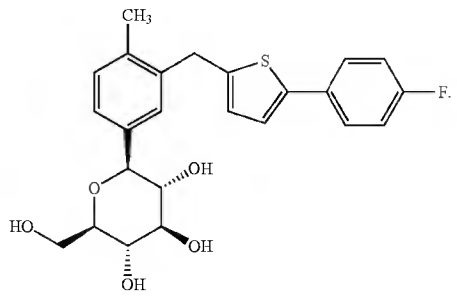
16. The method according to claim 1, wherein the compound is 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

17. The method according to claim 1, wherein the disease is type 1 or type 2 diabetes mellitus.

18. The method according to claim 17, which further comprises administering to a mammalian species in need of treatment another antidiabetic agent, an agent for treating diabetic complications, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an anti-atherosclerotic agent and/or a hypolipidemic agent.

19. The method according to claim 18, wherein said antidiabetic agent is at least one selected from the group consisting of insulin, insulin secretagogue, insulin sensitizers, biguanide compounds, sulfonylurea compounds, α-glucosidase inhibitors, PPARγ agonists, PPARα/γ dual agonists, dipeptidyl peptidase IV inhibitors, mitiglinide compounds, nateglinide compounds, glucagon-like peptide-1, PTP1B inhibitors, glycogen phosphorylase inhibitors, RXR modulators, and glucose 6-phosphatase inhibitors.

20. A method for treating or delaying the progression or onset of a disease selected from diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, and hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound having the following structure:



21. The method according to claim 20, wherein the disease is diabetes mellitus.

22. The method according to claim 21, wherein the disease is type 2 diabetes mellitus.

23. The method according to claim 20, wherein the disease is obesity.

24. The method according to claim 20, which further comprises administering another antidiabetic agent.

25. The method according to claim 24, wherein said antidiabetic agent is at least one selected from the group consisting of insulin, insulin secretagogue, insulin sensitizers, biguanide compounds, sulfonylurea compounds, α-glucosidase inhibitors, PPARγ agonists, PPARα/γ dual agonists, dipeptidyl peptidase IV inhibitors, mitiglinide compounds, nateglinide compounds, glucagon-like peptide-1, PTP1B inhibitors, glycogen phosphorylase inhibitors, RXR modulators, and glucose 6-phosphatase inhibitors.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,222,219 B2
APPLICATION NO. : 13/174814
DATED : July 17, 2012
INVENTOR(S) : Sumihiro Nomura et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE CLAIMS:

In claim 13, at column 219, line 43, change "claim 4" to --claim 3--.

Signed and Sealed this
Sixteenth Day of October, 2012

David J. Kappos
Director of the United States Patent and Trademark Office

US008785403B2

(12) **United States Patent**
Nomura et al.

(10) **Patent No.: US 8,785,403 B2**
(45) **Date of Patent: *Jul. 22, 2014**

(54) **GLUCOPYRANOSIDE COMPOUND**

(75) Inventors: **Sumihiro Nomura**, Kawaguchi (JP); **Eiji Kawanishi**, Kitamoto (JP); **Kiichiro Ueta**, Wako (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/494,602**

(22) Filed: **Jun. 12, 2012**

(65) **Prior Publication Data**

US 2012/0258913 A1 Oct. 11, 2012

Related U.S. Application Data

(60) Continuation of application No. 13/174,814, filed on Jul. 1, 2011, now Pat. No. 8,222,219, which is a division of application No. 13/005,757, filed on Jan. 13, 2011, now Pat. No. 8,202,984, which is a division of application No. 11/045,446, filed on Jan. 31, 2005, now Pat. No. 7,943,788, which is a continuation-in-part of application No. PCT/JP2004/011312, filed on Jul. 30, 2004.

(60) Provisional application No. 60/491,534, filed on Aug. 1, 2003.

(51) **Int. Cl.**

C07H 5/02	(2006.01)
A01N 43/04	(2006.01)
A61K 31/70	(2006.01)

(52) **U.S. Cl.**

USPC **514/23**; 536/122

(58) **Field of Classification Search**

None

See application file for complete search history.

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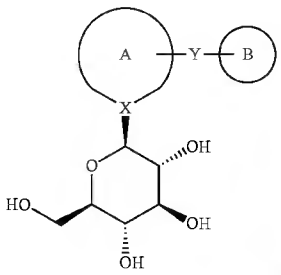
(57) **ABSTRACT**

A compound of the formula:

(I)



wherein Ring A and Ring B are: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring or an optionally substituted unsaturated fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, and Ring B are independently an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring; X is a carbon atom or a nitrogen atom; Y is $—(CH_2)_n—$ (n is 1 or 2); or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

26 Claims, No Drawings

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Opposition to European Patent EP1651658B1 dated Oct. 16, 2013, including attachments: Letter filed by the patentee with the EPO on Apr. 18, 2011, and Comparative Experiments filed with the EPO by the patentee on Apr. 18, 2011.

GLUCOPYRANOSIDE COMPOUND

TECHNICAL FIELD

This application is a Continuation of U.S. application Ser. No. 13/174,814, filed Jul. 1, 2011, which is a Divisional of U.S. application Ser. No. 13/005,757, filed Jan. 13, 2011, which is a Divisional of U.S. application Ser. No. 11/045,446, filed Jan. 31, 2005, which issued as U.S. Pat. No. 7,943,788 B2 on May 17, 2011. U.S. application Ser. No. 11/045,446 is a Continuation-In-Part of PCT International Application No. PCT/JP2004/011312 filed on Jul. 30, 2004, which designated the United States and on which priority is claimed under 35 U.S.C. §120, which claims priority of Provisional Application No. 60/491,534 filed on Aug. 1, 2003. The entire contents of each of the above applications are hereby incorporated by reference.

BACKGROUND ART

Diet therapy and exercise therapy are essential in the treatment of diabetes mellitus. When these therapies do not sufficiently control the conditions of patients, insulin or an oral antidiabetic agent is additionally used for the treatment of diabetes. At the present, there have been used as an antidiabetic agent biguanide compounds, sulfonylurea compounds, insulin resistance improving agents and α-glucosidase inhibitors. However, these antidiabetic agents have various side effects. For example, biguanide compounds cause lactic acidosis, sulfonylurea compounds cause significant hypoglycemia, insulin resistance improving agents cause edema and heart failure, and α-glucosidase inhibitors cause abdominal bloating and diarrhea. Under such circumstances, it has been desired to develop novel drugs for treatment of diabetes mellitus having no such side effects.

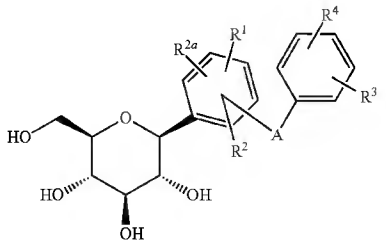
Recently, it has been reported that hyperglycemia participates in the onset and progressive impairment of diabetes mellitus, i.e., glucose toxicity theory. Namely, chronic hyperglycemia leads to decrease of insulin secretion and further to decrease of insulin sensitivity, and as a result, the blood glucose concentration is increased so that diabetes mellitus is self-exacerbated [cf., Diabetologia, vol. 28, p. 119 (1985); Diabetes Care, vol. 13, p. 610 (1990), etc.]. Therefore, by treating hyperglycemia, the aforementioned self-exacerbating cycle is interrupted so that the prophylaxis or treatment of diabetes mellitus is made possible.

As one of the methods for treating hyperglycemia, it is considered to excrete an excess amount of glucose directly into urine so that the blood glucose concentration is normalized. For example, by inhibiting sodium-dependent glucose transporter being present at the proximal convoluted tubule of kidney, the re-absorption of glucose at the kidney is inhibited, by which the excretion of glucose into urine is promoted so that the blood glucose level is decreased. In fact, it is confirmed that by continuous subcutaneous administration of phlorizin having SGLT inhibitory activity to diabetic animal models, hyperglycemia is normalized and the blood glucose level thereof can be kept normal for a long time so that the insulin secretion and insulin resistance are improved [cf., Journal of Clinical Investigation, vol. 79, p. 1510 (1987); ibid., vol. 80, p. 1037 (1987); ibid., vol. 87, p. 561 (1991), etc.].

In addition, by treating diabetic animal models with SGLT inhibitory agents for a long time, insulin secretion response and insulin sensitivity of the animals are improved without incurring any adverse affects on the kidney or imbalance in blood levels of electrolytes, and as a result, the onset and progress of diabetic nephropathy and diabetic neuropathy are prevented [cf., Journal of Medicinal Chemistry, vol. 42, p. 5311 (1999); British Journal of Pharmacology, vol. 132, p. 578 (2001), Ueta, Ishihara, Matsumoto, Oku, Nawano, Fujita, Saito, Arakawa, Life Sci., in press (2005), etc.].

From the above, SGLT inhibitors may be expected to improve insulin secretion and insulin resistance by decreasing the blood glucose level in diabetic patients and further prevent the onset and progress of diabetes mellitus and diabetic complications.

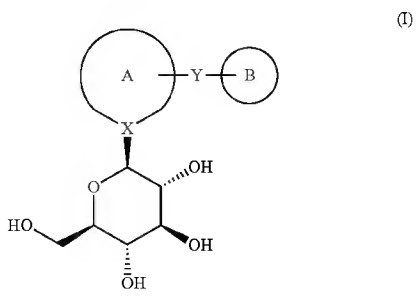
WO 01/27128 discloses an aryl C-glycoside compound having the following structure.



This compound is disclosed to be useful in the prophylaxis or treatment of diabetes mellitus, etc., as an SGLT inhibitor.

DISCLOSURE OF INVENTION

The present invention relates to a compound of the following formula I, or a pharmaceutically acceptable salt thereof, or a prodrug thereof:



(I)

wherein Ring A and Ring B are one of the followings: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring wherein Y is linked to the heterocyclic ring of the fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, wherein the sugar moiety X-(sugar) and the moiety —Y— (Ring B) are both on the same heterocyclic ring of the fused heterobicyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring;

X is a carbon atom or a nitrogen atom; and

Y is —$(CH_2)_n$— (wherein n is 1 or 2).

The compound of the formula I exhibits an inhibitory activity against sodium-dependent glucose transporter being present in the intestine and the kidney of mammalian species, and is useful in the treatment of diabetes mellitus or diabetic complications such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, obesity, and delayed wound healing.

BEST MODE FOR CARRYING OUT THE INVENTION

Hereinafter, the present compound (I) is illustrated in more detail.

The definitions for each term used in the description of the present invention are listed below.

The term "halogen atom" or "halo" means chlorine, bromine, fluorine and iodine, and chlorine and fluorine are preferable.

The term "alkyl group" means a straight or branched saturated monovalent hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkyl group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkyl group having 1 to 4 carbon atoms is more preferable. Examples thereof are methyl group, ethyl group, propyl group, isopropyl group, butyl group, t-butyl group, isobutyl group, pentyl group, hexyl group, isohexyl group, heptyl group, 4,4-dimethylpentyl group, octyl group, 2,2,4-trimethylpentyl group, nonyl group, decyl group, and various branched chain isomers thereof. Further, the alkyl group may optionally and independently be substituted by 1 to 4 substituents as listed below, if necessary.

The term "alkylene group" or "alkylene" means a straight or branched divalent saturated hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkylene group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkylene group having 1 to 4 carbon atoms is more preferable. Examples thereof are methylene group, ethylene group, propylene group, trimethylene group, etc. If necessary, the alkylene group may optionally be substituted in the same manner as the above-mentioned "alkyl group".

Where alkylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The term "alkenyl group" means a straight or branched monovalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. Preferable alkenyl group is a straight chain or branched chain alkenyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkenyl group having 2 to 4 carbon atoms is more preferable. Examples thereof are vinyl group, 2-propenyl group, 3-butenyl group, 2-butenyl group, 4-pentenyl group, 3-pentenyl group, 2-hexenyl group, 3-hexenyl group, 2-heptenyl group, 3-heptenyl group, 4-heptenyl group, 3-octenyl group, 3-nonenyl group, 4-decenyl group, 3-undecenyl group, 4-dodecenyl group, 4,8,12-tetradecatrienyl group, etc. The alkenyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "alkenylene group" means a straight or branched divalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. The straight chain or branched chain alkenylene group having 2 to 6 carbon atoms is preferable, and the straight chain or branched chain alkenylene group having 2 to 4 carbon atoms is more preferable. Examples thereof are vinylene group, propenylene group, butadienylene group, etc. If necessary, the alkylene group may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary.

Where alkenylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle (e.g., a fused benzene ring) together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The term "alkynyl group" means a straight or branched monovalent hydrocarbon chain having at least one triple bond. The preferable alkynyl group is a straight chain or branched chain alkynyl group having 2 to 6 carbon atoms, and the straight chain or branched chain alkynyl group having 2 to 4 carbon atoms is more preferable. Examples thereof are 2-propynyl group, 3-butynyl group, 2-butynyl group, 4-pentynyl group, 3-pentynyl group, 2-hexynyl group, 3-hexynyl group, 2-heptynyl group, 3-heptynyl group, 4-heptynyl group, 3-octynyl group, 3-nonynyl group, 4-decynyl group, 3-undecynyl group, 4-dodecynyl group, etc. The alkynyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The term "cycloalkyl group" means a monocyclic or bicyclic monovalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms is more preferable. Examples thereof are a monocyclic alkyl group and a bicyclic alkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, cyclodecyl group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. The cycloalkyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the condensed unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkylidene group" means a monocyclic or bicyclic divalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 6 carbon atoms is preferable. Examples thereof are a monocyclic alkylidene group and a bicyclic alkylidene group such as cyclopropylidene group, cyclobutylidene group, cyclopentylidine group, cyclohexylidene group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkylidene group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkenyl group" means a monocyclic or bicyclic monovalent unsaturated hydrocarbon ring having 4 to 12 carbon atoms and having at least one double bond. The preferable cycloalkenyl group is a monocyclic unsaturated hydrocarbon group having 4 to 7 carbon atoms. Examples thereof are monocyclic alkenyl groups such as cyclopentenyl

group, cyclopentadienyl group, cyclohexenyl group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkenyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "cycloalkynyl group" means a monocyclic or bicyclic unsaturated hydrocarbon ring having 6 to 12 carbon atoms, and having at least one triple bond. The preferable cycloalkynyl group is a monocyclic unsaturated hydrocarbon group having 6 to 8 carbon atoms. Examples thereof are monocyclic alkynyl groups such as cyclooctynyl group, cyclodecynyl group. These groups may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkynyl group may optionally and independently be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "aryl group" means a monocyclic or bicyclic monovalent aromatic hydrocarbon group having 6 to 10 carbon atoms. Examples thereof are phenyl group, naphthyl group (including 1-naphthyl group and 2-naphthyl group). These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the aryl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "unsaturated monocyclic heterocyclic ring" means an unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the preferable one is a 4- to 7-membered saturated or unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof are pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, 4,5-dihydrooxazole, triazole, isothiazole, thiadiazole, triazole, tetrazole, etc. Among them, pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, oxazole, and thiazole can be preferably used. The "unsaturated monocyclic heterocyclic ring" may optionally and independently be substituted by 1-4 substituents as mentioned below, if necessary.

The term "unsaturated fused heterobicyclic ring" means hydrocarbon ring comprised of a saturated or a unsaturated hydrocarbon ring condensed with the above mentioned unsaturated monocyclic heterocyclic ring where said saturated hydrocarbon ring and said unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO, or SO_2 within the ring, if necessary. The "unsaturated fused heterobicyclic ring" includes, for example, benzothiophene, indole, tetrahydrobenzothiophene, benzofuran, isoquinoline, thienothiophene, thienopyridine, quinoline, indoline, isoindoline, benzothiazole, benzoxazole, indazole, dihydroisoquinoline, etc. Further, the "heterocyclic ring" also includes possible N- or S-oxides thereof.

The term "heterocyclyl" means a monovalent group of the above-mentioned unsaturated monocyclic heterocyclic ring or unsaturated fused heterobicyclic ring and a monovalent group of the saturated version of the above-mentioned unsaturated monocyclic heterocyclic or unsaturated fused heterobicyclic ring. If necessary, the heterocyclyl may optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The term "alkanoyl group" means a formyl group and ones formed by binding an "alkyl group" to a carbonyl group.

The term "alkoxy group" means ones formed by binding an "alkyl group" to an oxygen atom.

The substituent for the above each group includes, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group. Each group as mentioned above may optionally be substituted by these substituents.

Further, the terms such as a haloalkyl group, a halo-lower alkyl group, a haloalkoxy group, a halo-lower alkoxy group, a halophenyl group, or a haloheterocyclyl group mean an alkyl group, a lower alkyl group, an alkoxy group, a lower alkoxy group, a phenyl group or a heterocyclyl group (hereinafter, referred to as an alkyl group, etc.) being substituted by one or more halogen atoms, respectively. Preferable ones are an alkyl group, etc. being substituted by 1 to 7 halogen atoms, and more preferable ones are an alkyl group, etc. being sub-

stituted by 1 to 5 halogen atoms. Similarly, the terms such as a hydroxyalkyl group, a hydroxy-lower alkyl group, a hydroxyalkoxy group, a hydroxy-lower alkoxy group and a hydroxyphenyl group mean an alkyl group, etc., being substituted by one or more hydroxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 hydroxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 hydroxy groups. Further, the terms such as an alkoxyalkyl group, a lower alkoxyalkyl group, an alkoxy-lower alkyl group, a lower alkoxy-lower alkyl group, an alkoxyalkoxy group, a lower alkoxyalkoxy group, an alkoxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, an alkoxyphenyl group, and a lower alkoxyphenyl group means an alkyl group, etc., being substituted by one or more alkoxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 alkoxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 alkoxy groups.

The terms "arylakyl" and "arylalkoxy" as used alone or as part of another group refer to alkyl and alkoxy groups as described above having an aryl substituent.

The term "lower" used in the definitions for the formulae in the present specification means a straight or branched carbon chain having 1 to 6 carbon atoms, unless defined otherwise. More preferably, it means a straight or branched carbon chain having 1 to 4 carbon atoms.

The term "prodrug" means an ester or carbonate, which is formed by reacting one or more hydroxy groups of the compound of the formula I with an acylating agent substituted by an alkyl, an alkoxy or an aryl by a conventional method to produce acetate, pivalate, methylcarbonate, benzoate, etc. Further, the prodrug includes also an ester or amide, which is similarly formed by reacting one or more hydroxy groups of the compound of the formula I with an α-amino acid or a β-amino acid, etc. using a condensing agent by a conventional method.

The pharmaceutically acceptable salt of the compound of the formula I includes, for example, a salt with an alkali metal such as lithium, sodium, potassium, etc.; a salt with an alkaline earth metal such as calcium, magnesium, etc.; a salt with zinc or aluminum; a salt with an organic base such as ammonium, choline, diethanolamine, lysine, ethylenediamine, t-butylamine, t-octylamine, tris(hydroxymethyl)aminomethane, N-methyl glucosamine, triethanolamine and dehydroabietylamine; a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; or a salt with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, etc.; or a salt with an acidic amino acid such as aspartic acid, glutamic acid, etc.

The compound of the present invention also includes a mixture of stereoisomers, or each pure or substantially pure isomer. For example, the present compound may optionally have one or more asymmetric centers at a carbon atom containing any one of substituents. Therefore, the compound of the formula I may exist in the form of enantiomer or diastereomer, or a mixture thereof. When the present compound (I) contains a double bond, the present compound may exist in the form of geometric isomerism (cis-compound, trans-compound), and when the present compound (I) contains an unsaturated bond such as carbonyl, then the present compound may exist in the form of a tautomer, and the present compound also includes these isomers or a mixture thereof. The starting compound in the form of a racemic mixture, enantiomer or diastereomer may be used in the processes for preparing the present compound. When the present compound is obtained in the form of a diastereomer or enantiomer, they can be separated by a conventional method such as chromatography or fractional crystallization.

In addition, the present compound (I) includes an intramolecular salt, hydrate, solvate or polymorphism thereof.

Examples of the optionally substituted unsaturated monocyclic heterocyclic ring of the present invention include an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxyl group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group wherein each substituent may optionally be further substituted by these substituents.

Examples of the optionally substituted unsaturated fused heterobicyclic ring of the present invention include an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidene-methyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenyl-carbonyl group, a cycloalkynyl-carbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl

group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxy-carbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxy-carbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cyclo-alkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cyclo-alkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclyl-carbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoyl-amino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkyl-sulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group, wherein each substituent may optionally be further substituted by these substituents.

Examples of the optionally substituted benzene ring of the present invention include a benzene ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, a heterocyclylsulfonyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group wherein each substituent may optionally be further substituted by these substituents. Moreover, examples of the optionally substituted benzene ring include a benzene ring substituted with an alkylene group to form an annelated carbocycle together with the carbon atoms to which they are attached, and also includes a benzene ring substituted with an alkenylene group to form an annelated carbocycle such as a fused benzene ring together with the carbon atoms to which they are attached.

Preferable examples of the optionally substituted unsaturated monocyclic heterocyclic ring include an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

Preferable examples of the optionally substituted unsaturated fused heterobicyclic ring include an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

Preferable examples of the optionally substituted benzene ring include a benzene ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group.

In another preferable embodiment of the present invention, the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group. an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkylthio group, an alkylsulfonyl group. an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, phenylsulfonyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, a mono- or di-alkylamino group, a carboxyl group, an alkoxycarbonyl group, a phenyl group, an alkyleneoxy group, an alkylenedioxy group, an oxo group, a carbamoyl group, and a mono- or di-alkylcarbamoyl group.

In a preferable embodiment, the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

In another preferable embodiment,

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

(2) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano

group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group. an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group; or

(3) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group;

wherein each of the above-mentioned substituents on Ring A and Ring B may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, an alkoxycarbonyl group, a carbamoyl group and a mono- or di-alkylcarbamoyl group.

In a more preferable embodiment of the present invention, Ring A and Ring B are

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group;

(2) Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a phenyl group, or a lower alkenylene group, and Ring B is (a) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, or a carbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group or a carbamoyl group; (b) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group. or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or

(3) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group.

In another more preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which is substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a phenyl group, and a lower alkenylene group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxy phenyl group, a lower alkylenedioxyphenyl group, a lower alkyleneoxy phenyl group, a mono- or di-lower alkylaminophenyl group, a carbamoyl phenyl group, a mono- or di-lower alkylcarbamoylphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, a lower alkoxyheterocyclyl group, a mono- or di-lower alkylaminoheterocycyclyl group, a carbamoylheterocyclyl group, and a mono- or di-lower alkylcarbamoyl group.

In another more preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is a benzene ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, and a lower alkoxyheterocyclyl group.

Further, in another preferable embodiment, Y is —CH_2— and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, and a lower alkoxyheterocyclyl group. In a more preferable embodiment of the present invention, X is a carbon atom and Y is —CH_2—.

Further, in another preferable embodiment, Ring A and Ring B are

(1) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, a phenyl group, and a lower alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, or a carbamoyl group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group or a carbamoyl group; and an oxo group,

(2) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group, and

Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, or a carbamoyl group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group or a carbamoyl group; and an oxo group,

a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a lower alkylene group,

(3) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group, Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group: a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group;

(4) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and a lower alkylene group, or

(5) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group.

In another preferable embodiment of the present invention, Y is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group, or a phenyl group. and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and an oxo group.

In another more preferable embodiment of the present invention, Y is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a substituent selected from a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and a lower alkylene group.

Preferable examples of unsaturated monocyclic heterocyclic ring include a 5- or 6-membered unsaturated heterocyclic ring containing 1 or 2 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are furan, thiophene, oxazole, isoxazole, triazole, tetrazole, pyrazole, pyridine, pyrimidine, pyrazine, dihydroisoxazole, dihydropyridine, and triazole. Preferable unsaturated fused heterobicyclic ring includes a 9- or 10-membered unsaturated fused heterocyclic ring containing 1 to 4 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are indoline, isoindoline, benzothiazole, benzoxazole, indole, indazole, quinoline, isoquinoline, benzothiophene, benzofuran, thienothiophene, and dihydroisoquinoline.

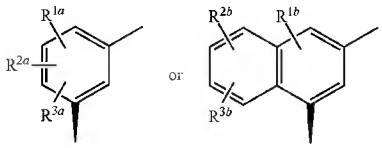
In a more preferred embodiment of the present invention, Ring A is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a phenyl group, and Ring B is a heterocyclic ring selected from the group consisting of thiophene, furan, benzofuran, benzothiophene, and benzothiazole, wherein the heterocyclic ring may optionally be substituted by a substituent selected from the following group: a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a lower alkylphenyl group, a lower alkoxyphenyl group, a thienyl group, a halothienyl group, a pyridyl group, a halopyridyl group, and a thiazolyl group.

In yet another preferred embodiment, Y is —CH_2—, Ring A is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring selected from the group con-

sisting of thiophene, dihydroisoquinoline, dihydroisoxazole, triazole, pyrazole, dihydropyridine, dihydroindole, indole, indazole, pyridine, pyrimidine, pyrazine, quinoline, and a isoindoline, wherein the heterocyclic ring may optionally substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

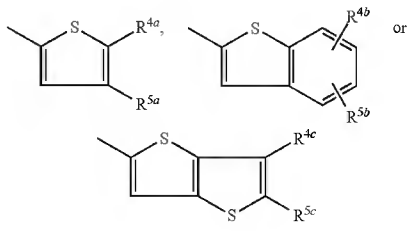
In a further preferred embodiment of the present invention, Ring A is a benzene ring which is substituted by a halogen atom or a lower alkyl group, and Ring B is thienyl group which is substituted by phenyl group or a heterocyclyl group in which said phenyl group and heterocyclyl group is substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

Further, in another aspect of the present invention, preferable examples of the compound of the formula I include a compound wherein Ring A is



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



wherein R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, a mono- or di-alkylamino group, a carbamoyl group, or a mono- or di-alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, a carbamoyl group, or a mono- or di-alkylcarbamoyl group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form an alkylene group; and

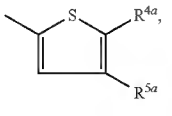
R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group or a haloalkoxy group.

More preferred is a compound wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;

R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group; and

R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

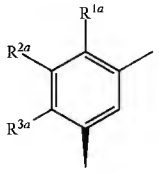
Further preferred is a compound in which Ring B is



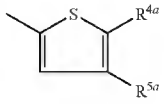
wherein R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, and R^{5a} is a hydrogen atom, or

R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group.

Further more preferred is a compound in which Ring A is



wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is

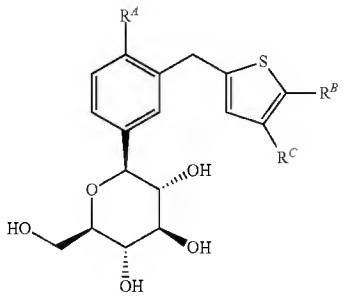


wherein R^{4a} is a phenyl group optionally substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a lower alkoxy group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group, and R^{5a} is a hydrogen atom, and Y is —CH_2—.

In more preferable embodiment, R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

In another preferable embodiment of the present invention, a preferable compound can be represented by the following formula IA:

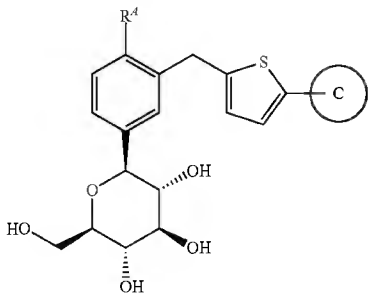
(IA)



wherein R^A is a halogen atom, a lower alkyl group or a lower alkoxy group; R^B is a phenyl group optionally substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group optionally substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; and R^C is hydrogen atom; or R^B and R^C taken together are a fused benzene ring which may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group.

In a preferable embodiment, R^A is a halogen atom or a lower alkyl group, R^C is hydrogen atom, and R^B is phenyl group substituted by 1-3 substituents selected from a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group. The chemical structure of such compounds are represented by the following formula (IA'):

(IA')



wherein R^A is a halogen atom, or a lower alkyl group, Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mono- or di-lower alkylamino group, a carbamoyl group, and a mono- or di-lower alkylcarbamoyl group.

In a more preferable embodiment, Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group,

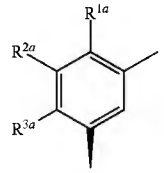
a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

Among them, a compound in which Ring C is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group is preferred.

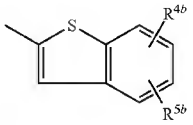
A preferred heterocyclyl group includes a 5- or 6-membered heterocyclyl group containing 1 or 2 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom, or a 9- or 10-membered heterocyclyl group containing 1 to 4 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. Specifically, a thienyl group, a pyridyl group, a pyrimidyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, a tetrazolyl group and an oxazolyl group are preferred.

In a further preferable embodiment, Ring C is a phenyl group substituted by a halogen atom or a cyano group, or a pyridyl group substituted by a halogen atom.

In another preferable embodiment of the present invention, preferred is a compound in which Ring A is



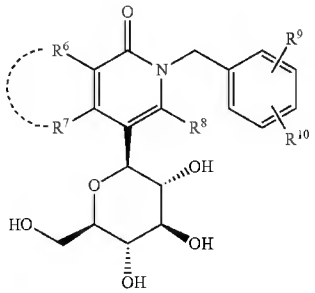
wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is



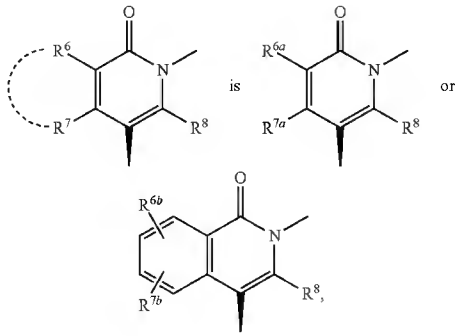
wherein R^{4b} and R^{5b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

In another aspect of the present invention, preferable examples of the compound I include a compound represented by the following formula IB:

(IB)

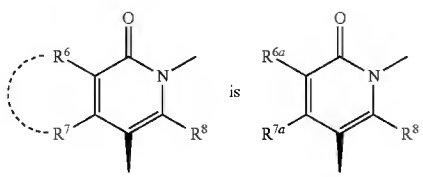


wherein R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group; and a group represented by:



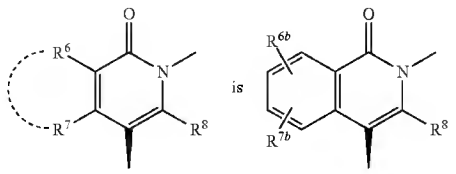
wherein R^{6a} and R^{7a} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group and R^{6b} and R^{7b} are each independently a hydrogen atom, a halogen atom, an alkyl group, a haloalkyl group, or an alkoxy group.

Among the compounds represented by the formula IB, more preferred is a compound in which R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a cycloalkoxy group, a halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, and a group represented by:



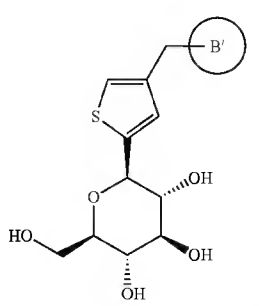
wherein R^{6a}, R^{7a} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a

cycloalkoxy group, a halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, or a group represented by:



wherein R^{6b} and R^{7b} are each independently a hydrogen atom. a halogen atom, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group.

In another aspect of the present invention, preferable examples of the compound I include a compound represented by the following formula IC:



(IC)

wherein Ring B' is an optionally substituted benzene ring, an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring.

Preferable examples of Ring B' include a benzene ring and a heterocyclic ring, both of which may have a substituent(s) selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a lower alkanoyl group; a mono- or di-lower alkylamino group; a lower alkoxycarbonyl group; a carbamoyl group; a mono- or di-lower alkylcarbamoyl group; a phenyl group optionally substituted by a substituent(s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; a heterocyclyl group optionally substituted by a substituent(s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; an alkylene group; and an oxo group.

More preferable examples of Ring B' include a benzene ring which may be substituted by a substituent selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom.

Preferred compound of the present invention may be selected from the following group:

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b] thiophen-2-ylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(5-thiazolyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-(5-phenyl-2-thienylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethylphenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene;

the pharmaceutically acceptable salt thereof; and the prodrug thereof.

Particularly Preferred compounds of the present invention include:

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof; and

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene, or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

The compound (I) of the present invention exhibits an excellent inhibitory activity against sodium-dependent glucose transporter, and an excellent blood glucose lowering effect. Therefore, the compound of the present invention is useful for treating or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension. In particular, the compound of the present invention is useful in the treatment or the prophylaxis of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy) or obesity, or is useful in the treatment of postprandial hyperglycemia.

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparation for oral administration includes, for example, solid preparation such as tablets, granules, capsules, powders, etc., or solution preparations, suspension preparations, or emulsion preparations, etc. Suitable pharmaceutical preparation for parenteral administration includes, for example, suppositories; injection preparations and intravenous drip preparations using distilled water for injection, physiological saline solution or aqueous glucose solution; or inhalant preparations.

The dosage of the present compound (I) or a pharmaceutically acceptable salt thereof may vary according to the administration routes, ages, body weight, conditions of a patient, or kinds and severity of a disease to be treated, and it is usually in the range of about 0.1 to 50 mg/kg/day, preferably in the range of about 0.1 to 30 mg/kg/day.

The compound of the formula I may be used, if necessary, in combination with one or more of other antidiabetic agents, one or more agents for treating diabetic complications, and/or one or more agents for treatment of other diseases. The present compound and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The other antidiabetic agents include, for example, antidiabetic or antihyperglycemic agents including insulin, insulin secretagogues, or insulin sensitizers, or other antidiabetic agents having an action mechanism different from SGLT inhibition, and 1, 2, 3 or 4 of these other antidiabetic agents may preferably be used. Concrete examples thereof are biguanide compounds, sulfonylurea compounds, α-glucosidase inhibitors, PPARγ agonists (e.g., thiazolidinedione compounds), PPARα/γ dual agonists, dipeptidyl peptidase IV (DPP4) inhibitors, mitiglinide compounds, and/or nateglinide compounds, and insulin, glucagon-like peptide-1 (GLP-1), PTP1B inhibitors, glycogen phosphorylase inhibitors, RXR modulators, and/or glucose 6-phosphatase inhibitors.

The agents for treatment of other diseases include, for example, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an anti-atherosclerotic agent and/or a hypolipidemic agent.

The SGLT inhibitors of the formula I may be used in combination with agents for treatment of diabetic complications, if necessary. These agents include, for example, PKC inhibitors and/or ACE inhibitors.

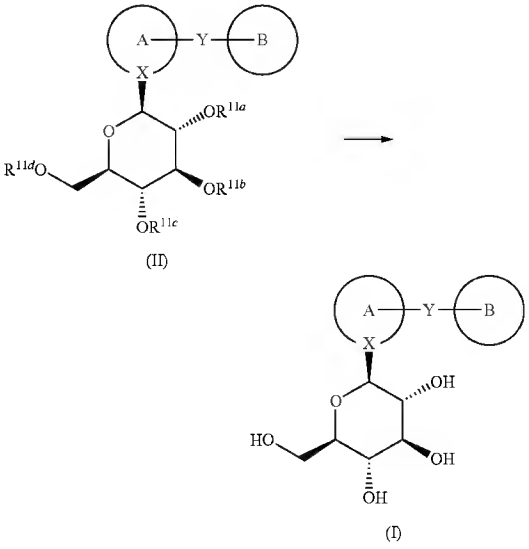
The dosage of those agents may vary according to ages, body weight, and conditions of patients, and administration routes, dosage forms, etc.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, dogs, etc., for example, in the dosage form of tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The present compound of the formula I may be prepared by the following Processes.

Process 1

The compound of the formula I may be prepared by a method as shown in the following scheme:



wherein R^{11a} is a hydrogen atom or a protecting group for a hydroxy group, and R^{11b}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group, and other symbols are as defined above.

The compound of the formula I may be prepared by deprotecting the compound of the formula II.

In the compound of the formula II, the protecting group for hydroxy group may be any conventional protecting groups, and a benzyl group, an acetyl group, and an alkylsily group such as a trimethylsilyl group may be used. Further, the protecting group for hydroxy group may form acetal or silylacetal together with adjacent hydroxy groups. Examples of such protecting group include an alkylidene group such as an isopropylidene group, a sec-butylidene group, etc., a benzylidene group, or a dialkylsilylene group such as di-tert-butylsilylene group, etc., which can be formed, for example, by combining R^{11c} and R^{11d} at the terminal thereof.

The deprotection can be carried out according to the kinds of protecting group to be removed, for example, by conventional processes such as reduction, hydrolysis, acid treatment, fluoride treatment, etc.

For example, when a benzyl group is to be removed, the deprotection can be carried out by (1) catalytic reduction using a palladium catalyst (e.g., palladium-carbon, palladium hydroxide) under hydrogen atmosphere in a suitable solvent (e.g., methanol, ethanol, ethyl acetate); (2) treatment with an dealkylating agent such as boron tribromide, boron trichloride, boron trichloride.dimethylsulfide complex, or iodotrimethylsilane in a suitable solvent (e.g., dichloromethane); or (3) treatment with a lower alkylthiol such as ethanethiol in the

presence of a Lewis acid (e.g., boron trifluoride.diethyl ether complex) in a suitable solvent (e.g., dichloromethane).

When a protecting group is removed by hydrolysis, the hydrolysis can be carried out by treating the compound of formula II with a base (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, sodium ethoxide, etc.) in a suitable solvent (e.g., tetrahydrofuran, dioxane, methanol, ethanol, water, etc.).

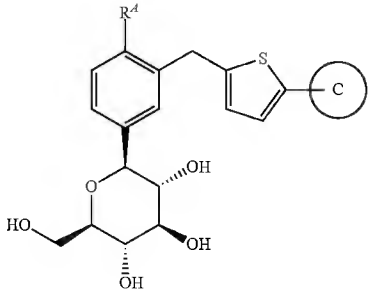
Acid treatment can be carried out by treating the compound of formula II with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

In case of the fluoride treatment, it can be carried out by treating the compound of formula II with a fluoride (e.g., hydrogen fluoride. hydrogen fluoride-pyridine, tetrabutylammonium fluoride, etc.) in a suitable solvent (e.g., acetic acid, a lower alcohol (methanol, ethanol, etc.), acetonitrile, tetrahydrofuran, etc.).

The deprotection reaction can be preferably carried out under cooling or with heating, for example, at a temperature of from 0° C. to 50° C., more preferably at a temperature of from 0° C. to room temperature.

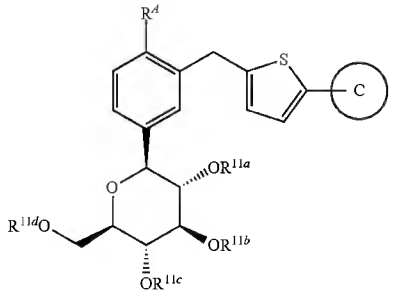
Accordingly, a compound of formula (IA'):

(IA')



wherein the symbols are the same as defined above, can be prepared by deprotecting a compound of formula (II-A):

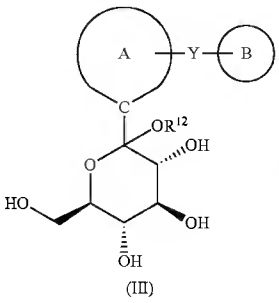
(II-A)



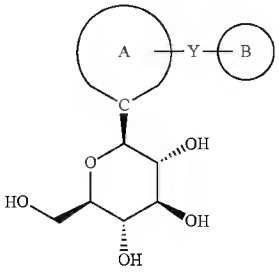
wherein the symbols are the same as defined above, as described above.

Process 2

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(III)



(I-a)

wherein R^{12} is a lower alkyl group, and other symbols are as defined above.

The compound of the formula I-a may be prepared by reducing the compound of the formula III.

The reduction can be carried out by treatment with a silane reagent, in the presence of an acid, in a suitable solvent or in the absence of a solvent.

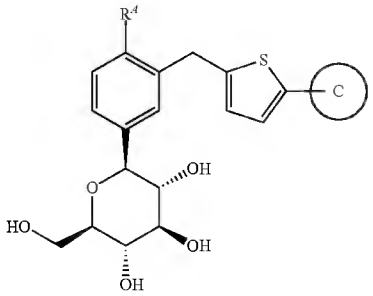
As the acid, for example, a Lewis acid such as boron trifluoride.diethyl ether complex, titanium tetrachloride, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid. etc., may preferably be used.

As the silane reagent, for example, a trialkylsilane such as triethylsilane, triisopropylsilane, etc. may preferably be used.

As the solvent, any kinds of solvent may be used as long as it does not affect the reaction, and for example, acetonitrile, dichloromethane, or an acetonitrile/dichloromethane mixture may preferably be used.

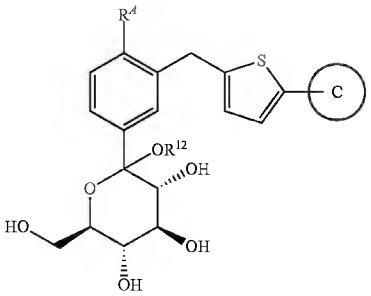
Accordingly. the compound of the formula (IA'):

(IA')



wherein the symbols are the same as defined above, can be prepared by reducing a compound of formula (III-A):

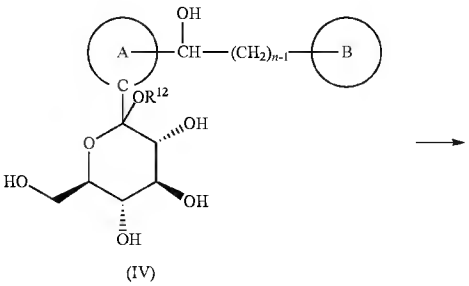
(III-A)



wherein the symbols are the same as defined above, as described above.

Process 3

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(IV)

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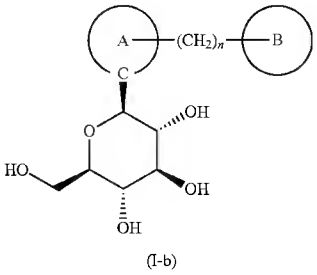


(I-b)

wherein the symbols are as defined above.

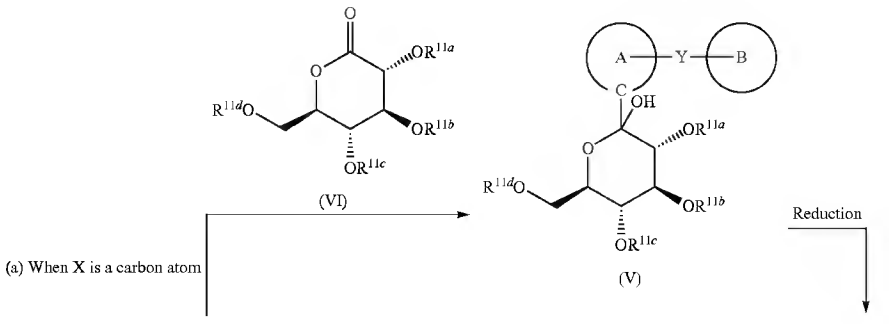
Namely, the compound of the formula I-b may be prepared by reducing the compound of the formula IV.

The reduction can be carried out in a manner similar to Process 2. In other words, it can be carried out by treatment with a silane reagent (e.g., triethylsilane, etc.), in the presence of a Lewis acid (e.g., boron trifluoride diethyl ether complex, etc.), in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.).

The compound of the present invention thus obtained may be isolated and purified by a conventional method well known in the organic synthetic chemistry such as recrystallization, column chromatography, etc.

The starting compound represented by the formula (II), (III) or (IV) may be prepared by either one of the following steps (a)-(l).

Steps (a) and (b):



(a) When X is a carbon atom

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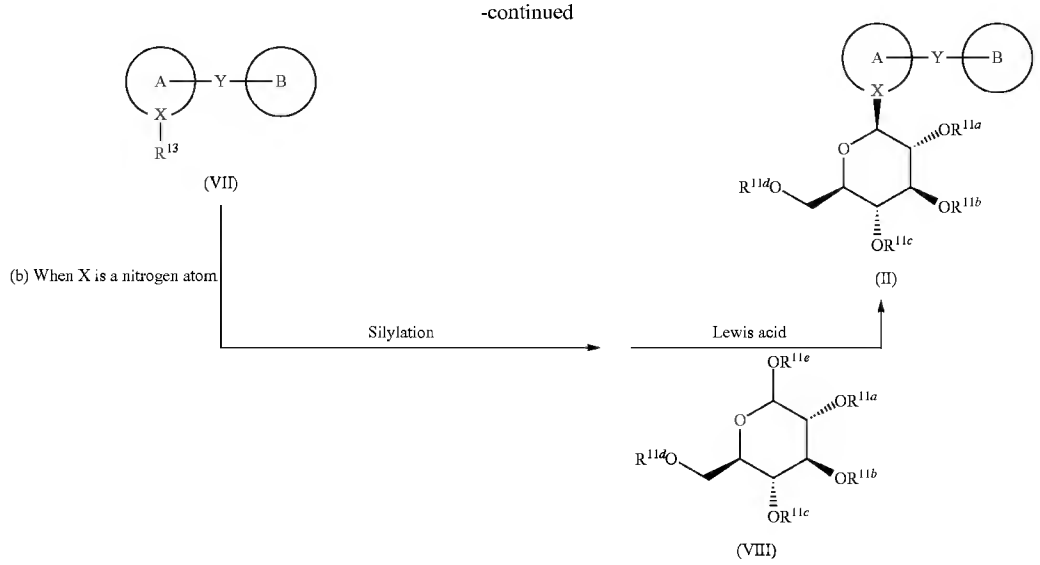


In the above scheme, R^{13} is (1) a bromine atom or an iodine atom when X is a carbon atom; or (2) a hydrogen atom when X is a nitrogen atom, R^{11e} is a protecting group for hydroxy group, and the other symbols are as defined above.

Step (a):

Among the compounds of the formula II, the compound wherein X is a carbon atom may be prepared by coupling the compound of the formula VII with the compound of the formula VI to give the compound of formula V, followed by reduction of the compound of the formula V.

The coupling reaction can be carried out by lithiating the compound of the formula VII, followed by reacting the resultant with the compound of the formula VI.

In particular, the compound of the formula VII can be treated with an alkyllithium, followed by reacting the resultant with the compound of the formula VI. As the alkyllithium, methyl lithium, n-butyl lithium, t-butyl lithium, etc. are preferably used. The solvent may be any solvent which does not disturb the reaction, and ethers such as tetrahydrofuran, diethyl ether, etc., are preferably used. This reaction can be carried out from under cooling (e.g., at −78° C.) to room temperature.

The reduction can be carried out in a manner similar to Process 2. Namely, it can be carried out by treating the compound of formula V with a silane reagent (e.g., triethylsilane, etc.) in the presence of a Lewis acid (e.g., boron trifluoride.diethyl ether complex, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.).

Step (b)

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by silylating the compound of the formula VII in a solvent, followed by reacting the resultant with the compound of the formula VIII (e.g., an α- or β-D-glucose pentaacetate, etc.) in the presence of a Lewis acid.

The silylation reaction can be carried out by treating the compound of formula VII with a silylating agent in a solvent. The silylating agent includes, for example, N,O-bis(trimethylsilyl)acetamide, 1,1,1,3,3,3-hexamethyl-disilazane, etc.

The solvent may be, for example, halogenated hydro-carbons such as dichloromethane, dichloroethane, chloroform, etc., ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, etc., acetonitrile, etc.

This reaction is preferably carried out under cooling or with heating, for example, at a temperature of from 0° C. to 60° C., preferably at a temperature of from room temperature to 60° C.

The reaction with the compound of the formula VIII can be carried out in a solvent in the presence of a Lewis acid.

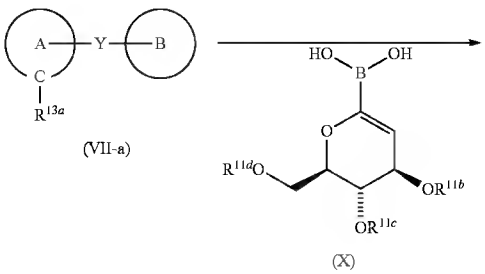
The Lewis acid includes, for example, trimethylsilyl trifluoromethanesulfonate, titanium tetrachloride, tin tetrachloride, boron trifluoride.diethyl ether complex.

The solvent may be, for example, halogenated hydro-carbons such as dichloromethane, dichloroethane, chloroform, etc., acetonitrile, etc.

This reaction can be carried out under cooling or with heating, for example, at a temperature of from 0° C. to 100° C., preferably at a temperature of from room temperature to 60° C.

Step (c):

Among the compounds of the formula II, the compound wherein X is a carbon atom and R^{11a} is a hydrogen atom may be prepared by a method as shown in the following scheme:



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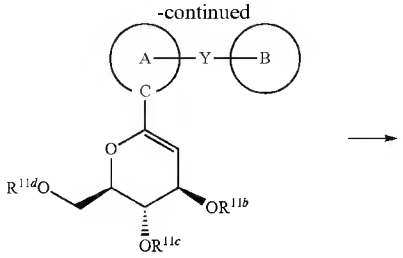
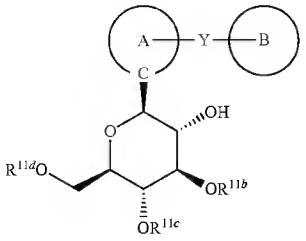


(IX)

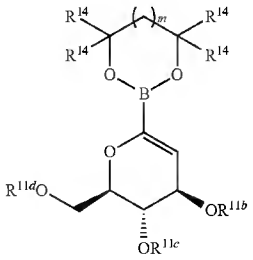


(II-a)

wherein R^{13a} is a bromine atom or an iodine atom, and the other symbols are as defined above.

Namely, the compounds of the formula II-a may be prepared by coupling the compound of the formula VII-a with the compound of the formula X or an ester thereof to give the compound of the formula IX, followed by hydrating the compound of the formula IX.

The ester of the compound of the formula X includes, for example, a lower alkyl ester thereof, and a compound represented by the formula XI:



(XI)

wherein R^{14} is a lower alkyl group, m is 0 or 1, and the other symbols are as defined above.

The coupling reaction of the compound of the formula VII-a with the compound of the formula X or an ester thereof can be carried out in the presence of a base and a palladium catalyst in a suitable solvent.

The base includes an inorganic base such as an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), potassium fluoride, potassium phosphate, etc., and an organic base such as a tri-lower alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), a cyclic tertiary amine (e.g., 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,8-diazabicyclo[5.4.0]undeca-7-ene, etc.).

The palladium catalyst may be a conventional catalyst such as tetrakis(triphenyl)phosphinepalladium(0), palladium(II) acetate, palladium(II) chloride, bis(triphenyl)phosphine palladium(II) chloride, palladium(II) chloride.1,1-bis(diphenylphosphino)ferrocene complex, etc.

The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., amide solvents such as N,N-dimethylformamide, 1,3-dimethyl-2-imidazolidinone, etc., aromatic hydrocarbons such as toluene, xylene, etc., dimethylsulfoxide, water, and if desired, a mixture of two or more of these solvents.

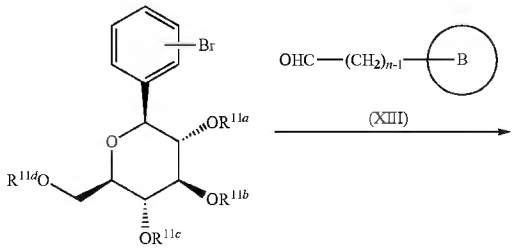
This reaction is preferably carried out with heating, for example, at a temperature of from 50° C. to a boiling point of the reaction mixture, and more preferably at a temperature of from 50° C. to 100° C.

The hydration reaction of the compound of the formula IX can be carried out, for example, by hydroboration, more specifically, by reacting with diborane, borane tetrahydrofuran complex, or 9-borabicyclononane, etc. in a suitable solvent, followed by treating with hydrogen peroxide solution in the presence of a base (e.g., an alkali metal hydroxide such as sodium hydroxide, etc.), or by treating with an oxidizing reagent such as sodium perborate, and oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) in a suitable solvent.

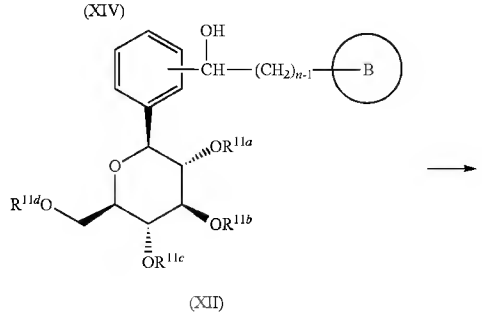
The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., water, and if desired, a mixture of two or more of these solvents. This reaction can be carried out at a temperature of a broad range such as under cooling or with heating, and preferably carried out at a temperature of from −10° C. to a boiling point of the reaction mixture.

Step (d):

Among the compound of the formula II, the compound wherein Ring A is a benzene ring may be prepared in a method as shown in the following scheme:



(XIV)



(XII)

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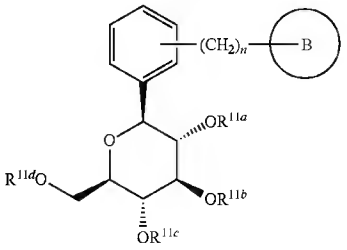


(II-b)

wherein the symbols are as defined above.

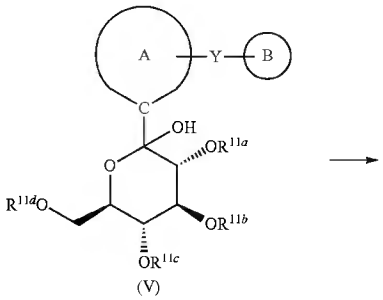
Namely, the compounds of the formula II-b may be prepared by coupling the compound of the formula XIV with the compound of the formula XIII, to give the compound of the formula XII, followed by reduction of the compound of the formula XII.

The coupling reaction can be carried out in a manner similar to Step (a). Namely, it can be carried out by lithiating the compound of formula XIV with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound (XIII).

The reduction reaction can be carried out by (1) treatment with a silane reagent (e.g., trialkyl silane such as triethyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at −30° C. to 60° C., in the presence of a Lewis acid such as boron trifluoride diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane, or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., and a Lewis acid such as aluminum chloride, etc.).

Step (e):

The compound of the formula III may be prepared by a method as shown in the following scheme:



(V)

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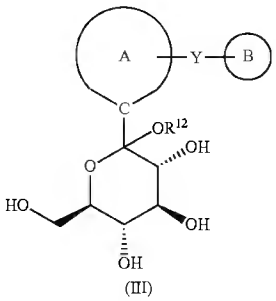


(III)

wherein the symbols are as defined above.

Namely, the compound of the formula III may be prepared by deprotecting the compound of the formula V which is a synthetic intermediate of Step (a), followed by treating the resultant compound with an acid in an alcohol solvent.

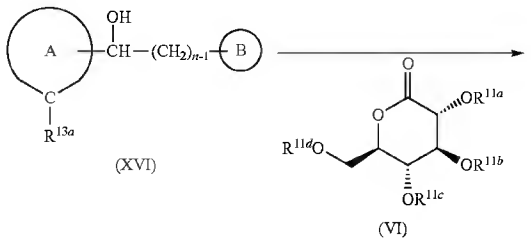
The deprotection reaction can be carried out in a manner similar to Process 1. Namely, it can be carried out by subjecting the compound V to an acid treatment, reduction, or a fluoride treatment, etc.

Following the deprotection reaction, the resultant compound is treated with an acid in a suitable alcohol. The acid includes, for example, an inorganic acid such as hydrochloric acid, nitric acid, sulfuric acid, etc., an organic acid such as p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc. The alcohol includes a conventional alkyl alcohol which does not disturb the reaction, for example, methanol, ethanol, n-propanol, i-propanol, n-butanol, etc.

Additionally, the deprotection reaction and acid treatment may be carried out in the same step, depending on the kind of the protecting group.

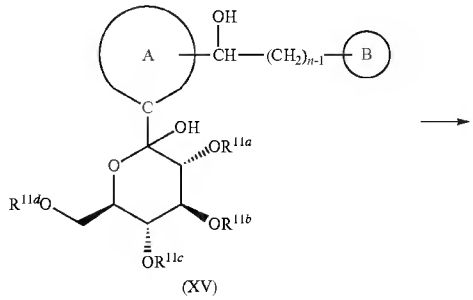
Step (f):

The compound of the formula IV may be prepared by a method as shown in the following scheme:



(XVI)

(VI)



(XV)

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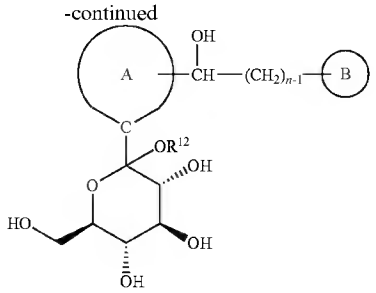


(IV)

wherein the symbols are as defined as above.

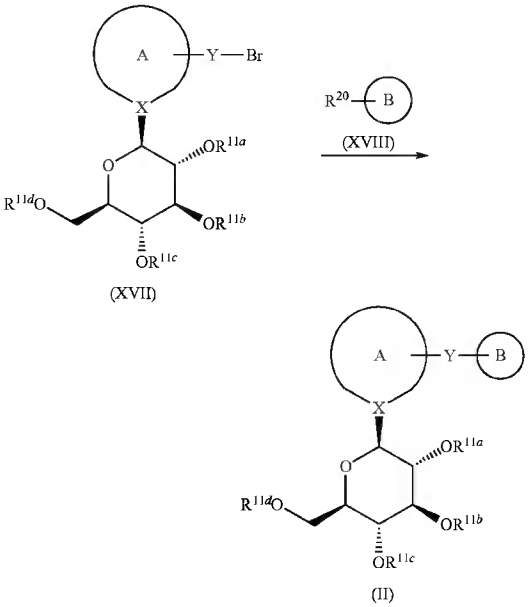
First, the compound of the formula XVI is coupled with the compound of the formula VI to give the compound of the formula XV. Then, after protecting groups are removed from the compound of the formula XV, the resultant is treated with an acid in an alcohol to give the compound of the formula IV.

The coupling reaction can be carried out in a manner similar to Step (a). Namely, the compound XVI is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc,) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound VI.

The removal of protecting groups and the acid treatment are carried out in a manner similar to Step (e). Namely, it can be carried out by subjecting the compound XV to reduction, acid treatment or fluoride treatment, depending on the kind of the protecting group to be removed, followed by treating the resultant with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

Step (g):

The compound of the formula II may be prepared by a method as shown in the following scheme:



(XVII)

(XVIII)

(II)

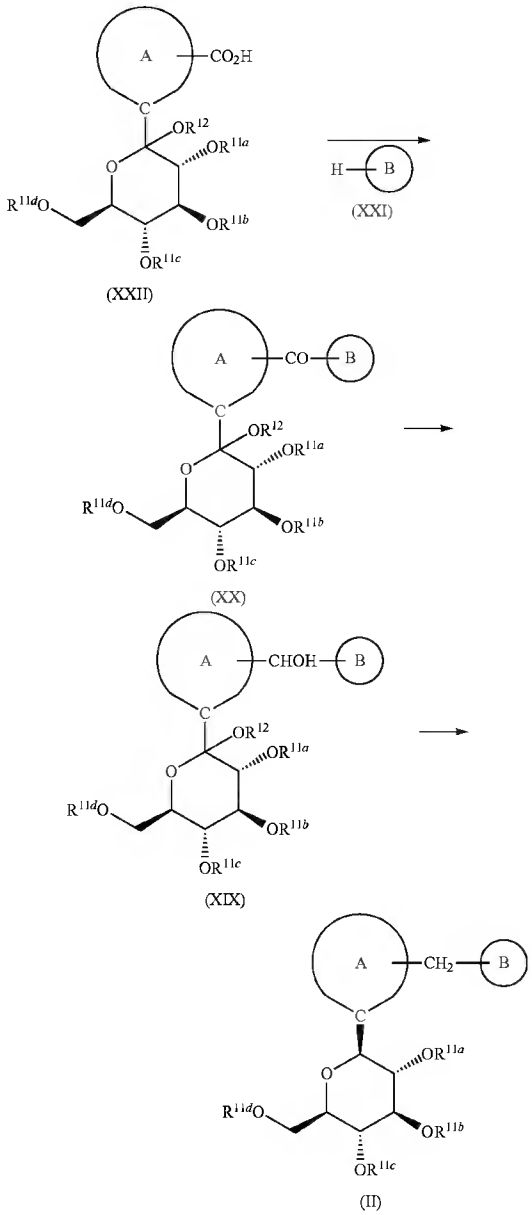
wherein R^{20} is a trialkylstannyl group, or a dihydroxyboryl group or an ester thereof, and the other symbols are as defined above. Examples of esters of dihydroxyboryl group include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol.

Namely, the compound of the formula II may be prepared by coupling the compound XVII with the compound XVIII in a suitable solvent, in the presence of a palladium catalyst, and in the presence or in the absence of a base.

The coupling reaction can be carried out in a manner similar to Step (c).

Step (h):

Among the compound of the formula II, the compound wherein n is 1 and X is a carbon atom may be prepared in a method as shown in the following scheme:



(XXII)

(XXI)

(XX)

(XIX)

(II)

wherein the symbols are as defined above.

Namely, the compound of the formula II may be prepared by the following steps: (1) treating the compound of the formula XXII with a halogenating agent in a suitable solvent or in the absence of a solvent, followed by condensation of the resultant with the compound of the formula XXI in the presence of a Lewis acid to give the compound of formula XX, (2) reducing the compound of formula XX, and (3) further reducing the compound of formula XIX.

The halogenating agent includes a conventional halogenating agent such as thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.

The solvent may be any solvent which does not disturb the reaction, and for example, dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc. may be mentioned.

Further, in the present reaction, the reaction suitably proceeds by adding a catalyst such as dimethylformamide, etc.

The condensation reaction of the compound (XXII) and the compound (XXI) can be carried out according to a conventional method as known as Friedel-Crafts reaction, in the presence of a Lewis acid and in a suitable solvent.

The Lewis acid includes aluminum chloride, boron trifluoride.diethyl ether complex, tin(IV) chloride, titanium tetrachloride, etc. which are conventionally used in Friedel-Crafts reaction.

The solvent includes halogenated hydrocarbons such as dichloromethane, carbon tetrachloride, dichloroethane, etc.

The reduction of the compound of formula XX can be carried out by treating the compound (XX) with borohydrides (e.g., sodium borohydride, sodium triacetoxyborohydride, etc.) in a suitable solvent (e.g., tetrahydrofuran, etc.).

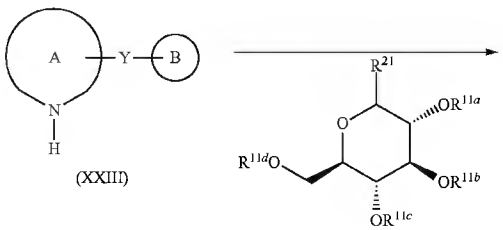
The present reaction can be carried out under cooling or with heating, for example, at a temperature of from −30° C. to 60° C.

The subsequent reduction reaction can be carried out by treating the compound of formula XIX with a silane reagent (e.g., trialkyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride.diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

The present reaction can be carried out under cooling or with heating, for example, at a temperature of from −30° C. to 60° C.

Step (i):

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by a method as shown in the following scheme:



(XXIII)

(XXIV)

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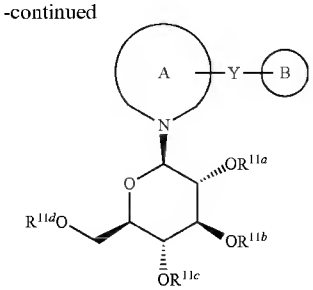


(II-d)

wherein R^{21} is a leaving group, and the other symbols are as defined above.

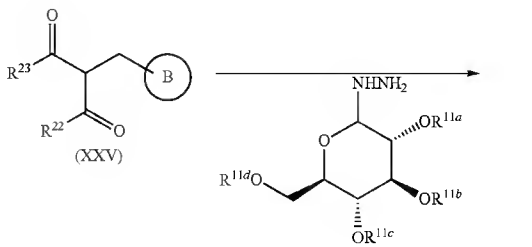
Examples of the leaving group include a halogen atom such as chlorine atom and bromine atom.

Namely, the compound of the formula II-d may be prepared by condensation of the compound of the formula XXIII with the compound of the formula XXIV.

The condensation reaction can be carried out in a suitable solvent such as acetonitrile, etc., in the presence of a base (e.g., an alkali metal hydroxide, such as potassium hydroxide, etc.).

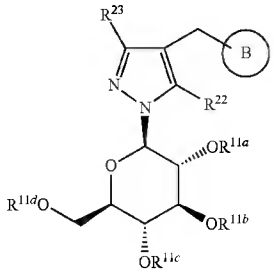
Step (j):

Among the compound of the formula II, the compound wherein Ring A is a pyrazole substituted by a lower alkyl group, X is a nitrogen atom and Y is —CH_2— may be prepared by a method as shown in the following scheme:



(XXV)

(XXVI)



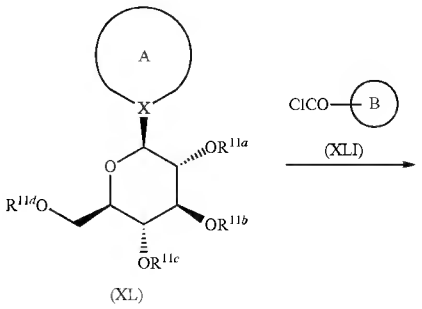
(II-e)

wherein R^{22} and R^{23} are each independently a lower alkyl group, and the other symbols are as defined above.

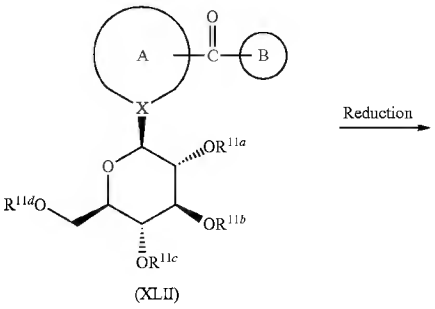
Namely, the compound II-e may be prepared by condensation of the compound of the formula XXV with the compound of the formula XXVI in a suitable solvent (e.g., ethers such as tetrahydrofuran, etc., an aromatic hydrocarbons such as toluene, etc.).

Step (k):

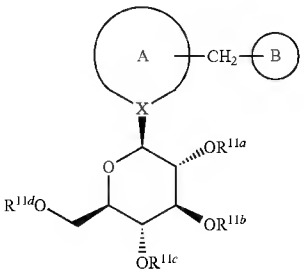
Among the compounds represented by formula (II), a compound wherein Y is —CH_2— group can be prepared by a method as shown in the following scheme:



(XL)



(XLII)



(II-f)

wherein the symbols are the same as defined above.

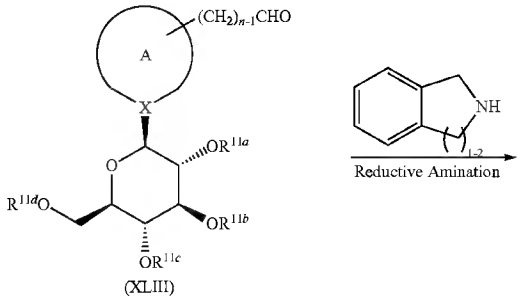
The compound (II-f) can be prepared by condensing a compound of formula (XL) with a compound of formula (XLI), and reducing a compound of formula (XLII).

The condensation reaction can be carried out in a similar manner as described in Step (h). Namely, the condensation reaction can be carried out in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, dichloroethane, etc.) in the presence of a Lewis acid (e.g., aluminum chloride, zinc chloride, titanium tetrachloride, etc.).

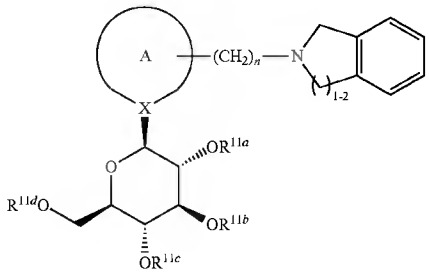
The reduction reaction can be carried out in a similar manner as described in Step (h).

Step (l)

Among the compounds represented by the formula (II), a compound wherein Ring B is an isoindolinyl or dihydroisoquinolinyl group can be prepared by a method as shown in the following scheme:



(XLIII)



(II-g)

wherein the symbols are the same as defined above.

A compound of formula (II-g) can be prepared by reductive amination of a compound of formula (XLIII) with isoindoline or dihydroisoquinoline. Reductive amination can be carried out in a suitable solvent (e.g., tetrahydrofuran, acetic acid, dichloroethane, etc.) in the presence of a reducing agent such as borohydrides (e.g., sodium borohydride, sodium triacetoxyborohydride) and aluminum hydrides (e.g., lithium aluminum hydride).

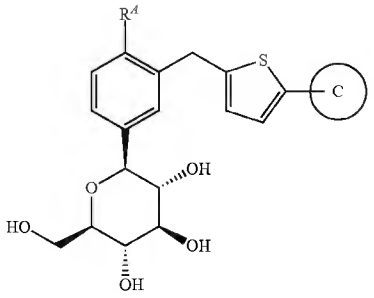
Further, the compound of the present invention may be converted to each other within the objective compounds of the present invention. Such conversion reaction may be carried out according to a conventional method, depending on the kind of the objective substituents. It may be preferable that functional groups in the compound would be protected before the conversion. The protective groups for the functional groups can be selected from conventional ones which can be removed by usual methods.

For example, a compound having as a substituent of Ring B an aryl group such as phenyl group or a heterocyclyl group may be prepared by coupling the compound in which substituents of the Ring B is a halogen atom such as a bromine atom, with a suitable phenylboronic acid, phenyltin, heterocyclylboronic acid, or heterocyclyltin.

The coupling reaction may be carried out in a manner similar to Step (c) or Step (g), or in a method as described in the following Examples.

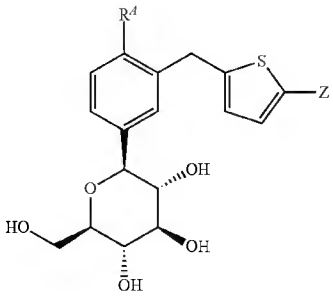
Accordingly, the compound of formula (IA'):

(IA')



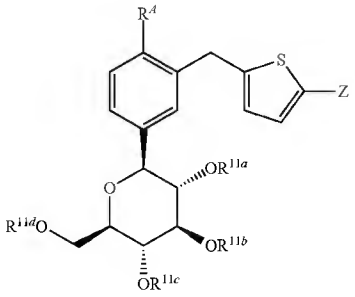
wherein the symbols are the same as defined above, can be prepared by (1) protecting a compound of formula (I-c):

(I-c)



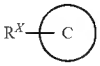
wherein Z is a halogen atom such as chlorine, bromine and iodine atom and R^A is the same as defined above, to afford a compound of formula (II-h):

(II-h)



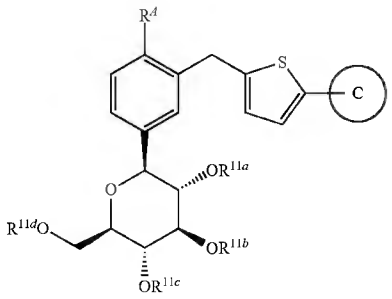
wherein the symbols are the same as defined above, (2) coupling the compound (II-h) with a compound of formula (XLIV):

(XLIV)



wherein R^X is $B(OH)_2$ or an ester thereof, or $Sn(lower\ alkyl)_3$, and Ring C is the same as defined above, to afford a compound of formula (II-A):

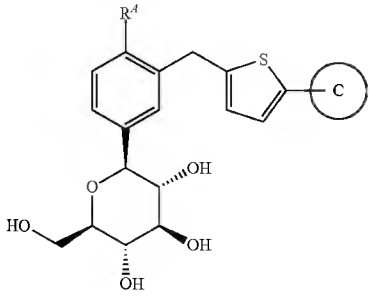
(II-A)



wherein the symbols are the same as defined above, and (3) removing the protecting groups. Examples of esters of $B(OH)_2$ include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol. Protection of hydroxyl groups can be carried out by conventional methods. Coupling reaction and deprotection can be carried out as described in Step (c) or (g) and Process 1, respectively.

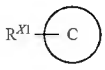
Additionally, the compound of formula (IA'):

(IA')



wherein the symbols are the same as defined above, can be prepared by (1) converting Z group of a compound of formula (II-h) to $B(OH)_2$ or an ester thereof, (2) coupling said compound with a compound of formula (XLV):

(XLV)



wherein R^{X1} is a halogen atom such as chlorine, bromine and iodine atom and Ring C is the same as defined above, and (3) removing the protecting groups.

Examples of esters of $B(OH)_2$ include an ester with a lower alkyl alcohol such as methanol and ethanol and an ester with a lower alkylene diol such as pinacol.

Conversion of a halogen atom to $B(OH)_2$ or an ester thereof can be carried out in a conventional method. For example, conversion of a halogen atom to $B(OH)_2$ can be carried out by treating the compound (II-h) with an alkyl lithium such as tert-butyl lithium in a suitable solvent (e.g., tetrahydrofuran),

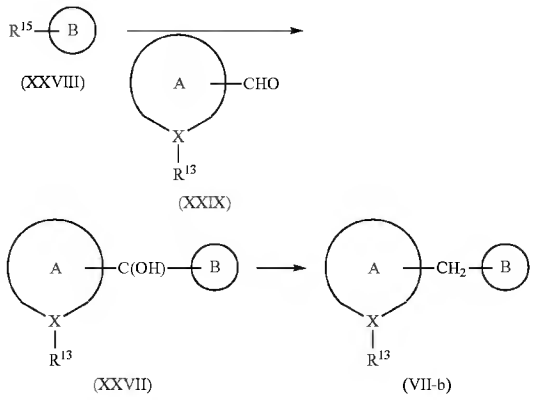
reacting the resulting compound with a tri-alkoxyborane in a suitable solvent (e.g., tetrahydrofuran), and hydrolyzing the resulting compound with an acid (such as acetic acid). And conversion of a halogen atom to an ester of $B(OH)_2$ can be carried out by treating the compound (II-h) with an alkyl lithium (such as tert-butyl lithium) in a suitable solvent (e.g., tetrahydrofuran), reacting the resulting compound with a tri-alkoxyborane in a suitable solvent (e.g., tetrahydrofuran), and reacting the resulting compound with an appropriate alcohol in a suitable solvent (e.g., tetrahydrofuran) or without solvent. Coupling reaction and deprotection can be carried out as described in Step (c) or (g) and Process 1, respectively.

In the present compound, the compound wherein heteroatom is oxidized (e.g., S-oxide, S,S-oxide, or N-oxide compounds) may be prepared by oxidizing a corresponding S-form or N-form.

The oxidation reaction can be carried out by a conventional method, for example, by treatment with an oxidizing agent (e.g., peracids such as hydrogen peroxide, m-chloroperbenzoic acid, peracetic acid, etc.) in a suitable solvent (e.g., halogenated hydrocarbons such as dichloromethane, etc.).

The starting compounds of the respective steps described above may be prepared by the methods as disclosed in Reference Examples or a process as mentioned below.

(1) Among the compounds of the formula VII, the compound wherein Y is $—CH_2—$ may be prepared by a method as shown in the following scheme:



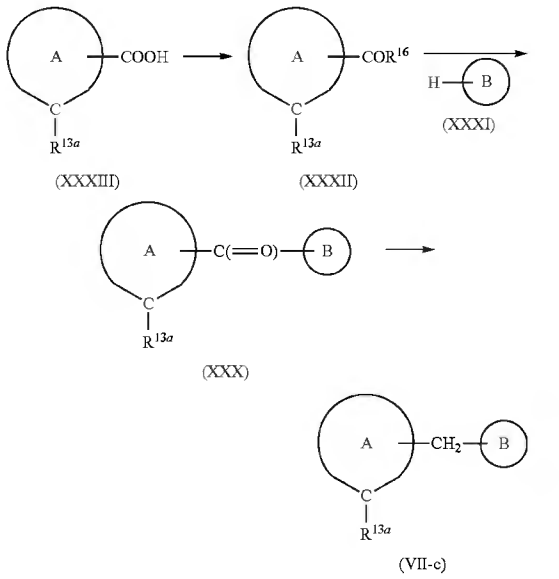
wherein R^{15} is a hydrogen atom or a halogen atom, and the other symbols are as defined above.

Namely, the compound of the formula VII-b may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXIX to give the compound of the formula XXVII, followed by reducing the obtained compound of the formula XXVII.

The coupling reaction of the present step may be carried out in a manner similar to Step (a). Namely, the compound of the formula XXVIII is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound of the formula XXIX.

The reduction reaction may be carried out in a manner similar to Step (d), more specifically, by (1) treatment with a silane reagent such as triethylsilane, etc., in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at −30° C. to 60° C., in the presence of a Lewis acid such as boron trifluoride.diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane, or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., a Lewis acid such as aluminum chloride, etc.).

(2) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is $—CH_2—$ may be prepared by a method as shown in the following scheme:



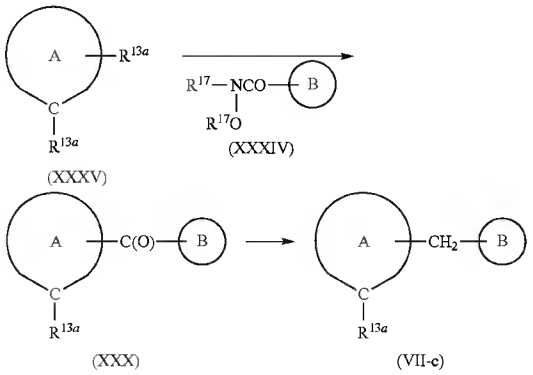
wherein R^{16} is a halogen atom, and the other symbols are as defined above.

The present process may be carried out in a manner similar to Step (h) as mentioned above.

Namely, the compound of the formula VII-c may be prepared by treating the compound of the formula XXXIII with a halogenating reagent (e.g., thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.) in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc.) or in the absence of a solvent, to give the compound of the formula XXXII, subsequently by condensing this compound with the compound of the formula XXXI in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, dichloroethane, etc.) in the presence of a Lewis acid (e.g., aluminum chloride, zinc chloride, titanium tetrachloride, etc.), to give the compound of the formula XXX, and further by reducing the obtained compound.

The reduction reaction can be carried out by treating with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride.diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

(3) Among the compounds of the formula VII, the compound wherein X is a carbon atom and Y is $—CH_2—$ may be prepared by a method as shown in the following scheme:

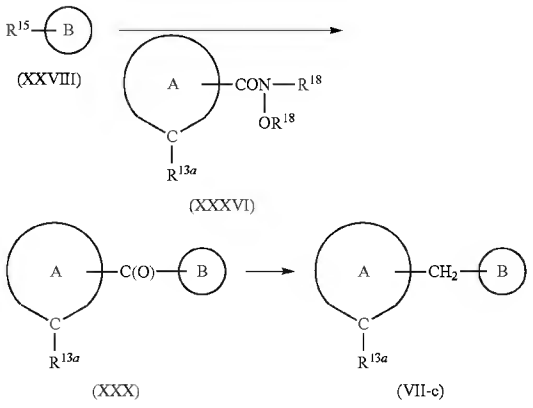


wherein R^{17} is a lower alkyl group, and the other symbols are as defined above.

The compound of the formula VII-c may be prepared by coupling the compound of the formula XXXV with the compound of the formula XXXIV to give the compound of the formula XXX, and subsequently by reducing the obtained compound.

The coupling reaction may be carried out in a manner similar to Step (a). Namely, the compound of the formula (XXV) is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the resultant with the compound (XXIV).

The reduction reaction may be carried out in a manner similar to Step (a). Namely, it can be carried out by treating the compound of formula XXX with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., boron trifluoride.diethyl ether complex, etc). (4) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is $-CH_2-$ may be prepared by a method as shown in the following scheme:



wherein R^{18} is a lower alkyl group, and the other symbols are as defined above.

Namely, the compound of the formula VII-c may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXXVI to give the compound of the formula XXX, and subsequently by reducing the compound.

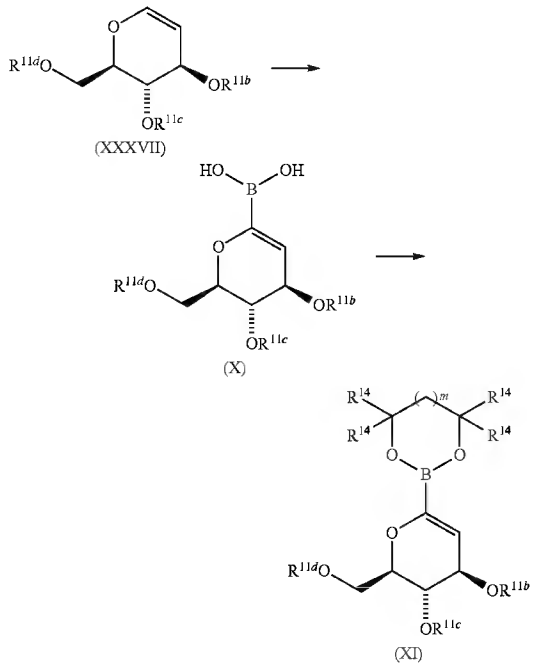
The present process may be carried out in a manner similar to Step (3). Namely, the compound of the formula (XXVIII) is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the resultant with the compound (XXXVI) to give the compound of the formula (XXX). Subsequently, the compound of the formula XXX is treated with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.) in the presence of an acid (e.g., boron trifluoride.diethyl ether complex, etc), to give the compound of the formula (VII-c).

The compound of the formula XIV wherein Ring A is a benzene ring is disclosed in WO 01/27128 pamphlet.

The compound of the formula VI is disclosed in WO 01/27128 or Benhaddu, S. Czernecki et al., Carbohydr. Res., vol. 260, p. 243-250, 1994.

The compound of the formula VIII may be prepared from D-(+)-glucono-1,5-lactone according to the method disclosed in U.S. Pat. No. 6,515,117.

The compound of the formula X and the compound of the formula XI may be prepared by the following Reaction Scheme:



wherein the symbols are as defined above.

First, the compound of the formula XXXVII is lithiated with t-butyl lithium in a suitable solvent (e.g., tetrahydrofuran, etc.) under cooling (e.g., −78° C.), followed by reacting with trimethyl borate to give the compound of the formula X.

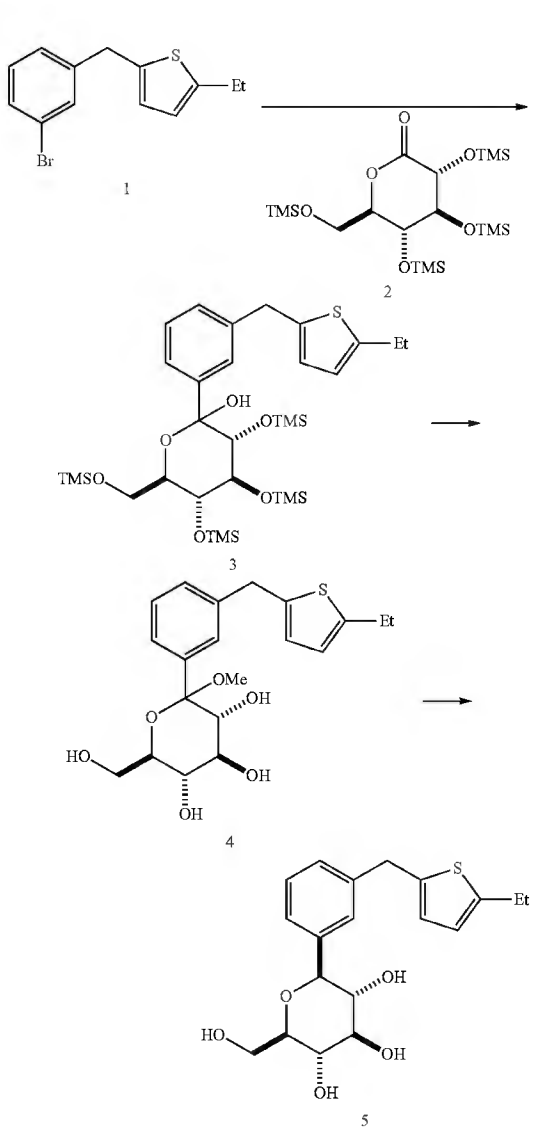
Then, the compound of the formula X is reacted with a 1,2-diol (e.g., pinacol, etc.) or 1,3-diol (e.g., 2,4-dimethyl-2, 4-pentanediol, etc.) to give the compound of the formula XI.

The other starting compounds are commercially available or are described in WO 01/27128 or WO 2004/080990, or may easily be prepared by a standard method well known to an ordinary skilled person in this field.

Hereinafter, the present invention will be illustrated by Examples and Reference Examples, but the present invention should not be construed to be limited thereto.

Example 1

1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienylmethyl) benzene



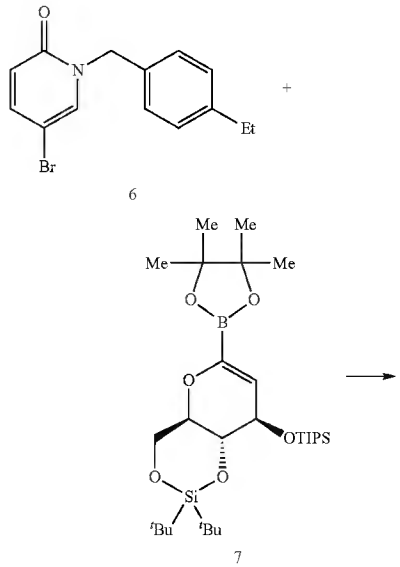
In the above scheme, Me is a methyl group, Et is an ethyl group, TMSO and OTMS are a trimethylsilyloxy group.

(1) 3-Bromo-(5-ethyl-2-thienylmethyl)benzene 1 (211 mg) was dissolved in tetrahydrofuran (2 ml)-toluene (4 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.29 ml), and the mixture was stirred at the same temperature for 30 minutes. Then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (233 mg) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for one hour to give a lactol compound 3. Without isolating this compound, a solution of methanesulfonic acid (0.1 ml) in methanol (5 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give a methyl ether compound 4 (136 mg) of the lactol. APCI-Mass m/Z 412 ($M+NH_4$).

(2) A solution of the above methyl ether compound 4 (100 mg) in dichloromethane (5 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triisopropylsilane (0.16 ml), and boron trifluoride.diethyl ether complex (0.10 ml). The mixture was stirred at the same temperature for 10 minutes, and warmed. The mixture was stirred at 0° C. for 1 hour and 20 minutes, and then further stirred at room temperature for 2 hours. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienylmethyl)benzene 5 (59 mg). APCI-Mass m/Z 382 ($M+NH_4$).

Example 2

5-(β-D-glucopyranosyl)-1-(4-ethylphenylmethyl)-1H-pyridin-2-one



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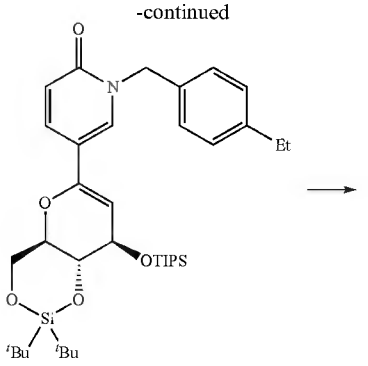

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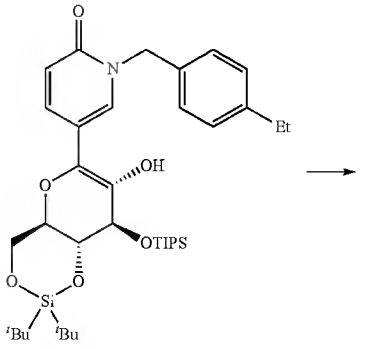

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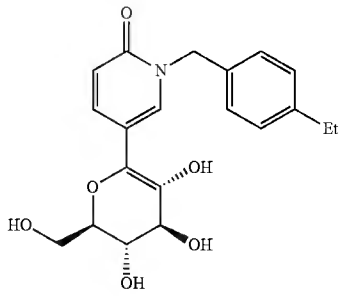

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In the above scheme, tBu is a tert-butyl group, OTIPS is a triisopropylsilyloxy group, and the other symbols are as defined above.

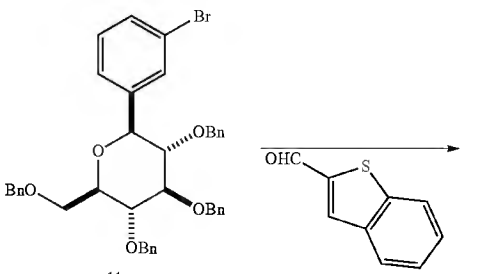
(1) 5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one 6 (293 mg) and boronic acid ester of glucal 7 (1.0 g) were dissolved in dimethoxyethane (5 ml). To the mixture were added bis(triphenyl)phosphine palladium(II)dichloride (35 mg) and 2M sodium carbonate (2.5 ml), and the mixture was heated with stirring under reflux under argon atmosphere for 5 hours. The mixture was cooled to room temperature, and the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-70:30) to give glucal derivative 8 (276 mg) as colorless powder. APCI-Mass m/Z 654 (M+H).

(2) A solution of glucal derivative 8 (260 mg) in tetrahydrofuran (5 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise a solution of borane.tetrahydrofuran complex (1.13 M tetrahydrofuran solution, 1.06 ml), and the reaction solution was stirred at the same temperature overnight. A mixture of an aqueous hydrogen peroxide solution (31%, 5.0 ml) and 3N aqueous sodium hydroxide solution (5.0 ml) was added to the reaction solution, and the mixture was warmed to room temperature, and stirred for 30 minutes. To the mixture was added 20% aqueous sodium thiosulfate solution (30 ml), and the mixture was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=96:4-66.34) to give C-glucoside compound 9 (59 mg) as colorless powder. APCI-Mass m/Z 672 (M+H).

(3) The above C-glucoside compound 9 (55 mg) was dissolved in tetrahydrofuran (2 ml), and thereto was added tetrabutyl ammonium fluoride (1.0 M tetrahydrofuran solution, 0.41 ml). The mixture was heated with stirring under reflux for 3 hours under argon atmosphere, and the reaction solution was cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-88:12) to give the desired 5-(β-D-glucopyranosyl)-1-(4-ethyl-phenylmethyl)1H-pyridin-2-one 10 (10 mg) as colorless powder. APCI-Mass m/Z 376 (M+H).

Example 3

1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)benzene



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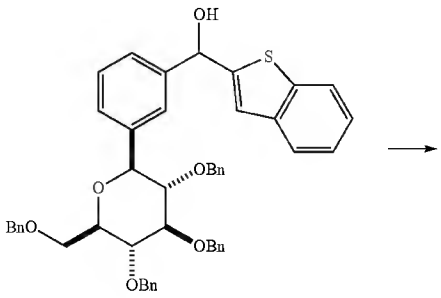

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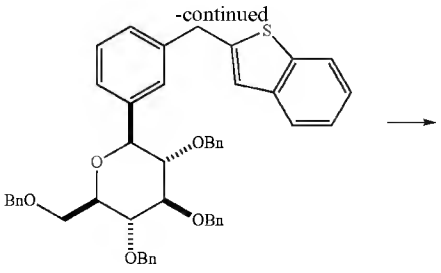
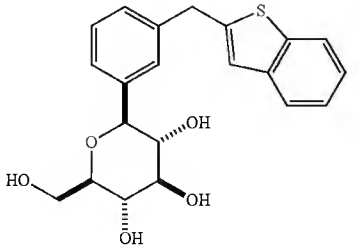


13



14

In the above scheme, Bn is a benzyl group.

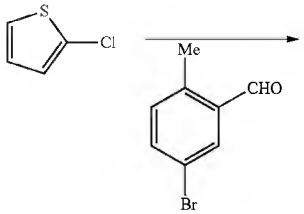
(1) β-m-Bromophenyl-tetra-O-benzyl-C-glucoside 11 (see WO 01/27128) (1.00 g) was dissolved in diethyl ether (60 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise t-butyl lithium (1.49 M pentane solution, 0.99 ml), and the mixture was stirred at the same temperature for 10 minutes. Then, a solution of 2-formylbenzo[b]thiophene (286 mg) in diethyl ether (2 ml) was added dropwise, and the mixture was further stirred at the same temperature for 30 minutes. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was warmed to room temperature. The mixture was extracted with diethyl ether, the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-50:50) to give an alcohol compound 12 (835 mg). APCI-Mass m/Z 780 ($M+NH_4$).

(2) A solution of the above alcohol compound 12 (820 mg) in dichloromethane (15 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (0.52 ml), and boron trifluoride.diethyl ether complex (0.20 ml). The reaction mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=94:6-75:25) to give the compound 13 (703 mg). APCI-Mass m/Z 764 ($M+NH_4$).

(3) A solution of the above compound 13 (690 mg) in dichloromethane (20 ml) was cooled to 0° C., and iodotrimethylsilane (0.66 ml) was added thereto and the mixture was stirred at room temperature for one hour. Addition of iodotrimethylsilane and stirring at room temperature were repeated in the same manner for 3 times. Total amount of the iodotrimethylsilane was summed up to 2.64 ml. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with diethyl ether twice, and washed with an aqueous sodium thiosulfate solution. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-89:11) to give the desired 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen2-ylmethyl)benzene 14 (180 mg). APCI-Mass m/Z 404 ($M+NH_4$).

Example 4

1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene



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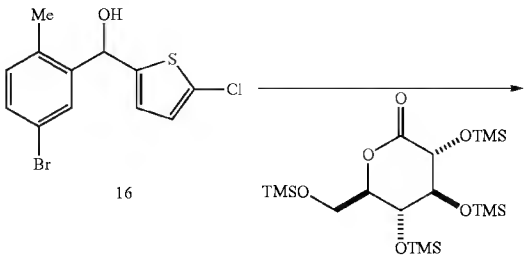
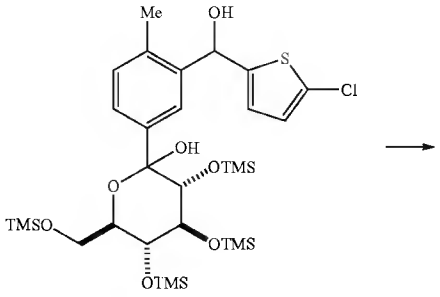


16

2



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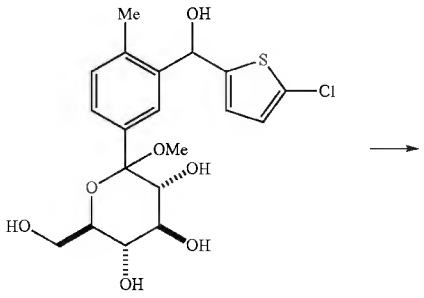

18

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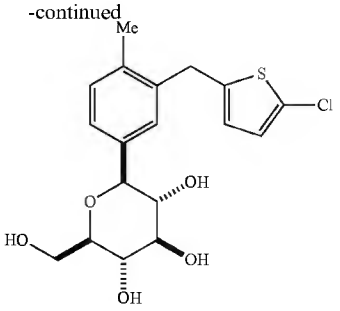


19

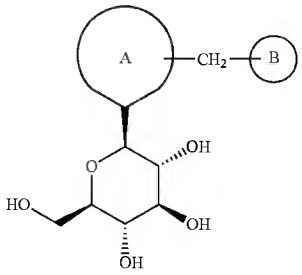
In the above scheme, the symbols are as defined above.

(1) A solution of 2-chlorothiophene (447 mg) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 2.61 ml). The mixture was stirred at the same temperature for one hour, and added dropwise thereto was a solution of 5-bromo-2-methylbenzaldehyde 15 (750 mg) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for 30 minutes to give a compound 16. Toluene (30 ml) was added, and further added dropwise thereto was n-butyl lithium (1.59 M hexane solution, 2.37 ml). The mixture was further stirred at the same temperature for 30 minutes, and a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (1.76 g) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for one and a half hours to give a lactol compound 17. Subsequently, a solution of methanesulfonic acid (1.22 ml) in methanol (25 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give a crude methyl ether compound 18, which was used in the subsequent step without further purification.

(2) A solution of the above crude methyl ether compound 18 in dichloromethane (25 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (3.01 ml), and boron trifluoride.diethyl ether complex (2.39 ml). The reaction mixture was warmed to 0° C., and stirred at the same temperature for 3 hours. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-92:8) to give the desired 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 19 (183 mg). APCI-Mass m/Z 402/404 ($M+NH_4$).

In a manner similar to the method disclosed in any of the above Examples 1 to 4, the compounds shown in Table 1 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out.

TABLE 1



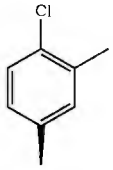
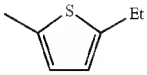
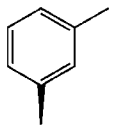
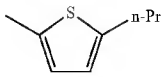
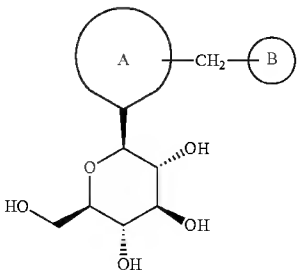
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
5			1	416/418 ($M + NH_4$)
6			1	396 ($M + NH_4$)

TABLE 1-continued



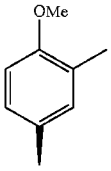
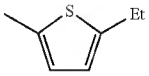
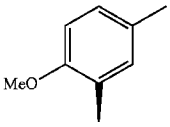
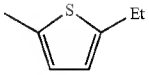
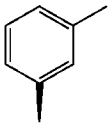
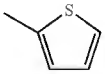
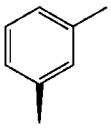
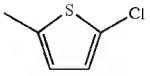
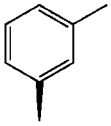
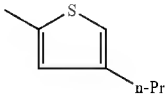
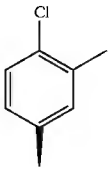
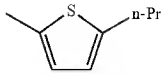
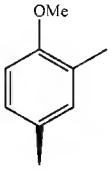
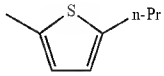
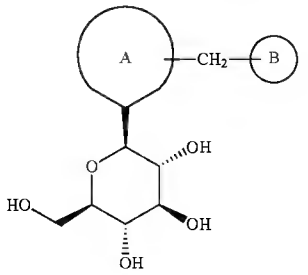
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
7			1	412 (M + NH_4)
8			1	412 (M + NH_4)
9			3	354 (M + NH_4)
10			3	388/390 (M + NH_4)
11			1	396 (M + NH_4)
12			1	430/432 (M + NH_4)
13			1	426 (M + NH_4)

TABLE 1-continued



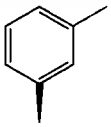
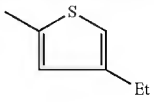
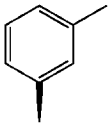
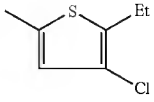
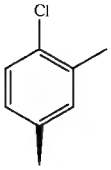
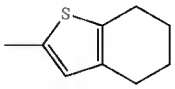
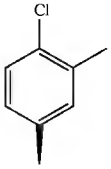
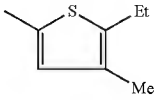
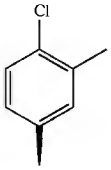
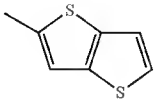
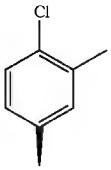
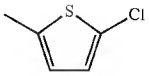
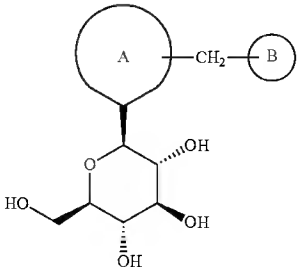
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
14			1	382 ($M + NH_4$)
15			1	416/418 ($M + NH_4$)
16			1	442/444 ($M + NH_4$)
17			1	430/432 ($M + NH_4$)
18			2	444/446 ($M + NH_4$)
19			1	422/424 ($M + NH_4$)

TABLE 1-continued



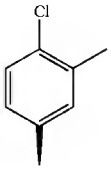
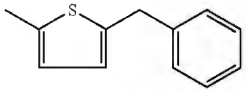
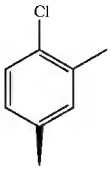
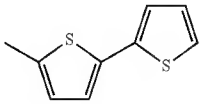
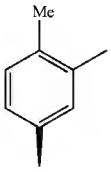
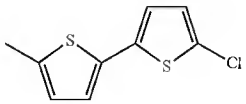
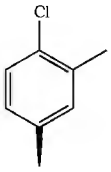
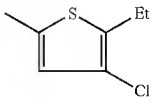
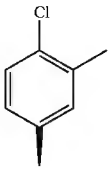
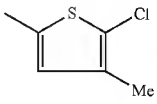
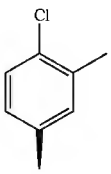
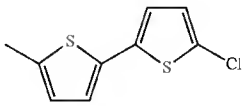
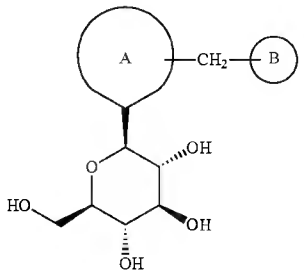
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
20			1	478/480 (M + NH_4)
21			2	470/472 (M + NH_4)
22			1	484/486 (M + NH_4)
23			1	450/452 (M + NH_4)
24			4	436/438 (M + NH_4)
25			1	504/506 (M + NH_4)

TABLE 1-continued



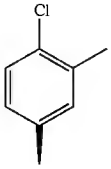
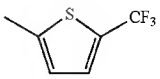
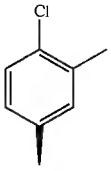
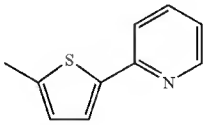
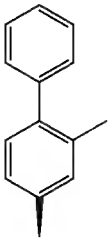
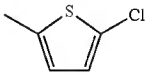
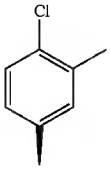
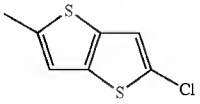
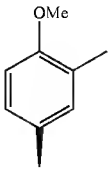
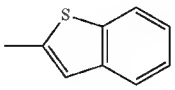
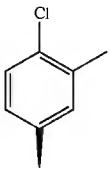
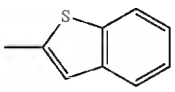
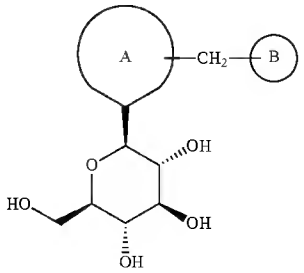
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
26			2	456/458 (M + NH_4)
27			1	448/450 (M + NH_4)
28			1	464/466 (M + NH_4)
29			4	478/480 (M + NH_4)
30			1	434 (M + NH_4)
31			1	438/440 (M + NH_4)

TABLE 1-continued



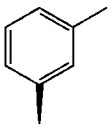
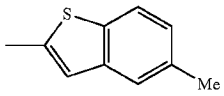
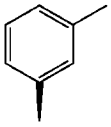
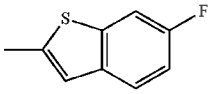
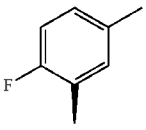
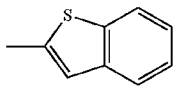
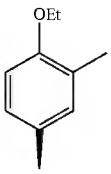
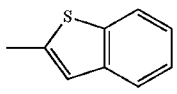
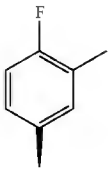
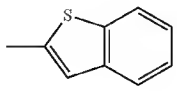
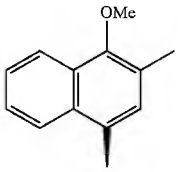
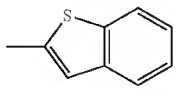
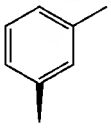
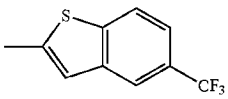
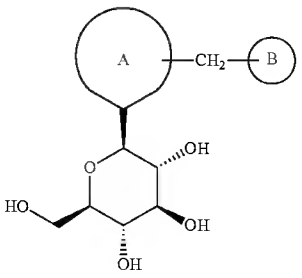
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
32			1	418 (M + NH_4)
33			1	422 (M + NH_4)
34			1	422 (M + NH_4)
35			1	448 (M + NH_4)
36			1	422 (M + NH_4)
37			1	484 (M + NH_4)
38			1	472 (M + NH_4)

TABLE 1-continued



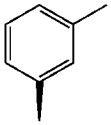
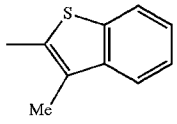
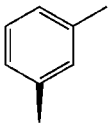
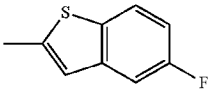
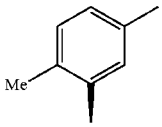
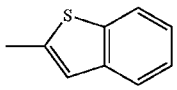
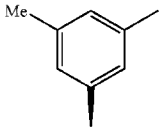
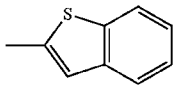
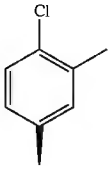
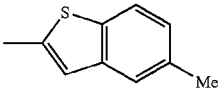
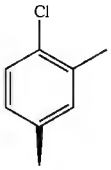
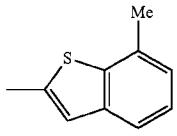
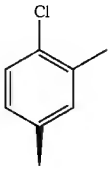
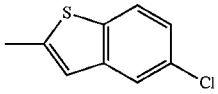
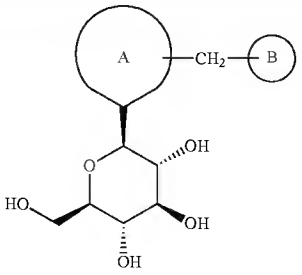
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
39			1	418 (M + NH_4)
40			1	422 (M + NH_4)
41			2	418 (M + NH_4)
42			1	418 (M + NH_4)
43			1	452/454 (M + NH_4)
44			1	452/454 (M + NH_4)
45			1	472/474 (M + NH_4)

TABLE 1-continued



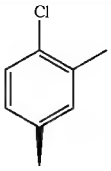
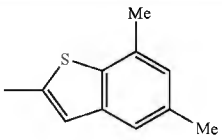
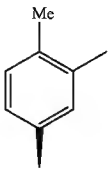
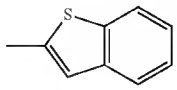
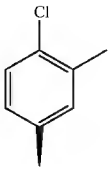
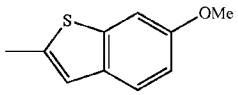
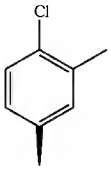
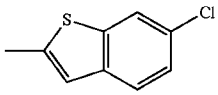
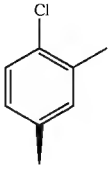
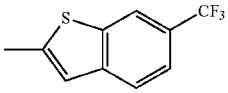
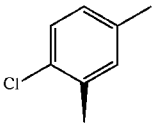
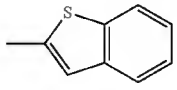
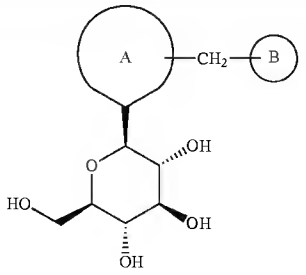
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
46			1	466/468 (M + NH_4)
47			1	418 (M + NH_4)
48			1	468/470 (M + NH_4)
49			1	472/474 (M + NH_4)
50			2	506/508 (M + NH_4)
51			2	438/440 (M + NH_4)

TABLE 1-continued



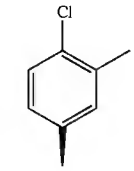
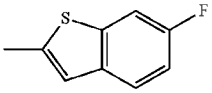
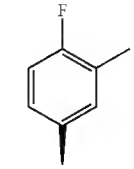
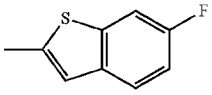
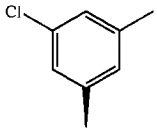
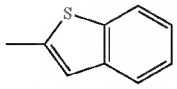
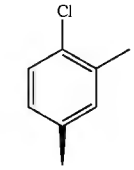
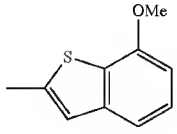
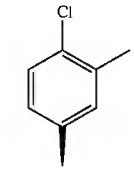
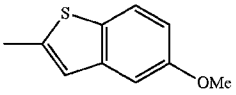
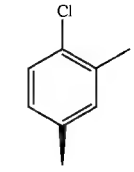
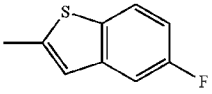
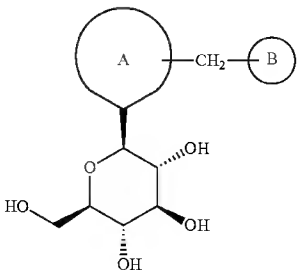
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
52			2	456/458 (M + NH_4)
53			2	440 (M + NH_4)
54			2	438/440 (M + NH_4)
55			1	468/470 (M + NH_4)
56			1	468/470 (M + NH_4)
57			2	456/458 (M + NH_4)

TABLE 1-continued



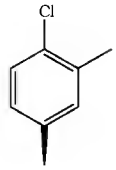
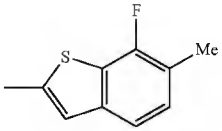
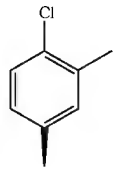
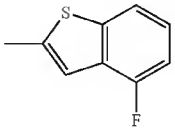
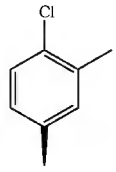
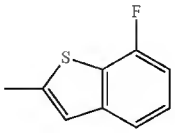
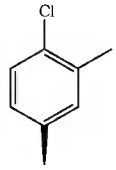
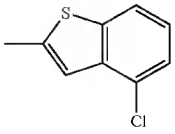
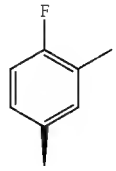
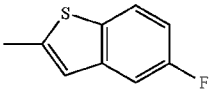
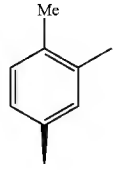
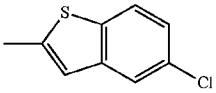
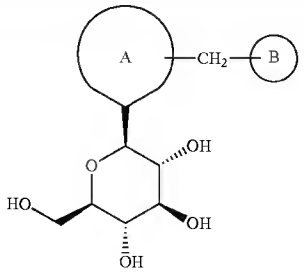
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
58			1	470/472 (M + NH_4)
59			2	456/458 (M + NH_4)
60			2	456/458 (M + NH_4)
61			2	472/474 (M + NH_4)
62			2	440 (M + NH_4)
63			4	452/454 (M + NH_4)

TABLE 1-continued



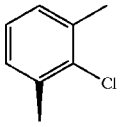
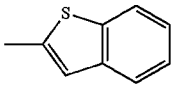
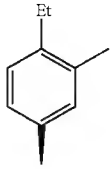
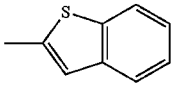
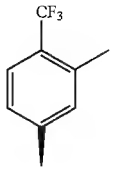
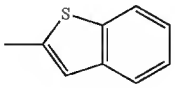
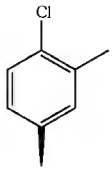
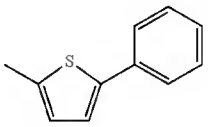
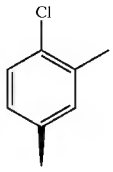
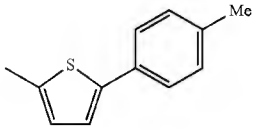
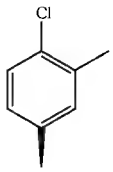
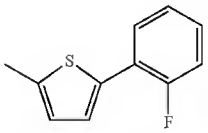
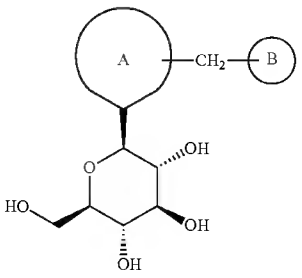
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
64			2	438/440 (M + NH_4)
65			1	432 (M + NH_4)
66			2	472 (M + NH_4)
67			1	464/466 (M + NH_4)
68			1	478/480 (M + NH_4)
69			1	482/484 (M + NH_4)

TABLE 1-continued



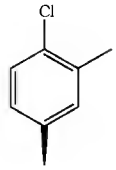
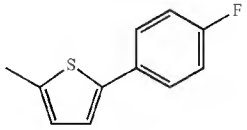
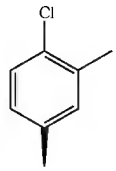
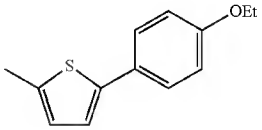
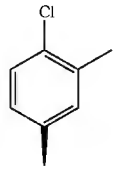
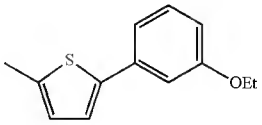
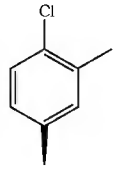
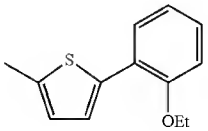
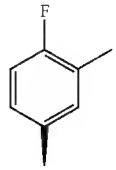
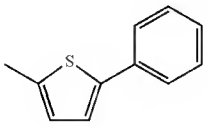
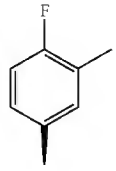
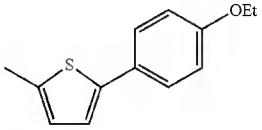
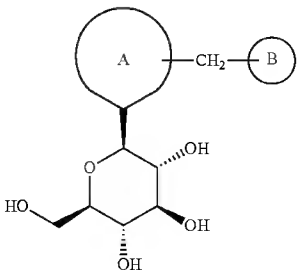
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
70			1	482/484 (M + NH_4)
71			1	508/510 (M + NH_4)
72			1	508/510 (M + NH_4)
73			1	508/510 (M + NH_4)
74			1	448 (M + NH_4)
75			1	492 (M + NH_4)

TABLE 1-continued



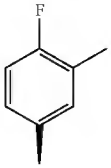
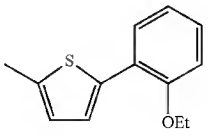
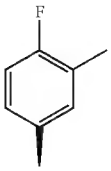
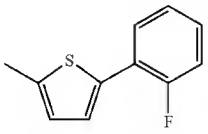
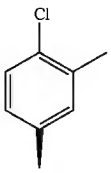
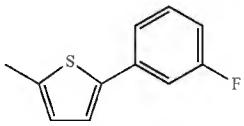
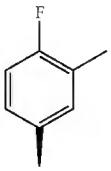
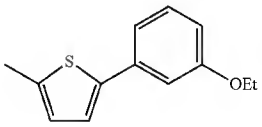
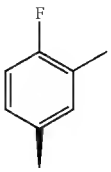
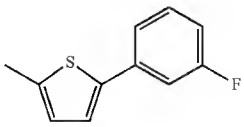
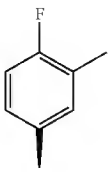
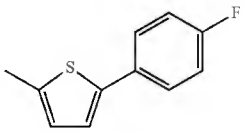
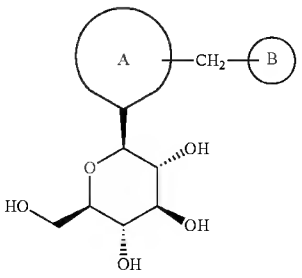
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
76			1	492 (M + NH_4)
77			1	466 (M + NH_4)
78			1	482/484 (M + NH_4)
79			1	492 (M + NH_4)
80			1	466 (M + NH_4)
81			1	466 (M + NH_4)

TABLE 1-continued



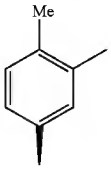
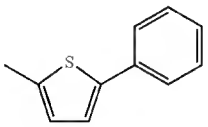
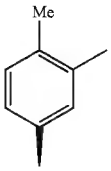
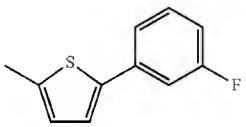
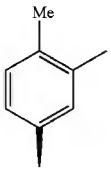
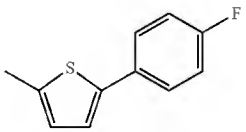
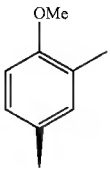
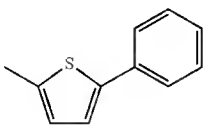
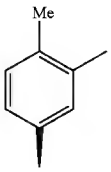
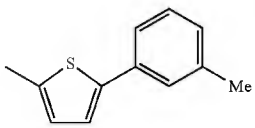
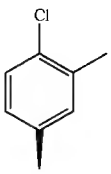
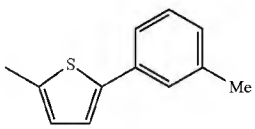
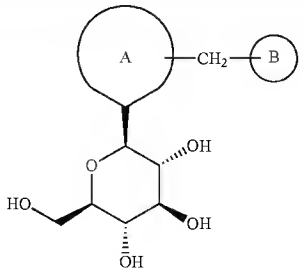
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
82			1	444 (M + NH_4)
83			1	462 (M + NH_4)
84			1	462 (M + NH_4)
85			2	460 (M + NH_4)
86			1	458 (M + NH_4)
87			1	478/480 (M + NH_4)

TABLE 1-continued



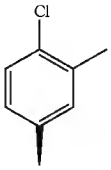
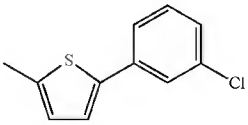
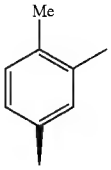
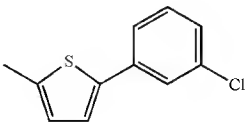
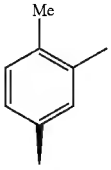
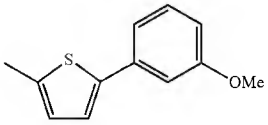
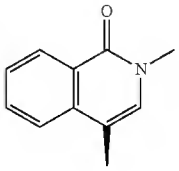
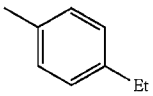
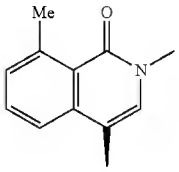
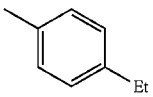
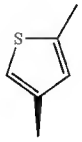
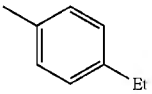
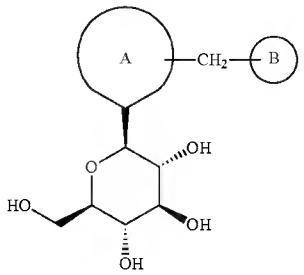
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
88			1	498/500 ($M + NH_4$)
89			1	478/480 ($M + NH_4$)
90			1	474 ($M + NH_4$)
91			2	426 (M + H)
92			2	440 (M + H)
93			2	382 ($M + NH_4$)

TABLE 1-continued



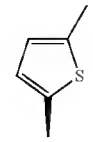
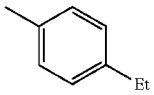
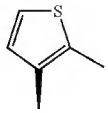
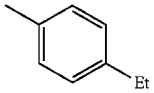
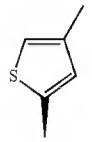
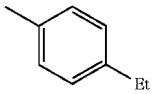
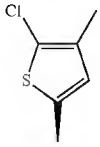
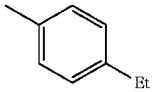
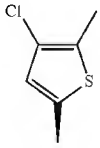
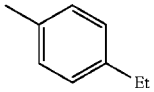
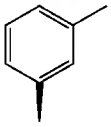
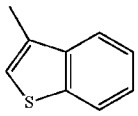
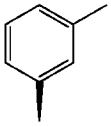
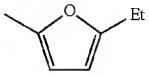
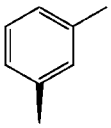
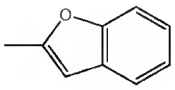
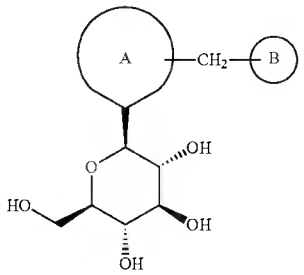
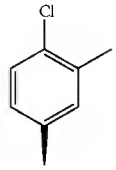
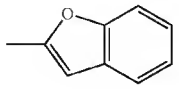
Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
94			2	382 (M + NH_4)
95			2	382 (M + NH_4)
96			2	382 (M + NH_4)
97			2	416/418 (M + NH_4)
98			2	416/418 (M + NH_4)
99			1	404 (M + NH_4)
100			1	366 (M + NH_4)
101			1	388 (M + NH_4)

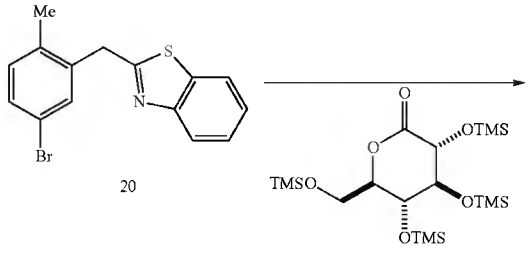
TABLE 1-continued

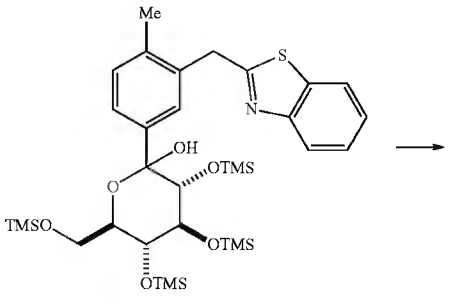


Examples	Ring A	Ring B	Prepa-ration Method	APCI-Mass (m/Z)
102			1	422/424 (M + NH_4)

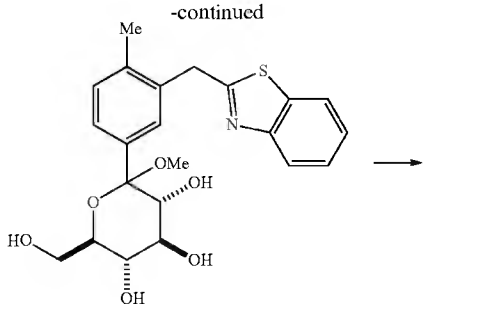
Example 103

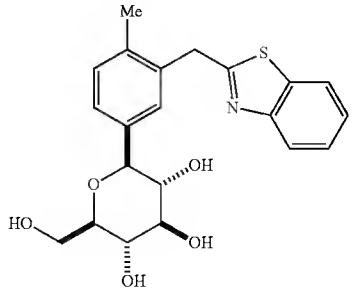
1-(β-D-glucopyranosyl)-3-(benzothiazol-2-ylm-ethyl)-4-methylbenzene





-continued





In the above scheme, the symbols are as defined above.

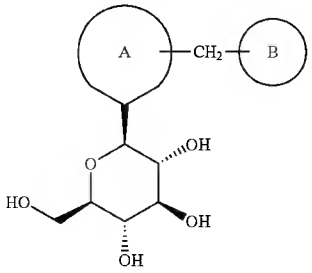
(1) 1-(benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene 20 (495 mg) was dissolved in tetrahydrofuran (5 ml)-toluene (10 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.67 ml), and successively was added dropwise t-butyl lithium (2.44 M pentane solution, 1.57 ml). The mixture was stirred at the same temperature for 10 minutes, and then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (2.17 g) in toluene (5 ml) was added drop-

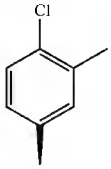
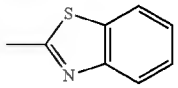
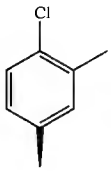
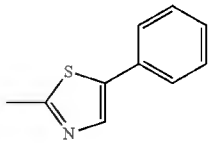
wise, and the mixture was further stirred at the same temperature for 15 minutes to give a lactol compound 21. Without isolating this compound, a solution of methanesulfonic acid (1.5 ml) in methanol (25 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution. and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give a methyl ether compound 22, which was used in the subsequent step without further purification.

(2) A solution of the above methyl ether compound 22 in dichloromethane (20 ml)-acetonitrile (10 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (1.24 ml), and boron trifluoride.diethyl ether complex (0.99 ml). The mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-85:15) to give 1-(β-D-glucopyranosyl)-3-(benzothiazol-2-ylmethyl)-4-methylbenzene 23 (200 mg) as colorless powder. APCI-Mass m/Z 402 (M+H).

In a manner similar to Examples 103, the compounds shown in Table 2 below were prepared from corresponding starting materials.

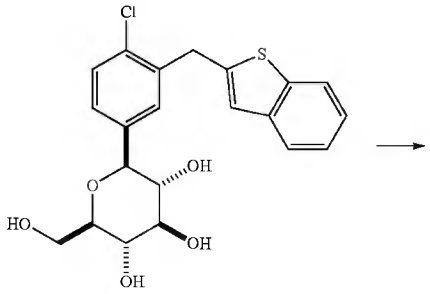
TABLE 2



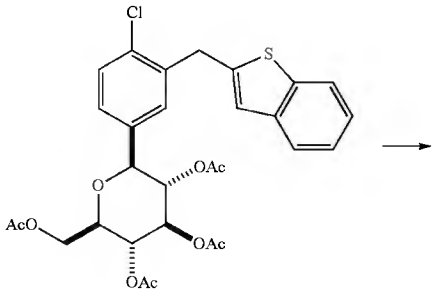
Examples	Ring A	Ring B	APCI-Mass (m/Z)
104			422/424 (M + H)
105			480/482 ($M + NH_4$)

Example 106

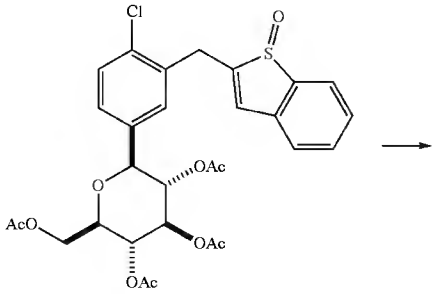
1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxy-benzo[b] thiophen-2-ylmethyl)benzene



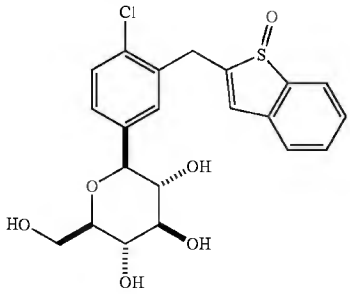
24



25



26



27

In the above scheme, AcO and OAc are an acetyloxy group.

(1) The compound 24 (9.61 g) obtained in Example 31 was dissolved in chloroform (100 ml), and to the mixture were added acetic anhydride (21.6 ml), pyridine (18.5 ml), and 4-dimethylaminopyridine (128 mg), and the mixture was

stirred at room temperature for 3.5 days. Then, Chloroform was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (200 ml). The solution was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over magnesium sulfate, and treated with activated carbon. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol to give a tetraacetate compound 25 (6.14 g). APCI-Mass m/Z 606/608 ($M+NH_4$).

(2) The above tetraacetate compound 25 (1.00 g) was dissolved in dichloromethane (20 ml), and under ice-cooling, m-chloroperbenzoic acid (439 mg) was added thereto, and the mixture was stirred a room temperature overnight. m-Chloroperbenzoic acid was further added thereto, and the mixture was stirred again at room temperature overnight. The reaction mixture was washed successively with 10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution, and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1-1:2) to give a sulfoxide compound 26 (295 mg). APCI-Mass m/Z 622/624 ($M+NH_4$).

(3) The above sulfoxide compound 26 (293 mg) was dissolved in a mixture of methanol (10 ml)-tetrahydrofuran (5 ml), and sodium methoxide (28% methanol solution, 2 drops) was added thereto, and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give 1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxybenzo[b]thiophen-2-ylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 454/456 ($M+NH_4$).

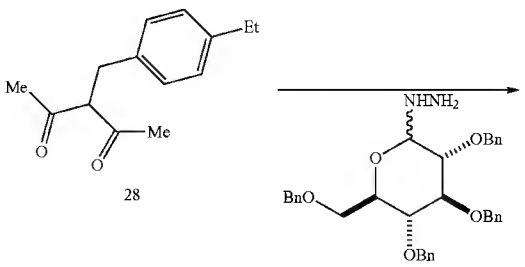
Example 107

1-(β-D-glucopyranosyl)-4-chloro-3-(1,1-dioxybenzo[b]thiophen-2-ylmethyl)benzene

The target compound was prepared in a manner similar to Example 106. APCI-Mass m/Z 470/472 ($M+NH_4$).

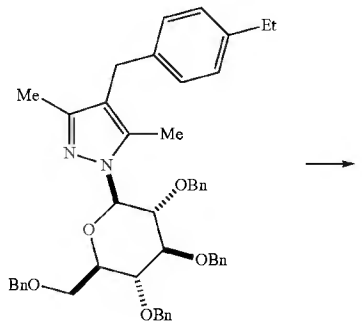
Example 108

3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole

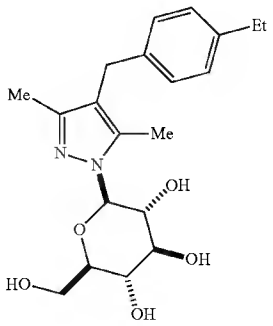


28 29

-continued



30



31

In the above scheme, the symbols are as defined above.

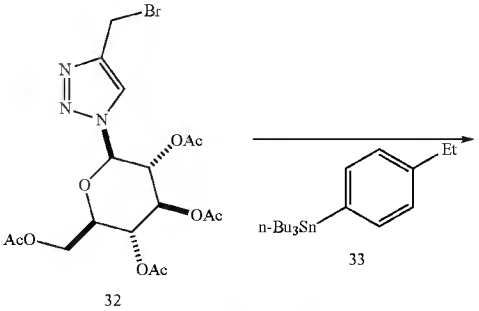
(1) 3-(4-ethylphenylmethyl)-2,4-pentanedione 28 (700 mg) and 2,3,4,6-tetra-O-benzyl-α,β-D-glucosehydrazone 29 (1.70 g) (See Schmidt, R. R. et al., *Liebigs Ann. Chem.* 1981, 2309) were dissolved in tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 18 hours under argon atmosphere. The solvent was evaporated under reduced pressure, and the residue was dissolved in toluene (20 ml), and the mixture was heated with stirring under reflux for 2 hours. The mixture was left alone until it was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-65:35) to give 3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)pyrazole 30 (299 mg) as a pale yellow semisolid. APCI-Mass m/Z 737 (M+H).

(2) The above tetrabenzyl compound 30 (294 mg) was dissolved in a mixture of ethanol (5 ml) and tetrahydrofuran (4 ml), and added thereto was palladium hydroxide (100 mg), and the mixture was stirred at room temperature for 16 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was crystallized from diethyl ether to give the desired 3,5-dimethyl-4-(4-ethylphe-

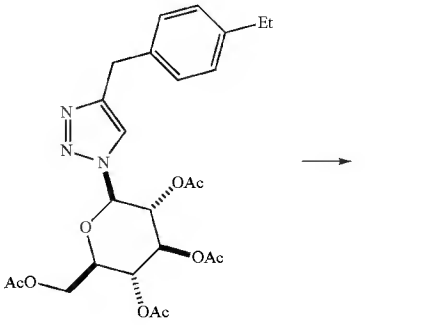
nylmethyl)-1-(β-D-glucopyranosyl)pyrazole 31 (118 mg) as colorless powder. APCI-Mass m/Z 377 (M+H).

Example 109

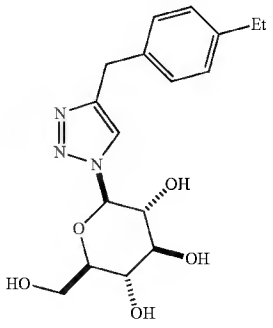
4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-1,2,3-triazole



32 33



34



35

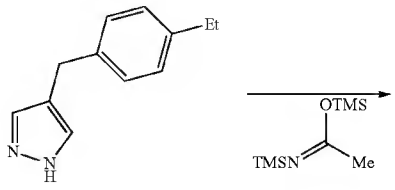
In the above scheme, n-Bu is n-butyl group, and other symbols are as defined above.

(1) A solution of 4-(bromomethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,3-triazole 32 (500 mg) (See Federico G. H. et al., *J. Med. Chem.* (1979) 29, 496), tri-n-butyl(4-ethylphenyl)tin 33 (604 mg) and tetrakis(triphenylphosphine)palladium (0) (59 mg) in tetrahydrofuran (10 ml) was stirred under heating at 70° C. for 12 hours under argon atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and then, an aqueous potassium fluoride solution was added thereto and the mixture was stirred at room temperature for one hour. Insoluble materials were filtered off, and the filtrate was washed with water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,3-triazole 34 (90 mg) as a colorless solid. APCI-Mass m/Z 518 (M+H).

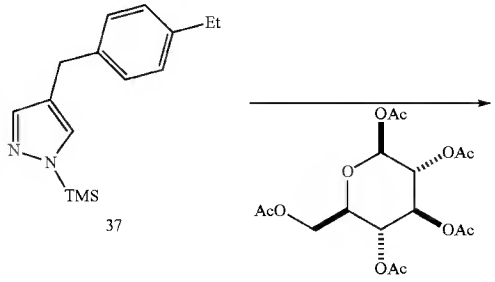
(2) From the above tetraacetate compound 34, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)1,2,3-triazole 35 was prepared in a manner similar to Example 106-(3) as a colorless solid. APCI-Mass m/Z 350 (M+H).

Example 110

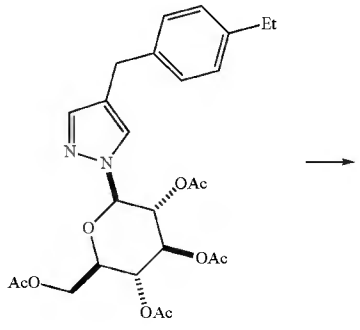
4-(4-Ethylphenylmethyl)-1-(β-D-glucopyranosyl) pyrazole



36

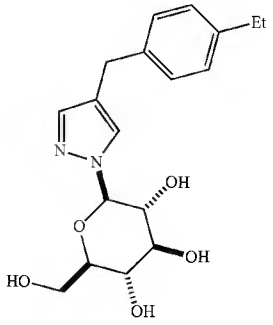


37 38



39

-continued



40

In the above scheme, TMS is a trimethylsilyl group, and other symbols are as defined above.

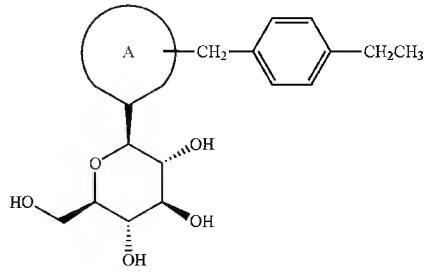
(1) To a solution of 4-(4-ethylphenylmethyl)pyrazole 36 (495 mg) in acetonitrile (2.0 ml) was added N,O-bis(trimethylsilyl)acetamide (1.05 ml), and the mixture was stirred under heating at 60° C. for 2.5 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure to give crude 4-(4-ethylphenylmethyl)-1-trimethylsilylpyrazole 37, which was used in the subsequent reaction without further purification.

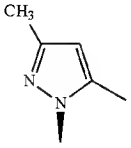
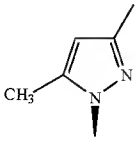
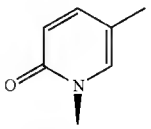
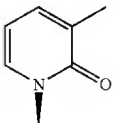
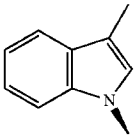
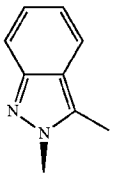
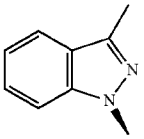
(2) The above N-silyl compound 37 was dissolved in dichloroethane (7.0 ml), and added thereto were molecular sieve 4A powder (500 mg), 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose 38 (1.04 g) and trimethylsilyl trifluoromethanesulfonate (0.51 ml). The mixture was stirred under heating at heating at 80° C. for 3 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and insoluble materials were filtered off. Subsequently, the filtrate was poured into a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with dichloromethane, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20-50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) pyrazole 39 (610 mg) as a colorless semisolid. APCI-Mass m/Z 517 (M+H).

(3) From the above tetraacetate compound 39, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole 40 was prepared in a manner similar to Example 106-(3) as colorless oil. APCI-Mass m/Z 349 (M+H).

In a manner similar to Example 110, the compounds shown in Table 3 below were prepared from corresponding starting materials.

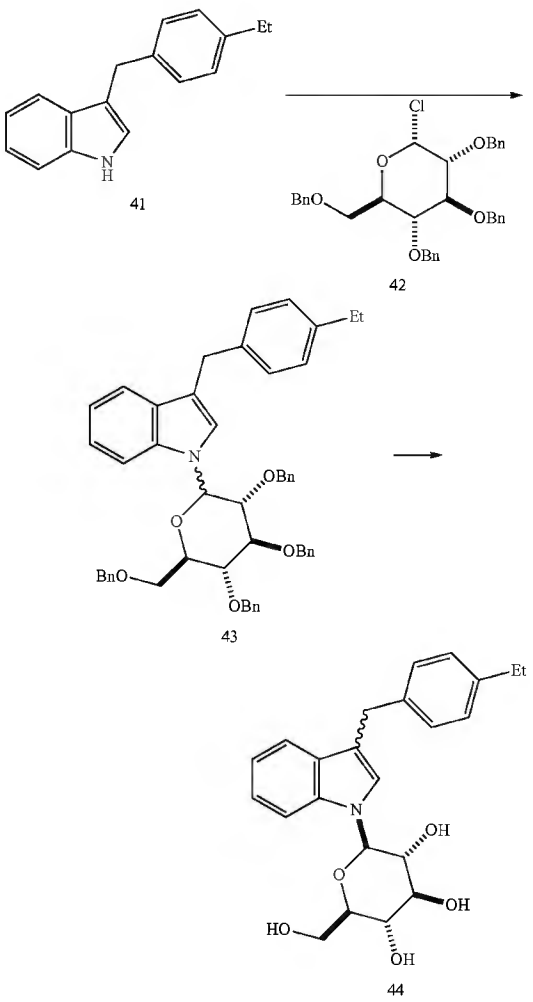
TABLE 3



Examples	Ring A	APCI-Mass (m/Z)
111		363 (M + H)
112		363 (M + H)
113		376 (M + H)
114		393 (M + NH_4)
115		415 (M + NH_4)
116		399 (M + H)
117		399 (M + H)

Example 118

3-RS-(4-ethylphenylmethyl)-1-(β-D-gluco-pyrano-syl)-2,3-dihydroindole



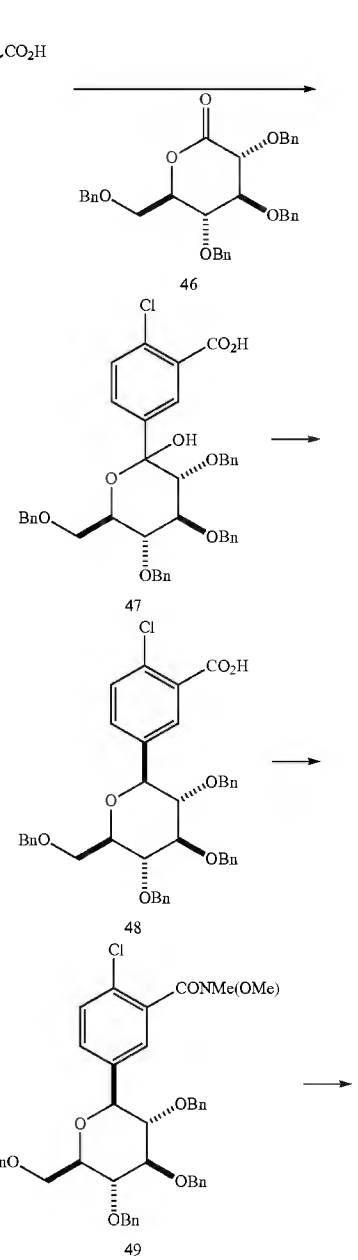
In the above scheme, the symbols are as defined above.

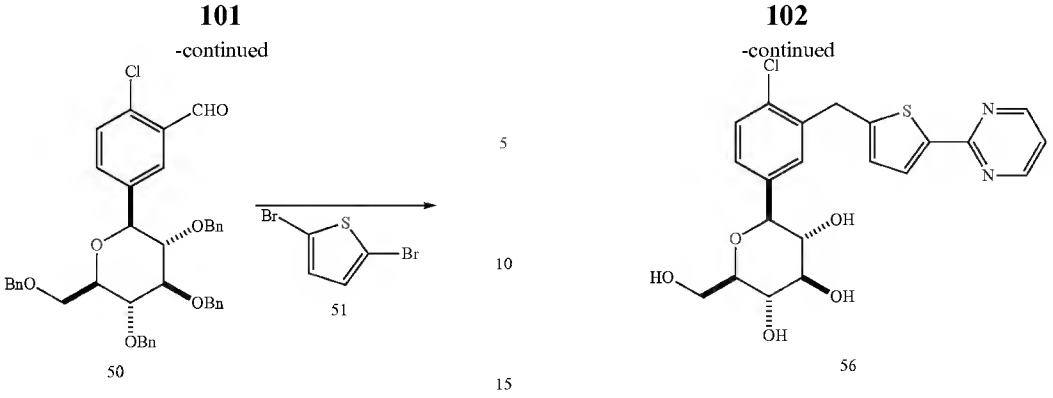
(1) To a suspension of potassium hydroxide power (953 mg) and sodium sulfate (6.0 g) in acetonitrile (50 ml) was added 3-(4-ethylphenylmethy)-1H-indole 41 (500 mg), and the mixture was stirred at room temperature for one hour under argon atmosphere. To the reaction mixture was added a solution of benzylchloro-α-D-glucose 42 (3.0 g) (see Cicchillo R. M. et al., *Carbohydrate Research* (2000) 328, 431) in acetonitrile (20 ml), and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 2N aqueous hydrochloric acid solution, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give 3-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-αβ-D-glucopyranosyl)-1H-indole 43 (1.04 g) as a pale yellow syrup. APCI-Mass m/Z 758 (M+H).

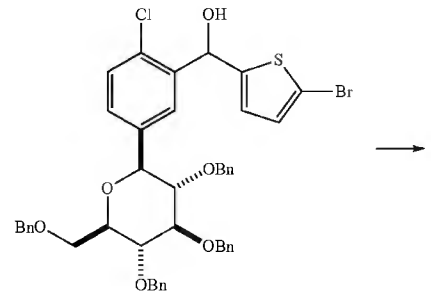
(3) From the above tetrabenzyl compound 43, the desired 3-RS-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-2,3-dihydroindole 44 was prepared in a manner similar to Example 108-(2) as pale pink powder. APCI-Mass m/Z 400 (M+H).

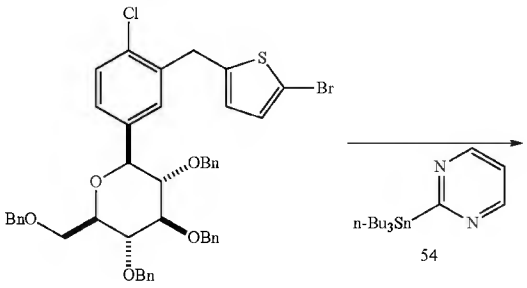
Example 119

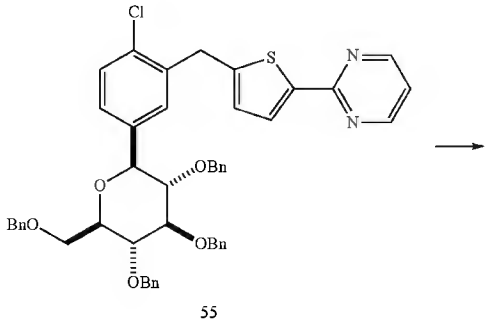
1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidi-nyl)-2-thienylmethyl)benzene











In the above scheme, the symbols are as defined above.

(1) To a solution of 5-bromo-2-chlorobenzoic acid 45 (1.22 g) in a mixture of tetrahydrofuran (20 ml)-toluene (20 ml) was added dropwise n-butyl lithium (2.44 M hexane solution, 4.26 ml) at −78° C. under argon atmosphere. The mixture was stirred at −78° C. for 30 minutes, and added dropwise thereto was a solution of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone 46 (2.16 g) in toluene (10 ml), and the mixture was further stirred at the same temperature for 2 hours. To the mixture was added a saturated aqueous ammonium chloride solution, and the mixture was warmed to room temperature. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude compound 47 as oil, which was used in the subsequent step without further purification.

(2) The above crude compound 47 was dissolved in dichloromethane (30 ml), and thereto were added dropwise triisopropylsilane (2.46 ml) and boron trifluoride.diethyl ether complex (1.52 ml) at −78° C. Subsequently, the mixture was stirred at 0° C. for one hour, and added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was further stirred for 20 minutes. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=100:1-50:1) to give a compound 48 (1.41 g) as oil.

(3) The compound 48 (1.41 g) was dissolved in dichloromethane (10 ml), and added thereto was oxalyl chloride (2 ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The compound was dissolved in chloroform (10 ml), and added dropwise to a solution of N,O-dimethylhydroxyamine hydrochloride (390 mg) and triethyl amine (1.12 ml) in chloroform (10 ml) at 0° C. The mixture was stirred at room temperature overnight, and the reaction mixture was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-2:1) to give a compound 49 (784 mg) as pale yellow oil. APCI-Mass m/Z 739/741 ($M+NH_4$).

(4) The compound 49 (1.22 g) was dissolved in tetrahydrofuran (20 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise diisobutylaluminum hydride (1.0 M toluene solution, 4.2 ml), and the mixture was stirred at the same temperature for 3 hours. Added thereto was 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) to give a compound 50 (771 mg) as pale yellow oil. APCI-Mass m/Z 680/682 ($M+NH_4$).

(5) 2,5-dibromothiophene 51 (1.31 g) was dissolved in tetrahydrofuran (30 ml) and the mixture was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.59 M hexane solution, 2.01 ml), and the mixture was stirred at the same temperature for 30 minutes. Added dropwise thereto was a solution of the above compound 50 (2.40 g) in tetrahydrofuran (15 ml), and the mixture was stirred at −78° C. for 2 hours. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate and washed with brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-4:1) to give a compound 52 (2.62 mg) as pale brown oil. APCI-Mass m/Z 842/844 ($M+NH_4$).

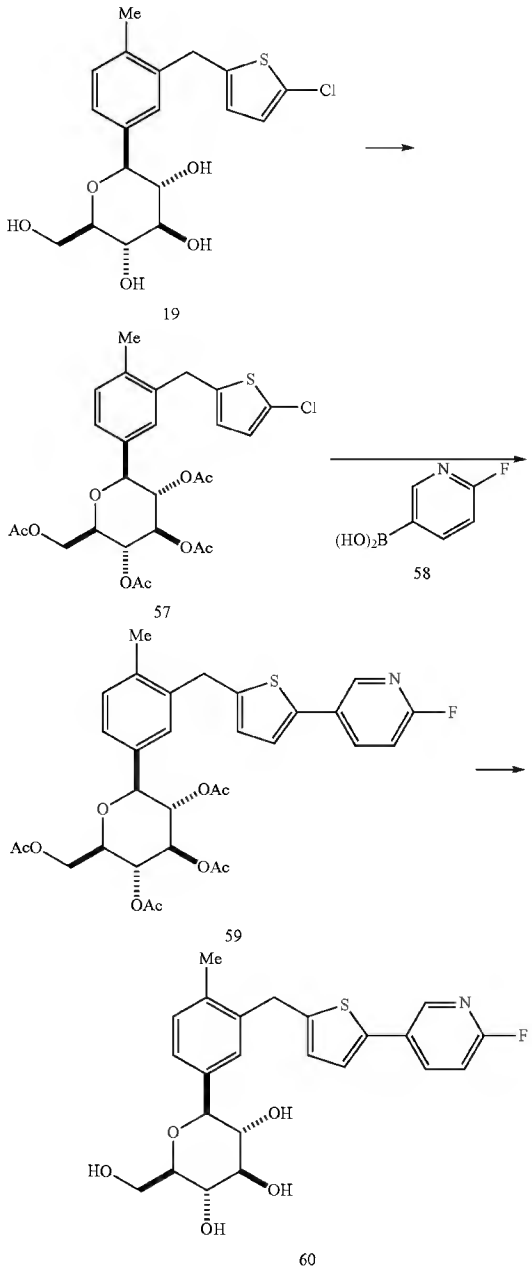
(6) The compound 52 was treated in a manner similar to Example 3-(2) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 as a pale yellow solid. APCI-Mass m/Z 826/828 ($M+NH_4$).

(7) A mixed solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene 53 (200 mg), tri-n-butyl(2-pyrimidinyl)tin 54 (137 mg) and bis(triphenylphosphine)palladium(II)dichloride (9 mg) in N-methyl-2-pyrrolidinone (5 ml) was stirred at 100° C. four 7 hours under argon atmosphere. The mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and subsequently with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-2:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 55 (93 mg) as pale brown oil. APCI-Mass m/Z 826/828 ($M+NH_4$).

(8) To a solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5(2-pyrimidinyl)-2-thienylmethyl)benzene 55 (90 mg) in ethanethiol (1.5 ml) was added boron trifluoride.ether complex (0.42 ml) at 0° C., and the mixture was stirred at room temperature overnight. The mixture was cooled again to 0° C., and added thereto were a saturated aqueous sodium hydrogen carbonate solution and an aqueous sodium thiosulfate solution. The mixture was extracted with ethyl acetate and tetrahydrofuran, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1-9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 56 (27 mg) as pale yellow powder. APCI-Mass m/Z 449/451 (M+H).

Example 120

1-(β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene



In the above scheme, the symbols are as defined as above.

(1) The compound 19 obtained in Example 4 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 as colorless crystals. APCI-Mass m/Z 570/572 ($M+NH_4$).

(2) A solution of the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene (200 mg), 6-fluoropyridine-3-boronic acid 58 (117 mg), tri-tert-butylphosphine.tetrafluoroboric acid adduct (24 mg), potassium fluoride (80 mg) and tris(dibenzylideneacetone)dipalladium (0) (27 mg) in tetrahydrofuran (8 ml) was stirred at room temperature for 2 days under argon atmosphere. Added thereto was a saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10-70:30) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59 (44 mg) as colorless crystals. APCI-Mass m/Z 631 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59 (39 mg) was dissolved in 1,4-dioxane (4 ml)-tetrahydrofuran (4 ml), and added thereto was 2N sodium hydroxide (2 ml). The mixture was stirred at room temperature for one hour. The mixture was made acidic by addition of an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and then dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the desired 1-(β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 60 (34 mg) as colorless powder. APCI-Mass m/Z 463 ($M+NH_4$).

Example 121

1-(β-D-glucopyranosyl)-4-chloro-3-(2-(5-phenyl-2-thienyl)ethyl)benzene

The target compound was obtained in a manner similar to Example 1, from 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)benzene. APCI-Mass m/Z 478/480 ($M+NH_4$).

Example 122

1-(β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120 (1) and 3-dimethylaminophenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 638 (M+H).

(2) the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 470 (M+H).

Example 123

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 (1.24 g) obtained in Example 119-(6), 3-cyanophenylboronic acid (270 ml), bis(triphenylphosphine)palladium (II)dichloride (54 mg) and 2M aqueous sodium carbonate solution (2.3 ml) in 1.2-dimethoxyethane (12 ml) was heated under reflux for 4 hours. The mixture was diluted with ethyl acetate and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate. and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:1-5:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene (1.12 g) as colorless oil. APCI-Mass m/Z 849/851 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 3-(3) to give the target compound as colorless powder. APCI-Mass m/Z 489/491 ($M+NH_4$).

Example 124

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (600 mg) obtained in Example 120-(1), tri-n-butyl(5-pyrimidinyl)tin (600 mg), tri-tert-butylphosphine.tetrafluoroboric acid adduct (116 mg), cesium fluoride (414 mg), and tris(dibenzylideneacetone)dipalladium (0) (91 mg) in 1,4-dioxane (18 ml) was heated under reflux at 100° C. for 3 hours under argon atmosphere. Insoluble materials were filtered off, and the filtrate was diluted with ethyl acetate and washed with brine. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-40:60) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5(5-pyrimidinyl)-2-thienylmethyl)benzene (266 mg) as colorless crystals. APCI-Mass m/Z 597 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5(5-pyrimidinyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 106-(3) to give the target compound as colorless powder. APCI-Mass m/Z 429 (M+H).

Example 125

1-(β-D-glucopyranosyl)-4-chloro-3-(2-phenyl-5-thiazolylmethylbenzene

The target compound was prepared in a manner similar to Example 1, starting from 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene. APCI-Mass m/Z 448/450 (M+H).

Example 126

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-pyridyl)-2-thienylmethyl)benzene

(1) 1-(β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene obtained in Example 19 was used and treated in a manner similar to Example 106-(1) to give 1-(2,

3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 590/592 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene and tri-n-butyl(3-pyridyl)tin were used and treated in a manner similar to Example 124 to give the target compound as colorless powder. APCI-Mass m/Z 448/450 (M+H).

Example 127

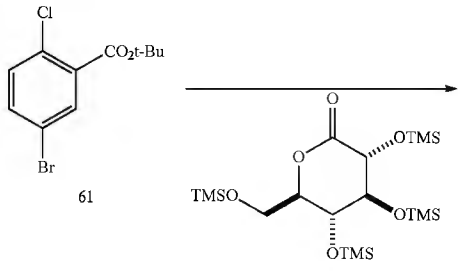
1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120-(1) and 3-cyanophenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-cyano phenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 637 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-methylbenzene was used and treated in a manner similar to Example 106-(3) to give the target compound as colorless powder. APCI-Mass m/Z 469 ($M+NH_4$).

Example 128

1-(β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene



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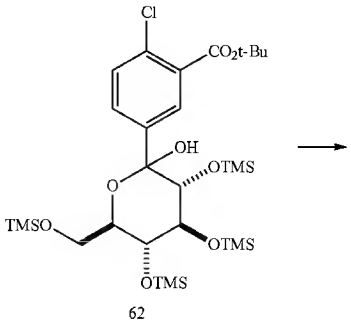

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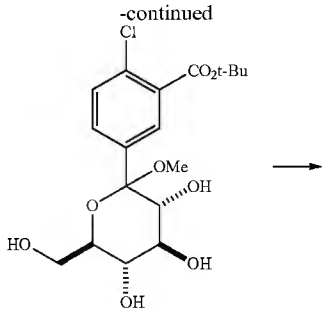

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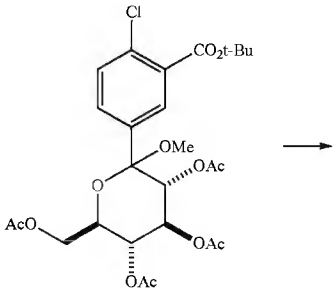

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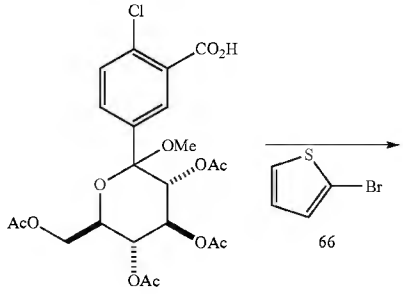

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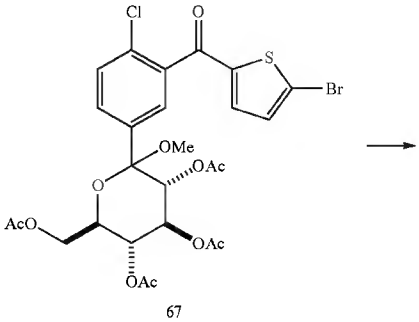

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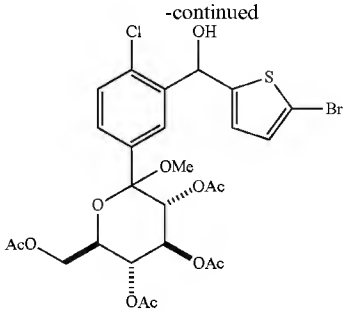

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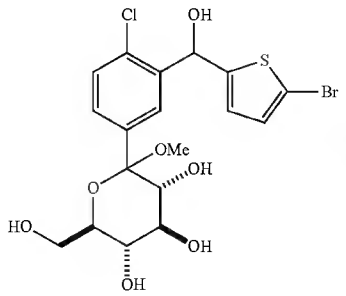

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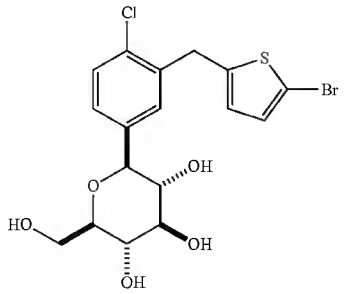

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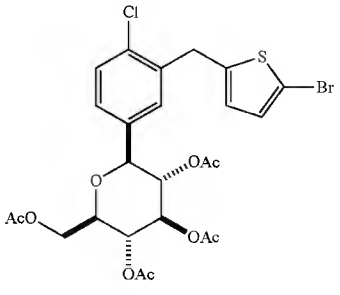

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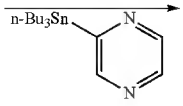

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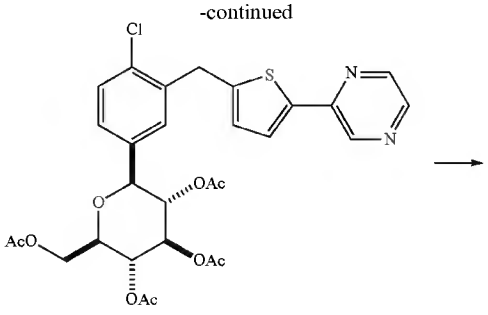

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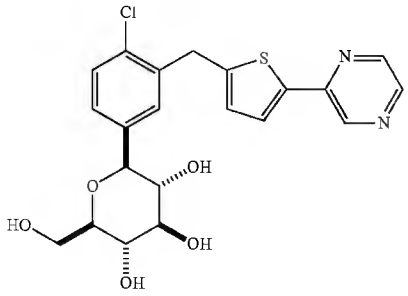


74

In the above scheme, the symbols are as defined above.

(1) A solution of mesityl bromide (4.74 g) in tetrahydrofuran (100 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise t-butyl lithium (1.43 M pentane solution, 33 ml). The mixture was stirred at −30 to −20° C. for one hour, and then, a mixed solution of t-butyl 5-bromo-2-chlorobenzoate 61 (4.94 g) and 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (11.10 g) in tetrahydrofuran (70 ml) was added dropwise thereto at −78° C. The mixture was stirred at the same temperature for one hour to give a compound 62. Without isolating this compound, a solution of methanesulfonic acid (3.75 ml) in methanol (50 ml) was added to the reaction solution, and the mixture was stirred at room temperature for 18 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution at 0° C., and the mixture was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give a methyl ether compound 63 (4.55 g) of the lactol as pale yellow powder. APCI-Mass m/Z 422/424 ($M+NH_4$).

(2) The compound 63 was treated in a manner similar to Example 106-(1) to give the compound 64. APCI-Mass m/Z 590/592 ($M+NH_4$).

(3) A solution of the above compound 64 (7.10 g) in formic acid (50 ml) was stirred at 50° C. for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene, twice, to give a compound 65 as colorless powder. Without further purification, this compound was dissolved in dichloromethane (50 ml). Added thereto were oxalyl chloride (1.3 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was dissolved in dichloroethane (50 ml),

without further purification. To the solution was added 2-bromothiophene 66 (2.63 g) and the mixture was cooled to 0° C. Added gradually thereto was aluminum chloride (8.26 g), and subsequently, the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-cold water, and the mixture was extracted with ethyl acetate. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1-5:1) to give a compound 67 (7.01 g) as pale yellowish powder. APCI-Mass m/Z 678/680 ($M+NH_4$).

(4) The above ketone compound 67 (7.01 g) was dissolved in ethanol (50 ml), and thereto was added sodium borohydride (401 mg), and the mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with successively with water, 2N aqueous hydrochloride acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a compound 68 as pale yellow powder, which was dissolved in methanol (50 ml) without further purification. To the solution, sodium methoxide (28% methanol solution, 5 drops) was added, and then the mixture was stirred at room temperature for 2.5 hours. The solvent was evaporated under reduced pressure to give a deacetylated compound 69 as pale yellow powder. Without further purification, it was dissolved in dichloromethane (170 ml)-acetonitrile (70 ml), and added thereto was triethylsilane (10.2 ml), and the mixture was cooled to 0° C. Added dropwise thereto was boron trifluoride.diethyl ether complex (8.1 ml), and the mixture was stirred at room temperature for 5 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 70 as pale brown powder. Without further purification, this was dissolved in dichloromethane (30 ml), and added thereto were acetic anhydride (10.0 ml), pyridine (8.57 ml) and 4-dimethylaminopyridine (258 mg), and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate, and the solution was washed successively with water, 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The solution was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (3.17 g) as colorless crystals. APCI-Mass m/Z 634/636 ($M+NH_4$).

(5) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (600 mg) was dissolved in 1,4-dioxane (11 ml). Added thereto were tri-n-butyl(pyrazinyl)tin 72 (720 mg), tetrakis(triphenylphosphine)palladium (0) (206 mg) and copper (I) iodide (51 mg), and the mixture was stirred under heating at 100° C. for 1.5 hours, under irradiation by a microwave (500 W). The mixture was diluted with ethyl acetate, the insoluble materials were filtered off, and the filtrate was washed with water. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-30:70), and crystallized from hexane-diethyl ether to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 (263 mg) as pale yellow crystals. APCI-Mass m/Z 617/619 (M+H).

(6) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 was used and treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 74 as colorless powder. APCI-Mass m/Z 449/451 (M+H).

Example 129

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)-benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482/484 ($M+NH_4$).

Example 130

1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120-(1) and 3-formylphenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 640 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene (100 mg) was dissolved in dichloromethane (2 ml), and added thereto was (diethylamino)sulfur trifluoride (0.30 ml). The mixture was stirred at room temperature overnight. Water was added to the mixture and the mixture was extracted with chloroform. The extract was washed with brine and dried over magnesium sulfate, and then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-1:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene (82 mg). APCI-Mass m/Z 662 ($M+NH_4$).

(3) The above obtained 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienyl methyl)-4-methylbenzene was used and treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

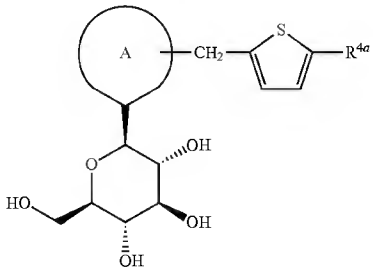
Example 131

1-(β-D-glucopyranosyl)-4-chloro-3-(6-phenyl-3-pyridylmethyl)benzene

5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 442/444 (M+H).

In a manner similar to the method disclosed in any of the above Examples, the compounds shown in Table 4 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out in the similar manner.

TABLE 4



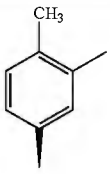
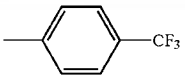
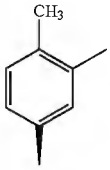
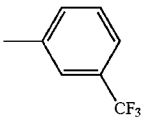
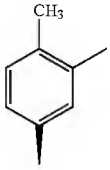
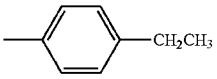
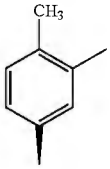
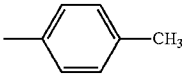
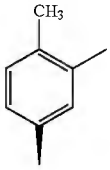
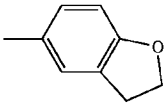
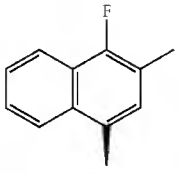
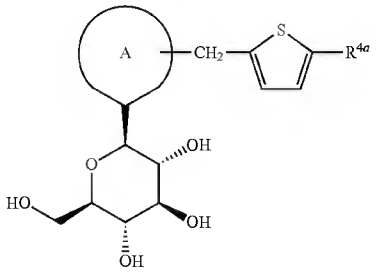
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
132			1	512 ($M + NH_4$)
133			1	512 ($M + NH_4$)
134			4	472 ($M + NH_4$)
135			4	458 ($M + NH_4$)
136			4	486 ($M + NH_4$)
137		Cl	1	456/458 ($M + NH_4$)

TABLE 4-continued



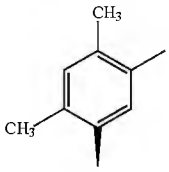
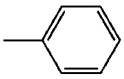
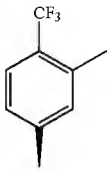
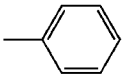
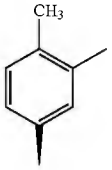
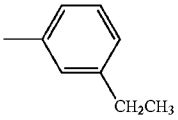
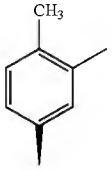
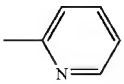
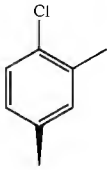
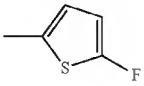
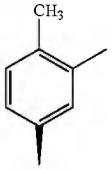
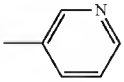
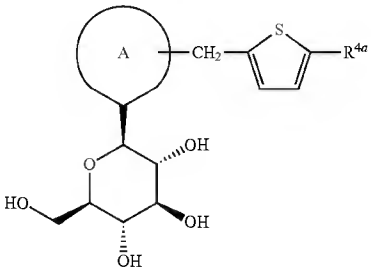
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
138			2	458 ($M + NH_4$)
139			2	498 ($M + NH_4$)
140			1	472 ($M + NH_4$)
141			1	428 ($M + H$)
142			4	488/490 ($M + NH_4$)
143			1	428 ($M + H$)

TABLE 4-continued



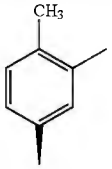
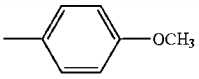
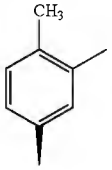
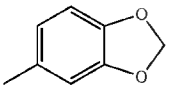
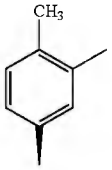
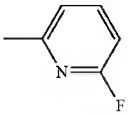
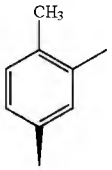
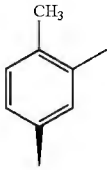
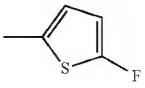
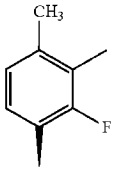
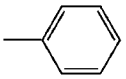
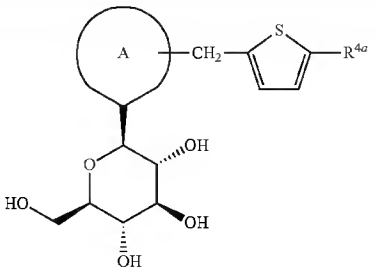
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
144			1	474 ($M + NH_4$)
145			1	488 ($M + NH_4$)
146			1	463 ($M + NH_4$)
147		CF_3	1	436 ($M + NH_4$)
148			1	468 ($M + NH_4$)
149			1	462 ($M + NH_4$)

TABLE 4-continued



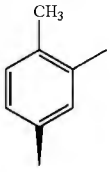
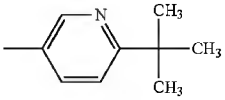
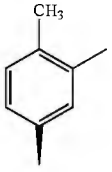
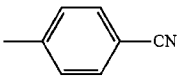
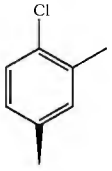
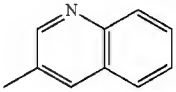
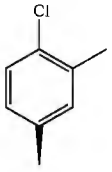
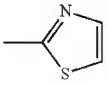
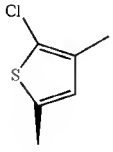
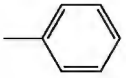
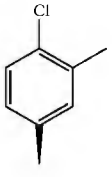
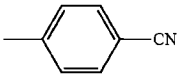
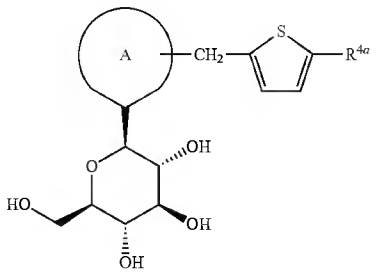
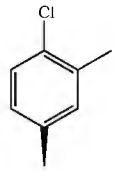
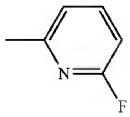
Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
150			103	484 (M + H)
151			124	469 ($M + NH_4$)
152			122	498/500 (M + H)
153			128	454/456 (M + H)
154			2	470/472 ($M + NH_4$)
155			122	489/491 ($M + NH_4$)

TABLE 4-continued



Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
156			122	466/468 (M + H)

Example 157

1-(β-D-glucopyranosyl)-4-chloro-3-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b]thiophen-2-yl-methyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 ($M+NH_4$).

Example 158

1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (12.0 g) obtained in Example 120-(1) was dissolved in tetrahydrofuran (120 ml) and methanol (360 ml), and added thereto were triethylamine (24.2 ml) and 10% palladium carbon catalyst (wet, 3.6 g), and the mixture was stirred at room temperature for 18 hours under hydrogen atmosphere under normal pressure. The insoluble materials were filtered off, washed with tetrahydrofuran, and the filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform, washed successively with a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution and water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3(2-thienylmethyl)benzene (7.79 g) as colorless crystals. APCI-Mass m/Z 536 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-methyl3-(2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 368 ($M+NH_4$).

Example 159

1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl3-(2-thienylmethyl)benzene (11.08 g) obtained in Example 158-(1) was dissolved in chloroform (100 ml), and added dropwise thereto at 0° C. was a solution of bromine (3.71 g) in chloroform (13 ml). The mixture was stirred at 0° C. for 1.5 hours, and then, at room temperature for 1 hour, and the mixture was poured into a 10% aqueous sodium thiosulfate solution and a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20-67:33) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (7.13 g) as a colorless solid. APCI-Mass m/Z 614/616 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 446/448 ($M+NH_4$).

Example 160

1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 3-bromobenzadlehyde was treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 430 ($M+NH_4$).

Example 161

1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (500 mg)

obtained in Example 159-(1) was dissolved in N,N-dimethylacetamide (10 ml), and added thereto were zinc cyanide (98 mg), tris(dibenzylideneacetone)dipalladium(0) (77 mg), 1,1'-bis(diphenylphosphino)ferrocene (47 mg) and zinc power (14 mg). The mixture was heated under stirring at 120° C. overnight. The reaction solution was cooled, diluted with ethyl acetate and water, and the insoluble materials were filtered off. The organic layer of the filtrate was washed twice with water and successively washed with brine. After drying the same over sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-50:50) to give 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene (207 mg) as colorless crystals. APCI-Mass m/Z 561 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 393 ($M+NH_4$).

Example 162

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(2pyridyl)-2-thienylmethyl)naphthalene

4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl) naphthalene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482 (M+H).

Example 163

1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 466/468 ($M+NH_4$).

Example 164

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and tri-n-butyl(2-pyrimidinyl)tin 54 were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 429 (M+H).

Example 165

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-thiazolyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and tri-n-butyl(2-thiazolyl)tin were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 434 (M+H).

Example 166

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethyl-3-pyridylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 394/396 (M+H).

Example 167

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b]thiophen-2-ylmethyl)benzene

6-Ethylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 466/468 (M+H).

Example 168

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro3-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene 71 (500 mg) obtained in Example 128-(4) was dissolved in 1,2-dimethoxyethane (15 ml), and added thereto were 6-fluoropyridine-3-boronic acid 58 (228 mg), tetrakis(triphenylphosphine)palladium(0) (94 mg) and cesium fluoride (738 mg). The mixture was heated under reflux for 30 minutes. The reaction solution was poured into a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=75:25-60:40) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene (454 mg) as a colorless solid. APCI-Mass m/Z 634/636 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl) benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 483 ($M+NH_4$), 466 (M+H).

Example 169

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-3-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 6-methoxypyridine-3-boronic acid were treated in a manner similar to Example 168 to give the target compound. APCI-Mass m/Z 478/480 (M+H).

Example 170

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-2-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl(6-methoxy-2-pyridyl)tin

(see Gros, Philippe; Fort, Yves. Synthesis (1999), 754-756) were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 478/480 (M+H).

Example 171

1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxo-2-isoindolinylmethyl)benzene

5-Bromo-2-chloro-1-(1-oxo-2-isoindolynilmethyl)benzene was treated in a manner similar to Example 2 to give the target compound. APCI-Mass m/Z 437/439 ($M+NH_4$).

Example 172

1-(β-D-glucopyranosyl)-4-chloro-3-(1-phenyl-4-pyrazolylmethyl)benzene

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 431/433 (M+H).

Example 173

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl(6-ethoxy-2-pyridyl)tin (see WO 00/74681) were treated in a manner similar to Example 128-(5) to give 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl) benzene as colorless crystals. APCI-Mass m/Z 660/662 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl) benzene (245 mg) was dissolved in tetrahydrofuran (5 ml), added thereto was a solution of sodium hydride (oil, 9 mg) in ethanol (5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10) to give the desired 1-(β-D-glucopyranosyl)-4-chloro3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene (145 mg) as colorless powder. APCI-Mass m/Z 492/494 (M+H).

Example 174

1-(β-D-glucopyranosyl)-4-chloro-3-(6-n-propyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b]thiophen-2-yl methyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 ($M+NH_4$).

Example 175

1-(β-D-glucopyranosyl)-4-chloro-3-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b] thiophen-2-ylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 500/502 ($M+NH_4$).

Example 176

1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-methylbenzene from Example 159-(1) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-formylphenyl)-2-thienylmethyl)-4-methylbenzene as a colorless solid. APCI-Mass m/Z 640 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-3-(5-(4-formylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 130-(2) to give the desired 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless crystals. APCI-Mass m/Z 662 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

Example 177

1-(β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2.3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and 3,4-difluorophenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-Oacetyl-β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless crystals. APCI-Mass m/Z 648 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 480 ($M+NH_4$).

Example 178

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 3-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 130-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 682/684 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example

120-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 514/516 ($M+NH_4$).

Example 179

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-Oacetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 130-(2) to give 1-(2,3,4,6-tetra-O-acetylβ-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 682/684 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-Dglucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 514/516 ($M+NH_4$).

Example 180

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethyl-3-fluorophenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and 3-fluoro-4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl)benzene as colorless foam. APCI-Mass m/Z 678/680 ($M+NH_4$).

(2) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl) benzene was treated in a manner similar to Example 178-(2) and (3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro3-(5-(4-difluoromethyl-3-fluorophenyl)-2-thienylmethyl)benzene as a colorless foam. APCI-Mass m/Z 532/534 ($M+NH_4$).

Example 181

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and (2-benzyloxymethyl-2H-tetrazol-5-yl) trin-butyltin (see *Tetrahedron Lett.* (2000) 2805) were treated in a manner similar to Example 128-(5) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-benzyloxymethyl-2H-tetrazol-5-yl)-2-thienylmethyl)-4-chlorobenzene as colorless solid. APCI-Mass m/Z 727/729 (M+H).

(2) A mixture of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-benzyloxymethyl-2H-tetrazol-5-yl)-2-thienylmethyl)-4-chlorobenzene (247 mg), 6M aqueous hydrochloric acid solution (2 ml) and methanol (20 ml) was refluxed overnight. The solvent was evaporated under reduced pressure and the residue was triturated with diethyl ether to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2-thienylmethyl)benzene (172 mg) as colorless powder. ESI-Mass m/Z 437/439 (M−H).

Example 182

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methyl-2H-tetrazol-5-yl)-2-thienylmethyl)benzene

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(1H-tetrazol-5-yl)-2-thienylmethyl)benzene (140 mg) obtained in Example 181 was dissolved in dimethylformamide (5 ml) and added thereto were methyl iodide (100 μl) and potassium carbonate (220 mg). The mixture was stirred at room temperature overnight. The reaction solution was poured into water and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methyl-2H-tetrazol-5-yl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 470/472 ($M+NH_4$).

Example 183

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-fluoro-4-formylphenyl)-2-thienylmethyl) benzene (272 mg) obtained in Example 180-(1) was dissolved in N-methyl-2-pyrrolidone (10 ml) and added thereto was hydroxylamine hydrochloride (34 mg). The mixture was heated under stirring at 117° C. overnight. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=3:1-2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3(5-(4-hydroxyimino-3-fluorophenyl)-2-thienylmethyl)benzene (177 mg) as colorless caramel. APCI-Mass m/Z 693/695 ($M+NH_4$).

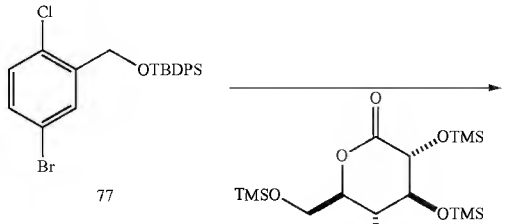
(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxyimino-3-fluorophenyl)-2-thienylmethyl)benzene (175 mg) was dissolved in chloroform (5 ml) and added thereto was 1,1'-carbonyldiimidazole (46 mg). The mixture was stirred at room temperature overnight. 1,1'-Carbonyldiimidazole (92 mg) was further added thereto, and the mixture was stirred at 40° C. for 6 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was separated and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene (158 mg) as colorless caramel. APCI-Mass m/Z 675/677 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)-benzene was treated in a manner similar to Example 106-(3) to give desired 1-(β-D-glucopyranosyl)-4-chloro-3-

(5-(4-cyano-3-fluorophenyl)-2-thienylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 507/509 ($M+NH_4$).

Example 184

1-(β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene



77

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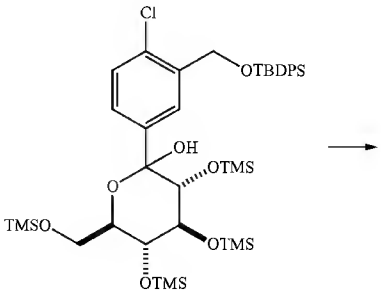
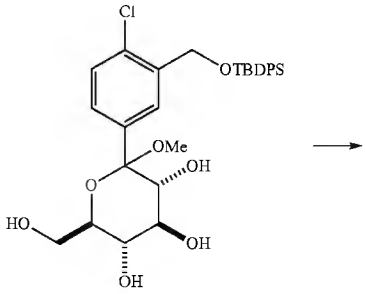


78



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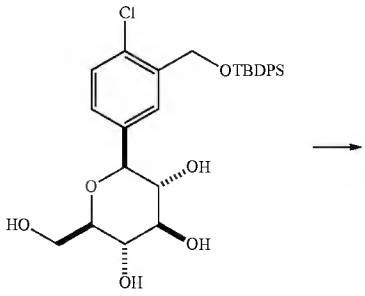

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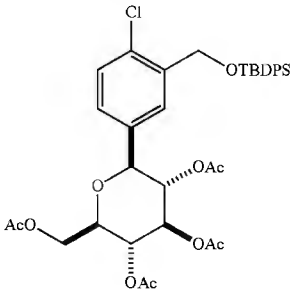
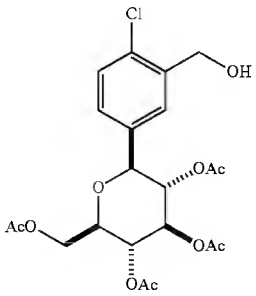
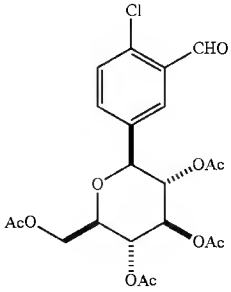


81



82



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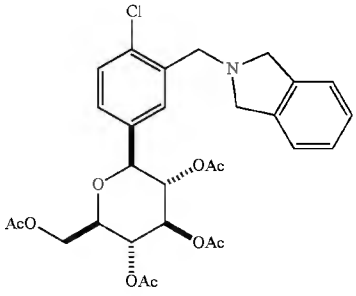

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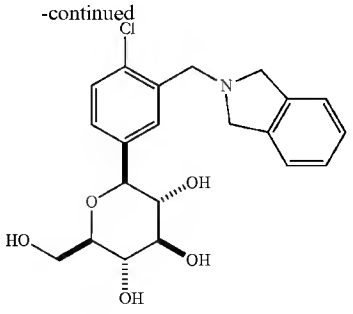


85

(In the above scheme, OTBDPS is a tert-butyldiphenylsilyloxy group, and the other symbols are the same as defined above.)

(1) A mixed solution of 5-bromo-2-chloro-1-(tert-butyldiphenylsilyloxymethyl)benzene 77 (10.83 g) and 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see U.S. Pat. No. 6,515,117) (13.2 g) in tetrahydrofuran (400 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise tert-butyl lithium (1.60 M pentane solution, 30.9 ml), and the mixture was stirred at the same temperature for 30 minutes to give a compound 78. Without isolating this compound, a solution of methanesulfonic acid (6.12 ml) in methanol (200 ml) was added to the reaction solution, and the reaction mixture was warmed to room temperature, and stirred at the same temperature for 15 hours. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=93:7) to give a methyl ether compound 79 (9.71 g) as colorless powder. APCI-Mass m/Z 590/592 ($M+NH_4$).

(2) A solution of the above methyl ether compound 79 (3.46 g) in dichloromethane (70 ml) was cooled to 0° C. under argon atmosphere, and thereto were added dropwise successively triethylsilane (2.89 ml) and boron trifluoride.diethyl ether complex (2.28 ml). The mixture was stirred at the same temperature for 1 hour. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-94:4) to give 1-(β-D-glucopyranosyl)-4-chloro-3-(tert-butyldiphenylsilyloxymethyl)benzene 80 (2.52 g) as colorless powder. APCI-Mass m/Z 560/562 ($M+NH_4$).

(3) The above compound 80 (4.12 g) was treated in a manner similar to Example 106-(1) to give the compound 81 (5.44 g). APCI-Mass m/Z 728/730 ($M+NH_4$).

(4) A mixed solution of the above compound 81 (5.44 g), acetic acid (1.29 ml) in tetrahydrofuran (60 ml) was cooled to 0° C. under argon atmosphere, and thereto was added tetrabutyl ammonium fluoride (1.0 M tetrahydrofuran solution, 8.43 ml). The mixture was stirred at the same temperature for 30 minutes, and then further stirred at room temperature for 15 hours. The mixture was diluted with ethyl acetate and washed successively with 0.4 M aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-1:1) to give the compound 82 (2.97 g) as a colorless solid. APCI-Mass m/Z 490/492 ($M+NH_4$).

(5) A solution of the above compound 82 (1.60 g) in dichloromethane (50 ml) was cooled to 0° C. under argon atmosphere, and thereto was added Dess-Martin periodinane (1.58 g). The mixture was warmed to room temperature and stirred at the same temperature for 3 hours. The mixture was diluted with ethyl acetate, and insoluble materials were filtered off. The filtrate was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1-1:1) to give 5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-chlorobenzaldehyde 83 (1.35 g) as colorless crystals. APCI-Mass m/Z 488/490 ($M+NH_4$).

(6) To a mixed solution of the above 5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-chlorobenzaldehyde 83 (325 mg), 2,3-dihydro-1H-isoindole (98 mg), acetic acid (82 mg) in 1,2-dichloroethane (5 ml) was added sodium triacetoxyborohydride (219 mg). The mixture was stirred at room temperature for 3 hours, and cooled to 0° C. A saturated aqueous sodium hydrogen carbonate solution was added thereto to basify the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:0-1:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 84 (234 mg) as a colorless solid. APCI-Mass m/Z 574/576 (M+H).

(7) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 84 was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(1,3-dihydro-isoindol-2-ylmethyl)benzene 85 as colorless powder. APCI-Mass m/Z 406/408 (M+H).

Example 185

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(3-cyano-4-fluorophenyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and 4-fluoro-3-formylphenylboronic acid were used and treated in a manner similar to Example 177-(1) and Example 183 to give the title compound as colorless powder. APCI-Mass m/z 487 ($M+NH_4$).

Example 186

1-(β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-methylbenzene (597 mg) obtained in Example 159-(1) was dissolved in N-methyl-2-pyrrolidone (10 ml) and added thereto were tri-n-butyl(2-cyano-5-pyridyl)tin (590 mg), dichlorobis(triphenylphosphine)palladium(II) (70 mg) and copper(I) iodide (19 mg). The mixture was heated under stirring at 100° C. for 4 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over mag-

nesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (351 mg) as colorless powder. APCI-Mass m/Z 621 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (62 mg) was dissolved in a mixture of tert-butanol (3 ml)-tetrahydrofuran (3 ml) and added thereto was sodium tert-butoxide (48 mg). The mixture was stirred at room temperature for 3.5 hours. Sodium tert-butoxide (19 mg) was further added thereto, and the mixture was stirred at room temperature for 1 hour. To the mixture was added a saturated aqueous ammonium chloride solution at 0° C., and the mixture was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=19:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(2cyano-5-pyridyl)-2-thienylmethyl)-4-methylbenzene (23 mg) as colorless powder. APCI-Mass m/Z 470 ($M+NH_4$).

Example 187

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) was treated in a manner similar to Example 186-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl) benzene as colorless powder. APCI-Mass m/Z 641/643 (M+H).

(2) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 186-(2) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2cyano-5-pyridyl)-2-thienylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 490/492 ($M+NH_4$).

Example 188

1-(β-D-glucopyranosyl)-3-(5-(2-carbamoyl-5-pyridyl)-2-thienylmethyl)-4-chlorobenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene obtained in Example 187-(1) was treated in a manner similar to Example 106-(3) to give the mixture of 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-cyano-5-pyridyl)-2-thienylmethyl)benzene and 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene. This mixture was dissolved in methanol, and sodium methoxide (28% methanol solution, 1 drop) was added thereto, and the mixture was stirred at 60° C. for 6 hours. The reaction solution was cooled and the solvent was evaporated under reduced pressure to give pure 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene. APCI-Mass m/Z 505/507 (M+H).

(2) The above 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-methoxyimidoyl-5-pyridyl)-2-thienylmethyl)benzene was suspended in tetrahydrofuran, and sodium hydride (60% mineral oil suspension, 2 equivalent) was added thereto, and the mixture was stirred under reflux for 3 hours. The reaction solution was cooled and to the mixture was added a saturated aqueous ammonium chloride solution at 0° C., and the mixture was extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1-5:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(2-carbamoyl-5-pyridyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow powder. APCI-Mass m/Z 491/493 (M+H).

Example 189

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene

(1) 5-bromo-2-fluorobenzaldehyde and 2-chlorothiophene were used and treated in a manner similar to Example 4 and Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 574/576 ($M+NH_4$). mp 130-131° C.

(2) The above compound was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 540 ($M+NH_4$). mp 119-121° C.

(3) The above compound was treated in a manner similar to Example 159-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluorobenzene as colorless crystals. APCI-Mass m/z 618/620 ($M+NH_4$). mp 127-129° C.

(4) The above compound and 3-cyanophenylboronic acid were used and treated in a manner similar to Example 168 to give the title compound as colorless powder. APCI-Mass m/z 473 ($M+NH_4$).

Example 190

1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(2-thiazolyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluorobenzene obtained in Example 189-(3) and tri-n-butyl(2-thiazolyl)tin were used and treated in a manner similar to Example 128 to give the title compound as colorless crystals. APCI-Mass m/z 438 ($M+NH_4$). mp 161.5-162° C.

Example 191

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-ethoxycarbonylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and 4-cyanophenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 657/659 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (128 mg) was suspended in ethanol (2 ml) and added thereto was a concentrated hydrochloric acid aqueous solution (1 ml). The mixture was heated reflux for 8.5 hours. The reaction solution was cooled and diluted with ethyl acetate and water. The organic layer was washed with water and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-ethoxycarbonylphenyl)-2-thienylmethyl)benzene (39 mg) as pale yellow foam. APCI-Mass m/Z 536/538 ($M+NH_4$).

Example 192

1-(β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (128 mg) obtained in Example 191-(1) was dissolved in acetic acid (2 ml) and added thereto was a concentrated hydrochloric acid aqueous solution (2 ml). The mixture was refluxed for 6.5 hours. To the mixture was added a 10% aqueous sodium hydroxide solution at 0° C., and the mixture was washed with ethyl acetate. The aqueous layer was acidified by adding concentrated hydrochloric acid, and extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by washing with a mixture of ethyl acetate and diethyl ether to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (49 mg) as pale brown powder. ESI-Mass m/Z 489/491 (M−H).

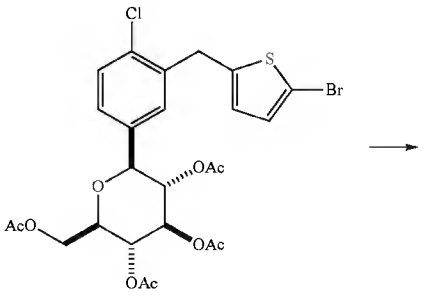
Example 193

1-(β-D-glucopyranosyl)-3-(5-(4-carbamoylphenyl)-2-thienylmethyl)-4-chlorobenzene

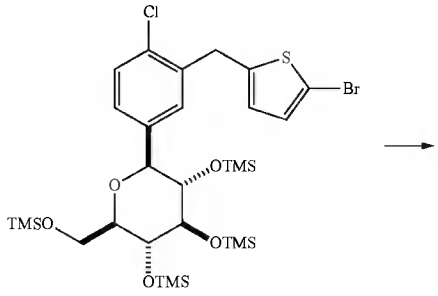
1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-cyanophenyl)-2-thienylmethyl)benzene (282 mg) obtained in Example 191-(1) was suspended in ethanol (5 ml) and added thereto was a 6N aqueous sodium hydroxide solution (0.37 ml). The mixture was stirred at room temperature for 10 minutes. To the mixture was added a 30% aqueous hydrogen peroxide solution (0.2 ml), and the mixture was stirred at room temperature for 1.5 hours and at 45° C. for 3 hours. To the mixture was added water (20 ml) and the mixture was cooled. The powder was collected by filtration and washed with diethyl ether and dried to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-carbamoylphenyl)-2-thienylmethyl)-4-chlorobenzene (176 mg) as colorless powder. APCI-Mass m/Z 507/509 ($M+NH_4$).

Example 194

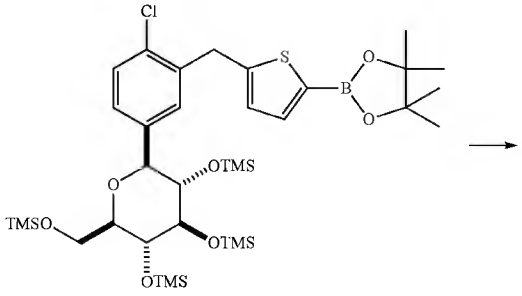
1-(β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene



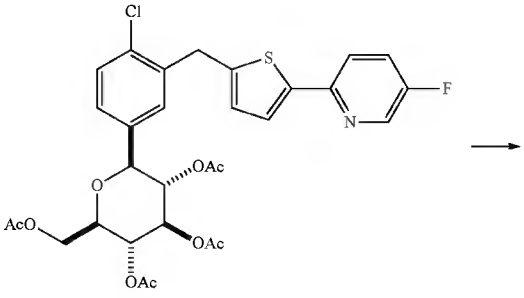
71



86



87



88

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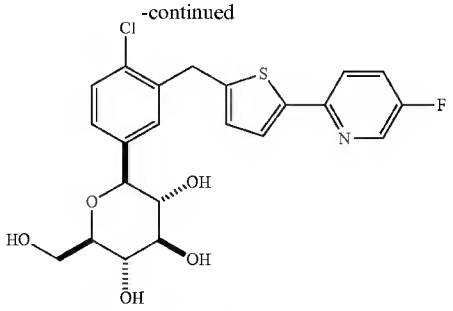


89

In the above scheme, the symbols are defined as above.

(1) The 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (750 mg) obtained in Example 128-(4) was dissolved in a mixture of methanol (8 ml)-tetrahydrofuran (8 ml), and sodium methoxide (28% methanol solution, 1 drop) was added thereto, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 ml), and thereto were added pyridine (0.69 ml) and 4-dimethylaminopyridine (15 mg). The mixture was cooled to 0° C., and thereto was added trimethylsilyl trifluoromethanesulfonate (1.54 ml). The mixture was stirred at room temperature for 3 days. To the mixture was added water, and the mixture was extracted with diethyl ether. The extract was washed with successively with water, a saturated aqueous ammonium chloride solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the compound 86 (900 mg) as colorless oil.

(2) A mixed solution of the above compound 86 (900 mg), triisopropoxyborane (252 mg) in tetrahydrofuran (22 ml) was cooled to −78° C. under argon atmosphere. Thereto was added dropwise tert-butyl lithium (1.46 M pentane solution, 0.9 ml), and the mixture was stirred at the same temperature for 1 hour. The mixture was warmed to room temperature, and thereto was added pinacol (2.24 g). The mixture was stirred at the same temperature overnight. The mixture was diluted with ethyl acetate, and washed successively with water and brine. The solvent was evaporated under reduced pressure to give the compound 87, which was used in the subsequent reaction without further purification.

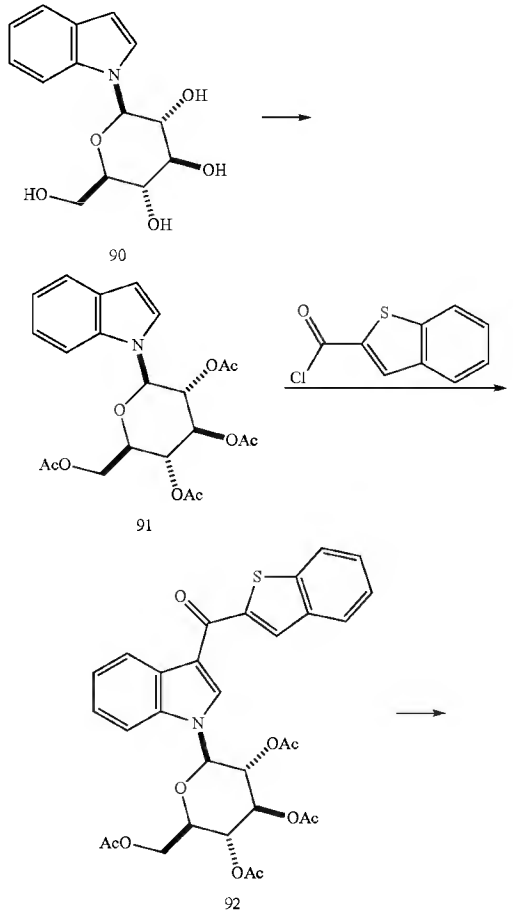
(3) The whole amount of the above compound 87 was dissolved in dimethoxyethane (20 ml), and thereto were added 2-bromo-5-fluoropyridine (460 mg), tetrakis(triphenylphosphine)palladium(0) (150 mg) and cesium fluoride (1.4 g). The mixture was stirred at 80° C. for 3 hours. The mixture was cooled to room temperature, acidified with 2 M aqueous hydrochloric acid solution, and stirred at the same temperature overnight. Under ice-cooling, the reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was passed through silica gel column chromatography (chloroform:methanol=100:0-88:12) to give crude oil, which was dissolved in dichloromethane (20 ml). To the mixture were added acetic anhydride (0.71 ml), pyridine (0.61 ml), and 4-dimethylaminopyridine (13 mg), and the mixture was stirred at room temperature for 1 hour. Then, dichloromethane was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The

mixture was washed successively with 2 M aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:0-3:2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene (218 mg) as a colorless solid. APCI-Mass m/Z 634/636 (M+H).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl) benzene 88 was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(5-fluoropyridin-2-yl)-2-thienylmethyl)benzene 89 as a colorless solid. APCI-Mass m/Z 466/468 (M+H).

Example 195

1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)-indole

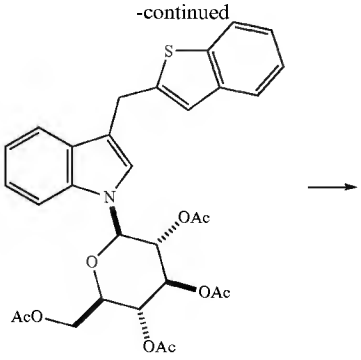


90

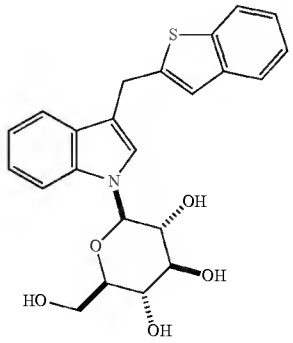
91

92

-continued



93



94

In the above scheme, the symbols are defined as above.

(1) 1-(β-D-glucopyranosyl)indole 90 (see *Eur. J. Med. Chem.* (2004) 39, 453-458) was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indole 91 as colorless crystals. APCI-Mass m/Z 465 ($M+NH_4$).

(2) Benzo[b]thiophene-2-carboxylic acid (598 mg) was suspended in dichloromethane (10 ml). Added thereto were oxalyl chloride (0.39 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was dissolved in dichloroethane (30 ml). To the solution was added 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indole 91 (1 g) obtained above, and the mixture was cooled to 0° C. Added gradually thereto was aluminum chloride (2.09 g), and subsequently, the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-cold water, and the mixture was extracted with chloroform. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-5:4) to give Benzo[b]thiophen-2-yl (1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-indol-3-yl)ketone 92 (570 mg) as colorless crystals. APCI-Mass m/Z 608 (M+H).

(3) The above Benzo[b]thiophen-2-yl (1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-indol-3-yl)ketone 92 (440 mg) was dissolved in tetrahydrofuran (6 ml) and ethanol (3 ml). To the solution was added sodium borohydride (137 mg), and the mixture was stirred at room temperature for 60 minutes. The reaction mixture was quenched with cold aqueous HCl solution (0.5 N), and extracted with ethyl acetate. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The resultant residue was dissolved in dichloromethane (8 ml) and acetonitrile (4 ml), and the mixture was cooled to 0° C. under argon atmosphere. To the mixture were added triethylsilane (0.58 ml) and boron trifluoride.diethyl ether complex (0.46 ml). After 30 minutes, the mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the organic layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The resultant residue was dissolved in chloroform (20 ml), and to the mixture were added acetic anhydride (0.16 ml), triethylamine (0.2 ml), and 4-dimethylaminopyridine (15 mg), and the mixture was stirred at room temperature for 30 minutes. Then, the solution was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (hexane:ethyl acetate=8:2-6:4) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(benzo-[b]thiophen-2-ylmethyl)indole 93 (290 mg). APCI-Mass m/Z 611 ($M+NH_4$).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)indole 93 (336 mg) was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)indole 94 (208 mg) as a colorless powder. APCI-Mass m/Z 443 ($M+NH_4$).

Example 196

1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-fluoronaphthalene

(1) The 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene obtained in Example 137 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 624/626 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-fluoronaphthalene was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 590 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-fluoronaphthalene was treated in a manner similar to Example 19-(1) to give 1-(2,3,4,6-tetra-

O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 668/670 ($M+NH_4$).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-fluoronaphthalene and 3-cyanophenylboronic acid were treated in a manner similar to Example 168 to give 1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienylmethyl)-4-fluoronaphthalene. APCI-Mass m/Z 523 ($M+NH_4$).

Example 197

1-(β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene obtained in Example 128-(4) and 4-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)aniline were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow powder. APCI-Mass m/Z 630/632 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene as pale yellow foam. APCI-Mass m/Z 479/481 ($M+NH_4$).

Example 198

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoyl-phenyl)-2-thienylmethyl)benzene

(1) 1-(β-D-Glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (637 mg) obtained in Example 192 was dissolved in a mixture of dichloromethane (10 ml)-tetrahydrofuran (5 ml) and added thereto were acetic anhydride (1.22 ml), pyridine (1.05 ml) and 4-dimethylaminopyridine (32 mg). The mixture was stirred at room temperature overnight. The solvents were evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 2N hydrochloric acid aqueous solution and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:1-50:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (687 mg) as pale yellow powder. ESI-Mass m/Z 657/659 (M−H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-carboxyphenyl)-2-thienylmethyl)-4-chlorobenzene (198 mg) was dissolved in dichloromethane (5 ml) and added thereto were oxalyl chloride (1 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature for 3.5 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was suspended in tetrahydrofuran (4 ml), without further purification. To the suspension was added a 2.0 M solution of methylamine in tetrahydrofuran (1.5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)benzene (218 mg) as pale yellow powder. APCI-Mass m/Z 689/691 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)-benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylcarbamoylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 521/523 ($M+NH_4$).

Example 199

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonyl-aminophenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene (126 mg) obtained in Example 197-(1) was dissolved in dichloromethane (3 ml) and added thereto were methanesulfonyl chloride (48 mg) and pyridine (48 mg). The mixture was stirred at room temperature for 3.5 hours. To the mixture was added 2N hydrochloric acid aqueous solution at 0° C. and extracted with ethyl acetate. The organic layer was washed with water, aqueous sodium hydrogen carbonate solution and successively washed with brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1-1:2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene (154 mg) as yellow caramel. ESI-Mass m/Z 706/708 (M−H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-methylsulfonylaminophenyl)-2-thienylmethyl)benzene as yellow foam. ESI-Mass m/Z 538/540 (M−H).

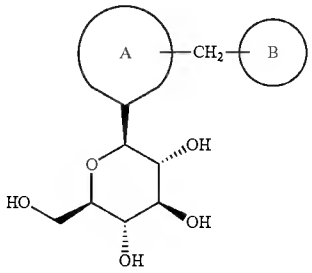
Example 200

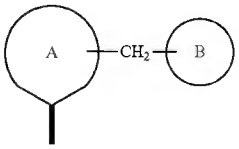
1-(β-D-glucopyranosyl)-3-(5-(4-acetylaminophenyl)-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-aminophenyl)-2-thienylmethyl)-4-chlorobenzene (126 mg) obtained in Example 197-(1) was treated in a manner similar to Example 106-(1) and (3) to give the target compound as colorless powder. APCI-Mass m/Z 521/523 ($M+NH_4$).

The compounds shown in Table 5 below were prepared in a manner similar to one of the above Examples from the corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out.

TABLE 5





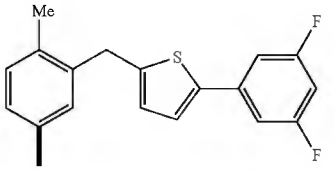
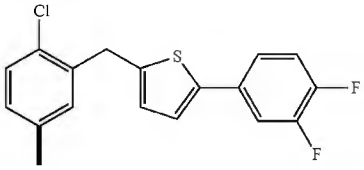
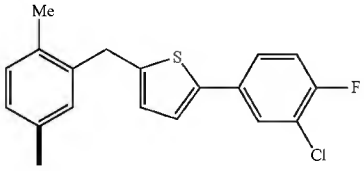
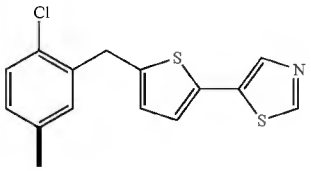
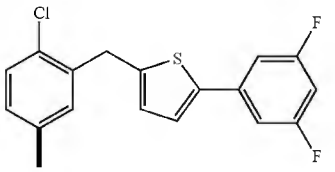
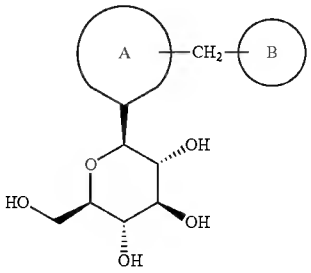
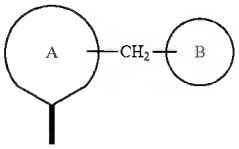
Examples		Preparation Method	APCI-Mass (m/Z)
201		177	480 ($M + NH_4$)
202		168	500/502 ($M + NH_4$)
203		177	496/498 ($M + NH_4$)
204		128	454/456 ($M + H$)
205		168	500/502 ($M + NH_4$)

TABLE 5-continued





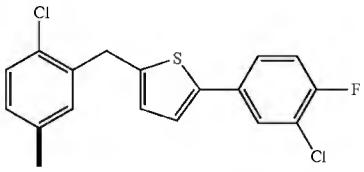
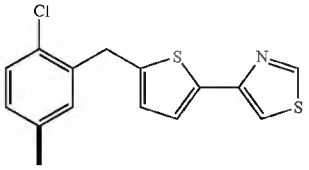
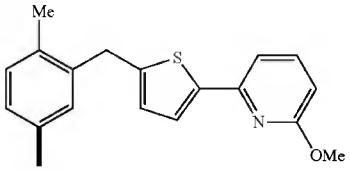
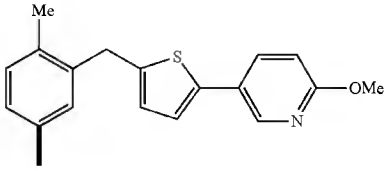
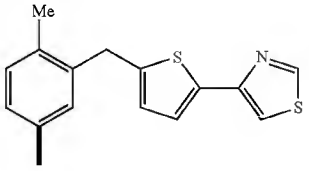
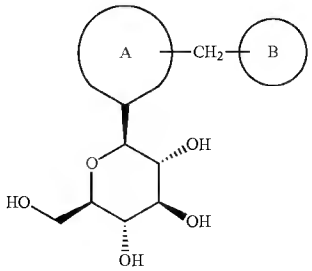
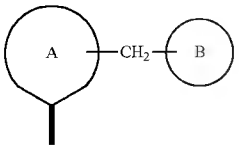
Examples		Preparation Method	APCI-Mass (m/Z)
206		168	516/518 ($M + NH_4$)
207		128	454/456 (M + H)
208		164	458 (M + H)
209		177	458 (M + H)
210		164	434 (M + H)

TABLE 5-continued





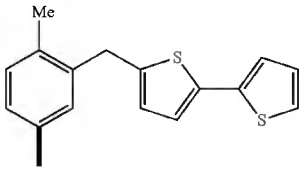
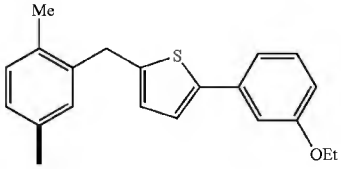
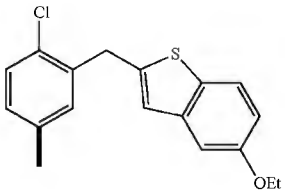
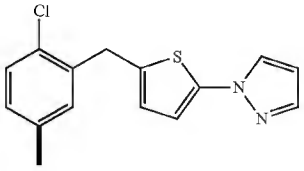
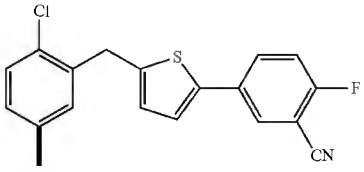
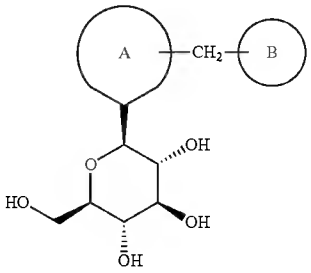
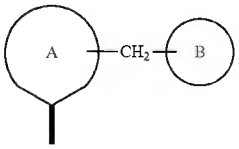
Examples		Preparation Method	APCI-Mass (m/Z)
211		177	450 (M + NH_4)
212		177	488 (M + NH_4)
213		1	482/484 (M + NH_4)
214		2	437/439 (M + H)
215		183	507/509 (M + NH_4)

TABLE 5-continued





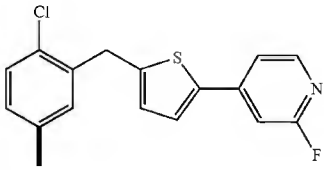
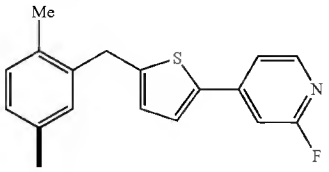
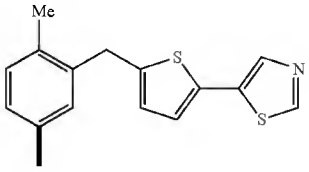
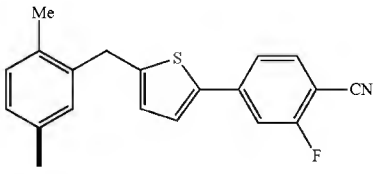
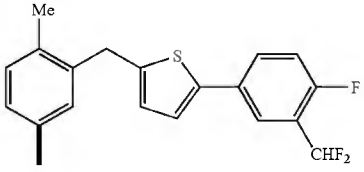
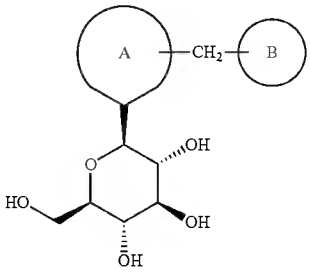
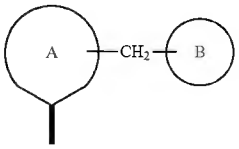
Examples		Preparation Method	APCI-Mass (m/Z)
216		168	466/468 (M + H)
217		177	446 (M + H)
218		164	434 (M + H)
219		185	487 (M + NH_4)
220		176	512 (M + NH_4)

TABLE 5-continued





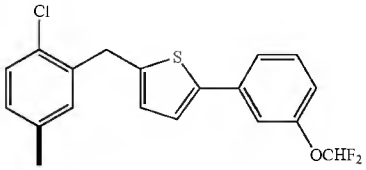
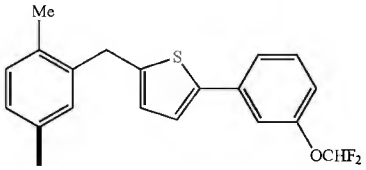
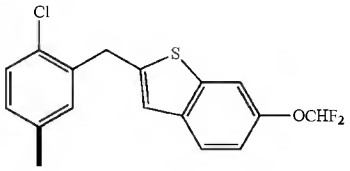
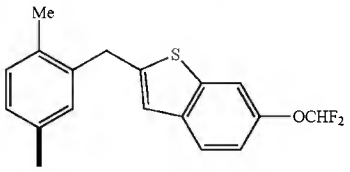
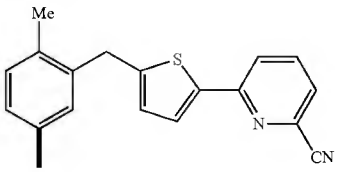
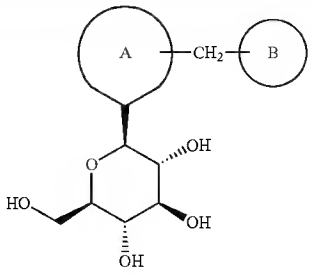
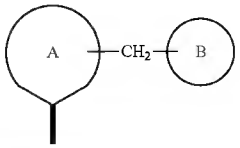
Examples		Preparation Method	APCI-Mass (m/Z)
221		168	530/532 ($M + NH_4$)
222		177	510 ($M + NH_4$)
223		2	504/506 ($M + NH_4$)
224		2	484 ($M + NH_4$)
225		186	470 ($M + NH_4$)

TABLE 5-continued





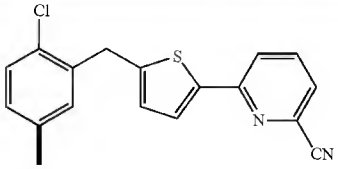
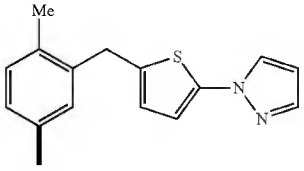
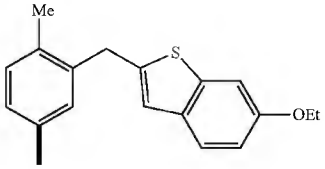
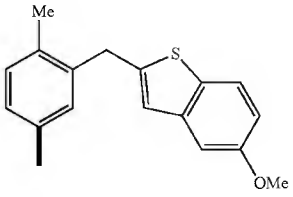
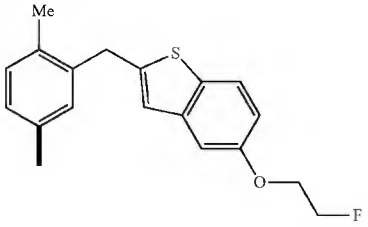
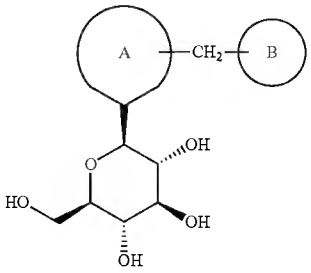
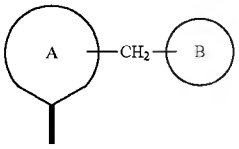
Examples		Preparation Method	APCI-Mass (m/Z)
226		187	490/492 ($M + NH_4$)
227		2	417 (M + H)
228		1	462 ($M + NH_4$)
229		1	448 ($M + NH_4$)
230		1	480 ($M + NH_4$)

TABLE 5-continued





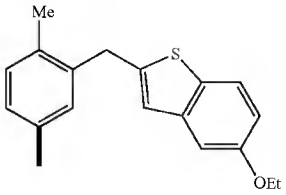
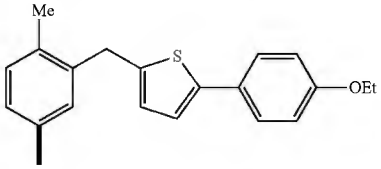
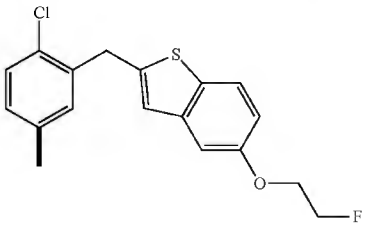
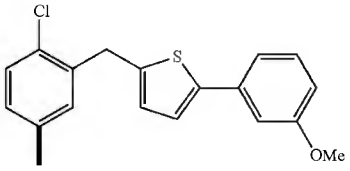
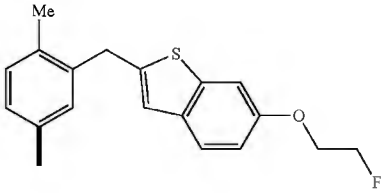
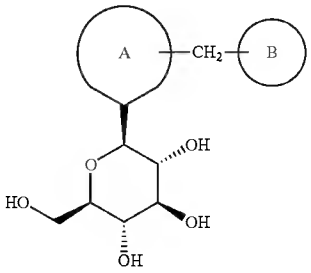
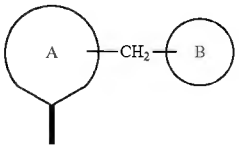
Examples		Preparation Method	APCI-Mass (m/Z)
231		1	462 (M + NH_4)
232		177	488 (M + NH_4)
233		1	500/502 (M + NH_4)
234		168	494/496 (M + NH_4)
235		1	480 (M + NH_4)

TABLE 5-continued





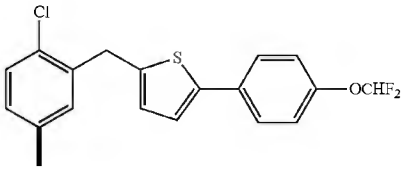
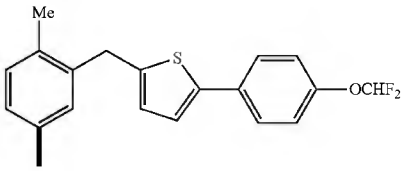
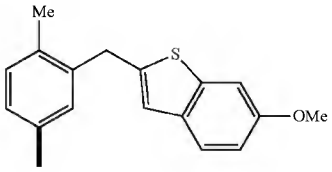
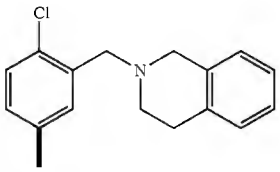
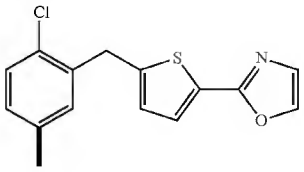
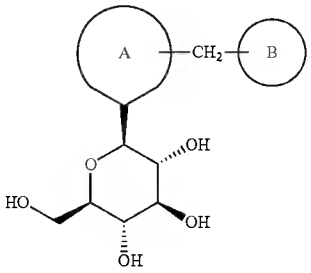
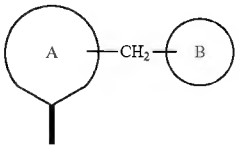
Examples		Preparation Method	APCI-Mass (m/Z)
236		168	530/532 (M + NH_4)
237		177	510 (M + NH_4)
238		1	448 (M + NH_4)
239		184	420/422 (M + H)
240		128	438/440 (M + H)

TABLE 5-continued





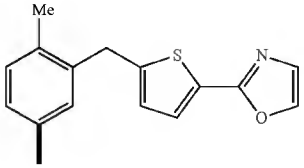
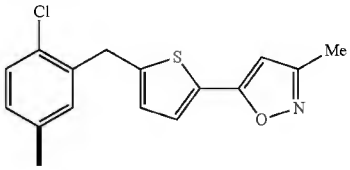
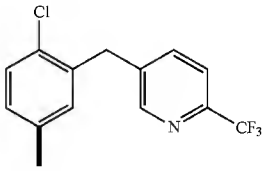
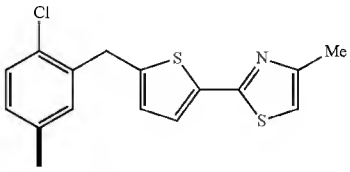
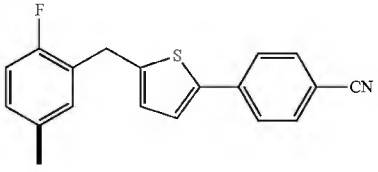
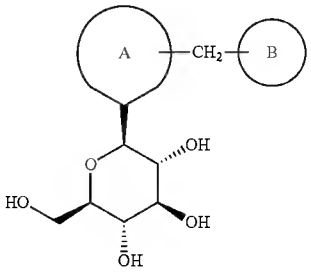
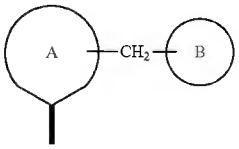
Examples		Preparation Method	APCI-Mass (m/Z)
241		164	418 (M + H)
242		128	469/471 ($M + NH_4$)
243		1	434/436 (M + H)
244		128	468/470 (M + H)
245		189	473 ($M + NH_4$)

TABLE 5-continued





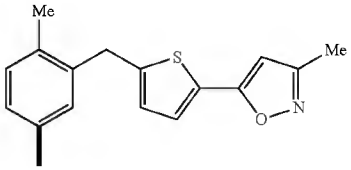
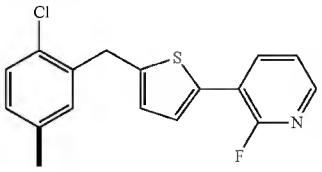
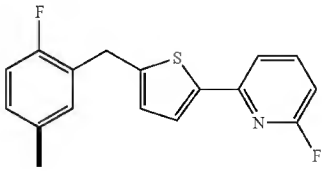
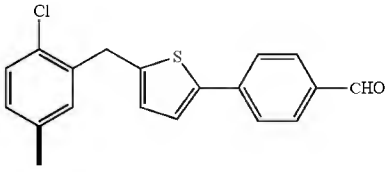
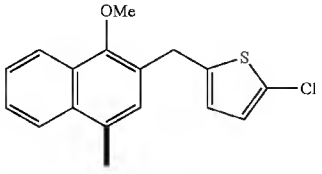
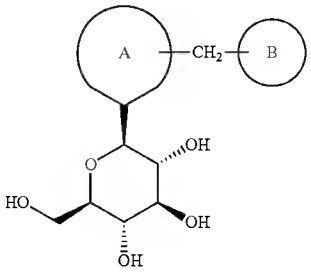
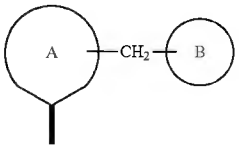
Examples		Preparation Method	APCI-Mass (m/Z)
246		164	449 (M + NH_4)
247		168	483/485 (M + NH_4)
248		189	467 (M + NH_4)
249		168	492/494 (M + NH_4)
250		1	468/470 (M + NH_4)

TABLE 5-continued





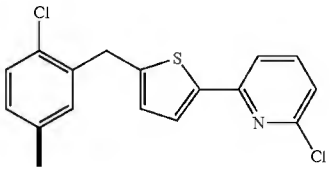
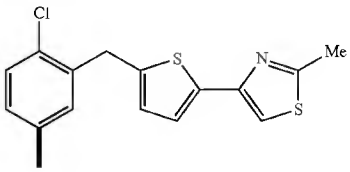
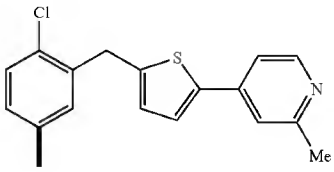
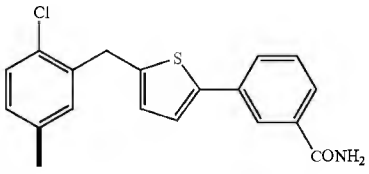
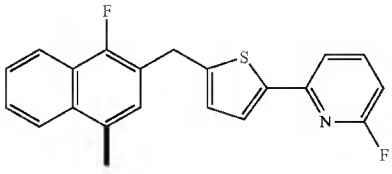
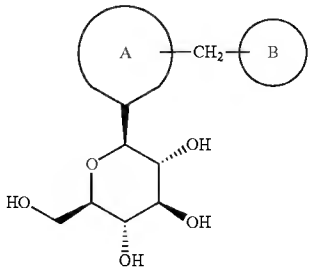
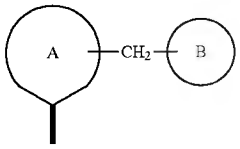
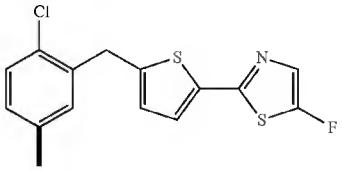
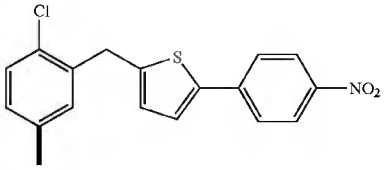
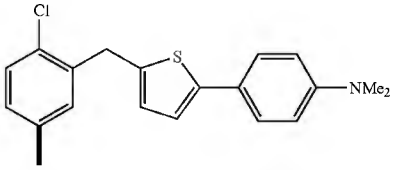
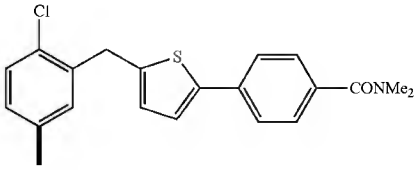
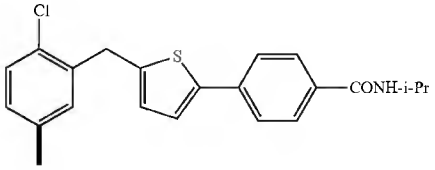
Examples		Preparation Method	APCI-Mass (m/Z)
251		168	499/501 ($M + NH_4$)
252		128	468/470 (M + H)
253		168	462/464 (M + H)
254		193	507/509 ($M + NH_4$)
255		196	517 ($M + NH_4$)

TABLE 5-continued

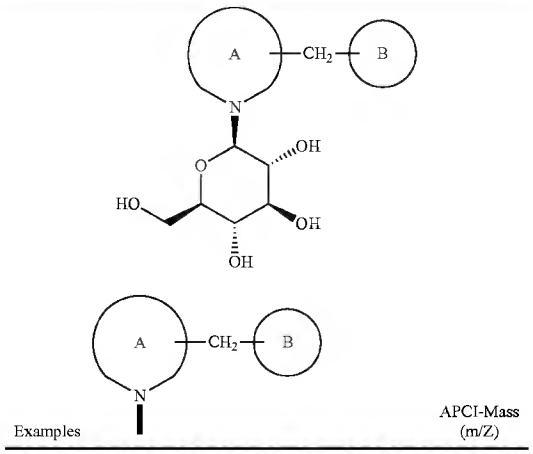


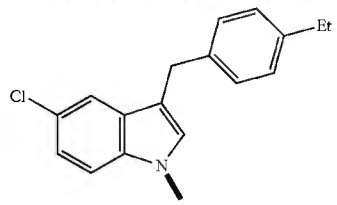
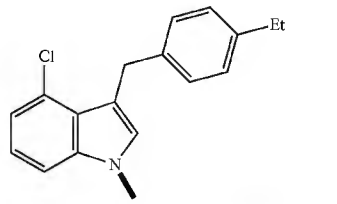
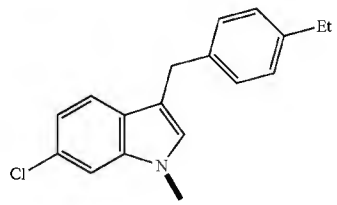


Examples		Preparation Method	APCI-Mass (m/Z)
256		1	472/474 (M + H)
257		168	509/511 ($M + NH_4$)
258		168	490/492 (M + H)
259		198	535/537 ($M + NH_4$)
260		198	549/551 ($M + NH_4$)

The compounds shown in Table 6 below were prepared in a manner similar to Example 195 from the corresponding starting materials.

TABLE 6



Examples		APCI-Mass (m/Z)
261		449/451 (M + NH_4)
262		432/434 (M + H)
263		449/451 (M + NH_4)

Example 264

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxymethylphenyl)-2-thienylmethyl)benzene

1-(β-D-Glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene (84 mg) obtained in Example 249 was dissolved in a mixture of ethanol (2 ml)-tetrahydrofuran (2 ml) and added thereto was sodium borohydride (7 mg). The mixture was stirred at room temperature for 1 hour. The mixture was quenched by 2N hydrochloric acid aqueous solution (3 drops) at 0° C., and the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-hydroxymethylphenyl)-2-thienylmethyl)benzene (82 mg) as colorless foam. APCI-Mass m/Z 494/496 (M+NH_4).

Example 265

1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)-4-methoxynaphthalene

(1) 1-(β-D-Glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methoxynaphthalene obtained in Example 250 was treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 636/638 (M+NH_4).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methoxynaphthalene was treated in a manner similar to Example 158-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 602 (M+NH_4).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-thienylmethyl)-4-methoxynaphthalene was treated in a manner similar to Example 159-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 680/682 (M+NH_4).

(4) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxynaphthalene and phenylboronic acid were treated in a manner similar to Example 168 to give the desired 1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)-4-methoxynaphthalene. APCI-Mass m/Z 510 (M+NH_4).

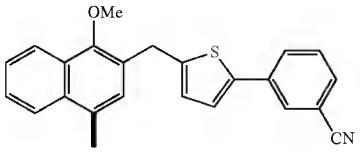
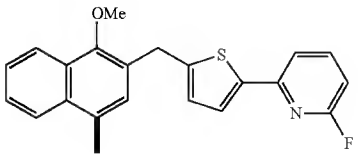
Example 266

1-(β-D-glucopyranosyl)-3-(5-(2-pyrimidinyl)-2-thienylmethyl)-4-methoxynaphthalene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methoxylnaphthalene obtained in Example 265-(3) and 2-tributylstannylpyrimidine were treated in a manner similar to Example 128-(5) and (6) to give 1-(β-D-glucopyranosyl)-3-(5-(2-pyrimidinyl)-2-thienylmethyl)-4-methoxylnaphthalene. APCI-Mass m/Z 495 (M+H).

The compounds shown in Table 7 below were prepared in a manner similar to Example 265 from the corresponding starting materials.

TABLE 7

Examples		APCI-Mass (m/Z)
267		535 (M + NH_4)
268		529 (M + NH_4)

Reference Example 1

3-Bromo-1-(5-ethyl-2-thienylmethyl)benzene

(1) A solution of 1,3-dibromobenzene (3.7 g) in tetrahydrofuran (25 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.55 ml). The reaction mixture was stirred at the same temperature for 10 minutes, and thereto was added dropwise a solution of 5-ethyl-2-thiophenecarboxaldehyde (2.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated ammonium chloride solution, and the reaction mixture was warmed to room temperature. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=97:3-85:15) to give 3-bromophenyl-5-ethyl-2-thienylmethanol (2.97 g) as a pale yellow syrup. APCI-Mass m/Z 279/281 (M+H−H_2O).

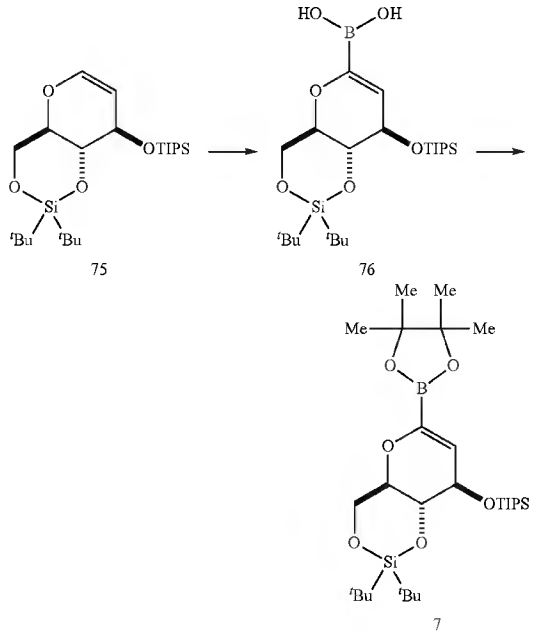
(2) The above 3-bromophenyl-5-ethyl-2-thienylmethanol (2.90 g) was dissolved in dichloromethane (38 ml), and the mixture was cooled to −78° C. under argon atmosphere. To the mixture were added triethylsilane (6.18 ml) and boron trifluoride diethyl ether complex (2.45 ml), and the mixture was gradually warmed to room temperature over a period of one hour. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the dichloromethane layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give the desired 3-bromo-(5-ethyl-2-thienylmethyl)benzene (2.57 g) as a colorless syrup. APCI-Mass m/Z 281/283 (M+H).

Reference Example 2

5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one

5-Bromo-1H-pyridin-2-one (1.04 g) and 4-ethylbenzyl bromide (1.43 g) were dissolved in N,N-dimethylformamide (15 ml), and thereto was added potassium carbonate (1.66 g). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and washed successively with water and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1-3:1) to give 5-bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one (1.58 g) as colorless crystals. APCI-Mass m/Z 292/294 (M+H).

Reference Example 3



75 76 7

In the above scheme, the symbols are as defined above.

(1) A solution of silylated glucal 75 (see Parker et al., Org. Lett. 2000, 2, 497-499) (7.00 g) in tetrahydrofuran (70 ml) was cooled to −78° C. under argon atmosphere. Thereto was added dropwise t-butyl lithium (1.45 M pentane solution, 49.0 ml) over a period of 10 minutes. The mixture was stirred at the same temperature for 15 minutes, and then warmed to room temperature, and further stirred for 30 minutes. The mixture was cooled again to −78° C., and thereto was added trimethyl borate (8.90 ml) in one portion. After 15 minutes, the reaction solution was warmed to room temperature over a period of one hour, and thereto was added water (100 ml) at 0° C. The mixture was stirred for 30 minutes, and extracted twice with diethyl ether. The extract was washed with water,

and then washed with brine. The resultant was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give the compound 76, which was used in the subsequent reaction without further purification.

(2) The whole amount of the above compound 76 was dissolved in toluene (65 ml), and thereto was added pinacol (2.24 g). The mixture was stirred at room temperature under argon atmosphere for 17 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, and the extract was washed with brine, dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the compound 7 (10.4 g) as a yellow semisolid, which was used in the subsequent reaction without further purification. APCI-Mass m/Z 569 (M+H).

Reference Example 4

5-Bromo-2-methylbenzaldehyde

(1) Methyl 5-bromo-2-methylbenzoate (see Japanese Unexamined Patent Publication No. 9-263549) (16.12 g) was dissolved in methanol (100 ml), and thereto was added 10% aqueous sodium hydroxide solution (50 ml). The mixture was stirred at 50° C. for 40 minutes. Under ice-cooling, the mixture was adjusted to pH 1 by addition of 10% aqueous hydrochloric acid solution, and diluted with water. Precipitated powder was collected by filtration, and dried to give 5-bromo-2-methylbenzoic acid (14.1 g). ESI-Mass m/Z 213/215 (M−H).

(2) The above 5-bromo-2-methylbenzoic acid (10.0 g) was suspended in dichloromethane (100 ml), and thereto were added oxalyl chloride (8.1 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-methylbenzoyl chloride. This benzoyl chloride was dissolved in dichloromethane (200 ml), and thereto was added N,O-dimethylhydroxylamine hydrochloride (12.3 g). To the mixture was added dropwise triethylamine (20 ml) at 0° C., and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate, and washed successively with water, 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.25 g) as oil. APCI-Mass m/Z 258/260 (M+H).

(3) A solution of the above N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.2 g) in tetrahydrofuran (100 ml) was cooled to −78° C. under argon atmosphere. To the mixture was added dropwise diisobutyl aluminum hydride (1.0 M toluene solution, 75 ml), and the mixture was stirred at the same temperature for one hour. 10% aqueous hydrochloric acid solution (50 ml) was added thereto, and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate twice, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was solidified to give 5-bromo-2-methylbenzaldehyde (8.73 g). APCI-Mass m/Z 213/215 (M+H+MeOH−H_2O).

Reference Example 5

5-Bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene

(1) 5-Bromo-2-chlorobenzoic acid (5.00 g) was suspended in dichloromethane (10 ml), and thereto were added oxalyl chloride (2.2 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 6 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzoyl chloride. This compound and 2-ethylthiophene (2.38 g) were dissolved in dichloromethane (20 ml), and thereto was added aluminum chloride (3.11 g) at 0° C. The mixture was stirred at the same temperature for one hour.

The reaction mixture was poured into a cold 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:1) to give 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) as an oil. APCI-Mass m/Z 329/331 (M+H).

(2) A solution of the above 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) in dichloromethane (50 ml)-acetonitrile (50 ml) was cooled under ice-cooling, and thereto were added dropwise triethylsilane (7.69 ml) and boron trifluoride.diethyl ether complex (6.1 ml). Subsequently, the mixture was stirred at room temperature for 3.5 hours, and was cooled again under ice-cooling. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene (4.52 g) as a colorless liquid.

Reference Example 6

3-Bromo-1-(5-n-propyl-2-thienylmethyl)benzene

3-Bromobenzoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 7

5-Bromo-(5-ethyl-2-thienylmethyl)-2-methoxybenzene

(1) A solution of 2-ethylthiophene (3.00 g) in tetrahydrofuran (36 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.56 M hexane solution, 17.1 ml). The mixture was stirred at the same temperature for 30 minutes, and cooled to −78° C., and thereto was added dropwise a suspension of 5-bromo-2-methoxybenzaldehyde (5.74 g) in tetrahydrofuran (60 ml). The mixture was stirred at the same temperature for 2 hours, warmed to 0° C., and thereto was added a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol (5.99 g) as a pale yellow syrup. APCI-Mass m/Z 309/311 (M+H−H_2O).

(2) The above 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol was treated in a manner similar to Reference Example 1-(2) to give 5-bromo-(5-ethyl-2-thienylmethyl)-2-methoxybenzene as oil. APCI-Mass m/Z 311/313 (M+H).

Reference Example 8

3-Bromo-1-(5-ethyl-2-thienylmethyl)-4-methoxybenzene

2-Ethylthiophene and 3-bromo-4-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 9

3-Bromo-1-(4-n-propyl-2-thienylmethyl)benzene

(1) 3-n-Propylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 7-(1) to give 3-bromophenyl-4-n-propyl-2-thienyl methanol. APCI-Mass m/Z 293/295 ($M+H-H_2O$).

(2) A solution of the above 3-bromophenyl-4-n-propyl-2-thienyl methanol (2.4 g) in acetonitrile (10 ml) was added dropwise to a mixed solution of chlorotrimethylsilane (4.54 ml) and sodium iodide (5.36 g) in acetonitrile (10 ml) at 0° C., over a period of 2 hours. The mixture was further stirred at room temperature for 5 minutes, and cooled again to 0° C. An aqueous solution (10 ml) of sodium hydroxide (1.0 g) was added thereto, and the mixture was stirred at 0° C. for 0.5 hours. The mixture was extracted with ethyl acetate, washed successively with an aqueous sodium thiosulfate solution, water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-1-(4-n-propyl-2-thienyl)benzene (1.97 g) as colorless oil.

Reference Example 10

5-Bromo-2-chloro-1-(5-n-propyl-2-thienylmethyl) benzene

5-Bromo-2-chlorobenozoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 11

5-Bromo-2-methoxy-1-(5-n-propyl-2-thienylmethyl) benzene

2-n-Propylthiophene and 5-bromo-2-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 325/327 (M+H).

Reference Example 12

3-Bromo-1-(4-ethyl-2-thienylmethyl)benzene

3-Ethylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 281/283 (M+H).

Reference Example 13

3-Bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene

(1) To a solution of 5-ethyl-2-thiophenecarboxaldehyde (6.0 g) in N,N-dimethylformamide (60 ml) was added N-chlorosuccinimide (8.57 g), and the mixture was stirred at room temperature for 2 hours, and subsequently stirred under heating at 60° C. for 2 hours. N-chlorosuccinimide (4.00 g) was further added thereto, and the mixture was further stirred under heating at 60° C. for 2 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=33:1) to give 4-chloro-5-ethyl-2-thiophenecarboxaldehyde (3.1 g) as colorless oil.

(2) The above 4-chloro-5-ethyl-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 1 to give 3-bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene as yellow oil. APCI-Mass m/Z 347/349 (M+H+MeOH).

Reference Example 14

5-Bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b] thiophen-2-ylmethyl)benzene

(1) To a solution of 4-keto-4,5,6,7-tetrahydrothianaphthene (9.83 g) in ethylene glycol (100 ml) were added hydrazine hydrate (10.4 ml) and potassium hydroxide (13.0 g), and the mixture was stirred under argon atmosphere at 190° C. for 4 hours. The reaction mixture was cooled to room temperature, and poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 4,5,6,7-tetrahydrothianaphthene (2.75 g) as colorless oil.

(2) The above 4,5,6,7-tetrahydrothianaphthene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl-methylbenzene as a colorless solid. APCI-Mass m/Z 341/343 (M+H).

Reference Example 15

5-Bromo-2-chloro-1-(5-ethyl-4-methyl-2-thienylmethyl)benzene

(3) 2-Acetyl-3-methylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 329/331 (M+H).

Reference Example 16

5-Bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl) benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chlorobenzaldehyde. APCI-Mass m/Z 233/235 (M+H+MeOH–H_2O).

(2) The above 5-bromo-2-chlorobenzaldehyde and thieno [3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans* 1 1997, 3465-3470) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 343/345 (M+H).

Reference Example 17

5-Bromo-2-chloro-1-(5-chloro-2-thienylmethyl)benzene

2-Chlorothiophene was treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 18

5-Bromo-2-chloro-1-(5-phenylmethyl-2-thienylmethyl)benzene

2-Benzoylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 377/379 (M+H).

Reference Example 19

5-Bromo-2-chloro-1-(5-(2-thienyl)-2-thienylmethyl) benzene

2,2'-Bithiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

Reference Example 20

5-Bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methylbenzene

(1) To a solution of 2-bromo-5-chlorothiophene (4.11 g), thiophene-2-boronic acid (4.00 g), tetrakis(triphenylphosphine)palladium (0) (1.20 g) and 2M aqueous sodium carbonate solution (31.3 ml) in dimethoxyethane (100 ml) was heated under reflux under argon atmosphere for 2.5 hours. The reaction mixture was cooled, and extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-chloro-2-thienyl)thiophene (3.37 g) as pale yellow oil.

(2) The above 2-(5-chloro-2-thienyl)thiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were used and treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methylbenzene as a colorless solid. APCI-Mass m/Z 383/385 (M+H).

Reference Example 21

5-Bromo-2-chloro-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene

2-Acetyl-3-chlorothiophene (see Japanese Unexamined Patent Publication No. 2000-34230) was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

Reference Example 22

5-Chloro-4-methylthiophene

The target compound was prepared according to a method described in Japanese Unexamined Patent Publication No. 10-324632.

Reference Example 23

5-Bromo-2-chloro-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)benzene

2-(5-Chloro-2-thienyl)thiophene and 5-bromo-2-chlorobenzoic acid were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 24

5-Bromo-2-chloro-1-(5-trifluoromethyl-2-thienylmethyl)benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 25

5-Bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl) benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol as colorless powder. APCI-Mass m/Z 380/382 (M+H).

(2) A solution of the above 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol (3.52 g) in trifluoroacetic acid (45 ml) was added to a solution of sodium borohydride (1.75 g) in trifluoroacetic acid (45 ml), and the mixture was stirred at room temperature for 4 hours. Trifluoroacetic acid was evaporated under reduced pressure. The residue was basified with an aqueous potassium hydroxide solution, and extracted with diethyl ether. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1-4:1) to give 5-bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl)benzene (2.42 g) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 26

5-Bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) and 2-chlorothiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene as colorless oil.

(2) To a solution of the above 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene (1.0 g) in dimethoxyethane (10 ml) were added phenylboronic acid (310 mg), bis(triphenylphosphine)palladium (II)dichloride (85 mg) and 2M aqueous sodium carbonate solution (3.8 ml), and the mixture was stirred at 50° C. overnight. Added thereto was a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene (683 mg) as oil.

Reference Example 27

2-Chlorothieno[3,2-b]thiophene

(1) A solution of thieno[3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans* 1 1997, 3465-3470) (1.27 g) in tetrahydrofuran (30 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 5.70 ml).

The mixture was stirred at 0° C. for 30 minutes, and cooled again to −78° C. Added thereto was a solution of hexachloroethane (2.14 g) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for one hour, and warmed to 0° C. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give 2-Chlorothieno[3,2-b]thiophene (1.19 g) as a solid.

Reference Example 28

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methoxybenzene

Thianaphthene was treated in a manner similar to Reference Example 7 to give the target compound. ESI-Mass m/Z 331/333 (M−H).

Reference Example 29

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-chlorobenzene

Thianaphthene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 30

3-Bromo-1-(5-methylbenzo[b]thiophen-2-ylmethyl) benzene

5-Methylbenzo[b]thiophene and 3-bromobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 31

3-Bromo-1-(6-fluorobenzo[b]thiophen-2-ylmethyl) benzene

(1) To a solution of 2,4-difluorobenzaldehyde (5.0 g) in dimethylsulfoxide (100 ml) were added methyl thioglycolate (3.45 ml) and triethylamine (10 ml), and the mixture was stirred at 80° C. overnight. The reaction mixture was poured into ice-cold water. The mixture was extracted with ethyl acetate, washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:1) to give 6-fluoro-2-methoxycarbonylbenzo[b]thiophene (1.32 g) as colorless powder. GC-EI-Mass m/Z 210 (M).

(2) The above 6-fluoro-2-methoxycarbonylbenzo[b] thiophene was treated in a manner similar to Reference Example 4-(1) to give 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid as colorless powder. ESI-Mass m/Z 195 (M−H).

(3) The above 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 4-(2) to give 6-fluoro-2-(N-methoxy-N-methylcarbamoyl) benzo[b]thiophene as colorless powder. APCI-Mass m/Z 240 (M+H).

(4) A solution of 1,3-dibromobenzene (493 mg) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 0.86 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of the above 6-fluoro-2-(N-methoxy-N-methylcarbamoyl)benzo[b]thiophene (500 mg) in tetrahydrofuran (3 ml). The mixture was warmed to room temperature, and added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-85:15) to give 3-bromophenyl 6-fluorobenzo [b]thiophen-2-yl ketone (479 mg) as a pale yellow solid. APCI-Mass m/Z 335/337 ($M+NH_4$).

(5) The above 3-bromophenyl 6-fluorobenzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 3-bromo-1-(6-fluorobenzo[b] thiophen-2-ylmethyl)benzene as a colorless solid.

Reference Example 32

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-fluorobenzene

Thianaphthene and 3-bromo-4-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 33

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethoxybenzene

Thianaphthene and 5-bromo-2-ethoxybenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 34

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-fluorobenzene

Thianaphthene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 35

2-(Benzo[b]thiophen-2-ylmethyl)-4-bromo-1-methoxynaphthalene

2,4-Dibromo-1-methoxynaphthalene (see J. Clayden, et al. *Org. Lett.*, 5, (2003) 831) and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 36

3-Bromo-1-(5-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

5-Trifluoromethylbenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 31-(3), (4), and (5) to give the target compound.

Reference Example 37

3-Bromo-1-(3-methylbenzo[b]thiophen-2-ylmethyl) benzene

3-Methylbenzo[b]thiophene-2-carboxaldehyde was treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 38

3-Bromo-1-(5-fluorobenzo[b]thiophen-2-ylmethyl) benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 31 to give the target compound.

Reference Example 39

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene

(1) 3-Bromo-4-methylbenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 3-bromo-4-methylbenzaldehyde as colorless crystals. APCI-Mass m/Z 213/215 (M+H+MeOH).

(2) The above 3-bromo-4-methylbenzaldehyde and thianaphthene were treated in a manner similar to Reference Example 7 to give (Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene as a colorless solid.

Reference Example 40

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-methylbenzene

3,5-Dibromotoluene and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 41

5-Bromo-2-chloro-1-(5-methylbenzo[b]thiophen-2-ylmethyl)benzene

5-Methylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 42

5-Bromo-2-chloro-1-(7-methylbenzo[b]thiophen-2-ylmethyl)benzene

7-Methylbenzo[b]thiophene (see Tilak, B. D. *Tetrahedron* 9 (1960) 76-95) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 43

5-Bromo-2-chloro-1-(5-chlorobenzo[b]thiophen-2-ylmethyl)benzene

5-Chlorobenzo[b]thiophene (see Tilak, B. D. *Tetrahedron* 9 (1960) 76-95) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 44

5-Bromo-2-chloro-1-(5,7-dimethylbenzo[b] thiophen-2-ylmethyl)benzene

5.7-Dimethylbenzo[b]thiophene (see Yoshimura, Y. et al., *J. Med. Chem.* 43 (2000) 2929-2937) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 45

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene

(1) A solution of thianaphthene (543 mg) in diethyl ether (20 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 1.74 ml). The reaction mixture was stirred at the same temperature for 3 hours. The reaction mixture was added dropwise to a solution of N-methoxy-N-methyl-5-bromo-2-methylbenzamide (1.15 g) obtained in Reference Example 4-(2) in diethyl ether (10 ml) cooled to −78° C. The mixture was warmed to room temperature and stirred for one hour. Added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-95:5) to give 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone (995 mg) as a pale yellow syrup. APCI-Mass m/Z 331/333 (M+H).

(2) The above 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 1-(benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene as colorless oil.

Reference Example 46

5-Bromo-2-chloro-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)benzene

6-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 47

5-Bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)benzene

(1) 4-Chloro-2-fluorobenzaldehyde was treated in a manner similar to Reference Example 31-(1) and (2) to give 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid as colorless crystals. ESI-Mass m/Z 211/213 (M−H).

(2) A solution of the above 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid (3.0 g) and copper powder (1.2 g) in quinoline (20 ml) was stirred at 210° C. for 40 minutes. The mixture was cooled to room temperature and diluted with diethyl ether, and insoluble materials were filtered off. The filtrate was washed successively with 10% aqueous hydrochloric

acid solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 6-chlorobenzo[b]thiophene (1.79 g) as colorless crystals.

(3) The above 6-chlorobenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give 5-bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)benzene as colorless crystals.

Reference Example 48

5-Bromo-2-chloro-1-(6-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

2-Fluoro-4-trifluoromethylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 49

1-Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-chlorobenzene

3-Bromo-4-chlorobenzoic acid was treated in a manner similar to Reference Example 39 to give the target compound.

Reference Example 50

5-Bromo-2-chloro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,4-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 51

5-Bromo-2-fluoro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)benzene

6-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 50 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 52

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-chlorobenzene

1-Chloro-3,5-dibromobenzene and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 53

5-Bromo-2-chloro-1-(7-methoxybenzo[b]thiophen-2-ylmethyl)benzene

7-Methoxybenzo[b]thiophene (see WO 02/094262) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

Reference Example 54

5-Bromo-2-chloro-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)benzene

5-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

Reference Example 55

5-Bromo-2-chloro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 56

5-Bromo-2-chloro-1-(7-fluoro-6-methylbenzo[b]thiophen-2-ylmethyl)benzene

2,3-Difluoro-4-methylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

Reference Example 57

5-Bromo-2-chloro-1-(4-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,6-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 58

5-Bromo-2-chloro-1-(7-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,3-difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 59

5-Bromo-2-chloro-1-(4-chlorobenzo[b]thiophen-2-ylmethyl)benzene

2-Chloro-6-fluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 60

5-Bromo-2-fluoro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)benzene

5-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 55 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 61

3-Bromo-2-chloro-1-(benzo[b]thiophen-2-ylmethyl)benzene

(1) 3-Bromo-2-chlorobenzoic acid (see Frederic Gohier et al., *J. Org. Chem.* (2003) δ 2030-2033.) was treated in a

manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-3-bromo-2-chlorobenzamide as oil. APCI-Mass m/Z 278/280/282 (M+H).

(2) The above N-methoxy-N-methyl-3-bromo-2-chlorobenzamide was treated in a manner similar to Reference Example 45 to give 3-bromo-2-chloro-1-(benzo[b]thiophen-2-ylmethyl)benzene as a colorless solid.

Reference Example 62

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethylbenzene

(1) To a solution of 2-ethylbenzoic acid (10.0 g) in dichloromethane (50 ml) were added oxalyl chloride (7.0 ml) and N,N-dimethylformamide (3 drops) and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The acid chloride was dissolved in methanol (60 ml) and the mixture was stirred at room temperature for 3 hours, and then, the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give methyl 2-ethylbenzoate, which was used in the subsequent step without further purification.

(2) The above methyl 2-ethylbenzoate was mixed with molecular sieve 13× (powder, 70 g), and while stirring the mixture, bromine (5.2 ml) was added dropwise thereto at 80° C. The mixture was further stirred at the same temperature for 1.5 hours. The mixture was cooled to room temperature, and added thereto were potassium carbonate (7.4 g), water (70 ml) and methanol (350 ml), and the mixture was stirred for 8 hours. Insoluble materials were filtered off, and suspended in a mixed solution of methanol (500 ml)-water (500 ml), and the mixture was stirred at room temperature overnight. Insoluble materials were filtered off and the filtrate was combined with the previously obtained filtrate, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was distilled under reduced pressure, to give methyl 5-bromo-2-ethylbenzoate (2.44 g). APCI-Mass m/Z 260/262 ($M+NH_4$).

(3) The above methyl 5-bromo-2-ethylbenzoate was treated in a manner similar to Reference Example 4-(1) and (2) to give N-methoxy-N-methyl-5-bromo-2-ethylbenzamide as colorless oil. APCI-Mass m/Z 272/274 (M+H).

(4) The above N-methoxy-N-methyl-5-bromo-2-ethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give 1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethylbenzene as oil.

Reference Example 63

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-trifluoromethylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-iodobenzamide as a pale yellow solid. APCI-Mass m/Z 370/372 (M+H).

(2) To a solution of the above N-methoxy-N-methyl-5-bromo-2-iodobenzamide (2.67 g) in N-methyl-2-pyrrolidinone (12 ml) were added copper (I) bromide (124 mg) and methyl fluorosulfonyl(difluoro)acetate (1.34 ml), and the mixture was stirred under heating for 1.5 hours. The reaction mixture was cooled to room temperature, and then, a diluted aqueous ammonia was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-85:15) to give N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide (1.59 g) as colorless oil. APCI-Mass m/Z 312/314 (M+H).

(3) The above N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give 1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-trifluoromethylbenzene as a colorless solid. ESI-Mass m/Z 369/371 (M−H).

Reference Example 64

5-Bromo-2-chloro-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 363/365 (M+H).

Reference Example 65

5-Bromo-2-chloro-1-(5-(4-methylphenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(4-methylphenyl)thiophene as colorless crystals. APCI-Mass m/Z 175 (M+H).

(2) The above 2-(4-methylphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-methylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 377/379 (M+H).

Reference Example 66

5-Bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)benzene

(1) 2-Fluorobromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-fluorophenyl)thiophene as a colorless liquid.

(2) The above 2-(2-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 381/383 (M+H).

Reference Example 67

5-Bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 4-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(4-fluorophenyl)thiophene as colorless powder.

(2) The above 2-(4-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)benzene as colorless powder.

Reference Example 68

5-Bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)benzene

(1) 2-Bromothiophene and 4-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-ethoxyphenyl)thiophene as a colorless solid. APCI-Mass m/Z 205 (M+H).

(2) The above 2-(4-ethoxyphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 407/409 (M+H).

Reference Example 69

5-Bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)benzene

(1) 2-Bromothiophene and 3-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethoxyphenyl)thiophene as colorless oil. APCI-Mass m/Z 205 (M+H).

(2) The above 2-(3-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H).

Reference Example 70

5-Bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 2-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-ethoxyphenyl)thiophene as a pale yellow solid.

(2) The above 2-(2-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H).

Reference Example 71

5-Bromo-2-fluoro-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

Reference Example 72

5-Bromo-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(4-Ethoxyphenyl)thiophene obtained in Reference Example 68-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 73

5-Bromo-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(2-Ethoxyphenyl)thiophene obtained in Reference Example 70-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 74

5-Bromo-2-fluoro-1-(5-(2-fluorophenyl)-2-thienylmethyl)benzene

2-(2-Fluorophenyl)thiophene obtained in Reference Example 66-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 365/367 (M+H).

Reference Example 75

5-Bromo-2-chloro-1-(5-(3-fluorophenyl)-2-thienylmethyl)benzene

(1) 2-Iodothiophene and 3-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-fluorophenyl)thiophene as oil.

(2) The above 2-(3-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give the target compound as powder.

Reference Example 76

5-Bromo-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(3-Ethoxyphenyl)thiophene obtained in Reference Example 69-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 77

5-Bromo-2-fluoro-1-(5-(3-fluorophenyl)-2-thienylmethyl)benzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 78

5-Bromo-2-fluoro-1-(5-(4-fluorophenyl)-2-thienylmethyl)benzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 79

5-Bromo-2-methyl-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a man-

ner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 343/345 (M+H).

Reference Example 80

5-Bromo-1-(5-(3-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 81

5-Bromo-1-(5-(4-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 82

5-Bromo-2-methoxy-1-(5-phenyl-2-thienylmethyl) benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 359/361 (M+H).

Reference Example 83

5-Bromo-2-methyl-1-(5-(3-methylphenyl)-2-thienyl-methyl)benzene

(1) 2-Bromothiophene and 3-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methylphenyl)thiophene as colorless oil.

(2) The above 2-(3-methylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 357/359 (M+H).

Reference Example 84

5-Bromo-2-chloro-1-(5-(3-methylphenyl)-2-thienyl-methyl)benzene

2-(3-Methylphenyl)thiophene obtained in Reference Example 83-(1) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 377/379/381 (M+H).

Reference Example 85

5-Bromo-2-chloro-1-(5-(3-chlorophenyl)-2-thienyl-methyl)benzene

(1) 2-Bromothiophene and 3-chlorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-chlorophenyl)thiophene as colorless oil.

(2) The above 2-(3-chlorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give the target compound as colorless oil.

Reference Example 86

5-Bromo-1-(5-(3-chlorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Chlorophenyl)thiophene obtained in Reference Example 85-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound as colorless oil.

Reference Example 87

5-Bromo-1-(5-(3-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) 3-Methoxybromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methoxyphenyl)thiophene as a yellow liquid. APCI-Mass m/Z 191 (M+H).

(2) The above 2-(3-methoxyphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound as yellow oil. APCI-Mass m/Z 373/375 (M+H).

Reference Example 88

4-Bromo-2-(4-ethylphenylmethyl)-2H-isoquinolin-1-one

4-Bromo-2H-isoquiolin-1-one (see EP0355750) was treated in a manner similar to Reference Example 2 to give the target compound. APCI-Mass m/Z 342/344 (M+H).

Reference Example 89

4-Bromo-2-(4-ethylphenylmethyl)-8-methyl-2H-isoquinolin-1one

(1) To a solution of 8-methyl-2H-isoquiolin-1-one (1.15 g) in dichloromethane (20 ml) was added dropwise a solution of bromine (1.26 g) in dichloromethane (4 ml) at room temperature. The mixture was stirred at the same temperature for one hour, and the solvent was evaporated under reduced pressure. The residue was crystallized from ether to give 4-bromo-8-methyl-2H-isoquinolin-1-one (1.86 g) as colorless crystals. APCI-Mass m/Z 238/240 (M+H).

(2) The above 4-bromo-8-methyl-2H-isoquinolin-1-one was treated in a manner similar to Reference Example 2 to give the target compound as colorless crystals. APCI-Mass m/Z 356/358M+H).

Reference Example 90

4-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) A solution of 4-bromo-2-thiophenecarboxaldehyde (4.78 g) in tetrahydrofuran (40 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise 4-ethylphenylmagnesium bromide (0.5 M tetrahydrofuran solution, 50 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel

column chromatography (hexane:ethyl acetate=97:3-84:16) to give 4-bromo-2-thienyl-4-ethylphenylmethanol (5.37 g) as colorless oil. APCI-Mass m/Z 279/281 (M+H–H_2O).

(2) The above 4-bromo-2-thienyl-4-ethylphenylmethanol was treated in a manner similar to Reference Example 1-(2) to give the target compound as colorless oil.

Reference Example 91

5-Bromo-2-(4-ethylphenylmethyl)thiophene

5-Bromo-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound. ESI-Mass m/Z 279/281 (M–H).

Reference Example 92

3-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) 2,3-Dibromothiophene and 4-ethylbenzaldehyde were treated in a manner similar to Reference Example 1-(1) to give 3-bromo-2-thienyl-4-ethylphenylmethanol as yellow oil. APCI-Mass m/Z 279/281 (M+H–H_2O).

(2) A solution of the above 3-bromo-2-thienyl-4-ethylphenylmethanol (12.4 g) in diethyl ether (10 ml) was added dropwise into a suspension of lithium aluminum hydride (2.6 g) and aluminum chloride (9.0 g) in diethyl ether (35 ml) at 0° C. Subsequently, the mixture was stirred at room temperature overnight, and then poured onto ice. The mixture was extracted with diethyl ether, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-2-(4-ethylphenylmethyl)thiophene (8.77 g) as colorless oil. APCI-Mass m/Z 279/281 (M+H).

Reference Example 93

5-Bromo-3-(4-ethylphenylmethyl)thiophene

5-Bromo-3-thiophenecarboxaldehyde (see Amishiro, N. et al., *Chem. Pharm. Bull.* 47 (1999) 1393-1403.) was treated in a manner similar to Reference Example 90 to give the target compound.

Reference Example 94

5-Bromo-2-chloro-3-(4-ethylphenylmethyl)thiophene

(1) 5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chloro-3-thiophenecarboxaldehyde as pale yellow oil. APCI-Mass m/Z 239/241/243 (M+H+MeOH–H_2O).

(2) The above 5-bromo-2-chloro-3-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound as colorless oil.

Reference Example 95

5-Bromo-3-chloro-2-(4-ethylphenylmethyl)thiophene

(1) A solution of diisopropylamine (6.8 ml) in tetrahydrofuran (75 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 30.5 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 3-chloro-2-thiophenecarboxylic acid (3.92 g) in tetrahydrofuran (40 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise 1,2-dibromo-1,1,2,2-tetrafluoroethane (6.0 ml). The mixture was stirred at the same temperature for one hour, and then, warmed to room temperature. The mixture was poured into a diluted aqueous hydrochloric acid solution, and the solution was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was crystallized from a mixed solvent of diisopropyl ether and hexane to give 5-bromo-3-chloro-2-thiophenecarboxylic acid (3.79 g) as a yellow solid. ESI-Mass m/Z 239/241 (M–H).

(2) The above 5-bromo-3-chloro-2-thiophenecarboxylic acid was treated in a manner similar to Reference Example 94 to give 5-bromo-3-chloro-2-(4-ethylphenylmethyl) thiophene as colorless oil.

Reference Example 96

3-Bromo-1-(benzo[b]thiophen-3-ylmethyl)benzene

Thianaphthene-3-carboxaldehyde was treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 97

3-Bromo-1-(5-ethyl-2-furylmethyl)benzene

(1) 5-Ethyl-2-furaldehyde was treated in a manner similar to Reference Example 1-(1) to give 3-bromophenyl-5-ethyl-2-furylmethanol as oil. APCI-Mass m/Z 263/265 (M+H–H_2O).

(2) The above 3-bromophenyl-5-ethyl-2-furylmethanol was treated in a manner similar to Reference Example 9-(2) to give the target compound as oil.

Reference Example 98

3-Bromo-1-(benzo[b]furan-2-ylmethyl)benzene

2-Benzo[b]furancarboxaldehyde was treated in a manner similar to Reference Example 97 to give the target compound.

Reference Example 99

1-(Benzo[b]furan-2-ylmethyl)-5-bromo-2-chlorobenzene

Benzo[b]furan and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 100

1-(Benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene

(1) Benzothiazole and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-methylphenyl-(benzothiazol-2-yl)methanol as pale yellow crystals. APCI-Mass m/Z 334/336 (M+H).

(2) To a solution of the above 5-bromo-2-methylphenyl-(benzothiazol-2-yl)methanol (2.60 g) in dichloromethane (30 ml)-toluene (10 ml) was added manganese(IV) oxide (3.42 g), and the mixture was stirred at room temperature for 3 hours. Insoluble materials were filtered off, and the filtrate was evaporated under reduced pressure to give 5-bromo-2-methylphenyl benzothiazol-2-yl ketone (2.45 g) as colorless crystals. APCI-Mass m/Z 332/334 (M+H).

(3) The above 5-bromo-2-methylphenyl benzothiazol-2-yl ketone was treated in a manner similar to Reference Example 14-(1) to give 1-(benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene as oil. APCI-Mass m/Z 318/320 (M+H).

Reference Example 101

1-(Benzothiazol-2-ylmethyl)-5-bromo-2-chlorobenzene

Benzothiazole and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 100 to give the target compound. APCI-Mass m/Z 338/340 (M+H).

Reference Example 102

5-Bromo-2-chloro-1-(5-phenyl-2-thiazolylmethyl) benzene

(1) A solution of thiazole (10.0 g), iodobenzene (2.63 ml), tetrakis(triphenylphosphine)palladium (0) (1.36 g) and potassium acetate (3.46 g) in N,N-dimethylacetamide (100 ml) was stirred under heating at 100° C. overnight. The solvent was evaporated under reduced pressure, and added to the residue was ethyl acetate. The mixture was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-90:10) to give 5-phenylthiazole (1.50 g) as a pale yellow solid. APCI-Mass m/Z 162 (M+H).

(2) The above 5-phenylthiazole and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 100 to give 5-bromo-2-chloro-1-(5-phenyl-2-thiazolylmethyl)benzene as a yellow solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 103

3-(4-Ethylphenylmethyl)-2,4-pentanedione

A suspension of sodium iodide (15.0 g) in acetonitrile (100 ml) was cooled to 0° C. under argon atmosphere, and thereto were added dropwise chlorotrimethylsilane (12.7 ml), 2,4-pentanedione (2.05 ml) and 4-ethylbenzaldehide (2.68 g), successively. The reaction mixture was stirred at room temperature for 17 hours, and further stirred at 60° C. for 10 hours. The reaction mixture was cooled to room temperature and poured into an aqueous sodium thiosulfate solution. The mixture was extracted with diethyl ether, and the extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) to give 3-(4-ethylphenylmethyl)-2,4-pentanedione (2.72 g) as pale yellow oil. APCI-Mass m/Z 219 (M+H).

Reference Example 104

Tri-n-butyl(4-ethylphenyl)tin

To a solution of magnesium (896 mg) in tetrahydrofuran (20 ml) was added dibromoethan (0.1 ml), and the mixture was stirred at room temperature for 15 minutes. Thereto was added dropwise a solution of 1-bromo-4-ethylbenzene (5.7 g) in tetrahydrofuran (20 ml), and subsequently, the mixture was stirred at room temperature for one hour. The reaction mixture was cooled to −78° C., and thereto was added dropwise tributyltin chloride (9.49 g). The mixture was stirred at the same temperature for 30 minutes, and then at room temperature for one hour. To the reaction mixture were added 10% aqueous potassium fluoride solution and ethyl acetate, and the mixture was stirred at room temperature for 30 minutes. Insoluble materials were filtered off. The organic layer of the filtrate was washed with water and brine successively, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by alumina column chromatography (hexane) to give the desired tri-n-butyl(4-ethylphenyl)tin (10.7 g) as colorless oil. EI-Mass m/Z 337 (M-Bu).

Reference Example 105

4-(4-Ethylphenylmethyl)pyrazole

(1) A mixed solution of 4-ethylbenzyl bromide (10.0 g), malononitrile (6.64 g), potassium carbonate (6.94 g) and tetra-n-butylammonium bromide (648 mg) in toluene (100 ml) was agitated at room temperature for 17 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate twice. The extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=6:1) to give 2-(4-ethylphenylmethyl)malononitrile (3.28 g) as a colorless solid.

(2) A solution of the above 2-(4-ethylphenylmethyl)malononitrile (1.30 g) and hydrazine hydrate (0.86 ml) in ethanol (35 ml) was heated under reflux for 4 hours. Hydrazine hydrate (0.43 ml) was further added thereto and the mixture was further heated under reflux for 4 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-diethyl ether to give 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (2.63 g) as pale pink powder. APCI-Mass m/Z 217 (M+H).

(3) The above 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (1.30 g) was added to 50% aqueous phosphoric acid solution (19 ml), and further added thereto was water (10 ml). The mixture was cooled to 0° C., and thereto was added dropwise an aqueous solution (4 ml) of sodium nitrite (912 mg). The mixture was stirred at the same temperature for 30 minutes, and further stirred at room temperature for 4 hours. The reaction mixture was cooled again to 0° C., 10% aqueous sodium hydroxide solution was added thereto to adjust pH of the reaction mixture to 7. The mixture was extracted with ethyl acetate, washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10) to give the desired 4-(4-ethylphenylmethyl)pyrazole (414 mg) as a pale brown semisolid. APCI-Mass m/Z 187 (M+H).

Reference Example 106

3-(4-Ethylphenylmethyl)-5-methyl-1H-pyrazole

(1) 4-Ethylphenylacetic acid (3.0 g) (see Japanese Unexamined Patent Publication 63-233975) was dissolved in dichloromethane (15 ml), and thereto were added oxalyl chloride (6.0 ml) and N,N-dimethylformamide (one drop). The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene to give a crude 4-ethylphenylacetyl chloride, which was used in the subsequent step without further purification.

(2) A suspension of magnesium chloride (1.74 g) in dichloromethane (30 ml) was cooled to 0° C., and thereto were added t-butyl acetoacetate (3.03 ml) and pyridine (2.96 ml), and successively was added a solution of the above 4-ethylphenylacetyl chloride in dichloromethane (30 ml). The mixture was stirred at the same temperature for 2.5 hours, and an aqueous citric acid solution was added thereto. The mixture was extracted with chloroform. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=15:1) to give t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate (4.75 g) as pale yellow oil. APCI-Mass m/Z 322 ($M+NH_4$).

(3) A solution of the above t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate in trifluoroacetic acid (60 ml) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate, and the mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (4.00 g) as yellow oil. APCI-Mass m/Z 205 (M+H).

(4) A solution of the above 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (3.98 g) and hydrazine hydrate (4.0 ml) in toluene (20 ml) was stirred under heating at 100° C. for 1.5 hours. The reaction mixture was cooled to room temperature, and washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:ethyl acetate=2:1) to give 3-(4-ethylphenylmethyl)-5-methyl-1H-pyrazole (3.12 g) as yellow oil. APCI-Mass m/Z 201 (M+H).

Reference Example 107

3-(4-Ethylphenylmethyl)-6-hydroxypyridine

(1) To a solution of 6-chloronicotinoyl chloride (10.0 g) and N,O-dimethylhydroxyamine hydrochloride (6.65 g) in dichloromethane (200 ml) was added dropwise triethylamine (17.2 g) at 0° C. Subsequently the mixture was stirred at room temperature overnight. The mixture was washed successively with water, 5% aqueous citric acid solution, water and brine, and then, dried over sodium sulfate. The solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-6-chloronicotinamide (11.73 g) as pale yellow oil. APCI-Mass m/Z 201/203 (M+H).

(2) A solution of the N-methoxy-N-methyl-6-chloronicotineamide (4.2 g) in tetrahydrofuran (40 ml) was cooled to 0° C., and thereto was added dropwise 4-ethylphenylmagnesium bromide (0.5 M tetrahydrofuran solution, 55 ml). The mixture was stirred at 0° C. for 4 hours, and then at the room temperature for 10 minutes. The reaction mixture was cooled again to 0° C., and added thereto was 10% aqueous hydrochloric acid solution. The mixture was extracted with ethyl acetate, and washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=20:1) to give 6-chloro-3-pyridyl 4-ethylphenyl ketone (3.68 g) as colorless crystals. APCI-Mass m/Z 246/248 (M+H).

(3) The above 6-chloro-3-pyridyl 4-ethylphenyl ketone (1.68 g) was dissolved in N-methyl-2-pyrrolidinone (20 ml), and thereto were added benzylalcohol (815 ml) and 60% sodium hydride (275 mg). The mixture was stirred at room temperature for 6 hours, and then at 90° C. for one hour. The reaction mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-95:5) to give 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.68 g) as colorless oil. APCI-Mass m/Z 318 (M+H).

(4) The above 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (865 mg) was dissolved in ethylene glycol (8.5 ml), and thereto were added hydrazine hydrate (0.44 ml) and potassium hydroxide (550 mg). The mixture was stirred under heating at 190° C. for 8 hours. The reaction mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water three times, and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-0:100) to give the desired 3-(4-ethylphenylmethyl)-6-hydroroxypyridine (256 mg) as colorless powder. APCI-Mass m/Z 214 (M+H).

Reference Example 108

3-(4-Ethylphenylmethyl)-2-hydroxypyridine

(1) 2-Chloronicotinoyl chloride was treated in a manner similar to Reference Example 107-(1), (2) and (3) to give 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone as colorless oil. APCI-Mass m/Z 318 (M+H).

(2) The above 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.69 g) was dissolved in ethanol (15 ml), and thereto was added sodium borohydride (403 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed with water and successively with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give crude 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol as colorless oil, which was used in the subsequent step without further purification.

(3) The above 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol was dissolved in methanol (10 ml), and thereto were added concentrated hydrochloric acid (1.0 ml) and 10% palladium-carbon (500 mg). The mixture was stirred at room temperature for 15 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with water and successively with brine, and dried over sodium sulfate. The solvent was evaporated under reduced

pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0-97:3) to give the desired 3-(4-ethylphenylmethyl)-2-hydroroxypyridine (307 mg) as a pale brown solid. APCI-Mass m/Z 214 (M+H).

Reference Example 109

3-(4-Ethylphenylmethyl)-1H-indole

(1) To a solution of indole (6.00 g) in methanol (60 ml) were added sodium hydroxide (2.25 g) and 4-ethylbenzaldehyde (7.56 g), and the mixture was stirred at room temperature for 3 days under argon atmosphere. Added thereto was water, and methanol was evaporated under reduced pressure. The residue was extracted with diethyl ether, and the extract was washed with water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-70:30) to give 4-ethylphenyl-(1H-indol-3-yl)methanol (2.10 g) as a colorless solid. APCI-Mass m/Z 234 (M+H−H_2O).

(2) The above 4-ethylphenyl-(1H-indol-3-yl)methanol was treated in a manner similar to Reference Example 1-(2) to give the desired 3-(4-ethylphenylmethyl)-1H-indole as colorless crystals. APCI-Mass m/Z 236 (M+H).

Reference Example 110

3-(4-Ethylphenylmethyl)-1H-indazole

(1) A mixture of zinc powder (712 mg) and dibromoethane (0.04 ml) in N,N-dimethylformamide (2.5 ml) were stirred under heating at 70° C. for 10 minutes under argon atmosphere. The reaction mixture was cooled to room temperature, and chlorotrimethylsilane (0.04 ml) was added thereto, and the mixture was stirred at room temperature for 30 minutes. To the activated zinc solution was added dropwise a solution of 4-ethylbenzyl bromide (1.74 g) in N,N-dimethylformamide (10 ml) at 0° C. over a period of 2 hours. Subsequently, the mixture was stirred at 0° C. for 2 hours, to prepare a solution of 4-ethylbenzylzinc bromide in N,N-dimethylformamide, which was used in the subsequent step without further purification.

(2) A solution of tris(dibenzylideneacetone)dipalladium (0) (167 mg) and tri(2-furyl)phosphine (135 mg) in tetrahydrofuran (20 ml) was stirred at room temperature for 5 minutes under argon atmosphere. Thereto were added 1-t-butoxycarbonyl-3-iodo-1H-indazole (2.0 g) and the above 4-ethylbenzylzinc bromide (N,N-dimethylformamide solution) at 0° C., and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into water, and the mixture was extracted with diethyl ether. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-92:8) to give 1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.37 g) as colorless oil. APCI-Mass m/Z 337 (M+H).

(3) The above 1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.35 g) was dissolved in methanol (15 ml), and added thereto was 28% sodium methoxide solution (methanol solution, 1.0 ml), and the mixture was stirred at room temperature for one hour. Added thereto was an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from hexane to give the desired 3-(4-ethylphenylmethyl)-1H-indazole (800 mg) as colorless crystals. APCI-Mass m/Z 237 (M+H).

Reference Example 111

5-Bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 4-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-trifluoromethylphenyl)thiophene as colorless crystals.

(2) The above 2-(4-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 425/427 (M+H+MeOH).

Reference Example 112

5-Bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 3-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-trifluoromethylphenyl)thiophene as colorless oil.

(2) The above 2-(3-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienylmethyl)benzene as colorless oil.

Reference Example 113

2-(4-Ethylphenyl)thiophene

2-Bromothiophene and 4-ethylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

Reference Example 114

2-(4-Methylphenyl)thiophene

2-Bromothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

Reference Example 115

2-(2,3-Dihydro-5-benzo[b]furanyl)thiophene

(1) 5,7-Dibromo-2,3-dihydrobenzo[b]furan (see WO 02/070020) (3.0 g) in diethyl ether was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.09 ml). The mixture was stirred at the same temperature for 30 minutes, and poured into a saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2,3-dihydrobenzo[b]furan (2.0 g) as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2,3-dihydrobenzo[b]furan and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give the desired 2-(2,3-dihydro-5-benzo[b]furanyl)thiophene as pale yellow crystals. APCI-Mass m/Z 203 (M+H).

Reference Example 116

4-Bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (1.04 g) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.58 M hexane solution, 4.43 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 1-bromo-4-fluoronaphthalene (1.50 g) in tetrahydrofuran (12 ml) at −78° C. The mixture was stirred at the same temperature for one hour, and thereto was added dropwise a solution of 5-chloro-2-thiophenecarboxaldehyde (1.07 g) in tetrahydrofuran (11 ml) at −78° C. The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by an aminosilane-treated silica gel column chromatography (hexane:ethyl acetate=3:1) to give 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol (2.00 g) as pale yellow powder. APCI-Mass m/Z 353/355 (M+H−H_2O).

(2) The above 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol was treated in a manner similar to Reference Example 1-(2) to give the desired 4-bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene as a yellow solid.

Reference Example 117

5-Bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl)benzene

(1) 2,4-dimethylbenzoic acid (20.0 g) was suspended in chloroform (100 ml), and thereto were added oxalyl chloride (6.8 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol (200 ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give methyl 2,4-dimethylbenzoate as pale yellow oil, which was used in the subsequent step without further purification.

(2) To a mixture of the above methyl 2,4-dimethylbenzoate (19.75 g) and activated aluminum neutral oxide (120 g) was added dropwise bromine (9.25 ml) while stirring at room temperature. The mixture was stirred at room temperature for 8 hours, and diluted with diethyl ether (1000 ml). Insoluble materials were filtered off, and washed with diethyl ether (500 ml). The combined filtrate was washed successively with 10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol (40 ml) to give methyl 5-bromo-2,4-dimethylbenzoate (6.34 g) as colorless crystals. APCI-Mass m/Z 243/245 (M+H).

(3) The above methyl 5-bromo-2,4-dimethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2,4-dimethylbenzoic acid as colorless crystals. ESI-Mass m/Z 227/229 (M−H)

(4) The above 5-bromo-2,4-dimethylbenzoic acid and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 357/359 (M+H).

Reference Example 118

5-Bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 117-(1) to give methyl 5-bromo-2-iodobenzoate as a brown solid.

(2) To a solution of the above methyl 5-bromo-2-iodobenzoate (4.65 g) in N-methyl-2-pyrrolydinone (20 ml) were added copper (I) bromide (235 mg) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.6 ml), and the mixture was stirred under heating at 120° C. for 1.5 hours. The reaction mixture was cooled, and added thereto were 10% aqueous hydrochloric acid solution and ethyl acetate. Insoluble materials were filtered off, and an organic layer of the filtrate was washed with water for 4 times, and subsequently washed with a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexan:ethyl acetate=80:1) to give methyl 5-bromo-2-trifluoromethylbenzoate (3.55 g) as colorless oil.

(3) The above methyl 5-bromo-2-trifluoromethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2-trifluoromethylbenzoic acid as pale brown crystals. ESI-Mass m/Z 267/269 (M−H).

(4) The above 5-bromo-2-trifluoromethylbenzoic acid and 2-phenylthiophene were treated in a manner similar to Reference Example 5-(1) to give 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone as pale yellow crystals. APCI-Mass m/Z 411/413 (M+H).

(5) To a mixed solution of the above 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone (670 mg) in methanol (20 ml)-tetrahydrofuran (10 ml) was added sodium borohydride (62 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in chloroform (10 ml)-acetonitrile (20 ml). Thereto was added triethylsilane (0.78 ml), and the mixture was cooled to 0° C. Thereto was added dropwise boron trifluoride.diethyl ether complex (0.52 ml). The mixture was stirred at room temperature for 45 minutes, and added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give the desired 5-bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethylbenzene (565 mg) as colorless oil.

Reference Example 119

5-Bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methylbenzene

(1) 1-Bromo-3-ethylbenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethylphenyl)thiophene as a pale yellow liquid.

(2) The above 2-(3-ethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give 5-bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methylbenzene as pale yellow oil. APCI-Mass m/Z 371/373 (M+H).

Reference Example 120

5-Bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl) benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol as colorless oil. APCI-Mass m/Z 360/362 (M+H).

(2) A solution of the above 5-bromo-2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol (1.59 g) in trifluoroacetic acid (40 ml) was cooled to 0° C., and thereto were added gradually sodium triacetoxyborohydride (4.68 g). The mixture was stirred at room temperature for one hour, and cooled again to 0° C. 10% aqueous sodium hydroxide solution was added thereto to basify the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give the desired 5-bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl)benzene (1.38 g) as a colorless solid. APCI-Mass m/Z 344/346 (M+H).

Reference Example 121

2-(5-Fluoro-2-thienyl)thiophene

2,2'-Bithiophene (7.40 g) in tetrahydrofuran (90 ml) was cooled to −78° C. under argon atmosphere, and thereto were added dropwise n-butyl lithium (1.59 M hexane solution, 28.0 ml). The mixture was stirred at 0° C. for one 30 minutes, and cooled again to −78° C. Added thereto was N-fluorobenzenesulfonimide (15.5 g), and the mixture was gradually warmed, and stirred at room temperature for 17 hours. The reaction mixture was poured into ice-cold water, and the solution was extracted with hexane twice, and the extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-fluoro-2-thienyl) thiophene (5.89 g) as colorless oil.

Reference Example 122

5-Bromo-2-methyl-1-(5-(3-pyridyl)-2-thienylmethyl) benzene

2-(3-Pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the target compound as colorless crystals. APCI-Mass m/Z 344/346 (M+H).

Reference Example 123

5-Bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) p-Bromoanisole and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-methoxyphenyl)thiophene as a pale yellow solid. APCI-Mass m/Z 191 (M+H).

(2) The above 2-(4-methoxyphenyl)thiophene and 4-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene as a pale yellow solid. APCI-Mass m/Z 373/375 (M+H).

Reference Example 124

5-bromo-2-methyl-1-(5-(1,2-Methylenedioxybenzen-4-yl)-2-thienylmethyl)benzene

4-Bromo-1,2-(methylenedioxy)benzene was treated in a manner similar to Reference Example 119 to give the target compound as colorless powder.

Reference Example 125

5-Bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl) benzene

(1) To a solution of 5-bromo-2-chlorobenzyl alcohol (10.66 g) in toluene (100 ml) solution were added thionyl chloride (10 ml), and pyridine (2 drops), and the mixture was stirred under heating at 100° C. overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, a 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride was dissolved in acetonitrile (100 ml), and the mixture was cooled to 0° C. Added thereto was tetraethylammonium cyanide (8.8 g), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetonitrile as a pale yellow solid, which was used in the subsequent step without further purification.

(3) The above 5-bromo-2-chlorophenylacetonitrile was added to water (90 ml)-sulfuric acid (75 ml), and the mixture was stirred under heating at 160° C. overnight. The mixture was further diluted with water, and cooled to 0° C. The solvent was removed by decant, and the residue was dissolved in diethyl ether. The solution was washed with water and brine, and extracted with 10% sodium hydroxide. To the extract was added concentrated hydrochloric acid to make the solution acidic. The precipitates were collected by filtration, and purified by silica gel column chromatography (chloroform) to give 5-bromo-2-chlorophenylacetic acid (6.67 g) as colorless crystals. ESI-Mass m/Z 247/249 (M−H).

(4) The above 5-bromo-2-chlorophenylacetic acid was treated in a manner similar to Reference Example 118-(4) and (5) to give the desired 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)benzene as a pale yellow solid. APCI-Mass m/Z 377/379 (M+H).

Reference Example 126

5-Bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl) 2methylbenzene

(1) 2-Bromo-6-fluoropyridine and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(6-fluoro-2-pyridyl)thiophene as yellow oil. APCI-Mass m/Z 180 (M+H).

(2) The above 2-(6-fluoro-2-pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the desired 5-bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl)-2-methylbenzene as a colorless solid. APCI-Mass m/Z 362/364 (M+H).

Reference Example 127

5-Bromo-2-methyl-1-(5-trifluoromethyl-2-thienylmethyl)benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the target compound as colorless oil.

Reference Example 128

5-Bromo-1-(5-(5-fluoro-2-thienyl)-2-thienylmethyl)-2-methylbenzene

5-Bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) and 2-(5-fluoro-2-thienyl)thiophene obtained in Reference Example 121 were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

Reference Example 129

3-Bromo-2-fluoro-6-methyl-1-(5-phenyl-2-thienylmethyl)benzene

4-Bromo-3-fluorotoluene and 5-phenyl-2-thiophenecarboxaldehyde were treated in a manner similar to Reference Example 116 to give the target compound as pale blue powders. APCI-Mass m/Z 361/363 (M+H).

Reference Example 130

5-Bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl) benzene

(1) 5-Bromo-2-chlorophenylacetic acid (2.0 g) obtained in Reference Example 125-(3) was dissolved in dichloromethane (40 ml), and thereto were added oxalyl chloride (0.77 ml) and N,N-dimethylformamide (one drop) at 0° C. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetyl chloride, which was used in the subsequent step without further purification.

(2) A solution of potassium t-butoxide (1.35 g) in tetrahydrofuran (20 ml) was cooled to 0° C., and thereto was added methyl isocyanoacetate (1.33 ml). Then, a solution of the above 5-bromo-2-chlorophenylacetyl chloride in tetrahydrofuran (20 ml) was added thereto, and the mixture was stirred at 0° C. for 2 hours, and then at room temperature overnight. The mixture was cooled again to 0° C. 10% aqueous citric acid solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)benzene (1.12 g) as a yellow solid. APCl-Mass m/Z 330/332 (M+H).

(3) The above 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)benzene (1.37 g) was heated under reflux in 6N aqueous hydrochloric acid solution (20 ml) overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol, and treated with carbon powder. The carbon powder was filtered off, and the filtrate was evaporated under reduced pressure to give crude 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene.hydrochloride (1.73 g) as a pale brown solid, which was used in the subsequent step without further purification. APCl-Mass m/Z 262/264 (M+H).

(4) A mixed solution of the above 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene.hydrochloride (1.70 g) in ethyl acetate (30 ml)-water (15 ml) was cooled to 0° C. Added thereto were benzoyl chloride (0.99 ml) and sodium hydrogen carbonate (2.39 g), and the mixture was stirred at the same temperature for 3 hours. The organic layer was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:ethyl acetate=95:5) to give 1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) as a colorless solid. APCI-Mass m/Z 366/368 (M+H).

(5) To a solution of the above 1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) in toluene (20 ml) was added Lawesson reagent (2.35 g), and the mixture was heated under reflux for 2 hours. The reaction mixture was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10) to give the desired 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene (512 mg) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 131

t-Butyl 5-bromo-2-chlorobenzoic acid

To a solution of 5-bromo-2-chlorobenzoic acid (11.75 g) in N,N-dimethylformamide (50 ml) was added 1,1'-carbonyldiimidazole (8.10 g), and the mixture was stirred under heating at 40° C. for one hour. Thereto were added t-butanol (7.40 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (7.60 g), and the mixture was further stirred under heating at 40° C. overnight. The mixture was diluted with diethyl ether, and washed successively with water (3 times), 2% aqueous hydrochloric acid solution (twice), a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give t-butyl 5-bromo-2-chlorobenzoate (12.53 g) as pale yellow oil.

Reference Example 132

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

(1) A solution of 5-bromo-2-chloro-1(6-methoxybenzo[b]thiophen-2-ylmethyl)benzene (2.70 g) obtained in Reference Example 46 in dichloromethane (27 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise boron tribromide (0.83 ml). The mixture was warmed to room temperature, and stirred for 30 minutes. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and subsequently, the reaction mixture was made acidic with a saturated aqueous citric acid solution. The mixture was extracted with chloroform, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from chloroform-hexane to give 5-bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene (2.01 g) as pale green crystals. ESI-Mass m/Z 351/353 (M−H).

(2) The above 5-bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene (500 mg) was dissolved in N,N-dimethylformamide (5 ml), and thereto were added iodoethane (0.23 ml) and potassium carbonate (390 mg). The mixture was stirred at room temperature for 2 days. Added thereto was water, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-80:20) to give the desired 5-bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene (492 mg) as pale pink oil. APCI-Mass m/Z 381/383 (M+H).

Reference Example 133

5-Bromo-2-chloro-3-(5-phenyl-2-thienylmethyl)thiophene

5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

Reference Example 134

6-Fluoro-2-pyridylboronic acid pinacol ester

A solution of 2-bromo-6-fluoropyridine (1.0 g) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere. and thereto was added a solution of n-butyl lithium (2.59 M hexane solution, 2.24 ml) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 45 minutes, and thereto was added dropwise a solution of triisopropoxyborane (1.28 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 2 hours, warmed, and further stirred at room temperature for one hour. Subsequently, a solution of pinacol (0.91 g) in tetrahydrofuran (10 ml) was added dropwise thereto, and stirred at room temperature for 20 minutes. Insoluble materials were filtered off. The filtrate was extracted with 2.5% sodium hydroxide, and the extract was cooled to 0° C., and was made weakly acidic with 2N aqueous hydrochloric acid solution. It was extracted with diethyl ether, washed with a small amount of brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was solidified with hexane to give 6-fluoro-2-pyridylboronic acid pinacol ester (850 mg) as a colorless solid. APCI-Mass m/Z 224 (M+H).

Reference Example 135

5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-chlorobenzamide as a colorless solid. APCI-Mass m/Z 278/280 (M+H).

(2) The above N-methoxy-N-methyl-5-bromo-2-chlorobenzamide and 2,5-dibromopyridine were treated in a manner similar to Reference Example 31-(4) to give 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone as a pale yellow solid. APCI-Mass m/Z 374/376 (M+H).

(3) The above 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone and phenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone as yellow crystals. APCI-Mass m/Z 372/374 (M+H).

(4) The above 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene as colorless crystals. APCI-Mass m/Z 358/360 (M+H).

Reference Example 136

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene obtained in Reference Example 132-(1) and 2-iodopropane were treated in a manner similar to Reference Example 132-(2) to give the titled compound. APCI-Mass m/Z 395/397 (M+H).

Reference Example 137

4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl)naphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (4.13 ml) in tetrahydrofuran (40 ml) was cooled to −78° C. under argon atmosphere, and added dropwise thereto was n-butyl lithium (2.44 M hexane solution, 10.0 ml). The mixture was stirred at the same temperature for 30 minutes, and added dropwise thereto at −78° C. was a solution of 1-bromo-4-fluoronaphthalene (5.0 g) in tetrahydrofuran (20 ml). The mixture was stirred at the same temperature for 1 hour, and added dropwise thereto at −78° C. was N,N-dimethylformamide (5.16 ml). The mixture was stirred at the same temperature for 1 hour, and added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from diisopropyl ether and hexane to give 4-bromo-1-fluoro-2-naphthaldehyde (4.43 g) as pale yellow crystals. APCI-Mass m/Z 267/269 ($M+NH_4$).

(2) The above 4-bromo-1-fluoro-2-naphthaldehyde and 2-(2-pyridyl)thiophene were treated in a manner similar to Reference Example 120 to give the desired 4-bromo-1fluoro-2-(5-(2-pyridyl)-2-thienylmethyl)naphthalene as colorless powder. APCI-Mass m/Z 398/400 (M+H).

Reference Example 138

5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene

(1) 5-Bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone (3.2 g) from Reference Example 135-(2) was dissolved in tetrahydrofuran (80 ml), and added thereto were triethylaluminium (1.0 M hexane solution, 9.9 ml), tetrakis(triphenylphosphine)palladium(0) (570 mg) and cerium(III) chloride (7.3 g), and the mixture was stirred at 30° C. for 1.5 hours. The reaction mixture was diluted with methanol, and the reaction solution was basified with a saturated aqueous sodium hydrogen carbonate solution. The insoluble materials were filtered off and, the filtrate was extracted with ethyl acetate and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=99:1-85:15) to give 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone (1.98 g) as a colorless solid. APCI-Mass m/Z 324/326 (M+H).

(2) The above 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene as a colorless oil. APCI-Mass m/Z 310/312 (M+H).

Reference Example 139

6-Ethylbenzo[b]thiophene

(1) 4-Bromo-2-fluorobenzaldehyde and ethyl thioglycolate were treated in a manner similar to Reference Example 31-(1) to give 6-bromo-2-ethoxycarbonylbenzo[b]thiophene as a colorless solid.

(2) The above 6-bromo-2-ethoxycarbonylbenzo[b]thiophene was treated in a manner similar to Reference Example 138-(1) to give 6-ethyl-2-ethoxycarbonylbenzo[b]thiophene as colorless oil. APCI-Mass m/Z 235 (M+H).

(3) The above 6-ethyl-2-ethoxycarbonylbenzo[b]thiophene (1.26 g) was dissolved in tetrahydrofuran (4 ml) and methanol (8 ml), and added thereto was lithium hydroxide monohydrate (677 mg), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in water and the solution was made acidic with a 10% aqueous hydrochloric acid solution. The precipitates were collected by filtration and washed with water to give 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid (1.15 g) as colorless crystals. ESI-I-Mass m/Z 205 (M−H).

(4) The above 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid was tread in a manner similar to Reference Example 47-(2) to give the desired 6-ethylbenzo[b]thiophene as colorless oil.

Reference Example 140

5-Bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl)benzene

(1) 5-Bromo-2-chlorobenzyl alcohol (3.0 g) was dissolved in toluene (30 ml), and added thereto were thionyl chloride (2.35 ml) and pyridine (two drops), and the mixture was heated under stirring at 100° C. for 2 hours. The mixture was cooled, washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride (3.34 g) as pale brown oil, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride (3.34 g) was dissolved in N,N-dimethylformamide (30 ml), and added thereto was potassium phthalimide (2.63 g), and the mixture was heated under stirring at 70° C. for 3 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from diisopropyl ether to give 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl)benzene (3.33 g) as colorless crystals. APCI-Mass m/Z 350/352 (M+H).

(3) The above 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl)-benzene (4.3 g) was dissolved in acetic acid (43 ml), and added thereto was zinc powder (8.02 g), and the mixture was heated at reflux for 3 days. The mixture was cooled and diluted with chloroform and it was basified with an aqueous sodium hydroxide solution. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=6:1-4:1) to give the desired 5-bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl)benzene (1.39 g) as colorless powder. APCI-Mass m/Z 336/338 (M+H).

Reference Example 141

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene

(1) A solution of 1-phenyl-4-bromopyrazole (see M. A. Khan, et al., Can. J. Chem., (1963) 41 1540) (2.23 g) in diethyl ether (30 ml) wad cooled to −78° C. under argon atmosphere, and added dropwise thereto was n-butyl lithium (1.59 M hexane solution, 6.9 ml). The mixture was stirred at −20° C. to −10° C. for 5 hours, and added dropwise thereto at the same temperature was a solution of 5-bromo-2-chlorobenzaldehyde (2.19 g) obtained in Reference Example 16-(1) in diethyl ether (30 ml). The mixture was stirred at the same temperature for 30 minutes, and added thereto was tetrahydrofuran (30 ml), and the mixture was stirred at 0° C. for further 30 minutes. A saturated aqueous ammonium chloride solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=83:17-80:20) to give 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol (831 mg) as yellow oil. APCI-Mass m/Z 363/365 (M+H).

(2) The above 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol was treated in a manner similar to Reference Example 120-(2) to give the desired 5-bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene as colorless powder. APCI-Mass m/Z 347/349 (M+H).

Reference Example 142

5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 132-(1) and

1-bromopropane were treated in a manner similar to Reference Example 132-(2) to give the target compound. APCI-Mass m/Z 395/397 (M+H).

Reference Example 143

5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene obtained in Reference Example 132-(1) and 1-bromo-2-fluoroethane were treated in a manner similar to Reference Example 132-(2) to give the target compound. APCI-Mass m/Z 399/401 (M+H).

Reference Example 144

5-Tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in WO 03/087104.

Reference Example 145

4-Tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in WO 03/087104.

Reference Example 146

Tri-n-butyl(6-methoxy-2-pyridyl)tin

The target compound was prepared according to a method described in P. Gros, et al., *Synthesis* (1999) 754.

Reference Example 147

5-Bromo-2-chloro-1-(5-ethoxybenzo[b]thiophen-2-ylmethyl)-benzene

(1) 5-Bromo-2-chloro-1-(5-methoxybenzo[b]thiophene-2-yl methyl)benzene obtained in Reference Example 54 was treated in a manner similar to Reference Example 132-(1) to give 5-bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene. ESI-Mass m/Z 351/353 (M−H).

(2) The above 5-bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)benzene and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-Bromo-2-chloro-1-(5-ethoxybenzo[b]thiophene-2-ylmethyl)-benzene. APCI-Mass m/Z 382/380 (M+H).

Reference Example 148

5-Bromo-2-chloro-1-(5-(1-pyrazolyl)-2-thienylmethyl)benzene

1-(2-thienyl)pyrazole (see: Chemica Scripta (1979) 13, 157-161) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 7 to give the title compound as colorless solid. APCI-Mass m/z 353/355 (M+H).

Reference Example 149

5-Bromo-2-chloro-1-(tert-butyldiphenylsilyloxymethyl)benzene

To a solution of 5-Bromo-2-chlorobenzylalcohol (5.15 g) in N,N-dimethylformamide (50 ml) was added diisopropylethylamine (19.8 ml) and tert-butyldiphenylchlorosilane (11.9 ml), and the mixture was stirred at room temperature for 2 days. Under ice-cooling, to the mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with successively with 0.4 M aqueous hydrochloric acid solution (twice), water, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by an aminosilane-treated silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(tert-butyldiphenylsiloxymethyl) benzene 77 (10.79 g) as colorless oil. APCI-Mass m/Z 476/478 ($M+NH_4$).

Reference Example 150

2-Fluoropyridin-4-boronic acid

The target compound was prepared according to a method described in *Tetrahedron* (2002) 58, 4369-4373.

Reference Example 151

3-Difluoromethoxybenzeneboronic acid

A solution of 3-(difluoromethoxy)benzene (3.0 g) and triisopropoxyborane (2.78 g) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (1.59 M hexane solution, 9.3 ml). The mixture was stirred at same temperature for 10 minutes, warmed, and further stirred at room temperature overnight. Thereto was added 3N aqueous hydrochloric acid solution (10 ml), and the mixture was stirred at room temperature for 5 minutes. The mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from hexane to give 3-difluoromethoxybenzeneboronic acid (1.6 g) as colorless crystals.

Reference Example 152

Tri-n-butyl(2-cyano-5-pyridyl)tin

5-Bromo-2-cyanopyridine was treated in a manner similar to the methods described in European Patent Publication No. 93-00867.

Reference Example 153

5-Bromo-2-chloro-1-(6-difluoromethoxybenzo[b]thiophen-2-yl-methyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene (1.8 g) obtained in Reference Example 132-(1) was dissolved in dimethylformamide (15 ml), and added thereto were methyl 2-chloro-2,2-difluoroacetate (1.63 ml) and potassium carbonate (2.28 g), and the mixture was stirred at 100° C. for 1.5 hours under argon atmosphere. The reaction mixture was acidified with 2N aqueous HCl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(6-difluoromethoxybenzo[b]thiophen-2-yl-methyl)benzene (695 mg) as a colorless solid. GC-Mass m/Z 402/404 (M+).

Reference Example 154

5-Bromo-1-(6-difluoromethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

(1) 6-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give 5-Bromo-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene. APCI-Mass m/Z 347/349 ($M+NH_4$).

(2) The above 5-bromo-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene was treated in a manner similar to Reference Example 132-(1) to give 5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene. ESI-Mass m/Z 331/333 (M−H).

(3) The above 5-bromo-1-(6-hydroxybenzo[b]thiophen-2-yl-methyl)-2-methylbenzene was treated in a manner similar to Reference Example 153 to give the desired 5-bromo-1-(6-difluoromethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene as colorless oil. GC-Mass m/Z 382/384 (M+).

Reference Example 155

(6-Cyanopyridin-2-yl)trimethyltin

2-Bromo-6-cyanopyridine (see Japanese Patent Publication 04-253974) (1.5 g) and hexamethylditin (2.69 g) were dissolved in dimethoxyethane (50 ml) and thereto was added tetrakis(triphenylphosphine)palladium(0) (972 mg). The mixture was refluxed for 5 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:1) to give (6-cyanopyridin-2-yl)trimethyltin (980 mg) as colorless oil. APCI-Mass m/Z 265/267/269 (M+H).

Reference Example 156

5-Bromo-2-methyl-1-(5-(1-pyrazolyl)-2-thienylmethyl)benzene

1-(2-thienyl)pyrazole (see Chemica Scripta (1979) 13, 157-161) and 5-bromo-2-methybenzaldehyde obtained in Reference Example 4 were used and treated in a manner similar to Reference Example 7 to give the title compound as colorless oil. APCI-Mass m/z 333/335 (M+H).

Reference Example 157

5-Bromo-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene obtained in Reference Example 154-(2) and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(6-ethoxybenzo[b]thiophene-2-ylmethyl)-2-methylbenzene as pale yellow wax. APCI-Mass m/Z 361/363 (M+H).

Reference Example 158

5-Bromo-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give 5-bromo-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene as colorless wax.

Reference Example 159

5-Bromo-1-(5-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)-2-methylbenzene

(1) 5-Bromo-1-(5-methoxybenzo[b]thiophene-2-ylmethyl)-2-methylbenzene obtained in Reference Example 158 was treated in a manner similar to Reference Example 132-(1) to give 5-bromo-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methyl benzene as colorless powder. ESI-Mass m/Z 331/333 (M−H).

(2) The above 5-bromo-1-(5-hydroxybenzo[b]thiophen-2-yl-methyl)-2-methylbenzene and 1-bromo-2-fluoroethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(5-(2-fluoroethyloxy)-benzo[b]thiophene-2-ylmethyl)-2-methylbenzene.

Reference Example 160

5-Bromo-1-(5-ethoxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Bromo-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methylbenzene obtained in Reference Example 159-(1) and iodoethane were treated in a manner similar to Reference Example 132-(2) to give the desired 5-bromo-1-(5-ethoxybenzo[b]thiophene-2-ylmethyl)-2-methylbenzene as colorless powder.

Reference Example 161

5-Bromo-2-chloro-1-(5-(2-fluoroethyloxy)benzo[b]thiophene-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(5-hydroxybenzo[b]thiophen-2-ylmethyl)-benzene obtained in Reference Example 147-(1) and 1-bromo-2-fluoroethane were treated in a manner similar to Example 132-(2) to give the target compound.

Reference Example 162

5-Bromo-1-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)-2-methylbenzene

5-Bromo-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)-2-methyl benzene obtained in Reference Example 154-(2) and 1-bromo-2-fluoroethane were treated in a manner similar to Example 132-(2) to give the target compound as colorless wax. APCI-Mass m/Z 379/381 (M+H).

Reference Example 163

4-(Difluoromethoxy)phenylboronic acid

A solution of (4-bromophenoxy)difluoromethane (3 g) and triisopropyl borate (3.42 ml) in tetrahydrofuran (15 ml) was cooled to −78° C. under argon atmosphere, and thereto was added a solution of n-butyl lithium (1.59 M hexane solution, 3.42 ml). The mixture was stirred at room temperature overnight. Added thereto was 6N aqueous hydrochloric acid at 0° C., and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure,

and the residue was triturated with cold hexane to give 4-(difluoromethoxy)phenylboronic acid (1.88 g) as colorless solid.

Reference Example 164

Tri-n-butyl(3-methyl-5-isooxazolyl)tin

The target compound was prepared according to a method described in Bioorg. & Med. Chem. Lett. (2003) 13, 4117-4120.

Reference Example 165

5-Bromo-2-chloro-1-(2-trifluoromethyl-5-pyridylmethyl)benzene

(1) A solution of 5-Bromo-2-trifluoromethylpyridine (5.3 g) (see Eur. J. Org. Chem. (2003) 1159-1168) in tetrahydrofuran (70 ml) was cooled to 0° C. under argon atmosphere, and thereto was added dropwise isopropylmagnesium chloride (1 mol/l tetrahydrofuran solution, 23.45 ml). The reaction mixture was stirred at the same temperature for 2 hours, and thereto was added dropwise a solution of 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) (5.15 g) in tetrahydrofuran (20 ml). The mixture was stirred at the same temperature for 60 minutes, and thereto was added a saturated ammonium chloride solution, and the reaction mixture was warmed to room temperature. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-85:15) to give (5-Bromo-2-chloro)phenyl-(2-trifluoromethyl-5-pyridyl)methanol (4.56 g) as a pale brown syrup. APCI-Mass m/Z 366/368 (M+H).

(2) The above (5-Bromo-2-chloro)phenyl-(2-trifluoromethyl-5-pyridyl)methanol (4.55 g) was dissolved in dichloromethane (50 ml) and toluene (50 ml), and added thereto was manganese(IV) oxide (5.39 g), and the mixture was stirred at room temperature overnight. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2-92:8) to give (5-Bromo-2-chloro)phenyl (2-trifluoromethyl-5-pyridyl)ketone (2.64 g) as a pale yellow syrup. APCI-Mass m/Z 364/366 (M+H).

(3) The above (5-Bromo-2-chloro)phenyl (2-trifluoromethyl-5-pyridyl)ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-Bromo-2-chloro-1-(2-trifluoromethyl-5-pyridylmethyl)benzene. APCI-Mass m/Z 350/352 (M+H).

Reference Example 166

4-Methyl-2-tributylstannanylthiazole

A solution of n-butyl lithium (2.71 M hexane solution, 3.9 ml) in tetrahydrofuran (10 ml) was cooled to −78° C. under argon atmosphere. and thereto was added dropwise a solution of 4-methylthiazole (1.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at same temperature for one hour and thereto was added dropwise a solution of tri-n-butyltin chloride (3.6 g) in tetrahydrofuran (10 ml). The mixture was stirred at same temperature for 30 minutes, warmed, and further stirred at room temperature overnight. Thereto was added water, and the mixture was extracted with diethyl ether. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by alumina column chromatography (hexane) to give the title compound (1.76 g) as oil. APCI-Mass m/z 386/388 (M+H)

Reference Example 167

2-Fluoropyridine-3-boronic acid

The target compound was prepared according to a method described in Tetrahedron (2002) 58, 3323-3328.

Reference Example 168

4-Bromo-2-(5-chloro-2-thienylmethyl)-1-methoxynaphthalene

2,4-Dibromo-1-methoxynaphthalene (see *Org. Lett.* (2003) 5, 831) and 5-chloro-2-thiophenecarboxaldehyde were treated in a manner similar to Reference Example 1 to give 4-Bromo-2-(5-chloro-2-thienylmethyl)-1-methoxynaphthalene.

Reference Example 169

2-(2-(6-Chloro)pyridine)-4,4,5,5-tetramethyl-1,3-dioxaborolane

The target compound was prepared according to a method described in *Tetrahedron* (2003) 59, 10043-10049.

Reference Example 170

2-Methyl-4-tri-n-butylstannanylthiazole

The target compound was prepared according to a method described in *Tetrahedron* (2003), 9979-9984.

Reference Example 171

2-(4-(2-Methyl)pyridine)-4,4,5,5-tetramethyl-1,3-dioxaborolane

The target compound was prepared according to a method described in United States Patent Publication No. 2003-024914.

Reference Example 172

1-(β-D-glucopyranosyl)-5-chloroindole

5-Chloro-2,3-dihydro-(1H)-indole was treated in a manner similar to the methods described in Eur. J. Med. Chem. (2004) 39, 453-458 to give the title compound. APCI-Mass m/z 314/316 (M+H)

Reference Example 173

5-Bromo-2-chloro-1-(5-(5-fluorothiazol-2-yl)-2-thienylmethyl)benzene

(1) 2-Bromothiazole (15.0 g) and 2-thiopheneboronic acid (14.0 g) were dissolved in dimethoxyethane (150 ml). To the mixture was added bis(triphenyl)phosphine palladium(II)dichloride (3.2 g) and 2M sodium carbonate (137 ml), and the mixture was refluxed under argon atmosphere for 2 hours.

The mixture was cooled to room temperature, and the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was collected, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=96:4) to give 2-(2-thienyl) thiazole (9.87 g) as oil. APCI-Mass m/z 168 (M+H)

(2) The above compound (3.17 g) was treated in a manner similar to Reference Example 121 to give 5-fluoro-2-(2-thienyl)thiazole (1.58 g) as oil. APCI-Mass m/z 186 (M+H)

(3) The above compound (1.58 g) was dissolved in chloroform (16 ml), cooled to 0° C., and thereto was added dropwise a solution of bromine (1.43 g) in chloroform (15 ml). The mixture was stirred at the same temperature for one hour, warmed, and further stirred at room temperature for one hour. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform. The extract was washed with 10% aqueous sodium thiosulfate solution, brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=97:3) to give 2-(5-bromo-2-thienyl)-5-fluorothiazole (1.81 g) as a pale yellow solid.

(4) The above compound (300 mg) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-chloro-1-(5-(5-fluorothiazol-2-yl)-2-thienylmethyl)benzene (199 mg) as a pale yellow powder.

Reference Example 174

1-(β-D-glucopyranosyl)-4-chloroindole

(1) 4-Chloroindole (3.15 g) was dissolved in trifluoroacetic acid (32 ml), thereto was added triethylsilane (8.3 ml) and the mixture was heated at 50° C. with stirring for 30 minutes. The resultant mixture was cooled to room temperature, and trifluoroacetic acid was evaporated under reduced pressure. To the residue was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate twice. The organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0-80:20) to give 4-chloro-2,3-dihydro-(1H)-indole (2.89 g) as colorless oil. APCI-Mass m/z 154/156 (M+H)

(2) The above 4-chloro-2,3-dihydro-(1H)-indole was treated in a manner similar to described in Eur. J. Med. Chem. (2004) 39, 453-458 to give the title compound. APCI-Mass m/z 314/316 (M+H)

Reference Example 175

1-(β-D-glucopyranosyl)-6-chloroindole

6-Chloroindole was treated in a manner similar to Reference Example 174 to give the title compound. APCI-Mass m/z 314/316 (M+H).

Pharmacological Experiment

1. Assay for SGLT2 Inhibition

Test Compounds:

Compounds described in the above examples were used for the SGLT2 inhibition assay.

Method:

CHOK1 cells expressing human SGLT2 were seeded in 24-well plates at a density of 400,000 cells/well in F-12 nutrient mixture (Ham's F-12) containing 10% fetal bovine serum, 400 μg/ml Geneticin, 50 units/ml sodium penicillin G (Gibco-BRL) and 50 μg/ml streptomycin sulfate. After 2 days of culture at 37° C. in a humidified atmosphere containing 5% CO_2, cells were washed once with the assay buffer (137 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 50 mM Hepes, and 20 mM Tris, pH 7.4) and incubated with 250 μl of the buffer containing test compounds for 10 min at 37° C. Test compounds were dissolved in DMSO. The final concentration of DMSO was 0.5%. The transport reaction was initiated by addition of 50 μl [^{14}C]-methyl-α-D-glucopyranoside (^{14}C-AMG) solution (final concentration, 0.5 mM). After incubation for 2 hours at 37° C., the uptake was stopped by aspiration of the incubation mixture, the cells were washed three times with ice-cold PBS. Then, cells were solubilized with 0.3 N NaOH and aliquots were taken for determination of radioactivity by a liquid scintillation counter. Nonspecific AMG uptake was defined as that which occurred in the presence of 100 μM of phlorizin, a specific inhibitor of sodium-dependent glucose cotransporter. Specific uptake was normalized for the protein concentrations measured by the method of Bradford. The 50% inhibitory concentration (IC_{50}) values were calculated from dose-response curves by least square method.

Results:

Results are shown in the following table:

Test Compounds (Example No.)	IC50 (nM)
69	7.9
70	7.0
71	6.6
72	4.6
78	1.7
79	9.0
80	6.8
83	1.3
84	2.2
86	2.8
87	3.4
88	2.6
89	3.0
90	2.0
120	3.4
122	8.2
123	1.4
127	1.3
130	2.4
140	5.9
142	5.6
144	4.1
145	4.0
146	2.2
148	2.8
151	2.5
155	1.7
156	1.1
168	2.3
169	3.6
170	3.5
173	8.0
176	7.7

-continued

Test Compounds (Example No.)	IC50 (nM)
177	6.7
178	5.1
179	9.8
183	9.5
185	5.6
186	5.4
187	4.3
188	1.6
189	2.4
190	3.1
191	7.7
192	7.4
193	0.9
194	2.6
197	2.0
201	8.2
202	8.7
204	1.4
207	0.6
208	2.4
209	3.9
210	1.0
211	1.2
212	2.6
213	5.6
214	1.5
215	4.3
216	3.3
217	3.6
218	2.4
219	6.7
221	5.5
222	1.8
223	3.1
224	5.9
225	1.5
226	1.2
227	3.2
228	3.6
229	2.7
230	4.0
231	3.5
232	4.0
233	2.9
234	2.4
235	2.6
236	4.4
237	2.8
238	1.6
240	1.2
241	1.0
242	4.6
244	1.2
246	6.4
247	2.5
248	5.1
249	4.3
250	4.2
251	3.6
252	1.4
253	1.6
254	1.7
255	6.5
256	3.1
257	3.3
260	2.3
264	1.5
265	3.4
266	3.2
267	1.5
268	2.5

2. Urinary Glucose Excretion Test in Rats

Test Compounds:

Compounds described in the above examples were used for the urinary glucose excretion test in rats.

Methods:

6-week-old male Sprague-Dawley (SD) rats were housed in individual metabolic cages with free access to food and water from 2 days prior to the experiment. On the morning of the experiment, rats were administered vehicle (0.2% carboxymethyl cellulose solution containing 0.2% Tween80) or test compounds (30 mg/kg) by oral gavage at a volume of 10 ml/kg. Then, urine of the rat was collected for 24 hours, and the urine volume was measured. Subsequently, the glucose concentration in urine was quantified using the enzymatic assay kit and the daily amount of glucose excreted in urine per individual was calculated.

Results:

Urinary glucose amount ranges are depicted by A and B. These ranges are as follows: A≥2000 mg; 2000 mg>B≥1000 mg.

Test compounds (Example No.)	Urinary glucose
22	A
25	B
69	B
70	A
81	B
83	A
84	A
88	B
89	B
120	A
123	A
127	A
133	B
140	B
142	A
144	B
146	A
148	B
151	B
155	A
156	A
168	A
169	B
170	B
177	A
178	B
189	B
194	A
195	B
204	A
207	A
208	A
209	B
210	B
214	B
216	A
217	B
221	B
223	A
226	B
227	B
228	B
229	B
230	A
231	B
232	B
233	B
235	A
236	B
237	B
238	A
247	A

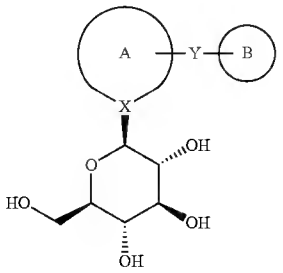
-continued

Test compounds (Example No.)	Urinary glucose
248	B
251	A
252	B

What is claimed is:

1. A pharmaceutical composition comprising

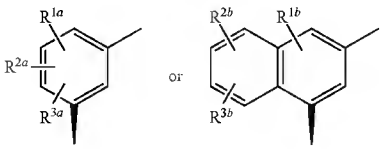
(i) a compound of Formula (I):



(I)

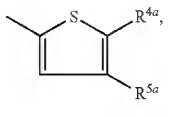
wherein

Ring A is



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



wherein R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, a mono- or di-alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, an alkyl group. a haloalkyl group, an alkoxy group, or a haloalkoxy group, where the heterocyclyl group is a thienyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, or a tetrazolyl group;

R^{5a} is a hydrogen atom;

X is a carbon atom; and

Y is $-(CH_2)_n-$ (wherein n is 1 or 2);

or a pharmaceutically acceptable salt thereof;

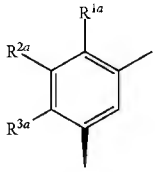
(ii) an antidiabetic agent selected from the group consisting of insulin, an insulin secretagogue, an insulin sensitizer, a biguanide compound, a sulfonylurea compound, an α-glucosidase inhibitor, a PPARγ agonist, a PPARα/γ dual agonist, a dipeptidyl peptidase IV inhibitor, a mitiglinide compound, a nateglinide compound, a glucagon-like peptide-1, a PTP1B inhibitor, a glycogen phosphorylase inhibitor, a RXR modulator, and a glucose 6-phosphatase inhibitor; and

(iii) a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim **1**, wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;

R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

3. The pharmaceutical composition according to claim **2**, wherein Ring A is

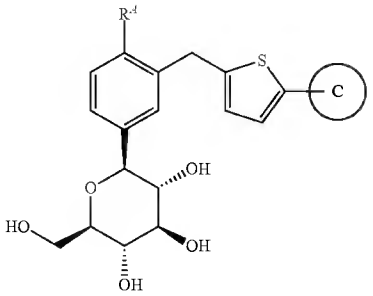


wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms;

R^{4a} is a phenyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, and Y is $-CH_2-$.

4. The pharmaceutical composition of claim **1**, wherein R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

5. The pharmaceutical composition according to claim **1**, wherein the compound is represented by the following formula:



wherein R^A is a halogen atom, or a lower alkyl group; and Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group; where the heterocyclyl group is a thienyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, or a tetrazolyl group; or a pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition according to claim **5**, wherein Ring C is a phenyl group substituted by 1-3 substituents selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

7. The pharmaceutical composition according to claim **5**, wherein Ring C is a phenyl group substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group.

8. The pharmaceutical composition according to claim **5**, wherein Ring C is a phenyl group substituted by a halogen atom or a cyano group, or a pyridyl group substituted by a halogen atom.

9. The pharmaceutical composition according to claim **1**, wherein the compound is selected from the group consisting of:

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethyl-phenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene; and

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene;

or a pharmaceutically acceptable salt thereof.

10. The pharmaceutical composition according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyano-phenyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

14. The pharmaceutical composition according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

15. The pharmaceutical composition according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

16. The pharmaceutical composition according to claim **1**, wherein the compound is 1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-3-pyridyl)-2-thienylmethyl]benzene, or a pharmaceutically acceptable salt thereof.

17. The pharmaceutical composition according to claim **1**, wherein said antidiabetic agent is a biguanide compound.

18. The pharmaceutical composition according to claim **1**, wherein said antidiabetic agent is a dipeptidyl peptidase IV inhibitor.

19. The pharmaceutical composition according to claim **1**, wherein said antidiabetic agent is insulin.

20. The pharmaceutical composition pharmaceutical composition according to claim **1**, wherein said antidiabetic agent is an insulin secretagogue.

21. The pharmaceutical composition according to claim **1**, wherein said antidiabetic agent is a sulfonylurea compound.

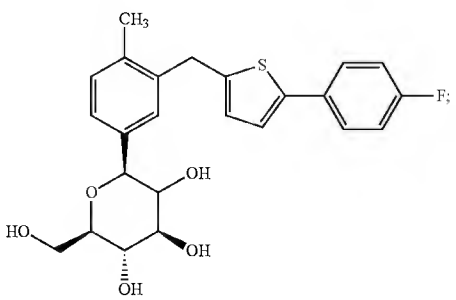
22. The pharmaceutical composition according the claim **1**, wherein said antidiabetic agent is an α-glucosidase inhibitor.

23. The pharmaceutical composition according to claim **1**, wherein said antiabetic agent is a PPARγ agonist.

24. The pharmaceutical composition according to claim **1**, wherein said antidiabetic agent is a PPARα/γ dual agonist.

25. A pharmaceutical composition comprising

(i) a compound having the following structure or a pharmaceutically acceptable salt thereof:



(ii) an antidiabetic agent selected from the group consisting of insulin, an insulin secretagogue, an insulin sensitizer, a biguanide compound, a sulfonylurea compound, an α-glucosidase inhibitor, a PPARγ agonist, a PPARα/γ dual agonist, a dipeptidyl peptidase IV inhibitor, a mitiglinide compound, a nateglinide compound, a glucagon-like peptide-1, a PTP1B inhibitor, a glycogen phosphorylase inhibitor, an RXR modulator, and a glucose 6-phosphatase inhibitor; and

(iii) a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim **25**, wherein the antidiabetic agent is a biguanide compound.

* * * * *

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 2021-1876

Short Case Caption: Mitsubishi Tanabe Pharma Corporation v. Zydus Pharmaceuticals (USA) Inc.

Filing Party/Entity: Defendant-Appellant Zydus Pharmaceuticals (USA) Inc.

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Date: July 6, 2021 Signature: /s/ Jay Deshmukh

Name: Jay Deshmukh