No. 19-2011

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CONCERT PHARMACEUTICALS, INC.,

Appellant,

v.

INCYTE CORPORATION,

Appellee,

KATHERINE K. VIDAL, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office

Intervenor.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board, No. IPR2017-01256

BRIEF OF APPELLANT CONCERT PHARMACEUTICALS, INC.

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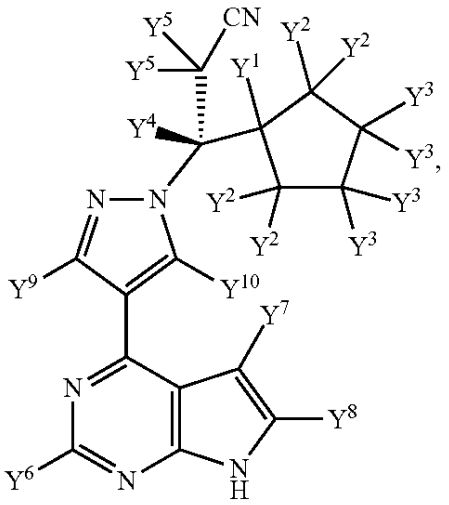
June 27, 2022

CLAIMS AT ISSUE

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is a hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9, and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

2. The compound of claim **1,** in which Y^4 is hydrogen and each Y^5 is hydrogen.

3. The compound of claim **1,** in which each Y^2 is deuterium and each Y^3 is hydrogen.

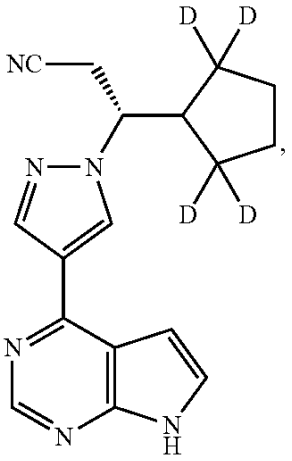
4. The compound of claim **1,** in which each Y^2 is hydrogen and each Y^3 is deuterium.

5. The compound of claim **1,** in which each Y^2 is deuterium and each Y^3 is deuterium.

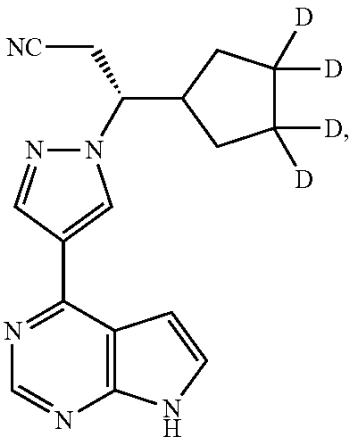
6. The compound of claim **1,** in which Y^6, Y^7 and Y^8 are each hydrogen.

7. The compound of claim **1,** in which the compound is selected from the group consisting of:

Compound 107

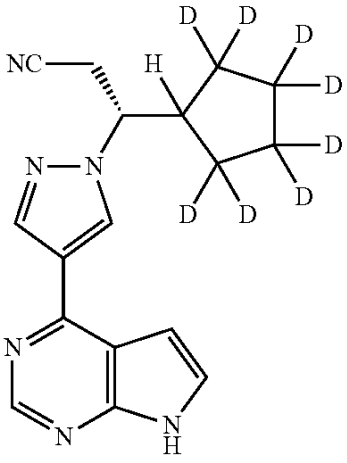


Compound 103



and

Compound 111

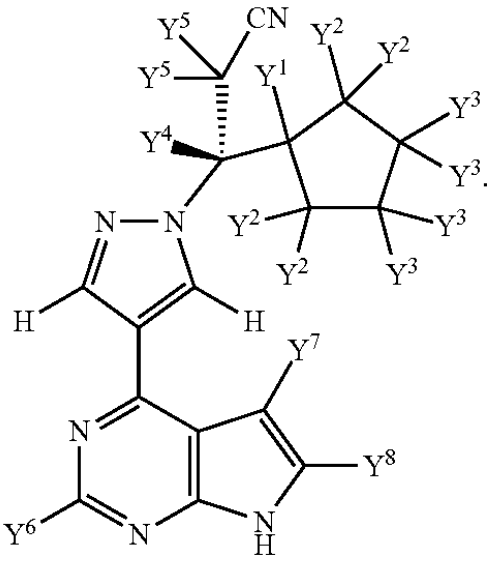


or a pharmaceutically acceptable salt of any of the foregoing.

8. A pharmaceutical composition comprising the compound of claim **1**, and a pharmaceutically acceptable carrier.

9. A compound of Formula I:

Formula I



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium; each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7 and Y^8 are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

10. The compound of claim **9**, in which Y^4 is hydrogen and each Y^5 is hydrogen.

11. The compound of claim **9**, in which each Y^2 is deuterium and each Y^3 is hydrogen.

12. The compound of claim **9**, in which each Y^2 is hydrogen and each Y^3 is deuterium.

13. The compound of claim **9**, in which each Y^2 is deuterium and each Y^3 is deuterium.

14. The compound of claim **9**, in which Y^6, Y^7 and Y^8 are each hydrogen.

15. A pharmaceutical composition comprising the compound of claim **9**, and a pharmaceutically acceptable carrier.

CERTIFICATE OF INTEREST

Counsel for Appellant Concert Pharmaceuticals, Inc., certifies the following:

1. **Represented Entities.** Provide the full names of all entities represented by undersigned counsel in this case. Fed. Cir. R. 47.4(a)(1).

   Concert Pharmaceuticals, Inc.

2. **Real Party in Interest.** 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. Fed. Cir. R. 47.4(a)(2).

   None.

3. **Parent Corporations and Stockholders.** 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. Fed. Cir. R. 47.4(a)(3).

   None.

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).

   Marta E. Delsignore (Goodwin Procter LLP)
   Cynthia L. Hardman and Sarah J. Fischer (formerly of Goodwin Procter LLP)

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).

   None.

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.

June 27, 2022

/s/ *William M. Jay*
William M. Jay

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TABLE OF AUTHORITIES

Cases:

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GLOSSARY

'149 Patent	U.S. Patent No. 9,249,149 [Appx1425-1446, Exhibit 1001 below]
AA	alopecia areata
ADME	absorption, distribution, metabolism, and excretion
AUC	area under the curve, *i.e.*, total drug exposure
Board	Patent Trial and Appeal Board
C_{max}	maximum plasma concentration
Concert	Appellant Concert Pharmaceuticals, Inc.
Concert Backgrounder	Concert Pharmaceuticals, Inc., PRECISION DEUTERIUM CHEMISTRY BACKGROUNDER [Appx1738-1743, Exhibit 1006 below]
CTP-543	Concert's novel deuterated version of ruxolitinib
EPO	Erythropoietin
IFN-γ	interferon gamma
Incyte	Appellee Incyte Corporation
IPR	*Inter partes* review
JAK1	Janus Kinase 1
JAK2	Janus Kinase 2
KIE	kinetic isotope effect
PTAB	Patent Trial and Appeal Board
PTO	United States Patent and Trademark Office
Rodgers	U.S. Patent No. 7,598,257 [Appx1744-1933, Exhibit 1007 below]
Shilling	Adam D. Shilling et al., *Metabolism, Excretion, and Pharmacokinetics of [^{14}C]INCB018424, a Selective Janus Tyrosine Kinase ½ Inhibitor, in Humans*, 38 DRUG METABOLISM & DISPOSITION 2023 (2010) [Appx1729-1737, Exhibit 1005 below]

STATEMENT OF RELATED CASES

No appeal in or from the same *inter partes* review proceedings was previously before this or any other appellate court.

Counsel is aware of no case pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal.

INTRODUCTION

Concert Pharmaceuticals' '149 Patent claims novel chemical compounds with surprising therapeutic advantages. Most notably, the claimed molecules possess superior pharmacokinetic properties that allowed Concert to develop an unexpectedly safe and effective treatment for alopecia areata (AA)—a condition that, until recently, had no FDA-approved therapy. In recognition of that discovery, the FDA granted Concert's product both "Fast Track" and "Breakthrough Therapy" designations, which expedite the agency's review of drugs to fill unmet medical needs.

No one could have foreseen those results. Concert created its new compounds by replacing hydrogen with deuterium at certain key locations of a prior-art molecule. That replacement process, known as deuteration, is notoriously unpredictable. While the prior art taught that deuteration *could* alter a drug's pharmacokinetic properties—*i.e.*, the properties that govern how the body processes the drug—there was no way to predict whether deuteration *would* do so, much less whether any change would be clinically beneficial, harmful, or neutral.

Only by actually creating deuterated compounds was Concert able to discover their unexpected benefits. The prior-art compound on which Concert experimented, ruxolitinib, had been approved to treat certain forms of blood cancer. But its toxic side-effects made it much less suitable for non-life-threatening conditions like AA. By replacing hydrogen with deuterium at select places in the ruxolitinib molecule,

Concert discovered that one of the resulting compounds, known as "CTP-543," displays unexpectedly superior pharmacokinetic properties. Those improvements—including a lower likelihood of toxic side-effects—give CTP-543 a significantly better risk-benefit profile that allows it to satisfy the long-felt need for a viable AA treatment.

None of that mattered to the Patent Trial and Appeal Board. The Board deemed every one of the claimed compounds obvious, holding that, so long as a skilled artisan would have considered deuteration *potentially* beneficial, and would have found it *technically possible* to synthesize a given compound, that compound is obvious no matter how unpredictable the clinical effects of the modification. In reaching that conclusion, the Board repeatedly misapplied settled precedent.

The Board's decision first went awry in analyzing whether a skilled artisan would have been motivated to modify ruxolitinib. Under this Court's decisions regarding novel chemical compounds, the Board needed to assess whether a skilled artisan would have been motivated to pursue the "*specific* molecular modifications" claimed in the '149 Patent—*i.e.*, to create the unique deuterated compounds that Concert invented. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added). But the Board thought it enough that the prior art supplied an abstract motivation to deuterate *any* molecule with known metabolic "hot spots"—a category that encompasses virtually *all* FDA-approved drugs.

The Board also believed that sufficient motivation could be inferred from the fact that deuterated and non-deuterated molecules would have some "similar properties, in general." Appx27. But in the pharmaceutical arts, pharmacokinetic properties are often key distinguishing features—and the effect of deuteration on *those* properties was not known.

The Board erred even more dramatically at the next stage of the analysis. The Board should have assessed whether a skilled artisan would have had a "reasonable expectation" that the claimed modifications "would result in beneficial changes"—*i.e.*, "would cause [the] compound to be more efficacious or less toxic." *Takeda*, 492 F.3d at 1360-1361. Ducking that question, the Board instead asked only whether a skilled artisan would have found it technically possible to synthesize the compounds identified in the '149 Patent—*regardless* of whether they were likely to possess any useful properties. That was the wrong inquiry: the question is "not only [whether the] prior art elements are *capable of being physically combined*, but also [whether] the combination would have *worked for its intended purpose*." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (emphasis added).

The Board made equally critical errors in disregarding significant objective indicia that Concert's invention is not obvious. Concert presented strong evidence of *two* unexpected results. First, CTP-543 remains in the "therapeutic window"—

i.e., above the level required to treat AA, but below the level where toxic side-effects are likely—for significantly longer than ruxolitinib. Second, CTP-543 provides disproportionate improvement in slowing metabolism for those patients who are the fastest metabolizers of ruxolitinib. These unexpected results have allowed Concert to develop CTP-543 as a fast-tracked treatment for AA. Yet the Board dismissed them on the theory that they represent "merely a difference in degree," not a difference in kind. That holding is inconsistent with precedent, and would render the vast majority of unexpected results in pharmaceutical inventions categorically irrelevant.

Finally, the PTAB failed to appreciate that Concert's innovation meets a long-felt need for a suitable AA treatment. The Board refused to give this factor any weight—even though Concert's drug showed such great promise in treating AA that the FDA fast-tracked it for that purpose—because the agency had not yet *approved* the drug. That flawed reasoning would place an inappropriate pharmaceutical-specific limit on the long-felt-need inquiry.

This Court has made clear that "predictability is a touchstone of obviousness." *DePuy*, 567 F.3d at 1326. If accepted, the Board's errors will undermine innovation by rendering new and innovative compounds obvious despite significant *unpredictability* in the art. Any one of those missteps is sufficient to warrant reversal.

JURISDICTIONAL STATEMENT

The Board issued its final written decision on April 8, 2019. Appx1-53. Concert filed a notice of appeal on June 7, 2019. Appx1420-1424. Following the Supreme Court's decision in *United States v. Arthrex, Inc.*, 141 S. Ct. 1970 (2021), this Court remanded the matter to allow Concert to request Director review of the Board's decision. Dkt. No. 56, at 2. That request was denied on January 14, 2022, Appx54-56, and Concert filed an amended notice of appeal on March 17, 2022, Appx11461-11466. This Court has jurisdiction under 28 U.S.C. §1295(a)(4)(A) and 35 U.S.C. §§141(c) and 319.

STATEMENT OF THE ISSUES

1. Whether the PTAB relied on the wrong legal standard in determining structural obviousness, because it ignored whether a skilled artisan:

(a) would have been motivated to deuterate ruxolitinib to alter its pharmacokinetic properties;

(b) would have been motivated to make the specific molecular modifications claimed in the '149 Patent; and

(c) would have had a reasonable expectation that the claimed modifications would lead to desired improvements in the compound's characteristics.

2. Whether the PTAB erred in disregarding objective indicia of nonobviousness.

3. Whether the official who denied Concert's request for Director review was a properly appointed "principal officer" of the Executive Branch.

STATEMENT OF THE CASE

I. Scientific and Factual Background.

A. The Clinical Importance of a Drug's Pharmacokinetic Properties.

Whether a drug is clinically useful depends on a number of factors. At a minimum, a drug must have suitable "selectivity" and "potency"—properties that describe how well the drug "interacts with its intended target" in the body. Appx9578; *see* Appx7919; Appx8225, Appx8246-8263. But equally important is how the body processes the drug—*i.e.*, the drug's pharmacokinetic properties. *See* Appx7919; Appx8225-8246; Appx9578. Even if a drug is selective and potent, its safety and efficacy will depend on the suitability of those pharmacokinetic properties—including the body's absorption, distribution, metabolism, and excretion (ADME) of the drug. *See* Appx1428(1:23-24); Appx8225-8246; Appx9578. For this reason, "[p]oor ADME properties" are "a major reason for the failure of drug candidates in clinical trials." Appx1428(1:23-24).

B. Deuteration's Unpredictable Effect on a Drug's Pharmacokinetic Properties.

One potential—though unpredictable—way to alter a drug's ADME properties is through deuteration. Appx1428(2:5-10). Deuteration exploits a significant difference between two isotopes of hydrogen. Appx2377. The more common isotope, known as "protium" (or, more simply, "hydrogen"),[1] has a nucleus consisting of a single proton. Appx1982; Appx2377. The rarer isotope, known as "deuterium," has a nucleus consisting of one proton and one neutron. Appx1982; Appx2377. Deuterium forms stronger bonds with carbon than hydrogen does—meaning it takes more energy to break a carbon-deuterium bond than a carbon-hydrogen bond. Appx1428(2:10-12); Appx1982. Because hydrogen and deuterium are almost identical in size and shape, deuteration typically has little or no effect on a drug's selectivity and potency. Appx1739. But by virtue of deuterium's increased bond strength, deuteration *may* affect a drug's pharmacokinetic properties. Appx1428(2:12-15); Appx9578-9579. A metabolic change caused by deuteration is called a kinetic isotope effect (KIE).

It is difficult, if not impossible, to predict whether deuteration will result in a KIE for any *particular* drug compound: without experimentation, a skilled artisan generally cannot say whether deuteration will affect a drug's ADME properties *at*

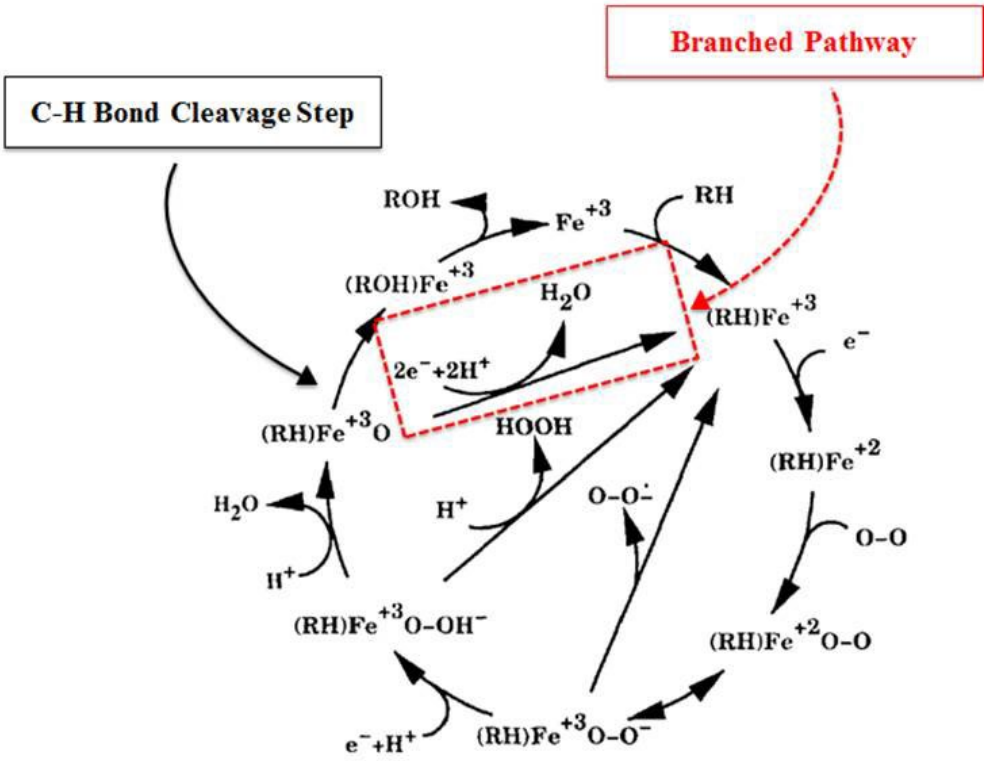
[1] In this brief, "hydrogen" refers exclusively to protium.

all, let alone whether the deuterated drug's properties will be therapeutically better, worse, or the same. That is because the biological processes involved in metabolism are extraordinarily complex. The way in which the body metabolizes a specific drug depends on a number of variables—each of which introduces an additional layer of unpredictability in forecasting the effects of deuteration. At least four variables are relevant here.

1. Unpredictability Resulting from the Nature of the Catalytic Cycle.

First, it is difficult to tell, *ex ante*, how deuteration will affect the catalytic cycle—*i.e.*, the chain of chemical reactions through which an enzyme (the catalyst) interacts with and metabolizes the drug in question (the substrate).

Most drugs are metabolized in the body by an enzyme in the CYP450 family. Appx9566; Appx9680. There are at least 57 different CYP450 enzymes, Appx9681-9682, and each drug-enzyme pair "is a unique reaction with its own kinetics and metabolic pathways," Appx9566; *see* Appx2849. The schematic below depicts a generic CYP450 catalytic cycle. The eight arrows forming the edge of the circle represent the eight steps through which a CYP450 enzyme metabolizes the substrate (RH) into a metabolite (ROH). Appx9567; Appx9841-9842. The overall rate of the cycle is determined by its slowest step—the "rate-limiting" step—which acts as a bottleneck. Appx9566.



Appx9569; *see also* Appx2849; Appx9841-9842.

One way deuteration might produce a KIE is by altering one of the last steps in the cycle—the cleavage of a carbon-hydrogen (C-H) bond (labeled in the diagram above). Appx9567; Appx9569-9570. *If* that step is rate-limiting in a particular drug's metabolic cycle, then deuteration may slow the rate of metabolism (because, as discussed, a carbon-deuterium bond is harder to break than a carbon-hydrogen bond). Appx1428(2:10-12); Appx1982. But the carbon-hydrogen bond cleavage step is generally *not* rate-limiting. Appx9570; *see also* Appx9017; Appx9273-9275.

Another way deuteration might produce a KIE is via a "branched" pathway in the catalytic cycle. The image above depicts three such pathways crossing the inte-

rior of the circle. Increasing the strength of the carbon-hydrogen bond through deuteration can help "shunt" the metabolic process into the pathway boxed in red, returning the enzyme and drug to an earlier stage of the cycle and thus slowing the rate of metabolism. Appx9566-9572; Appx9839-9842; Appx9863-9864. But whether such a branched pathway exists when a *particular* drug is metabolized by a *particular* CYP450 enzyme cannot be known without experimentation. Appx9570; Appx9572; Appx9839-9842; Appx9863-9864; Appx9867.

In short, the complexity of the catalytic cycle makes the effect of deuteration on the metabolism of any given compound unpredictable.

2. Unpredictability Resulting from Metabolic Switching.

A second layer of unpredictability arises from "metabolic switching." Studies have frequently observed that, when deuterium is substituted for hydrogen at one metabolic site on a drug molecule, metabolism can "switch" to a different location on the molecule. Appx9195; Appx9573-9574; *see* Appx2843-2848. If that occurs, the overall rate of metabolism may remain unchanged or even speed up. Appx2843 (reporting a "dramatic decrease in the [carbon-hydrogen] bond cleavage rate" from deuteration that nevertheless failed to change the overall reaction rate); *see* Appx2379. Metabolic switching can also increase the formation of undesirable or toxic metabolites. Appx9579. A skilled artisan would have been well aware that metabolic switching would contribute to the unpredictability of deuteration's effect

on a drug, even when deuterium is substituted at a metabolic hot spot. Appx2846; Appx2861; Appx2904; Appx8136; Appx9211; Appx9220; Appx9302-9304.

3. Unpredictability Resulting from Masking *In Vivo*.

Even if deuteration produces a KIE in a highly controlled lab environment (*i.e.*, *in vitro*), skilled artisans still cannot predict whether deuteration will produce a KIE in a living organism (*in vivo*). Because of the "complexity" of biological processes in the body and the existence of "competing effects," an *in vitro* KIE often does not manifest itself *in vivo*. Appx1982-1983. In particular, ADME processes unrelated to deuteration will often "mask" *in vivo* any KIE that is observed *in vitro*. *See* Appx1982-1983; Appx9565; *see also* Appx9686-9691. *In vivo* masking "ha[s] made the application of deuterium to drug discovery highly unpredictable and challenging." Appx2783.

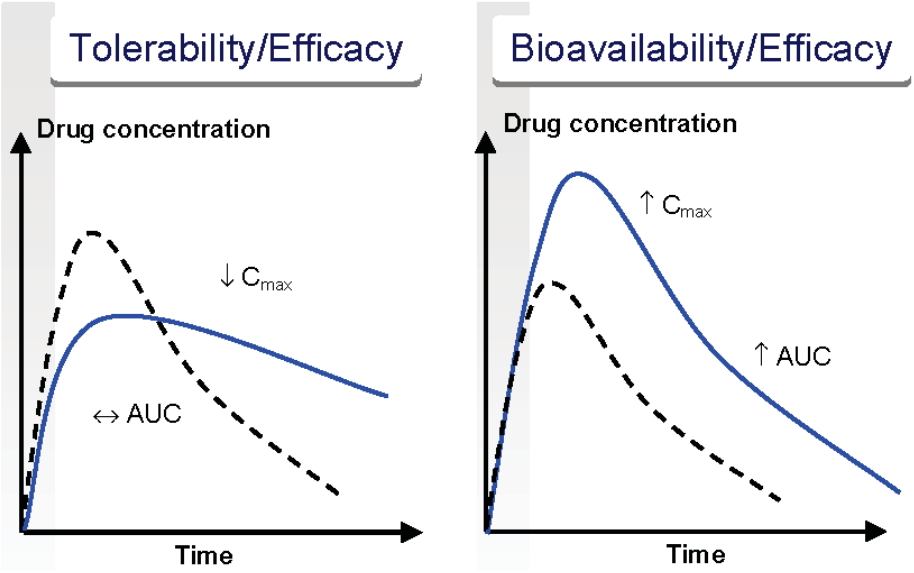
Even Appellee Incyte's expert acknowledged that *in vitro* "experimental parameters" may not be "probative" of how "tested analogs would actually perform *in vivo*." Appx1516. As he explained, an *in vitro* KIE "is not necessarily relevant to the 'success' of a deuterated analog" because "what is rate limiting *in vivo* may differ from the *in vitro* results." Appx1512.

4. Unpredictable Effects on Clinical Outcomes.

Finally, even if a skilled artisan overcame all these hurdles—*i.e.*, even if she could say with confidence that deuteration would affect the catalytic cycle to produce a KIE *and* that metabolic switching would not preclude the KIE *and* that the KIE would be expressed *in vivo*—she still could not predict whether the effect of deuteration on the drug's clinical profile would be *desirable*. Not every change is for the better. "[E]ven if expressed *in vivo*," Incyte's expert conceded, "the KIE that results from deuteration must have an effect on a pharmacokinetic parameter of . . . interest in order to make deuterium substitution useful." Appx2395. Yet a skilled artisan could not predict *ex ante* whether deuteration's effect on the pharmacokinetic properties of a drug like ruxolitinib would be positive, negative, or inconsequential.

A drug's pharmacokinetic properties are described by several parameters, including the drug's maximum concentration in a patient's body (C_{max}), the amount of time it takes for that concentration to decrease by 50% (half-life), and the patient's total exposure to the drug over time. Those parameters can be graphically represented by a pharmacokinetic curve—a chart that plots the concentration of the drug in the blood (on the *y*-axis) over a period of time (on the *x*-axis). The peak of the curve is the C_{max} value, the rate of decrease reflects the half-life, and the area under the curve (AUC) shows the patient's the total exposure. Appx9122; Appx9563-9564.

The images below—from the Concert Backgrounder, a reference on which the Board based its decision—display just two of the ways in which deuteration can affect a drug's pharmacokinetic curve. The dashed black line represents the curve of a hypothetical non-deuterated compound, while the solid blue line represents the curve for its deuterated analog:



Appx1739. In the left-hand panel, deuteration produces a pharmacokinetic curve with a different shape: it *maintains* total exposure (AUC) while *lowering* maximum concentration (C_{max}). In the right-hand panel, meanwhile, deuteration shifts the curve upward: it *raises* the drug's AUC and C_{max}. For drugs whose side-effects are "dose-dependent"—meaning an increase in C_{max} causes an increase in toxicity—the effect of these two changes is markedly different. The left-hand panel reflects a welcome change: the same total exposure with fewer side-effects. *See* Appx9265-9266. The right-hand panel, meanwhile, signifies an unwelcome change: greater

total exposure, but with a concomitant increase in toxic side-effects. *See* Appx9265-9266; Appx9579. In other words, a skilled artisan would have understood that an *in vivo* KIE, even if achieved for a deuterated compound, could just as readily produce an *undesirable* pharmacokinetic profile by increasing the risk of toxicity.

This simplified example shows why an *in vivo* KIE does not necessarily result in a positive therapeutic effect. And again, an *in vivo* KIE may not manifest *at all* (because of the unpredictable nature of the catalytic cycle and the effects of metabolic switching and *in vivo* masking). For all these reasons, a skilled artisan cannot predict whether deuterating a particular drug, even at its metabolic hot spots, will affect that drug's ADME properties—let alone whether any change will be clinically beneficial.

The FDA's treatment of deuterated compounds underscores this unpredictability. The agency has determined that a deuterated version of an existing drug is a "new chemical entity"—*i.e.*, the two are not the "same drug." *See* Appx10040-10041 (reflecting the award of new-chemical-entity exclusivity to the deuterated drug deutetrabenazine); *see also* Mem. from FDA Ctr. for Drug Evaluation & Research, CDER Exclusivity Board 5 (July 31, 2015), https://bit.ly/2TeRFKd; *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765-766 (D.C. Cir. 2010) (stating the agency's position that even minor structural differences "are capable of producing not only major changes in the activity of a drug but changes that are not readily predicted").

C. Ruxolitinib and Its Clinical Uses.

Ruxolitinib is a chemical compound that affects signaling proteins known as Janus Kinases 1 and 2 (JAK1 and JAK2), which coordinate the body's immune response. A hyperactive JAK1/JAK2 response can lead to certain autoimmune diseases. Ruxolitinib inhibits those overactive proteins, *see* Appx1428(2:53); Appx1729, though not without the potential for serious side-effects.

1. JAK Signaling.

Immune responses in the body are coordinated by regulatory molecules called cytokines. Appx8176. When a cytokine binds to a receptor on the surface of a cell, JAK1 and JAK2 activate a sequence of steps inside the cell that produce downstream biological effects. Appx8176. Proper JAK-cytokine signaling systems are important for immune function and the production of blood cells. Appx1428(2:53). For that reason, defects in the signaling process can lead to serious health conditions. For example, a hyperactive signaling process that increases immune function is the cause of a number of autoimmune diseases, including rheumatoid arthritis and AA. Appx1748(3:17-28).

2. Ruxolitinib.

Ruxolitinib is FDA-approved to treat life-threatening indications like myelofibrosis, a rare bone marrow/blood cancer "associated with dysregulated JAK1 and JAK2 signaling." Appx1717; Appx7060; *see* Appx1428-1429(2:66-3:3). Despite

its benefits, ruxolitinib comes with a number of serious side-effects, including blood-related toxicities such as anemia (low red blood cell count), thrombocytopenia (low blood platelet count), neutropenia (low white blood cell count), and lowered hemoglobin. *See* Appx7794-7795; Appx7827; Appx9472; Appx9479; Appx9484; *see also* Appx9574-9575. These side-effects occur with significant frequency. For example, in one placebo-controlled study, the percentage of individuals who experienced anemia, thrombocytopenia, or neutropenia while taking ruxolitinib was 96%, 70%, and 19% respectively (as compared to 87%, 31%, and 4% of patients taking a placebo). Appx7794; Appx9478-9479. The percentage of patients who experienced "severe" or "life-threatening or disabling"[2] versions of those conditions was 45%, 13%, and 7% respectively (as compared to 19%, 2%, and 1% of patients taking a placebo). Appx7794; Appx9478-9479.

These side-effects are serious. In one clinical study, for example, more than 40% of patients taking ruxolitinib for myelofibrosis required dose reduction or interruption due to thrombocytopenia, and a further 5% required dose reduction or interruption due to anemia. Appx9491-9492. Still other patients required at least one transfusion of packed red blood cells because of anemia. Appx9483; Appx9491-

[2] *See* National Cancer Institute, Common Terminology Criteria for Adverse Events v3.0 (CTCAE), cover (Aug. 9, 2006), https://bit.ly/2M1uH8v (explaining that a "Grade 3" designation describes a "[s]evere" side-effect, while a "Grade 4" designation describes a "[l]ife-threatening or disabling" side-effect).

9492. The severity of these side-effects limits the medical conditions for which ruxolitinib is an acceptable treatment. While serious adverse reactions like anemia and thrombocytopenia might be acceptable for treating a potentially fatal illness like cancer, they are far less tolerable for patients suffering from non-life-threatening conditions. Appx9382; Appx9580.

On the '149 Patent's priority date, a skilled artisan would have understood these toxic side-effects to be caused by the same mechanism that causes ruxolitinib's beneficial clinical effects. Ruxolitinib treats myelofibrosis by inhibiting the activity of JAK2. *See* Appx1717; Appx7697-7698; Appx7838; Appx9473. But inhibiting JAK2 also suppresses the activity of erythropoietin (EPO), a cytokine involved in red blood cell formation. *See* Appx7697-7698. A skilled artisan would thus have understood ruxolitinib's toxicities to be dose-dependent, such that increasing the drug's dosage would *also* increase the risk of its harmful side-effects like anemia. Appx9484; Appx9575; *see also* Appx9178 (testimony by Incyte's expert discussing the information at Appx1708, tbl. 3, and agreeing that it suggests that thrombocytopenia is dose-dependent); Appx9491-9492 (clinical study showing dose-reduction often required). It follows that a skilled artisan would have believed that slowing the drug's metabolism—including through deuteration—could *increase* the drug's already serious side-effects by increasing the patient's exposure to the drug before it breaks down through metabolism. Appx9575.

D. Alopecia Areata and the Potential for Treatment with Deuterated Ruxolitinib.

AA is one of the most common autoimmune disorders in the United States. Appx7824. An AA patient's immune system begins attacking the patient's own hair follicles, leading to unpredictable and sometimes total hair loss. Appx7824; Appx7833; Appx9380-9381. The disease often causes "significant disfigurement"—and, as a result, "psychological distress in affected individuals." Appx7824; *see* Appx9890-9892. Until June 2022, the FDA had not approved any systemic treatments for AA. *See* U.S. Food & Drug Admin., *FDA Approves First Systemic Treatment for Alopecia Areata* (June 13, 2022), https://bit.ly/3MP8dlS.

Concert recognized the potential for deuterated ruxolitinib to meet the long-felt need for a viable AA treatment. Ruxolitinib treats myelofibrosis through inhibition of the JAK-mediated EPO signaling pathway. *See* Appx7697-7698. But a different JAK-mediated pathway, the interferon gamma (IFN-γ) pathway, is now known to be relevant for treating AA. Appx7654-7655. That difference is significant. When a JAK inhibitor like ruxolitinib is used to treat blood cancers, efficacy and toxicity go hand in hand because they arise from the *same* underlying mechanism: inhibition of EPO. By contrast, when a JAK inhibitor is used to treat AA, efficacy and toxicity stem from *different* mechanisms: efficacy comes from inhibition of IFN-γ, while toxicity comes from inhibition of EPO. Appx7654-7655. Con-

cert discovered that ruxolitinib's inhibition of the IFN-γ pathway is much more potent than its inhibition of the EPO pathway. Appx7654-7655. For this reason, certain plasma concentrations of the drug could be effective for AA and still fall below the levels that would increase risks of toxic side-effects from inhibiting EPO.

E. CTP-543 and Its Unexpected Properties.

Concert invented CTP-543, a new chemical compound that differs from ruxolitinib by having deuterium rather than hydrogen at eight specific positions. While ruxolitinib has severe side-effects that make it an undesirable treatment for a non-life-threatening condition like AA, *see* Appx9382; Appx9580, CTP-543 has a markedly better risk-benefit profile for AA. Recognizing the promise of this therapy, the FDA granted CTP-543 "Fast Track" status in 2018. Appx10102. That designation exists to "expedite the review of drugs to treat serious conditions and fill an unmet medical need." U.S. Food & Drug Admin., *Fast Track* (Jan. 4, 2018), https://bit.ly/3xJ5DIK. More recently, the agency granted CTP-543 a "Breakthrough Therapy" designation, which is available when "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)." U.S. Food & Drug Admin., *Breakthrough Therapy* (Jan. 4, 2018), https://bit.ly/2y63x7e; *see* Press Release, Concert Pharmaceuticals Inc., *Concert Pharmaceuticals Receives FDA Breakthrough Therapy Designation*

for CTP-543 for the Treatment of Alopecia Areata (July 8, 2020), https://bit.ly/3tQz0I9.

In clinical trials, Concert found that CTP-543 demonstrated two separate, unexpected qualities that make it particularly promising for treating AA compared to ruxolitinib. First, CTP-543 possesses a "flatter" pharmacokinetic curve than ruxolitinib, meaning it spends a longer time in the "therapeutic window" for AA treatment, while plasma levels remain below the levels that would risk the toxic side-effects of EPO inhibition. Second, in a head-to-head comparison with ruxolitinib, individuals who most rapidly metabolize ruxolitinib experience the greatest relative increase in half-life with CTP-543.

1. Flatter Pharmacokinetic Curve.

CTP-543's first unexpected difference from ruxolitinib is its pharmacokinetic profile, which makes CTP-543 more efficacious at more tolerable doses. As discussed above, a skilled artisan would have worried that slowing ruxolitinib's metabolism through deuteration would *increase* the drug's already serious side-effects. *See supra*, p. 17. Concert discovered that, contrary to expectations, that is not the case.

Compared to ruxolitinib, CTP-543 has a longer half-life and greater total exposure (AUC) *without* a statistically significant change in its maximum plasma concentration (C_{max}). Appx7658-7659. In other words, CTP-543 stays in the body for

longer—and delivers greater exposure to the drug over that time—without increasing the peak concentration of the drug in the bloodstream. This advantage of CTP-543 is graphically represented by a "flatter" pharmacokinetic curve compared to that of ruxolitinib: for equally effective doses, CTP-543's pharmacokinetic curve rises to about the same C_{max} value, but tapers more gradually.

CTP-543's flatter pharmacokinetic curve provides an important clinical advantage. To effectively treat AA, ruxolitinib must have a certain minimum plasma concentration—at least 50 nanomoles per liter. Appx7655 tbl. 1; Appx7661 tbl. 5; Appx8086. But the risk of anemia-associated side-effects caused by inhibiting the EPO signaling pathway increases as the drug's plasma concentration rises above 677 nanomoles per liter. Appx7655 tbl. 1; Appx7661 tbl. 5; Appx8086. Accordingly, ruxolitinib's "therapeutic window" for AA lies between 50 and 677 nanomoles per liter. And CTP-543 remains in that window for significantly longer than the dose of ruxolitinib needed to produce the same inhibitory effect. Appx7661 tbl. 5. In light of that change, AA patients taking CTP-543 would likely experience the desired therapeutic effect "with comparatively fewer side effects." Appx9385-9386. That means CTP-543 "could provide a significant clinical benefit for patients." Appx9385-9386.

2. Disproportionate Benefits for Rapid Metabolizers.

CTP-543 demonstrates another unexpected benefit not predicted in the prior art: the more rapidly a subject metabolizes ruxolitinib, the greater the increase in half-life she experiences when given CTP-543. Appx7659-7660; Appx7704-7705; Appx9384. This property, too, is clinically significant. Because a faster metabolism results in a steeper decline in plasma concentrations, more rapid metabolizers experience a lesser therapeutic response from a given dose of ruxolitinib than other patients. Appx7923-7927. These rapid metabolizers are more likely to benefit from a given dose of CTP-543 because they experience a greater relative increase in half-life than less rapid metabolizers. With CTP-543, in other words, a greater percentage of the patient population will remain within the therapeutic window for longer. Appx9387.

The prior art did not teach this advantage of CTP-543. Indeed, Concert's experts testified that they know of *no other reported instances* of this effect in a drug metabolized by the same enzyme as ruxolitinib. Appx7660; Appx7707-7708. Incyte's experts likewise identified *no prior-art example* of such a result. A skilled artisan would have expected that if deuteration slowed metabolism, the percent increase in half-life would be similar across subjects. The inversely proportional relationship in the percentage increase in half-life was unexpected and is clinically significant: again, patients who would be least likely to benefit from ruxolitinib

would experience a disproportionally greater benefit with CTP-543. Appx9579-9580.

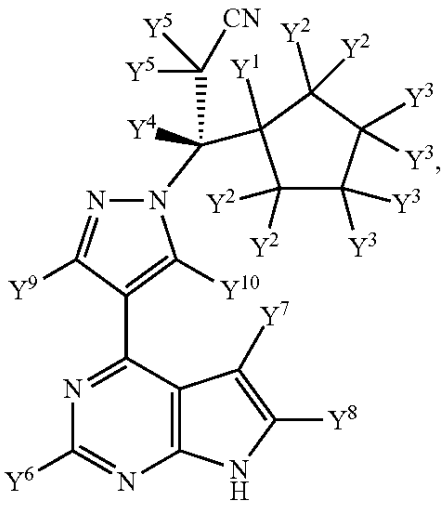
F. The '149 Patent.

The '149 Patent issued on February 2, 2016, and claims priority to a provisional application filed on June 15, 2012. Appx1425. The patent claims a number of specific deuterated ruxolitinib compounds, including CTP-543.

Of the '149 Patent's fifteen claims, Claims 1 and 9 are independent, while the remaining claims depend from those two. Claim 1 reads:

A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is a hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9, and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

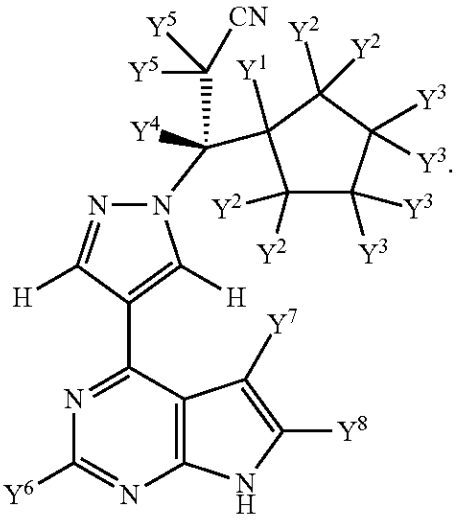
each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

Appx1445(36:17-53).

Claim 9 is identical to Claim 1, except it is directed to Formula I, which replaces the Y^9 and Y^{10} of Formula A with hydrogen atoms:

Formula I

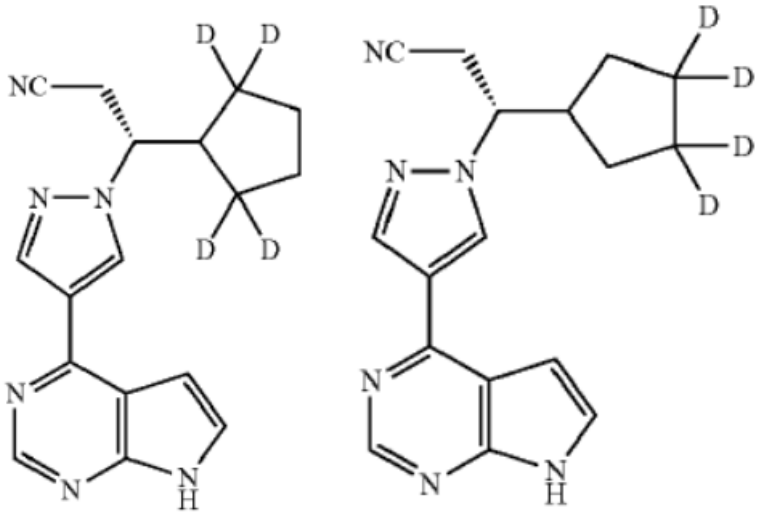


Appx1446(38:1-33).

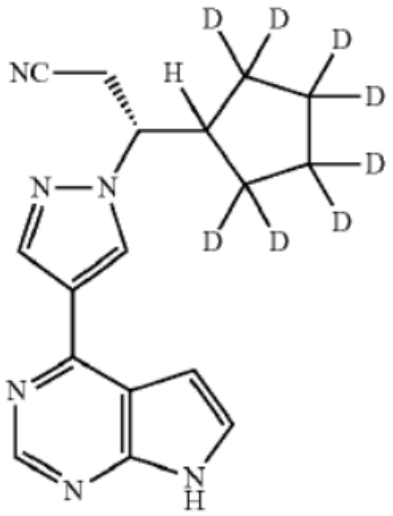
Claims 2-7 and 10-14 depend from Claims 1 and 9, respectively, and recite specific deuteration patterns of the compounds embodied in those claims. Appx1445-1446(36:54-37:40, 38:33-38:42). Finally, Claims 8 and 15 depend from

Claims 1 and 9, respectively, and recite a pharmaceutical composition of the compounds embodied in those claims plus a pharmaceutically acceptable carrier. Appx1446(37:44-45, 38:43-44).

In this proceeding, Incyte has focused its analysis on the three specific compounds recited in Claim 7: two "tetra-deuterated" compounds and one "octa-deuterated" compound. Appx11-12; *see* Appx1446(37:1-40). In the tetra-deuterated analogs, each of the four Y^2 *or* each of the four Y^3 is replaced with deuterium:



Appx12; *see* Appx1446(37:1-27). In the octa-deuterated analog, meanwhile, each Y^2 *and* each Y^3 is replaced with deuterium:



Appx11-12; *see* Appx1446(37:28-40).

Incyte asserts that Claims 1, 2, 5-7, 9, 10, 13, and 14 each read on the octa-deuterated analog, and that Claims 1-4, 6, 7, 9-12, and 14 each read on the "tetra-deuterated" analogs. Appx11-12. The octa-deuterated compound corresponds to CTP-543. Appx33 n. 12.

II. Procedural History.

A. Incyte's IPR Petition.

Incyte filed a petition for *inter partes* review of the '149 Patent, asserting that Claims 1-15 were obvious over three references.

First, Incyte relied on Rodgers, a patent that discloses and claims ruxolitinib. *See* Appx1744-1933.

Second, Incyte relied on Shilling, a published article that discloses that ruxolitinib is "a potent, selective inhibitor of [JAK] 1/2." Appx1729. According to Incyte, "Shilling teaches that oxidative metabolism occurs almost entirely on the

cyclopentyl ring of ruxolitinib at Y^2 and Y^3." Appx22. As Incyte's expert admitted, however, Shilling does not specify which of the several dozen CYP450 enzymes are involved in ruxolitinib's metabolism. Appx9180.

Third, Incyte relied on the Concert Backgrounder, a non-technical, non-peer-reviewed marketing paper. As its name suggests, the Concert Backgrounder provides general background information about "Precision Deuterium Chemistry" and Concert's business strategy as it relates to deuteration. Appx1738-1743. It does not discuss ruxolitinib at all. The Concert Backgrounder explains that "[d]euterium-substituted compounds retain their molecular shape and thus have selectivity and potency comparable to their hydrogen analogs." Appx1739. But "since deuterium is heavier than hydrogen," the document explains, "it forms significantly stronger bonds with carbon," which can "result[] in differentiated ADME." Appx1739.

Notably, the Concert Backgrounder cautions that "the magnitude and nature of the deuterium benefit cannot be predicted *a priori*." Appx1740. Instead, "CoNCERT must test multiple compounds in a range of assays to identify those that are differentiated." Appx1740. Illustrating the point, the document gives several divergent examples of "potential" changes to ADME properties that one might observe through deuteration—including the two images discussed above (at p. 13).

B. The PTAB's Decision.

After initially denying institution, the PTAB reversed itself and instituted review on whether Claims 1-15 of the '149 Patent are obvious over the combination of Rodgers, Shilling, and the Concert Backgrounder.[3] The Board applied the test set forth in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012), which asks "'whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts'" and "whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success." Appx20 (quoting *Otsuka*, 678 F.3d at 1291-1292). According to the Board, Incyte satisfied that test, and the claims of the '149 Patent were obvious over the asserted combination. Appx1-53.

Beginning with the lead-compound inquiry, the Board held that "whether a person of ordinary skill in the art would have chosen the prior art compound as a lead compound 'is 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.'" Appx20-21 (quoting

[3] The Board also instituted review on a second obviousness ground based on a different combination. Appx8. Because the Board did not resolve that obviousness ground, Appx37, it is not at issue in this appeal.

Otsuka, 678 F.3d at 1292). The Board determined "that the preponderance of the evidence supports finding that a person of ordinary skill in the art would have chosen ruxolitinib as a lead compound," because "Shilling states that ruxolitinib is 'a potent, selective inhibitor of Janus tyrosine kinase 1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis.'" Appx21 (quoting Appx1729).

On whether there was a "reason to make the claimed compound," Appx21 (capitalization omitted), the Board recited and adopted Incyte's arguments. Appx22-24. It agreed with Incyte "that the combined teachings of Rodgers, Shilling, and the Concert Backgrounder would have provided a person of ordinary skill in the art a reason to deuterate Rodgers's ruxolitinib compounds at their metabolic 'hot spots,' as identified by Shilling, in the manner taught by the Concert Backgrounder to achieve the *potential* benefits that the Concert Backgrounder disclosed, *e.g.*, improved safety, tolerability, and efficacy." Appx23-24 (emphasis added); *see also* Appx22 ("Petitioner asserts that the Concert Backgrounder explains that 'deuterium substitution has the *potential* to create new chemical entities with improved safety, tolerability, and efficacy'" (emphasis added)). The Board also concluded that "a motivation to make deuterated ruxolitinib compounds and compositions exist[ed] based upon the structural similarity between those claimed compounds and the prior art compounds." Appx24.

The Board rejected several contrary arguments. First, the Board dismissed evidence that a skilled artisan would have been dissuaded from deuterating ruxolitinib in light of its dose-dependent toxicity. According to the Board, any increase in side-effects could be "managed by dose adjustment." Appx25; *see* Appx24-26. Second, the Board rejected the argument that, given the uncertainty surrounding deuteration, a skilled artisan would have been motivated to pursue methods other than deuteration. Appx26-27. Finally, the Board disregarded Concert's argument that structural similarities were not enough to imply similarity between the claimed deuterated compounds and ruxolitinib. Appx27-28. Concert had explained that the drug's ADME properties—which could not be assumed based on structural similarities—were also relevant in comparing to the prior art. But the Board ignored these arguments: it relied only on the facts that "deuterium and hydrogen are very similar in size and electronic properties," and that "deuterium-substituted compounds retain their molecular shape and their basic electronic properties, and therefore, have selectivity and potency comparable to their hydrogen analogs." Appx28 (quotation marks omitted). In other words, without giving weight to the drugs' pharmacokinetic differences, the Board rested on the observation that "the claimed and prior art compounds have similar properties, *in general*." *Id.* (emphasis added).

Moving on to reasonable expectation of success, the Board asked "whether a person of ordinary skill in the art would have had a reasonable expectation of *successfully making the claimed invention*"—*i.e.*, successfully synthesizing the claimed compounds "in light of the prior art." Appx31 (emphasis added). It concluded that "the preponderance of the evidence supports [Incyte]'s assertion that the combined teachings of Rodgers, Shilling, and the Concert Backgrounder would have provided a person of ordinary skill in the art a reasonable expectation of *successfully deuterating* Rodgers's ruxolitinib compounds at their metabolic 'hot spots,' as identified by Shilling, and in the manner taught by the Concert Backgrounder." Appx31 (emphasis added). Concert had explained to the Board that "a person of ordinary skill in the art would have had no reasonable expectation of achieving either an *in vitro* or *in vivo* [KIE], and would not have been able to predict *a priori* the effect of deuteration on the clinical profile (*e.g.*, half-life) of the drug." Appx31 (citations omitted). In the Board's view, however, whether a skilled artisan would have reasonably expected any particular pharmacokinetic result from deuteration was irrelevant, because "the challenged claims do not recite any of those features." Appx31; *see also* Appx30 (noting that Concert's argument was not based "on whether a person of ordinary skill in the art could have reasonably expected to successfully synthesize the claimed octa- and tetra-deuterated ruxolitinib analogs").

The PTAB concluded its analysis by refusing to give any weight to objective indicia of nonobviousness. The Board did not dispute that, as Concert had explained, CTP-543 exhibited two important and clinically meaningful unexpected advantages: a flatter pharmacokinetic curve and a disproportionately large improvement in metabolism for more rapid metabolizers. *See* Appx33. Nevertheless, the Board disregarded both. In the Board's view, these unexpected properties were, "at most, results that differ in degree over the results observed with the closest prior art" because they involved "an increase in the same clinical activity observed with ruxolitinib," and because they could be "measured by percentages." Appx34-35. Concert also explained that its invention fulfilled a long-felt need, as shown by CTP-543's clinical promise to provide a treatment for AA. The Board did not dispute Concert's proof, but disregarded that factor as "unsupported" and "premature" for the sole reason that CTP-543 was not yet *FDA-approved* to treat AA. Appx35-37.

C. Concert's Request for Director Review.

Concert appealed to this Court. Before Concert filed its opening brief, this matter was held in abeyance pending the Supreme Court's resolution of *Arthrex*. *See* Dkt. No. 39, at 2; Appx11424-11429. Following the Supreme Court's decision, this Court remanded to the PTO to allow Concert to request Director review of the

Board's decision. *See* Dkt. No. 56, at 2. Andrew Hirshfeld—the official then "performing the functions and duties" of PTO Director on an interim basis—denied Concert's request. Appx54-55.

SUMMARY OF THE ARGUMENT

I. The Board applied the wrong legal standard to both the "motivation" and "reasonable expectation" components of the obviousness inquiry.

This Court has made clear that a motivation to create a new chemical compound—like the one claimed in the '149 Patent—does not arise merely because the new compound is "close enough" in structure to an existing one. There must also be an expectation that the new compound will function similarly to the prior-art compound. *See, e.g.*, *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009). Here, however, the Board thought it sufficient that the claimed deuterated compounds have the same basic structure as ruxolitinib and some similar properties "in general." Appx28. The Board thus ignored the pertinent properties of the deuterated compounds—their pharmacokinetic properties. Applying the proper test, the Board never would have found motivation: a skilled artisan could not have predicted the beneficial ADME properties of the deuterated compounds *ex ante*—indeed, she would have been discouraged from deuterating ruxolitinib given what was known about ruxolitinib's dose-dependent toxicities.

The Board also erred in the motivation inquiry because it failed to ask whether "the prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added). The Board found motivation based on a combination that, at best, provided a reason to deuterate *all* drugs. But the Board failed to show why a skilled artisan would have created the specific octa- and tetra-deuterated compounds here.

In addressing reasonable expectations, the Board disregarded whether a skilled artisan would have expected these claimed deuterated compounds to demonstrate any beneficial pharmacokinetic properties. According to the Board, it did not need to consider that question *at all*: what mattered was only whether a skilled artisan could *create* the deuterated compounds. But this Court's structural-obviousness decisions have always required some demonstration of desired properties. *See, e.g.*, *Takeda*, 492 F.3d 1360-1361. Under the proper test, a person of ordinary skill in the art would not have had a reasonable expectation that deuterating ruxolitinib would achieve a positive effect on ADME properties or metabolic processes.

II. The Board erred in disregarding two objective indicia of nonobviousness.

First, CTP-543 demonstrated two unexpected results: a flatter pharmacokinetic curve and a disproportionate benefit for rapid metabolizers. Both of these unexpected results make CTP-543 a more promising treatment for AA than ruxolitinib. The Board dismissed these unexpected results as "difference[s] in degree," Appx34-35, but its approach misreads the controlling precedent and would turn virtually *any* unexpected result into a difference in degree.

Second, CTP-543 satisfies a long-felt need for AA treatment. AA is a serious autoimmune disease that, as of 2012, had no viable treatment. CTP-543 satisfies that long-felt need. The PTAB's sole basis for reaching a contrary conclusion was that CTP-543 had not yet received final FDA marketing approval. But the relevant question is whether the claimed invention *in fact* satisfied a long-felt need, not whether it has jumped through all the hoops necessary to receive regulatory approval.

III. The official who denied Concert's request for Director review was not a properly appointed principal officer under *Arthrex*.

STANDARD OF REVIEW

"Obviousness is a question of law based on underlying findings of fact." *DSS Tech. Mgmt., Inc. v. Apple Inc.*, 885 F.3d 1367, 1373 (Fed. Cir. 2018) (quotation marks omitted). The Court reviews the Board's underlying factual findings for substantial evidence. *Id.* at 1374. It reviews the Board's legal conclusions *de novo*. *Id.*

Substantial-evidence review asks "whether a reasonable fact finder could have arrived at the agency's decision, which requires examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *PersonalWeb Techs., LLC v. Apple, Inc.*, 917 F.3d 1376, 1381 (Fed. Cir. 2019).

ARGUMENT

I. The PTAB applied the wrong legal standard to both stages of the structural obviousness inquiry.

Under 35 U.S.C. §103, a claimed compound that does not itself appear in the prior art is unpatentable only if "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012). In undertaking that inquiry, the Board committed three separate legal errors. It failed to ask whether a skilled artisan would have been motivated to alter ruxolitinib's *pertinent* properties—its pharmacokinetic properties. It failed to ask whether the prior art would have motivated the *specific* molecular modifications claimed in the '149 Patent. And it failed to ask whether a skilled artisan would have reasonably expected *desired changes* to ruxolitinib's pharmacokinetic properties. Any one of those errors warrants reversal. Together, they warp the structural-obviousness inquiry beyond recognition.

A. The PTAB failed to ask whether a skilled artisan would have been motivated to deuterate ruxolitinib to alter its pharmacokinetic properties.

"Any compound may look obvious once someone has made it and found it to be useful[.]" *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019). But a new compound is not obvious just because it is "close enough" to an existing one, or just because it has similar properties "in general" to a prior-art molecule. Instead, the correct inquiry focuses on what properties motivated the creation of the new compound. Only if the new compound would be expected to demonstrate *those properties* is an obviousness determination possible.

1. A motivation to create a claimed molecule can arise from structural similarities between that molecule and the prior art only if there is "an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (quotation marks omitted). In other words, structural similarity is not enough on its own: this Court's "cases recognize that the chemical arts are unpredictable and that similar structures do not always result in similar properties." *Anacor Pharm., Inc. v. Iancu*, 889 F.3d 1372, 1385 (Fed. Cir. 2018). Instead, "[t]he obviousness inquiry often depends on whether there is evidence demonstrating a nexus between *structural* similarities (or dissimilarities) and *functional* similarities (or dissimilarities)." *Id.* (emphasis added).

This Court has regularly applied that principle to reject assertions of obviousness where a compound's pertinent properties were unpredictable from the prior art. In *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006), for example, the Court considered whether the chemical compound clopidogrel bisulfate was obvious in light of a structural difference over the prior art. Clopidogrel bisulfate is one of two "enantiomers" of a chemical called MATTPCA: both enantiomers contain the same atoms but are "mirror images of each other." *Id.* at 1372. This structure gives each enantiomer different optical properties (*i.e.*, how the molecule interacts with polarized light), *id.*, but "two enantiomers generally have identical physical properties—such as melting at the same temperature and dissolving in solvents to the same extent," *Sanofi-Synthelabo v. Apotex Inc.*, 488 F. Supp. 2d 317, 328 (S.D.N.Y. 2006). MATTPCA, for its part, is a "racemate"—a mixture containing equal parts of both enantiomers—and thus "exhibits no optical activity." 470 F.3d at 1372.

Apotex argued that clopidogrel bisulfate was obvious over a prior-art patent that claimed MATTPCA. According to Apotex, a skilled artisan would have pursued clopidogrel bisulfate because she would have expected the compound to provide the same clinical benefits as MATTPCA with lower toxicity. 488 F. Supp. 2d at 336. But the district court held that "the prior art could not predict whether a single enantiomer . . . would have more acceptable pharmaceutical properties than

the racemate itself, whether one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole, or whether a single enantiomer would have both all of the activity and all of the toxicity." *Id.* at 337. This Court agreed. *See* 470 F.3d at 1378-1379. Although both the prior-art compound and the claimed enantiomer shared a beneficial pharmaceutical property (anti-platelet activity), the inability to predict a pertinent property (toxicity) rendered the patented compound nonobvious.

The Court reached a similar conclusion in *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009). There, the Court considered whether the chemical compound risedronate was obvious over a prior-art compound called 2-pyr EHDP. *Id.* at 993. Both compounds fall within the same class of molecules called bisphosphonates. *Id.* They are also "positional isomers" of each other, meaning that "they each contain the same atoms arranged in different ways." *Id.* at 995. As in *Sanofi-Synthelabo*, obviousness in *Procter & Gamble* turned on the claimed compound's toxicity and its "safety to efficacy ratio." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 536 F. Supp. 2d 476, 496 (D. Del. 2008). This Court explained that a skilled artisan would not have been motivated to make the necessary modifications to 2-pyr EHDP to arrive at risedronate because "the properties of bisphosphonates could not be anticipated based on their structure." 566 F.3d at 996.

These precedents reflect an important tenet of the obviousness inquiry: a motivation to modify does not arise merely because two compounds share a similar structure and *some* similar qualities. Instead, the prior art must show that a skilled artisan would have had reason to think the modified compound would have "functional similarities" to the prior-art compound, *Anacor*, 889 F.3d at 1385—*i.e.*, that the properties that *actually motivated the modification* would be at least similar.

2. The PTAB's analysis violated these principles. In holding that a skilled artisan would have been motivated to pursue the '149 Patent's deuterated compounds, the Board viewed it as sufficient that "deuterium and hydrogen are very similar in size and electronic properties" and that "deuterium-substituted compounds retain their molecular shape and their basic electronic properties, and therefore, have *selectivity and potency* comparable to their hydrogen analogs." Appx28 (emphasis added). In other words, the Board thought it enough that deuterated compounds have the same structure and "similar properties, in general," to compounds containing hydrogen rather than deuterium. *Id.*

The law requires a far more demanding inquiry. By focusing its motivation analysis on structural similarities like atomic size and molecular shape, the Board ignored the unpredictable effects of deuteration on the pharmacokinetic properties of ruxolitinib, especially those relevant to the balance of safety and efficacy. In particular, the Board completely disregarded the fact that a skilled artisan could not

have predicted the beneficial ADME properties of deuterated ruxolitinib *ex ante* given the unpredictability of deuteration. *See supra*, pp. 8-14.

The Board's observation that deuteration would not affect ruxolitinib's "selectivity and potency" (Appx28) does not salvage its incomplete analysis. As discussed, selectivity and potency are merely two of a drug's important properties: a drug must also have adequate *pharmacokinetic* properties to be clinically safe and effective. *See supra*, p. 6. That is, even a drug with superior selectivity and potency will be ineffectual if it is rapidly cleared from the body, or dangerous if it reaches toxic levels in the plasma. The Board erred by myopically focusing on ruxolitinib's selectivity and potency and failing to consider its unpredictable pharmacokinetics, which are central to the motivation the Board itself identified. As a result, the Board failed to answer the key question: whether a skilled artisan would be motivated by a belief that the claimed compounds shared *relevant* "functional similarities" with ruxolitinib. *Anacor*, 889 F.3d at 1385.

This Court's decision in *Sanofi-Synthelabo* confirms that the Board cannot simply ignore uncertainty regarding an invention's key properties (here, pharmacokinetics) merely by pointing to similarities in *other* properties. There, the structures of the prior-art racemate (MATTPCA) and the claimed invention (clopidogrel) were virtually *identical*: MATTPCA was a 50/50 mixture of clopidogrel and its "mirror image[]" enantiomer. 470 F.3d at 1372. And the "physical properties" of the two

enantiomers and the racemate—including their melting point and solubility—were "generally . . . identical." 488 F. Supp. 2d 328. Nevertheless, the Court agreed that a skilled artisan had no motivation to modify MATTPCA to isolate *one* enantiomer in light of "unpredictability" regarding the pertinent "pharmaceutical properties." 470 F.3d at 1379.

The same reasoning applies here. The Board erred in finding a motivation to deuterate based on "similar properties, in general," without analyzing whether—let alone concluding that—a deuterated compound was likely to have similar functionality *with respect to the allegedly motivating pharmacokinetic properties*.

3. Under the proper motivation inquiry, this is a straightforward case. Incyte offered no evidence to suggest that a skilled artisan would have expected the claimed deuterated compounds to enjoy any particular pharmacokinetic properties. To the contrary, Incyte's key reference concerning deuteration, the Concert Backgrounder, clearly warned that the effects of deuteration "cannot be predicted *a priori*." Appx1740. Indeed, it expressly highlighted an *undesirable* pharmacokinetic profile that could result from deuteration. Appx1739; *see supra*, pp. 13-14.

As discussed above, the unpredictable effect of deuteration stems from a number of sources. The nature of the CYP450 catalytic cycle is variable, and each drug-enzyme pair has its own unique kinetics, making it exceedingly difficult to anticipate whether deuteration would affect ruxolitinib's metabolism. *See supra*, pp. 8-10.

Deuteration might not produce an observable effect on overall metabolism as a result of "metabolic switching." *See supra*, pp. 10-11. Even if metabolic changes were observed *in vitro*, they might be masked *in vivo*. *See supra*, p. 11. And even if expressed *in vivo*, any KIE resulting from deuteration might not have affected ruxolitinib's ADME properties in a way that was clinically beneficial. *See supra*, pp. 12-14; *see also supra*, p. 14 (explaining that, for this reason, FDA practice would treat CTP-543 as a "new chemical entity" requiring its own clinical studies, and entitled to its own marketing exclusivity, regardless of the fact that the agency has previously approved ruxolitinib). Considering these effects together, a skilled artisan would have had no reason to expect the claimed compounds to possess improved pharmacokinetic properties over ruxolitinib.

In fact, the prior art actually taught skilled artisans away from attempting to modify ruxolitinib's pharmacokinetic properties through deuteration. *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015). The prior art taught that ruxolitinib had several significant dose-dependent side-effects. *See supra*, pp. 15-17. These serious conditions required dose reduction, interruption of treatment, and even blood transfusions in some patients; in one study, as many as 40% of participants required dose modification due to just one of these many side-effects. Appx9483; Appx9491-9492; *see supra*, pp. 16-17. Crucially, the prior art *also* taught that slowing metabolism—and producing a concomitant increase in C_{max}—

would exacerbate these side-effects. *See supra*, p. 17. That is because the *same* mechanism of action that led to ruxolitinib's beneficial clinical properties for its approved indications was known to cause its toxicities. *See id.* A skilled artisan thus would have viewed ruxolitinib as a particularly bad candidate for deuteration, because altering ruxolitinib's metabolism would have risked increasing the drug's toxic side-effects. *See id.*

The PTAB brushed aside these teachings on the theory that any "side effect[s] may be managed by dose adjustment"—*i.e.*, a clinician could lower a patient's dose to lower the side-effects. Appx25-26. But that misses the point entirely. Again, the prior art taught that ruxolitinib's beneficial properties and side-effects went hand-in-hand, moving in the same direction as the dosage changed. So while a skilled artisan may have known that lowering the dose of deuterated ruxolitinib could mitigate its toxic side-effects, she would also have expected that change to reduce its clinical efficacy. It is *that* unsatisfactory tradeoff that renders the PTAB's motivation finding incoherent: a skilled artisan has no reason to deuterate a drug *in the hopes of improving its clinical efficacy* if she fully expects that patients will need to take a correspondingly lower dose, *resulting in reduced clinical efficacy*. Or, stated even more simply: a skilled artisan had no reason to pursue a modification that, according to the prior art, would have been self-defeating at best.

B. The PTAB failed to ask whether a skilled artisan would have pursued the specific modifications claimed in the '149 Patent.

1. The motivation-to-modify inquiry is limited in another way: "to find a prima facie case of unpatentability," there must be "a showing that the prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (quotation marks omitted).

Again, *Sanofi-Synthelabo* and *Procter & Gamble* provide important guidance. In *Sanofi-Synthelabo*, this Court explained that, despite the prior art's teachings regarding enantiomers and salts generally, "nothing directed a chemist" wishing to reduce toxicity "to the particular enantiomer and salt, clopidogrel bisulfate, which is the limited subject matter of [the patent-in-suit]." 470 F.3d at 1379. That was so even though there were only two enantiomers from which to select. Likewise, in *Procter & Gamble*, the Court recognized that, given the "unpredictable nature of bisphosphonates at the time of the invention" and the state of knowledge regarding the prior-art compound's potency and toxicity, a skilled artisan "would not have been motivated to make the specific molecular modifications to make risedronate." 566 F.3d at 993.

In other words, motivation must be shown with particularity as to both the compound and the modification. It is not enough that the prior art would have motivated a skilled artisan to modify compound *x* in some nonspecific way. Nor is it

enough that the prior art would have motivated a skilled artisan to attempt modification *y* on some nonspecific compound. The challenger must show a motivation to make *the specific modified compound* claimed in the patent.

Here, neither a motivation to "modify ruxolitinib" nor a motivation to "deuterate" is a motivation to replace *four or eight particular hydrogen atoms* with deuterium. Without such a specific motivation, the skilled artisan would not arrive at the claimed compounds.

2. Once again, the PTAB ignored the appropriate inquiry. The Board held that the combined teachings of Rodgers, Shilling, and the Concert Backgrounder would have provided a skilled artisan with sufficient motivation to pursue the compounds claimed in the '149 Patent. Appx23-24. The Board's reasoning went as follows: (1) Rodgers discloses ruxolitinib; (2) Shilling teaches that oxidative metabolism occurs almost entirely on the cyclopentyl ring of ruxolitinib at Y^2 and Y^3 (*i.e.*, that those are its metabolic "hot spots"); and (3) the Concert Backgrounder teaches that deuteration has the potential to "create new chemical entities with improved safety, tolerability, and efficacy," and compounds should be selected for deuteration based on known metabolic "hot spots" and should be deuterated at some or all of these metabolic hot spots. Appx23-24.

That chain of inferences falls far short of demonstrating that a skilled artisan would have been motivated to produce the specific deuterated compounds claimed

in the '149 Patent. At most, the three references support a general motivation to deuterate compounds with known metabolic "hot spots." But as Incyte's own expert recognized, nearly *all* FDA-approved drugs have known metabolic hotspots. Appx9258-9261. Extending the Board's reasoning would lead to a conclusion that the prior art provides a skilled artisan with a reason to *deuterate all drugs*, based on the *potential* to create something new and valuable. Such reasoning fails to show why a skilled artisan would have *selected ruxolitinib* and deuterated it *in the particular manner claimed in the '149 Patent.* Motivation cannot be stated in such generalized terms. *Takeda*, 492 F.3d at 1361 ("[G]eneralization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other[.]").

The overbreadth of the PTAB's reasoning is perhaps best demonstrated by its treatment of the three particular compounds that were the focus of these proceedings: the one octa-deuterated and two tetra-deuterated compounds. The PTAB treated these three together, summarily concluding that a skilled artisan would have been motivated to "deuterate Rodgers's ruxolitinib compounds at their metabolic 'hot spots.'" Appx23. Even if that were correct, it does not explain why a person of ordinary skill in the art would have been motivated specifically to create the first tetra-deuterated compound (with deuteration at Y^2), as opposed to the second tetra-deuterated compound (with deuteration at Y^3), as opposed to the octa-deuterated

compound (with deuteration at Y^2 *and* Y^3)—let alone to create all three. The lack of a reasoned explanation for that key conclusion infects the PTAB's entire analysis.

Ultimately, the law asks whether the combination of the prior art teaches "specific molecular modifications." *Takeda*, 492 F.3d at 1356; *Procter & Gamble*, 566 F.3d at 993. The PTAB failed to answer that question altogether.

C. The Board disregarded whether a skilled artisan would have reasonably expected modifying the compound to result in beneficial changes.

The PTAB's application of §103 conflicts with this court's case law for an independent reason: the Board failed to ask whether a skilled artisan would have expected that deuterating ruxolitinib at several specific locations would produce a new compound with advantageous pharmacokinetic properties. According to the Board, it did not need to consider this question *at all*: what mattered was only whether a skilled artisan could physically create the claimed compounds, *regardless* of whether those compounds would be expected to work for their intended purpose. Appx31. But that is not the standard this Court has articulated. For that reason, too, the PTAB's decision should be reversed.

1. The second step of the obviousness analysis asks whether a skilled artisan would have "a reasonable expectation of success" in pursuing the claimed modifications. *Otsuka*, 678 F.3d at 1292. To prove the existence of such an expectation, a challenger must do more than show that a skilled artisan would have been able to

make the relevant modifications: the challenger must also show that the skilled artisan would have had a reasonable probability of achieving *the desired advantageous properties* of the claimed compound. *Cf. DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("[A] 'predictable result' . . . refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.").

This Court has repeatedly made that rule clear. In *Takeda*, for example, the Court considered whether it was obvious to modify the prior-art compound, "compound b," to form the claimed compound, pioglitazone, through two modifications known as "homologation" and "ring-walking." 492 F.3d at 1357. In conducting the reasonable-expectation analysis, the Court asked (1) whether the prior art provided a "reasonable expectation that [homologation of] compound b would *reduce or eliminate its toxicity*" and (2) whether ring-walking "would *result in beneficial changes*" (*i.e.*, whether it "would cause [compound b] to be more efficacious or less toxic"). *Id.* at 1360-1361 (emphasis added). In other words, even though the patent-in-suit claimed only the compound itself—not any of its particular properties—a reasonable likelihood of success meant more than just making the compound. The Court looked to the likelihood of achieving the *desired properties*, because without that likelihood, the skilled artisan would not make the attempt. *See id.* at 1353; *accord, e.g.*, *UCB,*

Inc. v. Accord Healthcare, Inc., 890 F.3d 1313, 1325 (Fed. Cir. 2018) (considering whether a skilled artisan would have had "a reasonable expectation [that modifications in question] would have yielded an *efficacious* anticonvulsant" (emphasis added)).

2. The Board departed from that precedent here. As Concert explained to the Board (*see* Appx31), a skilled artisan would have had no reasonable expectation of achieving an *in vivo* KIE from deuterating ruxolitinib—and certainly would not have been able to predict the advantageous effect of deuteration on the drug's clinical profile. *See supra*, pp. 8-13. That is, a skilled artisan would have had no expectation that deuterating ruxolitinib would improve the drug's pharmacokinetic properties so as to mitigate the risk of toxicity. *See id.* The Board did not dispute those facts—it just deemed them irrelevant on the ground that "the challenged claims [of the '149 Patent] do not recite any of those features." Appx31. According to the Board, the only question was whether a skilled artisan would have had "a reasonable expectation of successfully deuterating Rodgers's ruxolitinib compounds at their metabolic 'hot spots,' as identified by Shilling, and in the manner taught by the Concert Backgrounder." Appx31.

That holding is impossible to square with *Takeda*. There, as here, the challenged patent claimed the bare compound—without added limitations regarding its functional properties. *See* 492 F.3d at 1353. Yet *Takeda* did not conclude its

analysis by simply asking whether a skilled artisan could have *physically created* pioglitazone by applying homologation and ring-walking to compound b. *See id.* at 1360-1361. Instead, the Court asked whether those physical modifications would have led to "beneficial changes" in compound b, including reduced toxicity. *Id.* The same approach applies here: the question is not only whether it was physically possible to deuterate ruxolitinib at its metabolic hot spots, but also whether doing so was expected to improve its pharmacokinetic properties.

The PTAB's approach in this case also makes little sense in practice. The first part of the obviousness inquiry—motivation—clearly focuses on the artisan's *desired outcome*: does she have a reason to pursue *a particular result*? *See supra*, pp. 37-48. It only makes sense for the second part of the inquiry—expectation of success—to focus on the expectation of achieving *that outcome*: is she likely to achieve *that result*? In its inquiry, however, the PTAB failed to connect the motivation and reasonable expectation steps of the obviousness analysis, because the only reasonable expectation of success the Board required was expected success in making the claimed compounds. The Board's analysis never matched the motivation to any reasonable expectation of what would be achieved by making the compounds. The Court should reject that disjointed and illogical approach to the structural obviousness inquiry.

3. At the tail end of its reasonable expectation analysis, the Board asserted in passing that, "[i]nsofar as [the] motivation to [deuterate ruxolitinib at its known 'hot spots'] involved an expectation that these ruxolitinib analogs *may display* superior ADME properties as compared to non-deuterated ruxolitinib, we further find that . . . a skilled artisan would have had a reasonable expectation that the synthesized ruxolitinib analogs '*may display*' superior ADME properties . . . as explained above in our discussion of a motivation to combine." Appx32 (quotation marks and citations omitted). Even if a skilled artisan's belief that a particular art combination "may" result in benefits is enough for motivation to combine, it plainly is not enough for a reasonable expectation of success. After all, a skilled artisan could simultaneously believe that deuteration "may" be beneficial, "may" be disadvantageous, or "may" produce no change at all. Mere hopes about what "may" happen do not amount to a reasonable expectation of *success*: prior art that "provide[s] no more than hope" is "not enough to create a reasonable expectation of success in a highly unpredictable art such as this." *OSI Pharm., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019).

In suggesting otherwise, the Board effectively conflated the motivation and reasonable-expectation inquiries, draining the reasonable-expectation step of independent meaning. The Board's inability to find reasonable expectation of anything other than the *abstract possibility* of success only highlights that a skilled artisan

would *not* have had any reasonable expectation of success under the correct legal framework.

In any event, the Board's motivation finding is itself flawed. For the reasons discussed above, the pertinent question in assessing motivation is whether a skilled artisan would have sought the pharmacokinetic properties of deuterated ruxolitinib, and whether a skilled artisan would have been motivated to pursue the specific molecular modifications claimed in the '149 Patent to achieve those properties—not, as the PTAB would have it, whether the artisan would have generalized hopes of some similar properties. *See supra*, pp. 37-48. Having failed to explain what would motivate the artisan to make the claimed compounds, the Board cannot salvage its reasonable-expectation analysis by simply pointing back to that failed explanation.

4. Under the proper test, a person of ordinary skill in the art would not have had a reasonable expectation that deuterating ruxolitinib would have achieved a positive effect on ADME properties or metabolic processes so as to provide an improved toxicity profile. As discussed above, the pharmacokinetic properties of the claimed deuterated compounds were unpredictable *ex ante* in light of the nature of the catalytic process, the potential for metabolic switching, the likelihood of *in vivo* masking, and the fact that only some *in vivo* metabolic changes from deuteration result in positive changes to ADME. *See supra*, pp. 8-14. Indeed, even the Concert

Backgrounder—on which Incyte relies—highlights the unpredictability of deuteration and shows two distinctly different examples from among the various ways deuteration *might* affect the pharmacokinetic curve. *See* Appx1739. The PTAB's observation that deuterated compounds may have similar selectivity and potency misses the point: there was no reasonable expectation of success as to the *pharmacokinetic* properties that allegedly supplied the motivation to modify in the first place.

D. Accepting the Board's approach to structural obviousness would undermine innovation by making many new compounds obvious despite significant uncertainty and unpredictability.

As this Court has stressed, "predictability is a touchstone of obviousness." *DePuy*, 567 F.3d at 1326. The Board's motivation and reasonable expectation holdings remove predictability from the application of §103.

If accepted, the Board's logic would dramatically expand the number of compounds that, despite improving upon the prior art in a meaningful way, are nonetheless deemed obvious—effectively building hindsight bias into the structural obviousness inquiry. Here, the Board found a motivation to pursue the compounds in the '149 Patent based solely on general similarities between those compounds and ruxolitinib. And it found a realistic expectation of success based solely on the expectation that a skilled artisan could physically achieve the required deuteration, without looking back at *why* the artisan would make the deuterated compounds and

asking whether that skilled artisan could predict that deuteration "would have worked for [*that*] intended purpose." *DePuy*, 567 F.3d at 1326. But structurally similar molecules will often have *some* properties in common (as in *Sanofi-Synthelabo*, *see supra*, pp. 38-39, 41-42), and a trained chemist will often be able to piece together various molecules with a reasonable expectation of synthesizing a specific target chemical compound or structure having some properties in common. In short, if the approach taken by the Board is followed elsewhere, countless new compounds with advantageous properties will be deemed "obvious."

Nothing in §103 or this Court's case law requires invalidation of a patent for a new chemical compound without *any* showing of predictability. To the contrary, the relevant authorities show that the Board's approach is founded on legal error.

II. Objective indicia, including unexpected results and a long-felt need, demonstrate that the '149 Patent's claims are not obvious.

Where objective indicia of nonobviousness are present, they also "must be considered," as they "help[] inform the ultimate obviousness determination." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048-1049 (Fed. Cir. 2016) (en banc). Here, two objective indicia show that the '149 Patent is not obvious: unexpected results and the fulfillment of a long-felt need. The Board erred in its consideration of both.

A. CTP-543 exhibits unexpected results.

"Nonobviousness may be established when an invention yielded more than predictable results." *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (quotation marks and brackets omitted). "Unexpected results are useful to show the improved properties provided by the claimed compositions are much greater than would have been predicted." *Id.* (quotation marks omitted).

Here, the '149 Patent is supported by unusually strong evidence of *two* unexpected results: a different, flatter pharmacokinetic curve and a disproportionately large benefit for the fastest metabolizers. These results make it possible to use deuterated ruxolitinib in ways that could not have been anticipated. Yet, based on a combination of fundamental legal errors and a failure to understand the nature of these results, the PTAB refused to give these vital results any weight.

1. The PTAB erred in refusing to consider CTP-543's flatter pharmacokinetic curve.

a. Concert's clinical studies show that, relative to ruxolitinib, CTP-543 maintains drug levels within the desired therapeutic window for a longer period of time. *See supra*, p. 21. That is, CTP-543 is metabolized more slowly, but *without* a meaningful increase in C_{max}, which is associated with the drug's toxic side-effects. *See id.*. As a result, CTP-543 is more suitable than ruxolitinib for treating AA. *See*

id. While ruxolitinib's side-effects may be acceptable for treating the life-threatening diseases for which ruxolitinib is FDA-approved, they are undesirable for the treatment of AA. *See supra*, pp. 16-17.

The positive effect on the time in the therapeutic window was unexpected. As explained above, layers of uncertainty in the metabolism and clearance of the drug made it impossible to predict in advance what effect—if any—deuteration would have on ruxolitinib's pharmacokinetic profile. *See supra*, pp. 8-14. Yet the PTAB disregarded that unexpected outcome, dismissing it on the ground that deuteration's effect on ruxolitinib's ADME properties was "merely a difference in degree." Appx35 (citing *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013)). That conclusion, in turn, rested solely on the fact that deuteration's effect on the pharmacokinetic profile—the change it creates in the shape of the pharmacokinetic curve—can be expressed as an "*increased time* in the therapeutic window," a value that can be "measured by percentages." Appx35 (emphasis added).

b. The PTAB's simplistic holding misreads *Galderma* in two fundamental ways.

First, the Board took *Galderma* to say that any unexpected improvement that can be classified as a "difference in degree" is *categorically* irrelevant to the obviousness inquiry. Appx34-35. But *Galderma* does not establish such a hard-and-fast rule. *See* 737 F.3d at 739. To the contrary, this Court has made clear that while

"'differences in degree' of a known and expected property are not *as* persuasive in rebutting obviousness," they are nevertheless factors for consideration. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (emphasis added). In other words, the Board treated consideration of unexpected results as an on-off switch, but this Court has made clear that it is a sliding scale.

Second, the Board read *Galderma* to say that *any* unexpected result that can be expressed as a percentage change in a known property is an irrelevant "difference in degree." Appx34-35. But *Galderma* did not go so far: the decision said only that "an increase, by some percentage," of a certain property was "a difference in degree rather than kind, *where the modification of the percentage [was] within the capabilities of one skilled in the art at the time*." 737 F.3d at 739 (emphasis added). Here, nothing in the prior art suggested that the simultaneous modification of multiple properties making up ruxolitinib's pharmacokinetic profile *so as to provide a flatter pharmacokinetic curve* was "within the capabilities of one skilled in the art at the time." *Id.*; *see supra*, pp. 8-14.

If there were any doubt, this Court's post-*Galderma* decisions confirm that the PTAB is wrong in its all-percentage-differences-are-differences-in-degree reasoning. In *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265 (Fed. Cir. 2018), the Court held that a district court erred in disregarding an unexpected percentage improvement—"66% improved bioavailability"— where there was no evidence that a

skilled artisan would have *expected* that increase. *Id.* at 1274; *see also Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1374 (Fed. Cir. 2022) (discussing *Orexo*). The same is true here: Incyte offered no evidence that a skilled artisan would have expected CTP-543's flatter pharmacokinetic curve. The PTAB's decision to disregard that fact is inconsistent with *Orexo*.

The Board's decision is also logically flawed. Its reasoning is so sweeping that it would mean virtually no result is "unexpected," because many changes over the prior art can be expressed—in one way or another—as a percentage difference in some known property. For example, even if a structural modification increased a drug's potency by 5000%, the PTAB's *per se* approach would deem that difference an irrelevant change in "degree" because it could be expressed in percentage terms—notwithstanding dramatic differences in the ways in which the drug may be used. The PTAB erred in relying on such a bright-line rule.

c. Even if the law did allow the Board to disregard all "differences in degree," the unexpected results here are differences in kind. As described above, CTP-543's flatter pharmacokinetic curve provides a safer profile for an entirely new condition, AA, that could not be treated as safely by other drugs available on the priority date. *See supra*, pp. 18, 21.

That is a far cry from the "difference in degree" described in *Galderma*. There, the prior art taught that topical compositions containing 0.01% to 1% of the

drug adapalene could be used to treat acne, and that a 0.1% concentration was "optimal." 737 F.3d at 736-737. The patent at issue claimed a 0.3% adapalene composition—within the range disclosed by the prior art. *Id.* at 739. The patent owner argued that its patent was not obvious, however, because the 0.3% formulation displayed an "unexpected increase in efficacy" over the 0.1% formulation "by a small percentage." *Id.* This Court disagreed, holding that "the comparable tolerability of 0.1% and 0.3% adapalene does not indicate that the asserted claims are non-obvious." *Id.*

Unlike the improvement in *Galderma*, here the claimed invention is substantially different from the prior art in ways that allow for a potentially safer and more effective treatment of an entirely new condition. The pharmacokinetic differences demonstrated by the different shape of CTP-543's pharmacokinetic curve represents a fundamental shift in how the drug is metabolized and distributed in the body; it is thus a difference in kind. Moreover, the 0.3% composition in *Galderma* fell within the range that the prior art considered effective for acne treatment—the only thing that was "unexpected" was that it compared favorably to the "optimal" 0.1% treatment. Nothing in the prior art taught that CTP-543, a novel compound, would have properties that are especially beneficial for treating AA.

2. The PTAB misunderstood the unexpected and disproportionately large benefit experienced by the fastest metabolizers.

Different people metabolize drugs at different rates: some individuals rapidly metabolize a given drug, while others do so more slowly. Skilled artisans would have expected that, if deuteration succeeded in decreasing the rate of metabolism of ruxolitinib (thus increasing its half-life), the relative change would have been similar across all patients—*i.e.*, the half-life would increase by the same percentage for both slower and more rapid metabolizers. *See supra*, pp. 22-23. Contrary to those expectations, however, the relative change in half-life between ruxolitinib and CTP-543 demonstrated an *inverse* relationship to a given patient's rate of metabolism for ruxolitinib. *See id.* That is, the patients with the *shortest* half-life for ruxolitinib (*i.e.*, those who metabolized the drug most quickly) demonstrated the *greatest* relative increase in half-life with CTP-543—an effect not known in the prior art. *See id.*

It is not clear that the Board even grasped this unexpected result. The Board described the change as an "increase in the same clinical activity observed with ruxolitinib." Appx35. That inapt description fails to capture both the nature and importance of the unexpected benefit for more rapid metabolizers. As a result of this inverse relationship, a greater percentage of the patient population will remain within

the therapeutic window longer, because patients who would rapidly metabolize ruxolitinib are more likely to obtain a clinical response on CTP-543. *See supra*, pp. 22-23.

Even assuming that the Board understood the nature of this unexpected result, it erred in failing to analyze that result beyond the surface level. Rather than appreciate the wholly new property of CTP-543, the Board simply assumed that *any* change that can be expressed as a numeric change to some known property is a "difference in degree." Appx34-35. But that characterization fails to capture the meaningful difference here: the inverse relationship results in a substantial reduction in variability between patients in their response to the drug. That is a difference in kind; the result is different from any found in the prior art, and it substantially broadens the patient population who can access a viable AA therapy—a condition for which there was no treatment as of the priority date.

B. CTP-543 satisfies a long-felt need for AA treatment.

Still another consideration supports the nonobviousness of the '149 Patent: Concert's novel octa-deuterated compound, CTP-543, meets the longstanding need for a viable AA treatment. As this Court has explained, "[e]vidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *Apple*, 839 F.3d at 1056. That principle applies here.

The PTAB did not dispute the existence of a long-felt need for AA treatment. Appx35-37. Nor could it. As discussed above, AA is a serious autoimmune disease that causes hair loss and often leads to significant psychological distress. *See supra*, p. 18. In 2012, no suitable compound had been identified to treat the condition: any potential treatments promised little efficacy and carried potentially significant side-effects. Ruxolitinib, for example, poses a risk of anemia and thrombocytopenia that makes the drug unsuitable for chronic, maintenance treatment for AA. In short, there was a long-felt need for an AA treatment.

CTP-543 satisfies this long-felt need. Concert's clinical studies have shown that CTP-543 improves ruxolitinib's pharmacokinetic and ADME profile, resulting in a longer period of time following each dose during which the drug's plasma concentrations are within the safe and effective therapeutic window. *See supra*, p. 21. CTP-543 therefore provides a much more favorable profile than ruxolitinib for treating AA patients. *See id.* Even the FDA has recognized CTP-543's promise in satisfying the need for AA treatment: the agency granted CTP-543 "Fast Track" and "Breakthrough Therapy" designations, which expedite the review of therapies that treat serious conditions and fill unmet medical needs. *See supra*, pp. 19-20.

The PTAB did not dispute any of this evidence. Instead, the PTAB's sole basis for concluding that CTP-543 does not fulfill a long-felt need is that CTP-543 had not yet received final FDA marketing approval by the close of evidence.

Appx36-37. But the Board's reasoning is flawed: the relevant question is whether the claimed invention *in fact* satisfied a long-felt need that others had not solved, *see Apple*, 839 F.3d at 1056, not whether it had jumped through all the hoops necessary to receive particular regulatory approval.

This Court has already rejected logic akin to that adopted by the Board here. In *Procter & Gamble*, the challenger argued that the question of long-felt need should be measured "at the time the invention becomes available on the market, when it can actually satisfy that need." 566 F.3d at 998. The Court rejected that argument, explaining that "we look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need" showing that the solution was nonobvious as of that time. *Id.* The patented invention "met such a need" as of the "filing date," *id.*, even though it did not come on the market until *fifteen years later*. *See id.* at 998 n. 2; *Procter & Gamble*, 536 F. Supp. 2d at 496.

That reasoning cannot be squared with the PTAB's decision. Like the obviousness analysis generally, long-felt need is assessed as of "the filing date." *Procter & Gamble*, 566 F.3d at 998. Plainly that assessment cannot depend on achieving final FDA approval before even filing for a patent. Under the PTAB's approach, by contrast, the question of obviousness for a pharmaceutical compound would turn on when the invalidity challenge is brought and whether the FDA completes its review

before the factfinder does. That is wrong: an invention and its unexpected properties either are obvious on the date of filing or they are not.

Here, *all* available evidence in the record points towards the conclusion that CTP-543 satisfies the long-felt need for AA treatment—and Incyte has offered no evidence to the contrary. Indeed, the PTAB's single-minded focus on the question of final FDA marketing approval is particularly perverse in this case, because it led the Board to ignore what the FDA has *already said* on the subject of CTP-543—which is that, by all available evidence, CTP-543 is being developed to "treat [a] serious condition[] and fill an unmet medical need." *Supra*, p. 19.

III. Concert preserves its challenge relating to Director review.

Parties in IPRs are entitled to review by "an officer properly appointed to a principal office." *Arthrex*, 141 S. Ct. at 1985; *see also id.* at 1987 (plurality opinion); *id.* at 1997 (Breyer, J., concurring in the judgment in relevant part). The official who denied Concert's request for Director review, Andrew Hirshfeld, was not a properly appointed principal officer. He was not named by the President or confirmed by the Senate either to his permanent job, *see* 35 U.S.C. §3(b)(2)(A), or to his temporary leadership role of the PTO. Nor was he the "Acting Director" of the PTO within the meaning of the Vacancies Reform Act, because he was not the first assistant to the previous Director and had not been named Acting Director by "the President (and

only the President)." 5 U.S.C. §3345(a)(3). In short, he could not issue a final decision under *Arthrex*. This argument is now foreclosed by Circuit precedent, *see Arthrex, Inc. v. Smith & Nephew, Inc.*, 35 F.4th 1328, 1332-1340 (Fed. Cir. 2022), but Concert preserves it for purposes of further review. *See* Appx11447-11448 (making this argument below).

CONCLUSION

The Court should reverse the PTAB's decision.

June 27, 2022

Respectfully submitted.

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ADDENDUM TABLE OF CONTENTS

Agency Orders:

Patent:

Trials@uspto.gov
571.272.7822

Paper No. 119
Entered: April 8, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION,
Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2017-01256
Patent 9,249,149 B2

Before ERICA A. FRANKLIN, TINA E. HULSE, and RICHARD J. SMITH, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Incyte Corporation ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–15 of U.S. Patent No. 9,249,149 B2 (Ex. 1001, "the '149 patent"). Paper 1 ("Pet."). Concert Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). Initially, the Board denied institution of an *inter partes* review of those claims based upon all grounds asserted in the Petition, i.e., one anticipation and two obviousness grounds. Paper 9. Thereafter, Petitioner filed a Request for Rehearing relating to the two obviousness grounds asserted. Paper 12. The rehearing request was granted. Paper 13. On April 9, 2018, the Board instituted an *inter partes* review of claims 1–15 based upon one of the asserted obviousness grounds. Paper 14 ("Inst. Dec.").

On May 9, 2018, in view of *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), the Board modified the institution decision to include all of the challenged claims and all of the grounds asserted in the Petition. Paper 19. Subsequently, with Board authorization, the parties filed a Joint Motion to Limit the Petition, requesting that the Petition and *inter partes* review be limited to the two obviousness grounds asserted. Paper 20. The Board granted the joint motion and, thereby, removed the anticipation ground from this proceeding. Paper 21.

Thereafter, Patent Owner filed a Patent Owner Response to the Petition. Paper 27 ("PO Resp."). Petitioner filed a Reply to the Patent Owner Response. Paper 62 (sealed), Paper 70 (public), (collectively "Reply").[1] Patent Owner filed an Amended Sur-Reply to Petitioner's Reply

[1] The Board previously granted Patent Owner's Unopposed Motion for Entry of a modified version of the Default Standard Protective Order.

to Patent Owner's Response. Paper 85. Petitioner filed a Sur-Sur-Reply to Patent Owner's Amended Sur-Reply. Paper 89.

Patent Owner filed a Contingent Motion to Amend. Paper 44 ("Amend Mot."). Petitioner filed an Opposition to the Contingent Motion to Amend. Paper 63 (sealed), Paper 71 (public), (collectively, "Amend Opp."). Patent Owner filed an Amended Reply to Petitioner's Opposition to the Motion to Amend. Paper 84. Petitioner filed a Sur-Reply to Patent Owner's Reply to Opposition to Motion to Amend. Paper 93 (sealed), Paper 100 (public).

Petitioner filed a Motion for Additional Discovery. Paper 31. Patent Owner filed an Opposition to the Motion for Additional Discovery. Paper 33. Petitioner filed a Reply to the Opposition. Paper 42. We granted the motion, in part. Paper 54.

Petitioner also filed a Motion to Exclude. Paper 94 ("Exclude Mot."). Patent Owner filed an Opposition to the Motion to Exclude. Paper 102 ("Exclude Opp."). Petitioner filed a Reply to Patent Owner's Opposition. Paper 103.

Patent Owner filed a Motion to Submit Supplemental Information. Paper 105. Petitioner filed an Opposition to Patent Owner's Motion to Submit Supplemental Information. Paper 109 (sealed). We denied the motion. Paper 118.

Paper 16. The parties have filed a number of motions to seal, many of which are contested. The Board has addressed each of those motions. Papers 101 and 117.

On January 25, 2019, the parties presented arguments at an oral hearing. Paper 98. The hearing transcript has been entered in the record. Paper 113 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–15 of the '149 patent are unpatentable. *See* 35 U.S.C. § 316(e). Additionally, we deny the Contingent Motion to Amend. We also decide the Motion to Exclude in this Final Written Decision.

A. Related Proceedings

The parties identify pending U.S. Patent Application No. 14/570,954 as a related matter to this proceeding. Pet. 1; Paper 5, 1. The '149 patent is a continuation of that application.

B. The '149 Patent

The '149 patent is entitled "Deuterated Derivatives of Ruxolitinib," and issued on February 2, 2016. Ex. 1001, [54], [45]. According to the '149 patent, many current medicines suffer from poor adsorption, distribution, metabolism, and/or excretion ("ADME") properties that limit their use for certain indications. *Id.* at 1:20–23. For example, rapid metabolism can cause drugs to be cleared too rapidly from the body, decreasing the drugs' efficacy in treating a disease. *Id.* at 1:28–31. Another ADME limitation is the formation of toxic or biologically reactive metabolites. *Id.* at 1:39–40.

The cytochrome P450 enzyme ("CYP") is typically responsible for hepatic metabolism of drugs. *Id.* at 1:52–54. As such, the '149 patent identifies deuterium modification as a "potentially attractive strategy for improving a drug's metabolic properties." *Id.* at 2:5–6.

Deuterium modification involves replacing one or more hydrogen atoms of a drug with deuterium atoms in an attempt to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites. *Id.* at 2:6–10. Because deuterium forms stronger bonds with carbon than hydrogen, in certain cases, that stronger bond strength can positively impact the ADME properties of a drug, resulting in the potential for improved drug efficacy, safety, and/or tolerability. *Id.* at 2:11–15.

According to the '149 patent, however, studies measuring deuterium substitution's effect on overall metabolic stability have reported variable and unpredictable results. *Id.* at 2:32–35. The '149 patent explains that the effects of deuterium modification on a drug's metabolic properties are not predictable "even when deuterium atoms are incorporated at known sites of metabolism." *Id.* at 2:42–44. As such, the Specification states that determining whether and how deuterium modification affects the metabolism rate of a drug requires actually preparing and testing the deuterated drug. *Id.* at 2:44–47. Thus, the '149 patent states that "[t]he site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug." *Id.* at 2:49–52.

The Specification describes ruxolitinib phosphate as a heteroaryl-substituted pyrrolo [2,3-d]pyrimidine that inhibits Janus Associated Kinases 1 and 2 ("JAK1" and "JAK2"). Those "kinases mediate the signaling of a number of cytokines and growth factors important for hematopoiesis and immune function." *Id*. at 2:53–61. Ruxolitinib phosphate is an approved drug for treating patients with intermediate or high-risk myelofibrosis. *Id.* at 2:66–67. Other potential applications for the drug include treating essential

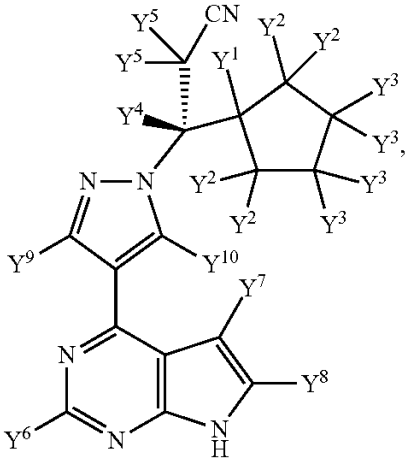
thrombocytopenia, psoriasis, and various forms of cancer. *Id.* at 3:3–6. Thus, according to the Specification, "[d]espite the beneficial activities of ruxolitinib, there is a continuing need for new compounds to treat the aforementioned diseases and conditions." *Id.* at 3:19–21.

C. Illustrative Claims

Petitioner challenges claims 1–15 of the '149 patent, of which claims 1 and 9 are the only independent claims. Claims 1 and 9 are illustrative and are reproduced below:

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is a hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9, and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

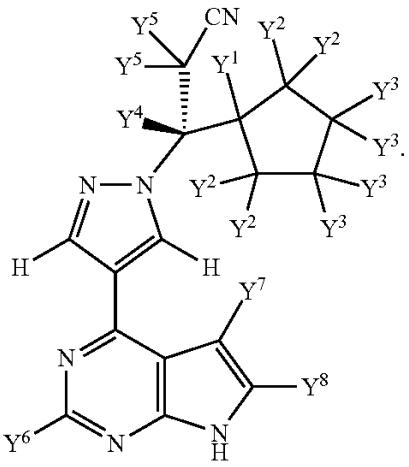
each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

Ex. 1001, 36:17–53.

Claim 9 is similar to claim 1, except that it is directed to Formula I, which is reproduced below:

Formula I



Formula I is similar to Formula A, except that Y^9 and Y^{10} of Formula A are both hydrogen in Formula I.

Claims 2–7 and 10–14 depend from claim 1 or claim 9 and recite specific deuteration patterns of ruxolitinib. Claims 8 and 15 depend from claim 1 and claim 9, respectively, and recite a pharmaceutical composition of claim 1 or claim 9, and a pharmaceutically acceptable carrier.

D. Instituted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–15 of the '149 patent on the following two obviousness grounds:

References	Basis	Claims challenged
Rodgers,[2] Shilling,[3] and Concert Backgrounder[4]	§ 103	1–15
Jakafi Label,[5] Shilling, and Concert Backgrounder	§ 103	1–15

Petitioner also relies on the Declarations of F. Peter Guengerich, Ph.D. (Ex. 1002), Jerry Shapiro, M.D. (Ex. 1117), and Ronald A. Thisted, Ph.D. (Ex. 1129). Patent Owner relies on the Declarations of Scott Harbeson, Ph.D. (Ex. 2001 and Ex. 2071, sealed; Ex. 2079, public), Thomas B. Baille, Ph.D., D.SC. (Ex. 2002), Julian Mackay-Wiggan, M.D., M.S. (Ex. 2048), Paul Ortiz de Montellano, Ph.D. (Ex. 2057), and Dr. Cameron Cowden, Ph.D. (Ex. 2122, sealed; Ex. 2123, public).

II. ANALYSIS

A. Person of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v.*

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[2] Rodgers et al., US 7,598,257 B2, issued Oct. 6, 2009 ("Rodgers," Ex. 1007).
[3] Shilling et al., *Metabolism, Excretion, and Pharmacokinetics of [^{14}C]INCB018424, a Selective Janus Tyrosine Kinase ½ Inhibitor, in Humans*, 38 DRUG METABOLISM AND DISPOSITION 2023–31 (2010) ("Shilling," Ex. 1005).
[4] CoNCERT Pharmaceuticals, Inc. PRECISION DEUTERIUM CHEMISTRY BACKGROUNDER ("Concert Backgrounder," Ex. 1006).
[5] Jakafi Prescribing Information (revised 11/2011) ("Jakafi Label," Ex. 1004).

VSI Int'l Inc., 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art as of June 15, 2012, would have had a "master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline," or a lesser degree with more experience. Pet. 9 (citing Ex. 1002 ¶¶ 15–18). Patent Owner asserts that human drug development experience "is a necessary part of the POSA definition." PO Resp. 40. Accordingly, Patent Owner asserts the following definition for a person of ordinary skill in the art at the time of the invention:

> A person of ordinary skill in the art would typically have had a master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline. Alternatively, the person of ordinary skill in the art may have had a lesser degree in one of those fields, but accompanied by more experience. To the extent necessary, a person of ordinary skill in the art may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds, developing drugs for human use, including analyzing human pharmacokinetic, pharmacodynamic, and ADME parameters and conducting and evaluating *in vitro* testing, human *in vivo* testing, and/or treating JAK1 or JAK2-mediated diseases and disorders in humans.

Id. at 39–40 (citing Ex. 2048 ¶ 5).

Based on the record as a whole, we determine that an appropriate description of the level of ordinary skill in the art incorporates Petitioner's definition with a portion of Patent Owner's definition, wherein,

> A person of ordinary skill in the art would typically have had a master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline. Alternatively, the person of ordinary skill in the art may have had a lesser degree in one of those fields, but accompanied by more experience. To the extent necessary, a person of ordinary skill in the art may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds and developing drugs for human use.

We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "'where the prior art itself reflects an appropriate level and a need for testimony is not shown'" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the Specification of the patent in which they appear. 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings).[6] Under that standard, and absent any

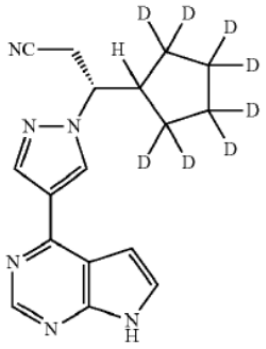
[6] A recent change to the claim construction standard for *inter partes* reviews does not apply here based on the filing date of the Petition. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (October 11, 2018) (amending 37 C.F.R. § 42.100(b), effective Nov. 13, 2018).

special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

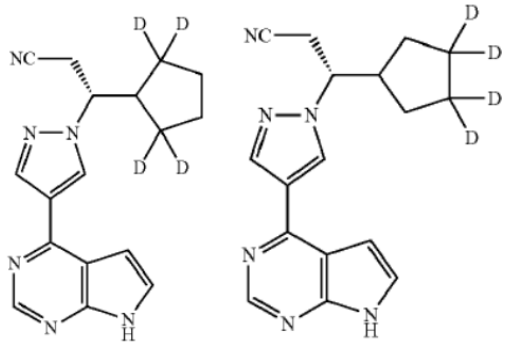
Petitioner asserts that the claim term "'D' or 'deuterium' is defined in the '149 [p]atent as meaning that the position has 'deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).'" Pet. 24 (quoting Ex. 1001, 3:65–43). We recognize that Specification definition and accept it as the broadest reasonable construction for the term.

The parties do not assert that any other claim term requires express construction for purposes of this Decision. We agree. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review)).

We note, however, that Petitioner limits its analysis to three compounds that it contends are covered by each of the claims. Specifically, Petitioner asserts that claims 1, 2, 5–7, 9, 10, 13, and 14 each read on the following "octa-deuterated" ruxolitinib analog, which is reproduced below:



Pet. 8. The "octa-deuterated" ruxolitinib analog replaces each Y^2 and Y^3 hydrogen with deuterium. Petitioner also asserts that claims 1–4, 6, 7, 9–12, and 14 each read on the following "tetra-deuterated" ruxolitinib analogs, which are reproduced below:



Id. The "tetra-deuterated" ruxolitinib analogs replace each Y^2 or each Y^3 hydrogen with deuterium. Patent Owner asserts that "the challenged claims cover variations [of] deuterated compounds," but does not dispute Petitioner's contention that the above-described three compounds are covered by the claims. PO Resp. 39.

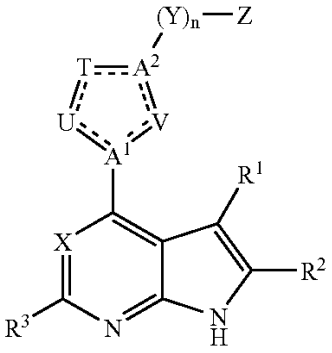
Having considered the compounds and the claims, we agree that the challenged claims encompass the three compounds as set forth by Petitioner.

C. Obviousness over Rodgers, Shilling, and Concert Backgrounder

Petitioner asserts that claims 1–15 are unpatentable as obvious over the combination of Rodgers, Shilling, and the Concert Backgrounder. Pet. 50–55. Patent Owner disagrees. PO Resp. 46–71.

1. Rodgers

Rodgers is a U.S. Patent directed to heteroaryl substituted pyrrolo[2,3-b]pyridines and heteroaryl substituted pyrrolo[2,3-b]pyrimidines that modulate the activity of Janus kinases and are useful in treating diseases related to the activity of Janus kinases. Ex. 1007, 1:18–22.[7] The compounds of Rodgers's invention have "Formula I," including pharmaceutically acceptable salt forms or prodrugs. *Id*. at 8:17–36. An illustration of Rodgers's Formula I is reproduced below:



Id. at 7:20–37. Rodgers's Formula I, reproduced above, includes numerous possibilities for each constituent member. *Id.* at 7:38–11:20. Rodgers states that its invention includes all stereoisomers, such as enantiomers and diastereomers (unless otherwise indicated). *Id.* at 31:32–34. Compounds of

[7] We use traditional patent citation for Rodgers and we cite to the original page numbers for Shilling and the Concert Backgrounder, rather than the page numbers assigned by Petitioner.

the invention also include "all isotopes of atoms occurring in the intermediates or final compounds. . . . For example, isotopes of hydrogen include tritium and deuterium." *Id.* at 32:13–17. Claims 1–3 recite ruxolitinib and its isomer. *Id.* at 374:12–20 (claims 1–3). Claim 4 recites a "composition comprising the compound of any one of claims 1 to 3 . . . and at least one pharmaceutically acceptable carrier." *Id*. at 374:21–23.

2. Shilling

Shilling teaches that ruxolitinib (INCB018424) is an orally active and "potent, selective inhibitor of Janus tyrosine kinase 1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis." Ex. 1005, 2023. Shilling discloses a study of the metabolism, excretion, and pharmacokinetics of ruxolitinib. *Id.* In its study, Shilling identifies two major metabolites of ruxolitinib: M18 (2-hydroxycyclopentyl ruxolitinib) and M16/M27 (3-hydroxycyclopentyl ruxolitinib). *Id.* at 2030.

3. Concert Backgrounder

The Concert Backgrounder discloses the product platform of "CoNCERT Pharmaceuticals, Inc." Ex. 1006, 2. The Concert Backgrounder explains the potential benefits of deuterium modification, including improved safety, better tolerability, and enhanced efficacy. *Id.* at 3. The Concert Backgrounder states, however, that "the magnitude and nature of the deuterium benefit cannot be predicted *a priori*, [so] CoNCERT must test multiple compounds in a range of assays to identify those that are differentiated." *Id.*

4. Public Accessibility of the Concert Backgrounder

As an initial matter, we address Patent Owner's contention that Petitioner has failed to carry its burden of proving that the Concert Backgrounder is a prior art printed publication. PO Resp. 40.

Whether a particular reference qualifies as a printed publication "is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis." *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). It is Petitioner's burden to prove that a relied upon cited reference is a printed publication. *Medtronic, Inc. v. Barry*, 891 F.3d 1368, 1380 (Fed. Cir. 2018) (citing *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350–51 (Fed. Cir. 2016)); *see also Jazz Pharms., Inc. v. Amneal Pharms., LLC*, 895 F.3d 1347, 1356 (Fed. Cir. 2018) (citation omitted) ("IPR Petitioner [] had the burden to prove that a particular reference is a printed publication.").

The Federal Circuit has explained that "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *Blue Calypso*, 815 F.3d at 1348 (quoting *Hall*, 781 F.2d at 899). "'A given reference is "'publicly accessible'" upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.'" *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

In the Petition, Petitioner asserts that the Concert Backgrounder is prior art under at least pre-AIA 35 U.S.C. § 102(b) because it was "publically accessible by at least January 27, 2009, as shown in the cached WebCite®

page (Ex. 1016)[8]." Pet 27. Petitioner asserts that the cached WebCite® page was "readily accessible to the public as indicated by the WebCite® description of its services." *Id*. at 27–28. As further evidence that the Concert Backgrounder was publicly accessible via the cached WebCite®, Petitioner also relies on Exhibit 1018,[9] a law review article published in 2009 that includes the same WebCite® page in the citation for the Concert Backgrounder. *Id*. at 28. Additionally, Petitioner asserts that the Concert Backgrounder was cited in an International Search Report for a Concert PCT application. *Id*.; Ex. 1021.[10] According to the International Search Report, the WebCite® Concert Backgrounder page was accessed on May 12, 2011. Ex. 1021, 3. In the Institution Decision, the Board made a preliminary determination that Petitioner's evidence provided a sufficient showing, at that stage in the proceeding, regarding the public accessibility of the Concert Backgrounder. Inst. Dec. 17.

In the Patent Owner Response, Patent Owner asserts that Petitioner has failed to meet its burden by relying "on a 'cached WebCite® page' to demonstrate public accessibility," because "availability on the internet alone is not sufficient to show public accessibility." PO Resp. 41. Patent Owner asserts that Petitioner has not provided "evidence that WebCite® was catalogued or indexed such that POSAs would have been able to access the Concert Backgrounder on WebCite®, whether through search engine results or by a search of WebCite® itself." *Id*. at 43. Patent Owner asserts that

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[8] WebCite®, page http://www.webcitation.org/5e81SGCnl (Ex. 1016).
[9] Kristen C. Buteau, *Deuterated Drugs: Unexpectedly Nonobvious?*, J. HIGH TECH. LAW 22–74 (2009) (Ex. 1018).
[10] International Search Report PCT/US2011/025472, published August 21, 2011 (Ex. 1021).

Petitioner's evidence establishes only that the Concert Backgrounder was available on WebCite® in 2009, and that the author of the law review article and the examiner who completed the International Search Report both "possessed the full WebCite address for the Concert Backgrounder." *Id*. at 44–45.

In response to the discovery requests that we authorized Petitioner to serve on Patent Owner relating to the Concert Backgrounder, Paper 54, Patent Owner admits that the Concert Backgrounder is "a true and correct copy of a document prepared by, or on behalf of, Patent Owner," but asserts that it does not have sufficient information to admit or deny (1) whether that document was prepared in 2007, (2) that the 2007 copyright date on the document is accurate, or (3) that the document was distributed to business partners between 2007 and 2009. Ex. 1139, 3–5. Patent Owner, however, acknowledges that it submitted an Information Disclosure Statement, dated November 7, 2011, which listed the Concert Backgrounder with a 2007 date, and "retrieved from the Internet: URL: http//www.webcitation.org/5e81SGCnl." *Id*. at 6. According to Patent Owner, that action "reflects Concert's practice of submitting to the Patent Office documents cited by an examiner in a European Search Report of a counterpart application." *Id*.

Thus, Petitioner has provided evidence that the specific webcitation.org website containing the Concert Backgrounder was disseminated and accessible to at least patent examiners and an author of a law review article before the critical date because those individuals interested in the art possessed the precise website URL that functioned as a link to the reference. Further, the evidence allows us to infer that Concert

Backgrounder was viewed or downloaded by those individuals before the critical date, as they referenced it in their own published documents. Those factors overcome the absence of evidence demonstrating that the website containing the article was indexed or catalogued in a manner that was findable by an internet search engine. As a result, we find Petitioner has demonstrated that the Concert Backgrounder was "'sufficiently accessible to the public interested in the art'" so as to allow a determination that the reference is a printed publication. *Blue Calypso*, 815 F.3d at 1348 (quoting *In re Cronyn*, 880 F.2d 1158, 1160 (Fed. Cir. 1989).

Moreover, as the Federal Circuit has explained, "the presence of a 'research aid' can also establish public accessibility." *Id*. at 1350 (citing *Bruckelmyer*, 445 F.3d at 1379). In the Reply, Petitioner asserts that the same link to access the document that was disseminated to and accessed by the patent examiners and law review article author was subsequently published by those individuals, before the critical date, in a search report, an Information Disclosure Sheet, and a law review article directed to deuterated drugs, allowing others interested and ordinarily skilled in the subject matter exercising reasonable diligence to similarly access the document using the same webcitation.org website. Pet. Reply 62, 23–26.

We have considered Patent Owner's arguments challenging the sufficiency of Petitioner's evidence, *see* PO Sur-Reply 2–4, however, it is apparent that the published items containing the webcitation.org URL would have provided a skilled artisan with a sufficient roadmap to the Concert Backgrounder. *See Blue Calypso*, 815 F.3d at 1350 ("An adequate roadmap . . . should at least provide enough details from which we can determine that an interested party is reasonably certain to arrive at the destination: the

potentially invalidating reference."). Indeed, the Federal Circuit has recognized that "a published article with an express citation to the potentially invalidating reference would similarly provide the necessary guidance." *Id.* Such is the case here.

Accordingly, based on the facts in this case, we determine that Petitioner's evidence demonstrating publication of the Concert Backgrounder on the internet, along with the dissemination of the website to patent examiners and an author of a law review article directed to the subject matter of the reference, provides "a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l*, 511 F.3d at 1194 (quotation marks and citation omitted).

Moreover, based upon the record as a whole, we find that Petitioner's evidence demonstrates that the patent documents and law review article published by those individuals function as "research aids" because they included as an express citation to the Concert Backgrounder a link to its location on the internet. Thus, we conclude that Petitioner has met its burden of demonstrating that the Concert Backgrounder was publicly accessible prior to the critical date so as to render it a "printed publication" under § 102(b). As a result, we recognize the Concert Backgrounder as prior art.

5. Obviousness Analysis

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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 the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

We generally follow a two-part inquiry to determine whether a new chemical compound would have been obvious over particular prior art compounds. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012). First, we determine "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.* at 1291. Second, we analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Id.* at 1292.

(a) Lead Compound

A lead compound is defined as "'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*, 678 F.3d at 1291 (quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). Stated another way, "a lead compound is 'a natural choice for further development efforts."' *Id*. (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). Importantly, the analysis of whether a person of ordinary skill in the art would have chosen the prior art compound as a lead compound "is 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." *Id.* at 1292 (citations omitted).

Based on our review of the record as a whole, we determine that the preponderance of the evidence supports finding that a person of ordinary skill in the art would have chosen ruxolitinib as a lead compound. It is "the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Otsuka*, 678 F.3d at 1292–93 (quotation marks and citation omitted). As Petitioner notes, Rodgers expressly claims ruxolitinib and its isomers. Pet. 50; Ex. 1007, claims 1–3. Moreover, Shilling states that ruxolitinib is "a potent, selective inhibitor of Janus tyrosine kinase1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis." Ex. 1005, Abstract.

Thus, we find that the Rodgers and Shilling demonstrate "useful properties" of ruxolitinib that would have led a person of ordinary skill in the art to choose ruxolitinib as a lead compound to make structurally similar compounds. *See Otsuka*, 678 F.3d at 1292–93. Patent Owner does not argue otherwise. Rather, Patent Owner asserts that there would have been a lack of motivation to modify ruxolitinib in the manner proposed by Petitioner, i.e., deuteration, and no reasonable expectation of success in doing so. PO Resp. 46–66. We address those arguments, in turn, below.

(b) Reason to Make the Claimed Compounds/Composition

Petitioner asserts that Rodgers discloses the compound and isomer that is ruxolitinib and teaches that the compounds of its invention include those in which hydrogen is replaced with deuterium isotopes. Pet. 50 (citing

Ex. 1007, 3[2]:13–17, Claims 1–3; Ex. 1002 ¶¶ 130, 133). According to Petitioner and its declarant, Dr. Guengerich, the "octa-deuterated" and "tetra-deuterated" ruxolitinib analogs recited in the challenged claims, *see* Pet. 25 (asserting which challenged claims read on the octa-deuterated or tetra-deuterated ruxolitinib analogs), differ only by the deuteration of the cyclopentyl ring (i.e., different isotopes of the same atom). Pet. 30 (citing Ex. 1002 ¶ 33). Petitioner asserts that a person of ordinary skill in the art would have been motivated to modify Rodgers's ruxolitinib compounds to yield the claimed subject matter based upon the teachings of Shilling and the Concert Backgrounder. *Id*. at 51.

In particular, Petitioner asserts that Shilling teaches that oxidative metabolism occurs almost entirely on the cyclopentyl ring of ruxolitinib at Y^2 and Y^3. Pet. 50–51 (citing Ex. 1002 ¶¶ 130–134; Ex. 1007, 3:13–17; Ex. 1005). Petitioner asserts that the Concert Backgrounder explains that "deuterium substitution has the potential to create new chemical entities with improved safety, tolerability, and efficacy" and that deuterium compounds useful for this technique are "based on drugs with known efficacy and safety that address clinically validated targets." *Id*. at 51–52 (citing Ex. 1006, 2; Ex. 1002 ¶¶ 71–73, 136). According to Dr. Guengerich, the Concert Backgrounder also teaches that compounds should be selected that have known "metabolic 'hot spots'" and should be deuterated at some or all of these metabolic hot spots. Ex. 1002 ¶ 136. Therefore, according to Petitioner, a person of ordinary skill in the art "would have been motivated to apply the techniques disclosed in the Concert Backgrounder to ruxolitinib and/or the deuterated ruxolitinib of Rodgers because ruxolitinib was a claimed compound of the invention in Rodgers and ruxolitinib contained

well-identified sites of oxidative metabolism in *in vivo* metabolism, as shown in Shilling." Pet. 54 (citing Ex. 1002 ¶¶ 135–136). Additionally, Petitioner asserts that Shilling and the Concert Backgrounder provide a motivation to make the recited tetra- and octa-deuterated ruxolitinib analogs and compositions because those references suggest that such analogs may display superior ADME properties. *Id*. at 31.

Further, Petitioner asserts that the motivation is supplied by the fact 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." Pet. 30 (quoting *Aventis Pharma Deutschland GmbH v. Lupin Ltd*., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (citing *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990)). According to Petitioner, a person of ordinary skill in the art would have known that "deuterium-substituted compounds retain their . . . selectivity and potency comparable to their hydrogen analogs." *Id*. (citing Ex. 1002 ¶ 55); Ex. 1013,[11] 5 ("At Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterated it.'").

Based upon our review of the record as a whole, we find that the preponderance of the evidence supports Petitioner's assertion that the combined teachings of Rodgers, Shilling, and the Concert Backgrounder would have provided a person of ordinary skill in the art a reason to deuterate Rodgers's ruxolitinib compounds at their metabolic "hot spots," as identified by Shilling, in the manner taught by the Concert Backgrounder to

[11] A. Yarnell, *Heavy-Hydrogen Drugs Turn Heads Again*, 87 CHEM. ENG'G NEWS 36–39 (2009) (Ex. 1013).

achieve the potential benefits that the Concert Backgrounder disclosed, e.g., improved safety, tolerability, and efficacy. We also determine that the preponderance of the evidence supports Petitioner's assertion that a motivation to make deuterated ruxolitinib compounds and compositions exists based upon the structural similarity between those claimed compounds and the prior art compounds, as evidenced by the testimony of Dr. Guengerich, Ex. 1002 ¶ 55, and the remarks by a Concert representative in an article published in the Chemical & Engineering News journal, Ex. 1013, 39. In reaching those determinations, we considered Patent Owner's arguments and found them deficient as explained in the following discussion.

Patent Owner asserts that a person of ordinary skill in the art would not have been motivated to modify ruxolitinib through deuteration because "the prior art taught that ruxolitinib had dose-limiting toxic side effects that could be exacerbated by slowing its metabolism" with a deuterium substitution. PO Resp. 47. In support of this argument, Patent Owner relies upon the similarly-stated testimony of its declarant, Dr. Ortiz de Montellano, *see id*. at 48 (citing Ex. 2057 ¶ 41), and upon cases wherein either "evidence that the chemical modification of [prior art compound] would have been unattractive to a person of ordinary skill for fear of disturbing the chemical properties whereby [the compound] function[ed] effectively," *Millennium Pharms. Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017), or "the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements," *DePuy Spine v. Medtronic Sofamor Danek Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). PO Resp. 48. According to Patent Owner, those cases apply here

because "ruxolitinib's dose-dependent toxicity would have dissuaded POSAs from trying to change the metabolic profile via deuteration." *Id*.

Although a person of ordinary skill in the art may have known that ruxolitinib exhibits dose-dependent side effects, Patent Owner and Dr. Ortiz de Montellano have not provided evidence that deuterating Rodgers's compounds would have been "unattractive to a person of ordinary skill for fear of disturbing the chemical properties" of those compounds, or that the skilled artisan would have found doing so would "undermine" the purpose of modifying such compounds, as in the cited cases. Nor have Patent Owner and Dr. Ortiz de Montellano offered other evidence that supports avoiding deuterating the drug based upon known dose-dependent side effects of ruxolitinib. *See* PO Resp. 47–48; Ex. 2057 ¶ 41.

For example, Patent Owner asserts that thrombocytopenia is a dose-dependent side effect of ruxolitinib. PO Resp. 10–11, 47. The journal article relied upon by Patent Owner teaches that such "events rarely led to treatment discontinuation . . . and were generally manageable with dose modifications, transfusions of packed red cells, or both." Ex. 2054, 795. In other words, as the side effect is dependent upon dose, the side effect may be managed by a dose adjustment.

Dr. Ortiz de Montellano acknowledged that teaching when he stated that hematological side effects of ruxolitinib "were known to be dose-dependent, as evidenced by recommendations to lower the dose of ruxolitinib if they occurred." Ex. 2057 ¶ 41 (citing Ex. 2054). Additionally, at his deposition, he responded affirmatively when asked "if you affect first-pass metabolism by deuteration, you can lower the dose of the deuterated drug to get the same area under the curve as the undeuterated drug?" Ex.

1088, 66:8–15. In other words, the dose of a deuterated drug may be lowered to achieve the same concentration as the undeuterated drug. In view of those acknowledgments, it is peculiar that Dr. Ortiz de Montellano's declaration testimony does not address whether a person of ordinary skill in the art would have managed side effects of deuterated ruxolitinib in the same manner. Without such consideration, we assign little weight to his conclusion that a person of ordinary skill in the art would have lacked motivation to deuterate ruxolitinib based upon known dose-dependent side effects of the undeuterated drug.

Patent Owner also asserts that, because "[d]euteration is relatively expensive and highly unpredictable," a person of ordinary skill in the art "would have pursued other clinically-validated strategies for increasing a drug's metabolic stability . . . such as the use of extended release dosage forms." PO Resp. 49 (citing Ex. 2057 ¶¶ 39, 43). According to Patent Owner, Petitioner has not shown "why POSAs would have been motivated to modify ruxolitinib's metabolism by deuteration, rather than other available methods for modifying metabolic profile." *Id*. Further, Patent Owner asserts that "the Petition merely sets forth some general reasons why POSAs might have been motivated to deuterate drugs generally, but provides no justification for why POSAs would have been motivated to deuterate ruxolitinib in particular to arrive at the claimed compounds." *Id*. at 49–50.

Insofar as Patent Owner argues that motivation to modify ruxolitinib with deuteration requires Petitioner to establish that a person of ordinary skill in the art would not have instead been motivated to modify the metabolic profile of ruxolitinib by using "other available methods" for doing

so, e.g., "use of extended release dosage forms," PO Resp. 49, we disagree. If that argument is intended to suggest that some prior art disclosing "other available methods" teaches away from the claimed invention, the argument fails as Patent Owner has not shown anything in the prior art describing such alternatives and criticizing, discrediting, or otherwise discouraging deuteration. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Further, we disagree with Patent Owner's assertion that Petitioner "provides no justification for why POSAs would have been motivated to deuterate ruxolitinib in particular to arrive at the claimed compounds." PO Resp. 49–50. As discussed above, Petitioner has shown persuasively how a person of ordinary skill in the art would have understood from Shilling that Rodgers's ruxolitinib compounds feature the metabolic "hot spots" targeted by the Concert Backgrounder for deuteration, and that the Concert Backgrounder teaches that such deuteration has the potential to improve the safety, tolerability, and efficacy of those compounds. *See* Pet. 31, 50–54.

Patent Owner asserts also that Petitioner's asserted motivation to modify ruxolitinib based upon structural similarities between the prior art compounds and the claimed compounds is deficient because Petitioner has not shown that "POSAs would have had 'an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." PO Resp. 52 (citing *Aventis*, 499 F.3d at 1301 (quoting *Dillon*, 919 F.2d at 692)). Patent Owner asserts that such similar properties cannot be assumed based upon similar structures. *Id*. at 54 (citing *Anacor Pharm., Inc. v. Iancu*, 889 F.3d 1372, 1385 (Fed. Cir. 2018) ("[T]he chemical arts are unpredictable and that similar structures do not always result in similar properties.")). Patent Owner asserts that Dr. Guengerich's reliance on the

Concert Backgrounder is insufficient, as that reference only suggests that deuterated drugs have not exhibited "any biologically relevant differences in target selectivity or potency" from the starting drugs. *Id*. at 56. According to Patent Owner, Dr. Guengerich "does not even assert that POSAs would have expected that *all* the relevant properties would be similar," i.e., pharmacokinetic and ADME properties as well. *Id*.

Petitioner asserts that it has provided sufficient evidence for a person of ordinary skill in the art to expect that deuterated ruxolitinib and Rodgers's ruxolitinib have similar properties. Pet. Reply 12–13. Based on the record as a whole, we agree with Petitioner. Petitioner's declarant, Dr. Guengerich, explains that "deuterium and hydrogen are very similar in size and electronic properties. Thus, deuterium-substituted compounds retain their molecular shape and their basic electronic properties, and therefore, have selectivity and potency comparable to their hydrogen analogs." Ex. 1002 ¶ 55. We find his explanation persuasive as it is based in chemistry and supported by the Concert Backgrounder. Further, we find that such testimony is sufficient to provide a skilled artisan with an expectation that the claimed and prior art compounds would have similar properties, in general. Petitioner further supports its position that those compared compounds would have been expected to have similar properties with the deposition testimony of Patent Owner's declarant, Dr. Harbeson, who explained that at Concert, "our experience has been that replacement of hydrogen with deuterium does not change the intrinsic biologic activity or pharmacology of the molecule. And therefore any deuterated analog of ruxolitinib we would presume to retain the same intrinsic biology and pharmacology." Ex. 1089, 97:4–18.

(c) Reasonable Expectation of Success

According to Petitioner and Dr. Guengerich, synthesizing the claimed octa- and tetra-deuterated ruxolitinib analogs from the known ruxolitinib compounds was well within the skill in the art at the time of the invention. Pet. 32–33 (citing Ex. 1002 ¶¶ 104–105). Additionally, Petitioner asserts that the skilled artisan would have expected those analogs to perform at least as well as ruxolitinib. *Id*. at 33 (citing Ex. 1002 ¶¶ 91–93, 104–105). In addition to Dr. Guengerich's testimony, Petitioner draws support for that assertion from the comments of a Concert representative in a published journal article explaining that he and his colleagues had "never seen any biologically relevant differences in target selectivity or potency of a drug when [they] deuterated it." *Id*. (quoting Ex. 1013, 5).

Petitioner and Dr. Guengerich further contend that an ordinarily skilled artisan would have expected improved metabolic stability over ruxolitinib based on Shilling and Concert Backgrounder. Pet. 33–39; Ex. 1002 ¶¶ 94–108. Petitioner asserts that Shilling's teaching that ruxolitinib metabolism is largely restricted to the cyclopentyl ring would have suggested to a skilled artisan that the compound was an ideal candidate for the deuteration disclosed by the Concert Backgrounder. *Id*. at 34 (citing Ex. 1002 ¶¶ 83–84).

In particular, Concert Backgrounder discloses an example of deuteration with the drug torcetrapib, wherein six of the twelve analogs demonstrated improved metabolic stability. Ex. 1002 ¶¶ 74–77. According to Dr. Guengerich, a person of ordinary skill in the art would have expected those six analogs to show enhanced metabolic stability based on known metabolic pathways of torcetrapib. *Id*. Dr. Guengerich explains that each

metabolite of torcetrapib is metabolized at least at one known position of the compound's structure. *Id*. When that position or "hotspot" is fully deuterated, metabolism is predictably altered. *Id*. ¶ 77. Thus, Dr. Guengerich considers the deuteration strategy disclosed in the Concert Backgrounder to be somewhat predictable. *Id*.

Moreover, Dr. Guengerich explains that a reasonable expectation of success would have been implicitly recognized by a person of ordinary skill in the art by the Concert Backgrounder's statement that deuteration "substantially reduced R&D [research and development] risk, time, and expense," which is due to the "relative ease and predictability of producing deuterated analogs of known pharmacologically-active compounds and suggests to a POSA a reasonable expectation of success." *Id*. ¶ 73.

Patent Owner asserts that Petitioner has not established that a person of ordinary skill in the art would have had a reasonable expectation of successfully making the claimed invention. PO Resp. 57–67. Patent Owner bases that contention not on whether a person of ordinary skill in the art could have reasonably expected to successfully synthesize the claimed octa- and tetra-deuterated ruxolitinib analogs from known ruxolitinib compounds. Indeed, Patent Owner does not contend that such a structural modification would not have been within the skill in the art and routine. Nor does Patent Owner assert that such analogs would not have been expected to remain effective in modulating the activity of Janus kinases or treating diseases related to activity of those kinases, as Rodgers discloses for undeuterated ruxolitinib. *See* PO Resp. 20–23, 66–67 and PO Sur-Reply 12–13 (addressing potential variable pharmacokinetic changes in deuterated ruxolitinib, i.e., potential dosage considerations).

Rather, Patent Owner bases its contention on assertions that a person of ordinary skill in the art would have had no reasonable expectation of achieving either an *in vitro* or *in vivo* kinetic isotope effect (KIE), i.e., metabolic change from deuterating ruxolitinib, PO Resp. 58–66, and would not have been able to predict *a priori* the effect of deuteration on the clinical profile (e.g., half-life) of the drug, *id*. at 66–67. However, as Petitioner correctly asserts, the challenged claims do not recite any of those features. Pet. Reply 15.

A reasonable expectation of success inquiry involves considering whether a person of ordinary skill in the art would have had a reasonable expectation of successfully making the *claimed invention* in light of the prior art. *See Amgen, Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.") (citing *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) ("[S]tated in the familiar terms of this court's longstanding case law, the record shows that a skilled artisan would have had a resoundingly 'reasonable expectation of success' in deriving the claimed invention in light of the teachings of the prior art.")).

Based upon our review of the record as a whole, we find that the preponderance of the evidence supports Petitioner's assertion that the combined teachings of Rodgers, Shilling, and the Concert Backgrounder would have provided a person of ordinary skill in the art a reasonable expectation of successfully deuterating Rodgers's ruxolitinib compounds at their metabolic "hot spots," as identified by Shilling, and in the manner taught by the Concert Backgrounder. Insofar as Petitioner's motivation to

do so involved an "expectation that these ruxolitinib analogs *may display* superior ADME properties as compared to non-deuterated ruxolitinib," Pet. 31 (emphasis added), we further find that Petitioner has established by a preponderance of the evidence that a skilled artisan would have had a reasonable expectation that the synthesized ruxolitinib analogs "may display" superior ADME properties, based upon the combined teachings of Shilling and the Concert Backgrounder, as explained above in our discussion of a motivation to combine. Patent Owner's arguments to the contrary attempt to avoid obviousness "by a showing of some degree of unpredictability in the art" despite the reasonable probability of success supplied by the structural similarity between the compounds and the motivation provided by the cited prior art that would have led a skilled artisan to modify known ruxolitinib compounds in the manner disclosed by the Concert Backgrounder. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. . . . [T]he expectation of success need only be reasonable, not absolute." (citations omitted)).

Based on the foregoing, we agree with Petitioner that one of ordinary skill in the art would have had a reason to deuterate Rodgers's ruxolitinib compounds, given the combined teachings of Rodgers, Shilling, and the Concert Backgrounder, and that those teachings would have provided a reasonable expectation that doing so would successfully yield the inventions of claims 1–15 of the '149 patent.

Our analysis continues with a discussion of Patent Owner's asserted secondary considerations of nonobviousness. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

(d) Secondary Considerations

Patent Owner asserts that the claimed invention yields unexpected results and satisfies a long-felt need. PO Resp. 67.

(i) Unexpected Results

According to the Federal Circuit, "[t]o be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

Patent Owner asserts that one specific deuterated ruxolitinib compound disclosed by the '149 patent, CTP-543,[12] exhibits "two important and clinically meaningful unexpected advantages." PO Resp. 68. First, Patent Owner asserts that CTP-543 provides an "increased time in the therapeutic window," when compared to prior art ruxolitinib. *Id*. More specifically, Patent Owner states that CTP-543 "has the potential to demonstrate an unexpected clinical benefit by maintaining safe and effective drug levels for a longer period." *Id*. Second, Patent Owner asserts that CTP-543 provides an "increased clinical response at a given dose," when

[12] The parties refer to Compound 111 disclosed in the '149 patent, Ex. 1001, 37:28–40, as "Compound 111," "CTP-543," and "octa-deuterated ruxolitinib," interchangeably.

compared to prior art ruxolitinib. *Id*. In particular, Patent Owner asserts that "individuals in Concert's Phase I study with the shortest ruxolitinib $t_{1/2}$ values unexpectedly had the greatest improvement in $t_{1/2}$ values when given CTP-543." *Id*. at 69.

Petitioner asserts that Patent Owner's secondary indicia of nonobviousness are not commensurate in scope with the challenged claims. Pet. Reply 2–3. Petitioner asserts also that Patent Owner's results relating to the "therapeutic window" for CTP-543 and its increased half-life for fast metabolizers would have been expected. *Id*. at 8–12. Additionally, Petitioner asserts that Patent Owner relies upon results demonstrating, at best, "an insignificant difference in degree." *Id*. at 7–8.

As the Federal Circuit has explained, "[u]nexpected results that 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 *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)).

Having reviewed the arguments and the evidence, we find that Patent Owner's asserted evidence of unexpected results demonstrates, at most, results that differ in degree over the results observed with the closest prior art, rather than in kind. Patent Owner plainly refers to the results as demonstrating an "*increased time* in the therapeutic window," and an "*increased clinical response* at a given dose," when compared to the closest prior art. PO Resp. 68 (emphasis added). Indeed, when describing the increased clinical response, Patent Owner asserts, "[w]here there is an observed KIE, the expectation is that there would be the same relative (percentage) increase in half-life for all metabolizers. . . . However, Concert

unexpectedly found that CTP-543 provides a *greater relative (percentage) increase in half-life* for more rapid ruxolitinib metabolizers." Paper 85, 15 (emphasis added). Even if commensurate in scope and taken as true and unexpected, Patent Owner's asserted results for CTP-543 demonstrate an increase in the same clinical activity observed with ruxolitinib, and therefore represent merely a difference in degree and not in kind. *See Galderma Labs., L.P.*, 737 F.3d at 739 (citing "*In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (finding increased efficacy, measured by percentages, to be a difference of degree and not of kind)"). Accordingly, the results asserted to demonstrate an "increased time in the therapeutic window" and an "increased clinical response at a given dose" for CTP-543 as compared to ruxolitinib are not of a "kind" so as to support a finding of nonobviousness of the challenged claims.

(ii) Long-Felt Need

Patent Owner asserts that "[t]here has been a long-felt need for an AA [alopecia areata] treatment that is not only effective, but also safe for prolonged use." PO Resp. 70. According to Patent Owner, "existing treatment options for AA patients in 2012 promised little efficacy and carried potentially significant side effects." *Id*. In particular, Patent Owner recognizes that the prior art ruxolitinib "may have potential use in moderating AA," however, the side effects of that drug include a risk of anemia and thrombocytopenia. *Id*. Patent Owner asserts that "Concert is developing CTP-543 as a first-in-class treatment satisfying the long-felt need for a safe and effective AA treatment." *Id*. Patent Owner submits that CTP-543 is "uniquely suited to meet this need" because deuteration confers a longer half-life and a longer time in the therapeutic window than ruxolitinib.

Id. at 71. According to Patent Owner and its declarant, Dr. Mackay-Wiggan, "[t]his increased time in the therapeutic window and potential for greater therapeutic response at a given dose show the promise of CTP-543 to help AA patients while mitigating the risk of undesirable side effects posed by ruxolitinib." *Id*. (citing Ex. 2048 ¶ 38). Additionally, Patent Owner asserts that "[t]he FDA's award of a 'Fast Track' designation to CTP-543 underscores the importance of the need satisfied by the octa-deuterated compound of the '149 patent." *Id*.

Petitioner asserts that Concert has not met the alleged long-felt need because, among other reasons, "CTP-543 is not 'FDA-approved' for anything, let alone AA." Pet. Reply 3.

Based upon our consideration of the arguments and the evidence, we find that Patent Owner's assertion that CTP-543 *has satisfied* a long-felt but unmet need for treating alopecia areata is unsupported. The pronouncement is premature. Indeed, Patent Owner and Dr. Mackay-Wiggan admit as much. Patent Owner describes meeting such long-felt need in terms of CTP-543 providing a "potential" treatment of AA with a lower dose and fewer side effects. PO Resp. 71. Similarly, Dr. Mackay-Wiggan describes Concert's data as "promising regarding the *potential* use of CTP-543 for the treatment of alopecia areata." Ex. 2048 ¶ 38 (emphasis added). At the oral hearing, counsel for Patent Owner candidly agreed that the contention is based upon the "likely efficacy" of CTP-543 to meet a need for treating AA from modeling performed, and that the FDA award of a Fast Track designation to CTP-543 indicates a "likelihood" that CTP-543 "will fulfill the long-felt need and meet the secondary consideration." Tr. 57:17–58:7.

Accordingly, we find that the evidence submitted relating to the "potential" or "likelihood" of CTP-543 treating alopecia areata does not demonstrate that it satisfies a long-felt unmet need so as to support a finding of nonobviousness of the challenged claims.

(e) *Conclusion as to Obviousness*

We base our final determination regarding obviousness upon an analysis of the foregoing arguments and evidence. In particular, we have considered the secondary considerations of nonobviousness and accorded them appropriate weight along with all of the *Graham* factors. *WBIP, LLC v. Kohler Co.*, 829 F. 3d 1317, 1328 (Fed. Cir. 2016). Accordingly, based upon the preponderance of the evidence, we conclude that the challenged claims are unpatentable as obvious over Rodgers, Shilling, and the Concert Backgrounder.

D. Remaining Ground of Obviousness

In the remaining ground of obviousness, Petitioner asserts that claims 1–15 are unpatentable over the combination of the Jakafi Label, Shilling, and the Concert Backgrounder. Pet. 26–43. Because Petitioner challenges the same claims in this ground as we just concluded were unpatentable over a similar combination of references and based upon a similar rationale as relied upon here, we decline to reach this ground.

III. PETITIONER'S MOTION TO EXCLUDE

Petitioner moves to exclude, in whole or in part, Exhibits 2001, 2002, 2019, 2048, 2057, 2071, 2078, 2079, 2099–2101, 2103, 2104, 2112, 2122, and 2123. Paper 94 ("Exclude Mot."). Patent Owner opposes the motion. Paper 102 ("Exclude Opp."). As the moving party, Petitioner has the burden

of proof to establish that it is entitled to the requested relief. 37 C.F.R. § 42.20(c).

A. Exhibits 2001, 2002, 2019, 2048, 2057, 2071, and 2079

Exhibit 2019 is referred to by Patent Owner as "Appendices to Declaration of Scott L. Harbeson, Ph.D (Exhibit 2001)." Ex. 2019, 1. Petitioner asserts that portions of Appendices 3 and 4 of Exhibit 2019 were relied upon in the declaration testimony of Patent Owner's declarants, Dr. Harbeson (Exhibits 2001, 2071, and 2079), Dr. Baille (Ex. 2002), Dr. Mackay-Wiggan (Exhibit 2048), and Dr. Ortiz de Montellano (Ex. 2057). Exclude Mot. 7. Petitioner contends that Appendices 3 and 4 are unauthenticated hearsay and should be excluded, along with the paragraphs in each of the above-mentioned declarations that rely upon those appendices, under Federal Rules of Evidence ("FRE") 802, 901 and 902. *Id*. at 1–9.

Patent Owner asserts that Petitioner's motion should be denied because "Petitioner failed to 'identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence.'" Exclude Opp. 2 (quoting 37 C.F.R. § 42.64(b)(1)). According to Patent Owner, Petitioner's Objections were directed to Exhibit 2019, as a whole, which represents seven appendices, whereas its motion is directed to only two of those appendices. *Id*.

Petitioner responds by noting that its objections specifically raise the bases for its motion to exclude. Paper 103, 2. We agree with Petitioner that its objections to Exhibits 2001, 2002, 2019, 2048, 2057, 2071, and 2079 complied with 37 C.F.R. § 42.64(b)(1). For example, the objections challenged Exhibit 2019 by asserting that it (a) lacks authentication under

FRE 901 and is not self-authenticating as the source of the exhibit, date of its creation, and author(s) are unidentified; (b) represents hearsay under FRE 802 by offering out of court statements of the unidentified author(s) for the truth of the matters asserted "(e.g., that certain experiments were conducted and generated certain results)," as hearsay within hearsay. Paper 18, 4. Further, in the objections of 2001, 2002, 2048, 2057, 2071, and 2079, Petitioner refers to the objection to Exhibit 2019 and sets forth the paragraphs of each challenged exhibit that it seeks to exclude based upon asserted reliance on Exhibit 2019 therein. *See* Paper 18, 1–3; Paper 32, 3–4. Moreover, we agree with Petitioner that the fact that its motion seeks to preserve its objections to those exhibits with regard to only a portion of Exhibit 2019, i.e., Appendices 3 and 4, does not render the objections encompassing those items insufficient, as they too were set forth with "sufficient particularity," as required.

Substantively, Patent Owner asserts that Dr. Harbeson's testimony regarding the source and content of the data in Appendices 3 and 4 is sufficient to authenticate those portions of Exhibit 2019. Exclude Opp. 3–4. Patent Owner characterizes Appendices 3 and 4 as a "summary" of pharmacokinetic data "excerpted from Concert's clinical study reports" relating to CTP-543 and relied upon by Dr. Harbeson in formulating his opinions. *Id*. at 6 n.2. According to Patent Owner, Dr. Harbeson demonstrated his familiarity with the study design, subjects, timing, dosages, sampling, and data acquisition and analysis. *Id*. at 4 (citing Ex. 2001 ¶¶ 2, 11–16). Regarding hearsay, Patent Owner asserts that Appendices 3 and 4 "reflect records of a regularly conducted activity and not hearsay." *Id*. at 7.

Patent Owner contends that if Appendices 3 and 4 are found to be unauthenticated hearsay, "the data and methodology presented in Exhibit 2019 is the sort that an expert would rely on, and as such, Exhibits 2001, 2002, 2048, and 2057 should not be excluded." *Id*. at 10.

Based upon our review of the arguments and evidence, we note that Petitioner demonstrates a strong case for finding that Appendices 3 and 4 of Exhibit 2019 have not been authenticated and likely contain hearsay. *See* Exclude Mot. 1–9 and Paper 103, 1–3. However, we decline to exclude that material. As we recognized in *Argentum Pharmaceuticals LLC v. Research Corp. Technologies, Inc*., Case IPR2016-00204, slip op. 52 (PTAB Mar. 22, 2017) (Paper 85), "under FRE 703, the proponent of an expert opinion may disclose otherwise inadmissible evidence underling that opinion to a jury, if the court determines that the 'probative value in helping the jury evaluate the opinion substantially outweighs [its] prejudicial effect.'" In this case, we conclude that our ability (and that of the declarant(s) for Petitioner) to evaluate the summary and methodology set forth in Appendices 3 and 4 that served as a basis for testimony provided by Patent Owner's declarants outweighs any prejudicial effect posed by those portions of Exhibit 2019. Indeed, when assigning weight, if any, to testimony based on Appendices 3 and 4, we may factor in the reliability of such information presented as a summary of data that was excerpted from clinical study reports.

Accordingly, we deny the Motion to Exclude with respect to Exhibits 2001, 2002, 2019, 2048, 2057, 2071, and 2079.

B. Exhibit 2078

Exhibit 2078 is a journal article titled "Effect of deuteration on metabolism and clearance of Nerispirdine (HP184) and AVE5638." Ex. 2078, 3831. Petitioner asserts that Exhibit 2078 appears to have been published in 2015, long after the 2012 priority date of the '149 patent. Exclude Mot. 9. Therefore, Petitioner asserts that the exhibit is irrelevant under FRE 401 and 402. *Id*.

Patent Owner acknowledges the post-priority date publication of Exhibit 2078 and asserts that such date "does not detract from its relevance" regarding the Patent Owner contentions regarding the unpredictability of effects of deuteration. Exclude Opp. 14. Further, Patent Owner asserts that arguments relating to the relevance of post-filing publication dates concern the weight given to that evidence and not its admissibility. *Id*. at 15.

We agree with Patent Owner that Petitioner's challenge of Exhibit 2078 is not a basis for excluding the exhibit. Rather, the post-filing publication date of a reference relied upon to indicate general knowledge of a person of ordinary skill in the art is a factor that we consider when we weigh the evidence. Further, as the Federal Circuit has explained, the Board may rely on "non-prior art evidence," in a limited capacity, i.e., in a supportive role, "e.g., indicating the level of ordinary skill in the art, what certain terms would mean to one with ordinary skill in the art, and how one with ordinary skill in the art would have understood a prior art disclosure." *Yeda Research v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018).

Accordingly, we deny Petitioner's Motion to Exclude with respect to Exhibit 2078.

C. Exhibits 2099–2101, 2103, 2104, and 2112

Exhibits 2099–2101, 2103, 2104, and 2112 were introduced at the deposition of Dr. Shapiro and were subsequently filed. Petitioner asserts that those exhibits have not been referenced in any briefing by Patent Owner. Exclude Mot. 9. According to the Petitioner, each of those exhibits should be excluded as irrelevant under FRE 401 and 402. *Id*. at 9–10. Further, Petitioner asserts that those exhibits should be excluded as untimely and improper new evidence. *Id*. at 10.

Patent Owner states that it "does not oppose exclusion of Exhibits 2099–2101, 2103, 2104, and 2112, which are not cited in any substantive paper." Exclude Opp. 1 n.1. Accordingly, we grant Petitioner's Motion to Exclude with respect to Exhibits 2099–2101, 2103, 2104, and 2112.

D. Exhibits 2122 and 2123

Exhibits 2122 (sealed) and 2123 (public) represent the declaration of Dr. Cowden, a Concert employee, filed with Patent Owner's Reply to Petitioner's Opposition to the Contingent Motion to Amend (Paper 84). Petitioner asserts that Dr. Cowden's testimony relating to tests performed on a sample of CTP-543 obtained by Concert from a third party (Carbogen) lacks foundation under FRE 602 because "Dr. Cowden has not established personal knowledge (1) that Carbogen retained the specific CTP-543 batch, (2) that Carbogen sent to Concert a representative sample of the specific CTP-543 batch, or (3) that the sample tested at Concert was the specific CTP-543 batch in issue." Exclude Mot. 11. Petitioner asserts also that, insofar as Dr. Cowden's testimony relies on quantitative nuclear magnetic resonance ("NMR") analysis, his testimony "constitutes improper lay testimony and/or expert testimony" as he has not been shown to be an expert

in quantitative NMR. *Id*. at 11–12. Therefore, Petitioner asserts that paragraphs 6, 8–13, 15–24, and Appendix A of Exhibits 2122 and 2123 should be excluded. *Id*. at 11–14.

Patent Owner asserts that "Dr. Cowden is an expert in NMR interpretation, as it relates to drug development," and that none of his declaration testimony should be excluded as improper expert testimony. Exclude Opp. 10–11. Further, Patent Owner asserts that Dr. Cowden provided sufficient foundation for his testimony regarding his knowledge about the specific CTP-543 batch at issue. *Id*. at 14 (citing Ex. 2122 ¶ 11).

Based upon our review of the declaration testimony and briefing, it appears as though Patent Owner offers the testimony of Dr. Cowden as that of a hybrid fact witness/expert, as he provides testimony regarding the analysis of a sample batch of CTP-543 at Concert, performed under his supervision, and he provides conclusions based upon the data generated from the sample. *See, e.g.*, Ex. 2123 ¶¶ 11, 24. Dr. Cowden begins his declaration by stating that he has "personal knowledge of the facts set forth in this Declaration." *Id.* ¶ 1. He testifies also that he is employed by Concert as the "Senior Director, Chemical Development." *Id*. ¶ 2. In terms of expertise, Dr. Cowden testified that he received his Ph.D. in synthetic organic chemistry, has over 18 years of experience in the field of process chemistry, and has "routinely used nuclear magnetic resonance (NMR) to analyze organic compounds." *Id*. ¶¶ 3–4. Patent Owner refers to Dr. Cowden as an expert in NMR interpretation, and also acknowledges that his testimony is based upon personal knowledge regarding the CTP-543 sample. Exclude Opp. 10–11.

In view of those facts, we do not find that Petitioner has met its burden of demonstrating that portions of Dr. Cowden's declaration should be excluded based upon FRE 602, 701, or 702. Petitioner's objections implicate the weight and sufficiency of the testimony, rather than its admissibility. We are in a position to discern whether Dr. Cowden's testimony should be entitled to weight, either as a whole or with regard to specific issues. Further, we note that Petitioner had the opportunity to address any alleged deficiencies regarding Dr. Cowden's personal knowledge or qualifications during a deposition. As Patent Owner has explained, Dr. Cowden was offered for such an examination, however, Petitioner declined. *See* Exclude Opp. 11 n.3.

Accordingly, we deny the Motion to Exclude with respect to Exhibits 2122 and 2123.

IV. PATENT OWNER'S CONTINGENT MOTION TO AMEND

Having concluded that claims 1–15 are unpatentable under 35 U.S.C. § 103 as obvious over Rodgers, Shilling, and the Concert Backgrounder, we next consider Patent Owner's Contingent Motion to Amend the claims of the '149 patent. Proposed amended claims are set forth in the Motion. Amend Mot. 26–31 (Appendix A). Patent Owner supports its Motion with the declarations of Scott Harbeson, Ph.D. (Ex. 2001 and Ex. 2071, sealed; Ex. 2079, public), Thomas B. Baille, Ph.D., D.SC. (Ex. 2002), Julian Mackay-Wiggan, M.D., M.S. (Ex. 2048), Paul Ortiz de Montellano, Ph.D. (Ex. 2057), and Dr. Cameron Cowden, Ph.D. (Ex. 2122, sealed; Ex. 2123, public), and the original disclosure of the '149 patent (U.S. Appl. No. 14/707,912) (Ex. 2037, 1–66) ("the '912 application"), and the original disclosure of related Provisional Application No. 61/660,428 (Ex. 2073)

("the '428 application"), to which the '912 application claims priority, (collectively, the "Applications"). Amend Mot. 4.

Pursuant to *Aqua Products, Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017), the Board assesses "the patentability of the proposed substitute claims without placing the burden of persuasion on the patent owner." *Id*. at 1296. The Court explained that the Patent Office may not place the burden of persuasion on a patent owner with respect to the patentability of substitute claims presented in a motion to amend. *See id*. at 1327; *see Bosch Auto. Serv. Sols. LLC v. Matal*, 878 F.3d 1027, 1040 (Fed. Cir. 2017).

As for procedural requirements regarding motions to amend, the Court stated that "the patent owner must satisfy the Board that the statutory criteria in [35 U.S.C.] § 316(d)(1)(a)–(b) and § 316(d)(3) are met and that any reasonable procedural obligations imposed by the Director are satisfied before the amendment is entered into the IPR." *Aqua Prods.*, 872 F.3d at 1305–06. In view of *Aqua Products*, the Board has issued guidance explaining,

> [A] patent owner still must meet the requirements for a motion to amend under 37 C.F.R. § 42.121 or § 42.221, as applicable. That is, a motion to amend must set forth written description support and support for the benefit of a filing date in relation to each substitute claim, and respond to grounds of unpatentability involved in the trial. Likewise, under 37 C.F.R. § 42.11, all parties have a duty of candor, which includes a patent owner's duty to disclose to the Board information that the patent owner is aware of that is material to the patentability of substitute claims, if such information is not already of record in the case.

See Memorandum "Guidance on Motions to Amend in view of *Aqua Products*" (Nov. 21, 2017) (https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf) ("Memorandum") at 2.

A. Reasonable Number of Substitute Claims

"A motion to amend may. . . propose a reasonable number of substitute claims. The presumption is that only one substitute claim would be needed to replace each challenged claim, and [that presumption] may be rebutted by a demonstration of need." 37 C.F.R. § 42.121(a)(3).

Patent Owner requests to substitute proposed claims 16–19 (the "Substitute Claims") for original claims 1, 8, 9, and 15. Amend Mot. 1. Specifically, Patent Owner submits proposed claim 16 to substitute original claim 1, proposed claim 17 to substitute original claim 8, proposed claim 18 to substitute original claim 9, and proposed claim 19 to substitute original claim 15. *Id*. Thus, the proposed claims 16–19 represent a one-for-one substitution for original claims 1, 8, 9, and 15, respectively.[13] Accordingly, we determine that Patent Owner has met the requirement of 37 C.F.R. § 42.121(a)(3).

B. Written Description Support

Pursuant to 37 C.F.R. § 42.121(b), a motion to amend in an *inter partes* review must set forth "[t]he support in the original disclosure of the patent for each claim that is added or amended," and "[t]he support in an

[13] Proposed substitute claims 16 and 18 are set forth as independent claims directed to a compound of Formula I. Proposed substitute claim 17 is directed to pharmaceutical composition comprising the compound of claim 16. Similarly, proposed substitute claim 19 is directed to a pharmaceutical composition comprising the compound of claim 18.

earlier-filed disclosure for each claim for which benefit of the filing date of the earlier filed disclosure is sought." In particular, the limitations added to the challenged claims must be supported *individually* by the application, from which Patent Owner claims priority, and the substitute claims also must be supported *as a whole* by that application. *Nichia Corp. v. Emcore Corp.*, Case IPR2012-00005, slip op. at 4 (PTAB June 3, 2013) (Paper 27).

The language of the proposed substitute claims does not need to be described *in ipsis verbis* in the original disclosure to support the proposed substitute claims. *Id.*; *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996). However, if the original disclosure does not use the precise terminology recited in a proposed claim, "mere citation to the original disclosure without any explanation as to why a person of ordinary skill in the art would have recognized that the inventor possessed the claimed subject matter as a whole may be similarly inadequate." *Nichia Corp.*, slip op. at 4. In other words, in such case, the question remains whether the disclosure reasonably would lead persons of ordinary skill in the art to the subject matter recited in the proposed claims. *See Fujikawa*, 93 F.3d at 1570.

Patent Owner asserts that each proposed claim finds written description support in the Applications. Amend Mot. 4–7. Specifically, Patent Owner asserts that the Applications each describe Compound 111, which discloses every limitation of proposed claims 16 and 18. *Id*. at 5. Additionally, Patent Owner asserts that the Applications also describe a pharmaceutical composition and a pharmaceutically acceptable carrier, as further recited in proposed claims 17 and 19. *Id*. at 7–8. We agree.

Petitioner disagrees only in a conditional manner. Amend Opp. 12. According to Petitioner, Concert improperly seeks to read particular "advantageous properties" of *in vitro* and *in vivo* KIE, and clinical profile into claims 16–19 by linking them to the claimed invention and asserting that a person of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the claimed invention. *Id*.. Petitioner states that "[i]f, however, the 'claimed invention' is read to require 'advantageous properties' for the purposes of a reasonable expectation of success, it necessarily follows from this disclaimer that there must be written description and enabling support for these 'advantageous properties.'" *Id*. at 13. We need not address that conditional argument because, as Petitioner correctly asserts, such "advantageous properties" are not recited in the original or proposed substitute claims.

Accordingly, we determine that Patent Owner has met the requirement of 37 C.F.R. § 42.121(b).

C. Respond to a Ground of Unpatentability Involved in the Trial

"A motion to amend may be denied where: (i) The amendment does not respond to a ground of unpatentability involved in the trial . . . ." 37 C.F.R. § 42.121(a)(2)(i).

Patent Owner asserts that the proposed substitute claims respond to the asserted grounds of unpatentability in the *inter partes* proceeding. Amend Mot. 8. Specifically, Patent Owner asserts:

> The Substitute Claims respond to the asserted grounds because as of 2012, (1) there was an affirmative motivation for POSAs not to combine the asserted references to arrive at the Substitute Claims, (2) there was no reasonable expectation of success in combining the asserted references to produce the compound or composition of the Substitute Claims, and (3)

> objective indicia support nonobviousness of the Substitute Claims. As to objective indicia, Concert's CTP-543 product under development has demonstrated unexpected beneficial results and a likelihood of satisfying a long-felt need. There is a nexus between these unexpected results and the Substitute Claims, as CTP-543 has the isotopic purity recited in claim 18 and is Compound 111 (*see* Ex. 2001, ¶4; Ex. 2079, ¶10), which, as explained above (*supra* Section III), is claimed by proposed claims 16 and 18.

Id. at 8–9. Patent Owner asserts further that "nothing in the asserted grounds addresses the claimed isotopic purity of proposed claims 18 and 19." *Id*. at 9.

Petitioner asserts that Patent Owner's motion to amend should be denied because the proposed substitute claims do not respond to a ground of unpatentability involved in the trial. Amend Opp. 10. Patent Owner asserts that proposed claims 16–19 read on Compound 111, which was shown to have been obvious in the Petition as it was a basis for the obviousness grounds. *Id*. (citing Amend Mot. 5; Pet 8–9, 26–43, 50–55). According to Petitioner, Patent Owner "does not, and cannot, explain how still claiming that obvious compound is responsive to either ground." *Id*.

Petitioner asserts that, in the motion to amend, Patent Owner merely repeats the same arguments that it presented in the Patent Owner Response regarding the challenged original claims, and that, by doing so, Patent Owner reveals that claims 16–19 are not patentably distinct from the original claims. *Id*. at 11 (citing PO Resp. 46–71; Amend Mot. 8–25). Petitioner notes that Patent Owner "neither mentions nor relies upon the added limitations of claims 16–19 anywhere in its arguments on motivation or reasonable expectation of success beyond relying on CTP-543 as an embodiment just as it does in the POR." *Id*. (citing Amend Mot. 9–19; PO

Resp. 30–37, 46–66). Petitioner notes also that Patent Owner relies on the same evidence and arguments regarding secondary considerations in its motion to amend for the proposed substitute claims as it did for the original claims in the Patent Owner Response. *Id*. (citing PO Resp. 36–37; Amend Mot. 22–23). Further, Petitioner asserts that the motion to amend does not address how the added limitation in claims 18 and 19 regarding isotopic purity responds to a ground of unpatentability. *Id*. at 12.

Based upon our review of the arguments and evidence, we agree with Petitioner that the motion to amend does not set forth how the proposed substitute claims respond to the asserted grounds of unpatentability. Insofar as the proposed substitute claims narrow the compounds of the challenged original claims, they have done so in a manner that still covers the compound that we have found to be obvious over the ground involving the combined teachings of Rodgers, Shilling, and the Concert Backgrounder. Patent Owner asserts that the proposed claims are not obvious over that ground for the same reasons asserted in the Patent Owner Response regarding the original claims, without identifying how analysis of the proposed substitute claims would be distinguished. Nor do we see how they could be as the same compound, i.e., Compound 111/CTP-543, is relied upon to represent the original claims and proposed substitute claims. Further, as Petitioner asserts, Patent Owner refers to the additional isotopic purity limitation in proposed claims 18 and 19, i.e., "wherein each position designated specifically as deuterium has at least 95% incorporation of deuterium," without explaining or providing evidence how that additional limitation, also covered by Compound 111/CTP-543, responds to the ground of unpatentability.

Patent Owner explains, in the Reply to Petitioner's Opposition to the Motion to Amend, that the proposed substitute claims respond to the ground because, "to the extent that the Board determines that the unexpected results offered by Concert are not commensurate in scope with the broader, original claims of the '149 Patent, those results are commensurate in scope with the narrower substitute claims 16–19." Paper 84, 11–12. However, our determination that Patent Owner's evidence did not demonstrate unexpected results was not based upon that contention. Rather, we determined that the results represented a difference in degree and not in kind. The proposed substitute claims do not respond to that deficiency.

Accordingly, because we find that Patent Owner has not met the requirement in 37 C.F.R. § 42.121(a)(2)(i) by proposing substitute claims that do not respond to a ground of unpatentability in the trial, the Motion to Amend is denied.

V. CONCLUSIONS

For the foregoing reasons, we conclude that Petitioner has shown by a preponderance of the evidence that the challenged claims of the '149 patent are unpatentable as obvious over Rodgers, Shilling, and the Concert Backgrounder. Additionally, we conclude that Petitioner has not established that it is entitled to have Exhibits 2001, 2002, 2019, 2048, 2057, 2071, 2078, 2079, 2122, and 2123 excluded. We conclude Petitioner is entitled to exclude Exhibits 2099–2101, 2103, 2104, and 2112. We also conclude that Patent Owner has not met the requirements of 37 C.F.R. § 42.121(a)(2)(i) for amending claims.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED claims 1–15 of the ’149 patent are unpatentable under 35 U.S.C. § 103 as obvious over Rodgers, Shilling, and the Concert Backgrounder;

FURTHER ORDERED that Petitioner’s Motion to Exclude is *denied* with respect to Exhibits 2001, 2002, 2019, 2048, 2057, 2071, 2078, 2079, 2122, and 2123, and *granted* with respect to Exhibits 2099–2101, 2103, 2104, and 2112;

FURTHER ORDERED that Patent Owner’s Contingent Motion to Amend is *denied*; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-01256
Patent 9,249,149 B2

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Paper 126
Entered: January 14, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE OFFICE OF THE UNDERSECRETARY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

_____

INCYTE CORPORATION,
Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner.

_____

IPR2017-01256
Patent 9,249,149 B2

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Before ANDREW HIRSHFELD, *Commissioner for Patents, Performing the Functions and Duties of the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office*.

ORDER

The Office has received a request for Director review of the Final Written Decision in this case. *See* Ex. 3100. The request was referred to Mr. Hirshfeld, Commissioner for Patents, Performing the Functions and Duties of the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office.

It is ORDERED that the request for Director review is denied; and

FURTHER ORDERED that the Patent Trial and Appeal Board's Final Written Decision in this case is the final decision of the agency.

IPR2017-01256
Patent 9,249,149 B2

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

(10) **Patent No.: US 9,249,149 B2**
(45) **Date of Patent: *Feb. 2, 2016**

(54) **DEUTERATED DERIVATIVES OF RUXOLITINIB**

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(60) Provisional application No. 61/660,428, filed on Jun. 15, 2012, provisional application No. 61/678,795, filed on Aug. 2, 2012, provisional application No. 61/917,589, filed on Dec. 18, 2013.

(51) **Int. Cl.**

C07D 487/04	(2006.01)
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A61K 45/06	(2006.01)
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(52) **U.S. Cl.**

CPC ***C07D 487/04*** (2013.01); ***A61K 31/519*** (2013.01); ***A61K 45/06*** (2013.01); *C07B 2200/05* (2013.01)

(58) **Field of Classification Search**

CPC C07D 487/04; A61K 31/519

See application file for complete search history.

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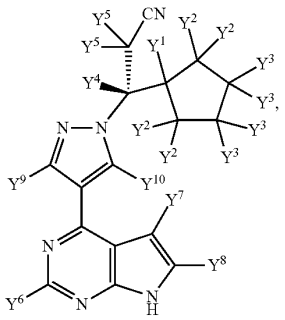
(57) **ABSTRACT**

The present invention in one embodiment provides a compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof; pharmaceutical compositions comprising the compound; and methods of treating the indications disclosed herein.

15 Claims, 1 Drawing Sheet

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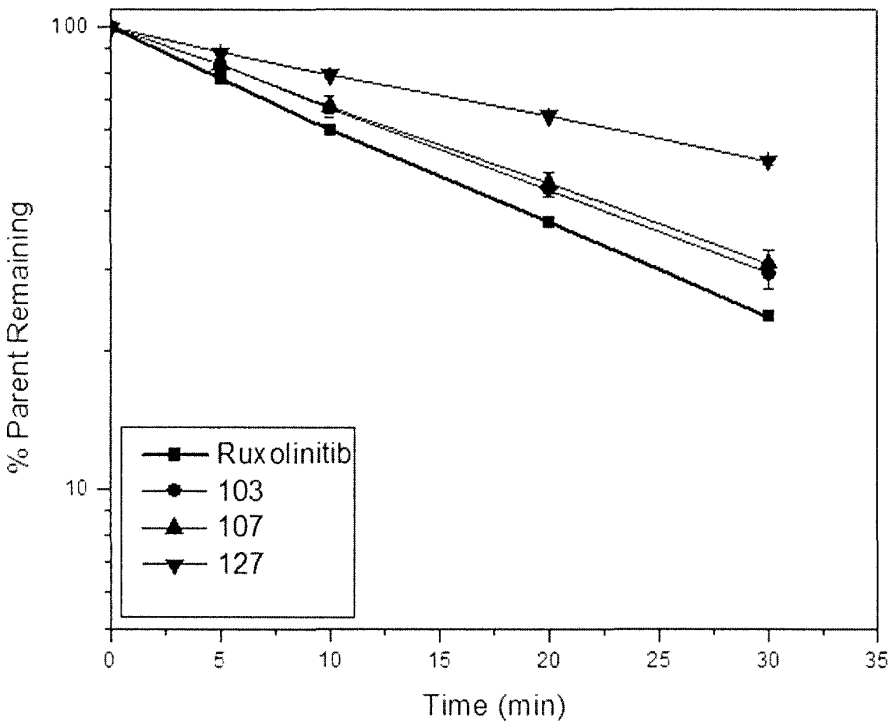

100
10
% Parent Remaining
Ruxolinitib
103
107
127
0
5
10
15
20
25
30
35
Time (min)

DEUTERATED DERIVATIVES OF RUXOLITINIB

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 14/570,954, filed Dec. 15, 2014, which is a continuation-in-part of International Application No. PCT/US2013/045919, which designated the United States and was filed on Jun. 14, 2013, published in English, which claims the benefit of U.S. Provisional Application No. 61/660,428, filed Jun. 15, 2012, and U.S. Provisional Application No. 61/678,795, filed Aug. 2, 2012. U.S. application Ser. No. 14/570,954 also claims the benefit of U.S. Provisional Application No. 61/917,589, filed Dec. 18, 2013. The entire teachings of the above applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use or limit their use in certain indications. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems such as poor patient compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment. A rapidly metabolized drug may also expose patients to undesirable toxic or reactive metabolites.

Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving the drug may experience toxicities, or the safe dosing of such drugs may be limited such that patients receive a suboptimal amount of the active agent. In certain cases, modifying dosing intervals or formulation approaches can help to reduce clinical adverse effects, but often the formation of such undesirable metabolites is intrinsic to the metabolism of the compound.

In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically responsible for their metabolism (see Kempf, D. J. et al., Antimicrobial agents and chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6 metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L et al., Clinical Pharmacology and Therapeutics, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at www.accessdata.fda.gov).

In general, combining drugs with cytochrome P450 inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme's activity can affect the metabolism and clearance of other drugs metabolized by that same enzyme. CYP inhibition can cause other drugs to accumulate in the body to toxic levels.

A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, M I et al, J Pharm Sci, 1975, 64:367-91; Foster, A B, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, D J et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, M B et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 ("Fisher")). Many of the examples in these references report a local deuterium isotope effect (an effect on the rate of metabolism at a specific site of deuteration in the substrate) rather than the effect of deuteration on the overall metabolic stability of the drug, i.e., the overall substrate consumption via metabolism. The reported results of those studies measuring deuterium substitution's effect on overall metabolic stability are variable and unpredictable. For some compounds deuteration caused decreased metabolic clearance in vivo. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. See, for example, Fukuto et al. (J. Med. Chem. 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

Ruxolitinib phosphate, is a heteroaryl-substituted pyrrolo [2,3-d]pyrimidines also known as 3(R)-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile phosphate and as (R)-3-(4-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2. These kinases mediate the signaling of a number of cytokines and growth factors important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

Ruxolitinib phosphate is currently approved for the treatment of patients with intermediate or high-risk myelofibrosis,

including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. Ruxolitinib phosphate is also currently in clinical trials for the treatment of essential thrombocythemia, pancreatic cancer, prostate cancer, breast cancer, leukemia, non-Hodgkin's lymphoma, multiple myeloma and psoriasis.

Three metabolites in humans have been identified as active, that resulting from hydroxylation at the 2-position on the cyclopentyl moiety, that resulting from hydroxylation at the 3-position on the cyclopentyl moiety and the ketone resulting from further oxidation at the 3-position on the cyclopentyl moiety. (See Shilling, A. D. et al., Drug Metabolism and Disposition, 2010, 38(11): 2023-2031; FDA Prescribing Information and US20080312258).

The most common hematologic adverse reactions associated with the dosing of ruxolitinib are thrombocytopenia and anemia. The most common non-hematologic adverse reactions are bruising, dizziness and headache.

Despite the beneficial activities of ruxolitinib, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

SUMMARY OF THE INVENTION

This invention relates to novel heteroaryl-substituted pyrrolo[2,3-d]pyrimidines, and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering an inhibitor of Janus-associated kinase with selectivity for subtypes 1 and 2 (JAK1/JAK2).

BRIEF DESCRIPTION OF THE DRAWINGS

The figure shows the results of metabolic stability testing of the referenced compounds.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "treat" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

"Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of ruxolitinib will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E et al., Seikagaku, 1994, 66:15; Gannes, L Z et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).

The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

The term "isotopologue" refers to a species in which the chemical structure differs from a specific compound of this invention only in the isotopic composition thereof.

The term "compound," when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues in toto will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues in toto will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

The invention also provides salts of the compounds of the invention.

A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid,

fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

The compounds of the present invention (e.g., compounds of Formula I or Formula A), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this invention can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present invention may exist as either a racemic mixture or a scalemic mixture, or as individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

The term "mammal" as used herein includes a human or a non-human animal, such as mouse, rat, guinea pig, dog, cat, horse, cow, pig, monkey, chimpanzee, baboon, or rhesus. In one embodiment, the mammal is a non-human animal. In another embodiment, the mammal is a human.

The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

"D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

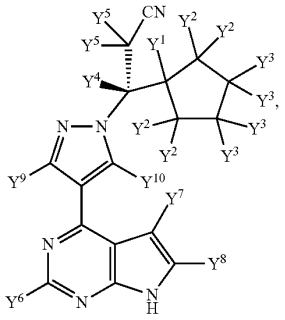
"Substituted with deuterium" refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

Throughout this specification, a variable may be referred to generally (e.g.,"each R") or may be referred to specifically (e.g., R^1, R^2, R^3, etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

Therapeutic Compounds

The present invention in one embodiment provides a compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is selected from hydrogen and deuterium;

each Y^2 is independently selected from hydrogen and deuterium, provided that each Y^2 attached to a common carbon is the same;

each Y^3 is independently selected from hydrogen and deuterium, provided that each Y^3 attached to a common carbon is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9, and Y^{10} are each independently selected from hydrogen and deuterium; provided that when Y^1 is hydrogen, each Y^2 and each Y^3 are hydrogen, Y^4 is hydrogen, and each of Y^6, Y^7, Y^8, Y^9, and Y^{10} is hydrogen, then each Y^5 is deuterium.

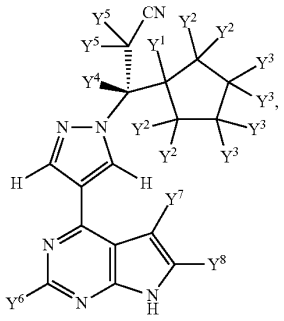
In one embodiment of Formula A each Y^2 is the same, each Y^3 is the same and each Y^5 is the same. In one aspect of this embodiment, each Y^2 is deuterium. In a further aspect each Y^3 is deuterium. In another further aspect each Y^3 is hydrogen. In another aspect of this embodiment, each Y^2 is hydrogen. In a further aspect each Y^3 is deuterium. In another further aspect each Y^3 is hydrogen. In one example of any of the foregoing aspects, Y^1 is deuterium. In another example of any of the foregoing aspects, Y^1 is hydrogen. In a more particular example of any of the foregoing aspects, Y^1 is deuterium, Y^4 is deuterium, and each Y^5 is deuterium. In another more particular example of any of the foregoing aspects, Y^1 is deuterium, Y^4 is deuterium, and each Y^5 is hydrogen. In another more particular example of any of the foregoing aspects, Y^1 is deuterium, Y^4 is hydrogen, and each Y^5 is deuterium. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is hydrogen, and each Y^5 is hydrogen. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is hydrogen, and each Y^5 is deuterium. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is deuterium, and each Y^5 is deuterium. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is deuterium, and each Y^5 is hydrogen.

In one embodiment, Y^6 is deuterium. In one aspect of this embodiment, each of Y^7 and Y^8 is deuterium. In another aspect of this embodiment, each of Y^7 and Y^8 is hydrogen.

In one embodiment, Y^6 is hydrogen. In one aspect of this embodiment, each of Y^7 and Y^8 is deuterium. In another aspect of this embodiment, each of Y^7 and Y^8 is hydrogen.

The present invention in one embodiment provides a compound of Formula I:

Formula I



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is selected from hydrogen and deuterium;

each Y^2 is independently selected from hydrogen and deuterium, provided that each Y^2 attached to a common carbon is the same;

each Y^3 is independently selected from hydrogen and deuterium, provided that each Y^3 attached to a common carbon is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, and Y^8 are each independently selected from hydrogen and deuterium; provided that when Y^1 is hydrogen, each Y^2 and each Y^3 are hydrogen, Y^4 is hydrogen, and each of Y^6, Y^7 and Y^8 is hydrogen, then each Y^5 is deuterium.

In one embodiment each Y^2 is the same, each Y^3 is the same and each Y^5 is the same. In one aspect of this embodiment, each Y^2 is deuterium. In a further aspect each Y^3 is deuterium. In another further aspect each Y^3 is hydrogen. In another aspect of this embodiment, each Y^2 is hydrogen. In a further aspect each Y^3 is deuterium. In another further aspect each Y^3 is hydrogen. In one example of any of the foregoing aspects, Y^1 is deuterium. In another example of any of the foregoing aspects, Y^1 is hydrogen. In a more particular example of any of the foregoing aspects, Y^1 is deuterium, Y^4 is deuterium, and each Y^5 is deuterium. In another more particular example of any of the foregoing aspects, Y^1 is deuterium, Y^4 is deuterium, and each Y^5 is hydrogen. In another more particular example of any of the foregoing aspects, Y^1 is deuterium, Y^4 is hydrogen, and each Y^5 is hydrogen. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is hydrogen, and each Y^5 is hydrogen. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is hydrogen, and each Y^5 is deuterium. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is deuterium, and each Y^5 is deuterium. In another more particular example of any of the foregoing aspects, Y^1 is hydrogen, Y^4 is deuterium, and each Y^5 is hydrogen.

In one embodiment, Y^6 is deuterium. In one aspect of this embodiment, each of Y^7 and Y^8 is deuterium. In another aspect of this embodiment, each of Y^7 and Y^8 is hydrogen.

In one embodiment, Y^6 is hydrogen. In one aspect of this embodiment, each of Y^7 and Y^8 is deuterium. In another aspect of this embodiment, each of Y^7 and Y^8 is hydrogen.

In one embodiment, the compound is a compound of Formula I wherein Y^6, Y^7 and Y^8 are each hydrogen and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1 (below):

TABLE 1

Exemplary Embodiments of Formula I

Cmpd	Y^1	Each Y^2	Each Y^3	Y^4	each Y^5
100	H	H	H	D	H
101	H	H	H	H	D
102	H	H	H	D	D
103	H	H	D	H	H
104	H	H	D	D	H
105	H	H	D	H	D
106	H	H	D	D	D
107	H	D	H	H	H
108	H	D	H	D	H
109	H	D	H	H	D
110	H	D	H	D	D
111	H	D	D	H	H
112	H	D	D	D	H
113	H	D	D	H	D
114	H	D	D	D	D
115	D	H	H	H	H
116	D	H	H	D	H
117	D	H	H	H	D
118	D	H	H	D	D
119	D	H	D	H	H
120	D	H	D	D	H
121	D	H	D	H	D
122	D	H	D	D	D
123	D	D	H	H	H
124	D	D	H	D	H
125	D	D	H	H	D
126	D	D	H	D	D
127	D	D	D	H	H
128	D	D	D	D	H
129	D	D	D	H	D
130	D	D	D	D	D

or a pharmaceutically acceptable salt thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

In one embodiment, the compound is a compound of Formula I wherein Y^6, Y^7 and Y^8 are each D and the compound is selected from any one of the compounds (Cmpd) set forth in Table 2 (below):

TABLE 2

Exemplary Embodiments of Formula I

Cmpd	Y^1	Each Y^2	Each Y^3	Y^4	each Y^5
200	H	H	H	D	H
201	H	H	H	H	D
202	H	H	H	D	D
203	H	H	D	H	H
204	H	H	D	D	H
205	H	H	D	H	D
206	H	H	D	D	D
207	H	D	H	H	H
208	H	D	H	D	H
209	H	D	H	H	D
210	H	D	H	D	D
211	H	D	D	H	H
212	H	D	D	D	H
213	H	D	D	H	D
214	H	D	D	D	D
215	D	H	H	H	H
216	D	H	H	D	H

TABLE 2-continued

Exemplary Embodiments of Formula I

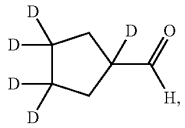
Cmpd	Y^1	Each Y^2	Each Y^3	Y^4	each Y^5
217	D	H	H	H	D
218	D	H	H	D	D
219	D	H	D	H	H
220	D	H	D	D	H
221	D	H	D	H	D
222	D	H	D	D	D
223	D	D	H	H	H
224	D	D	H	D	H
225	D	D	H	H	D
226	D	D	H	D	D
227	D	D	D	H	H
228	D	D	D	D	H
229	D	D	D	H	D
230	D	D	D	D	D
231	H	H	H	H	H

or a pharmaceutically acceptable salt thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

The following compounds are useful for making various compounds of this invention:

22



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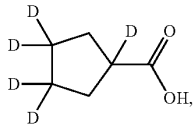

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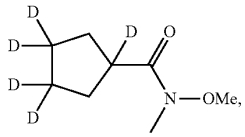

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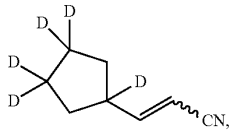

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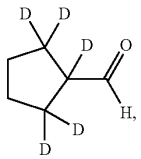

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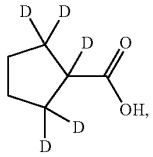

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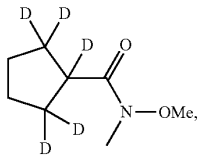

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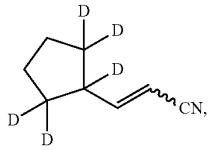

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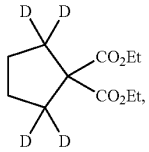

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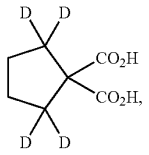

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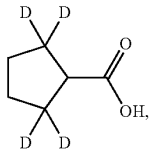

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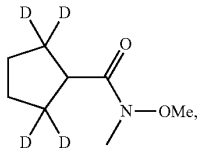

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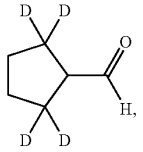

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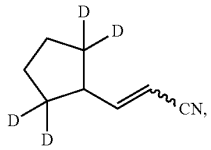

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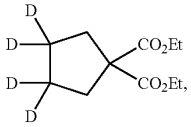

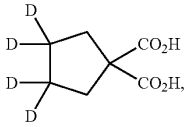

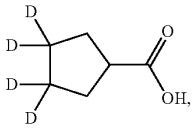

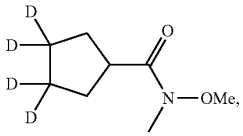

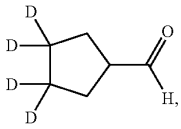

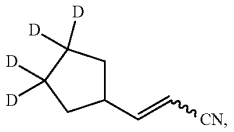

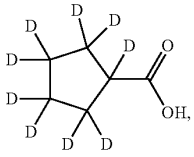

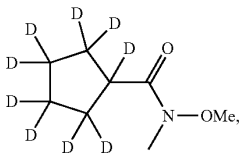

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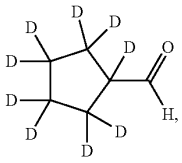

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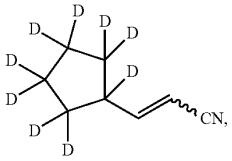


or a salt thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

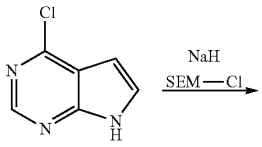
The synthesis of compounds of Formula I or Formula A may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis and Examples disclosed herein. Relevant procedures analogous to those of use for the preparation of compounds of Formula I or Formula A and intermediates thereof are disclosed, for instance, in U.S. Pat. No. 7,598,257 and in Organic Letters, 2009, 11(9): 1999-2009.

Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Synthesis

Compounds of Formula I or Formula A may be prepared in a manner analogous to those syntheses presented in U.S. Pat. No. 7,598,257 and in Organic Letters, 2009, 11(9): 1999-2009 using appropriately deuterated starting materials.

Compounds of Formula I or Formula A may also be prepared as shown in the schemes below.



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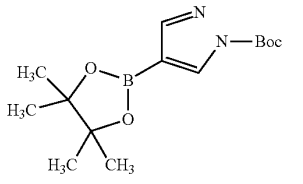

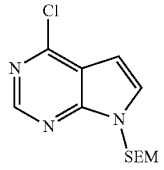

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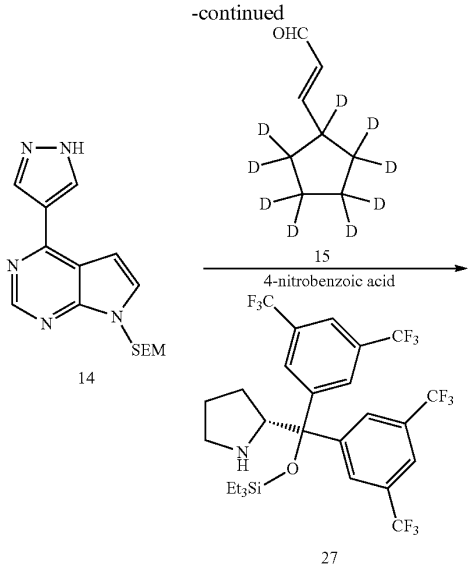
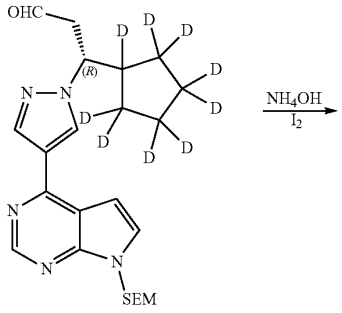
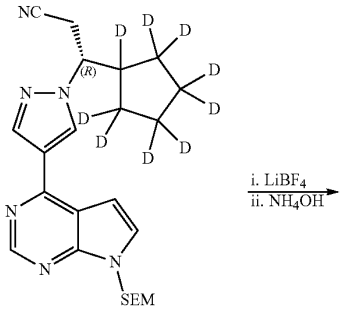
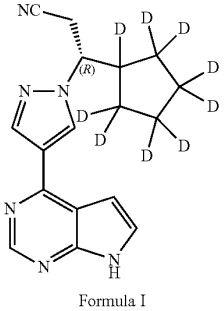


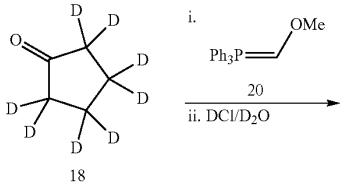


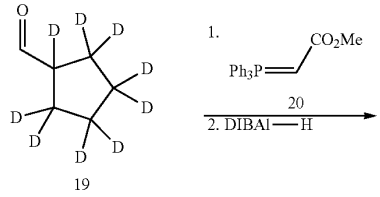


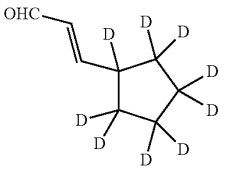


Scheme 1 discloses an exemplary preparation of the compound of formula I wherein Y^1, each Y^2 and each Y^3 are deuterium and Y^4, each Y^5, Y^6, Y^7 and Y^8 are hydrogen. In a manner analogous to that described in WO 2010/083283, commercially available, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine 11 (Aldrich) is treated with sodium hydride and SEM chloride to afford 12, which is reacted with commercially available 13 to provide 14. Instead of 11, 4-bromo-7H-pyrrolo[2,3-d]pyrimidine may also be used in the first step to provide the SEM-protected 4-bromo-7H-pyrrolo[2,3-d]pyrimidine (analogous to 12) which can be reacted with 13 to provide 14. Reaction of 14 with 15, prepared as disclosed in Scheme 2a below, is performed in a manner analogous to that described in Lin, Q. et al. Org. Lett. 2009, 11, 1999, to give 16. The reaction is performed in the presence of chiral ligand 27, prepared as described in Lin, Q. et al. 16 is converted to 17 by treatment with NH_4OH and I_2. The SEM protecting group of 17 is then deprotected with $LiBF_4$ and NH_4OH to give a compound of Formula I.

Scheme 2a. Preparation of Compound 15.

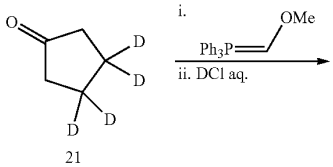






As shown in Scheme 2a, commercially available 18 is treated with phosphonium ylide 20 and DC1/D_2O to provide 19, which is treated with 20 and DiBA1-H to afford 15.

Scheme 2b. Preparation of Compound 23.



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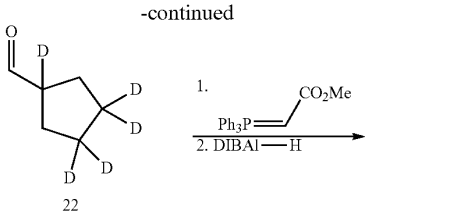

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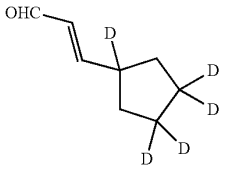

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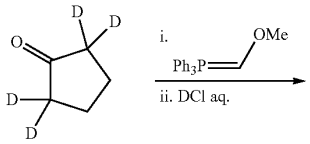
Scheme 2c. Preparation of Compound 26.



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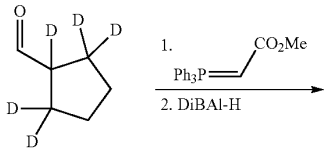

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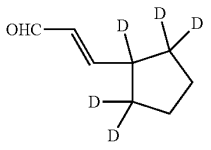

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Compounds analogous to 15 may also be prepared. For example, as shown in Scheme 2b, commercially available 21 may be converted to 23 in a manner analogous to that disclosed in Scheme 2a. As another example, as shown in Scheme 2c, commercially available 24 may be converted to 26 in a manner analogous to that disclosed in Scheme 2a and Scheme 2b. 23 may be converted, in a manner similar to that disclosed in Scheme 1, to a compound of formula I wherein Y^1 and each Y^3 are deuterium and Y^4, each Y^2, each Y^5, Y^6, Y^7 and Y^8 are hydrogen. Likewise, 26 may be converted, in a manner similar to that disclosed in Scheme 1, to a compound of formula I wherein Y^1 and each Y^2 are deuterium and Y^4, each Y^3, each Y^5, Y^6, Y^7 and Y^8 are hydrogen.

The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R^1, R^2, R^3, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

Additional methods of synthesizing compounds of Formula I or Formula A and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene, T W et al., *Protective Groups in Organic Synthesis,* 3rd Ed., John Wiley and Sons (1999); Fieser, L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette, L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

Compositions

The invention also provides pyrogen-free pharmaceutical compositions comprising an effective amount of a compound of Formula I or Formula A (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See U.S. Pat. No. 7,014,866; and United States patent publications 20060094744 and 20060079502.

The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administra-

tion. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, Md. (20th ed. 2000).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz J D and Zaffaroni A C, U.S. Pat. No. 6,803,031, assigned to Alexza Molecular Delivery Corporation.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or com-

binations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

Where an organ or tissue is accessible because of removal from the subject, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as ruxolitinib. Such agents include those indicated as being useful in combination with ruxolitinib.

Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from myelofibrosis, including primary myelofibrosis, polycythemia vera, post-polycythemia vera myelofibrosis, chronic idiopathic myelofibrosis, post-essential thrombocythemia myelofibrosis, and essential thrombocythemia, pancreatic cancer, prostate cancer, breast cancer, leukemia, non-Hodgkin's lymphoma, multiple myeloma, psoriasis and alopecia areata.

In one embodiment, the second therapeutic agent is selected from lenalidomide, panobinostat, capecitabine, exemestane, and combinations thereof.

In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder.

The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., Cancer Chemother. Rep, 1966, 50: 219. Body surface area may be approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

In one embodiment, an effective amount of a compound of this invention can range from 1 mg to 500 mg, such as 5 mg to 100 mg, such as 5 mg to 50 mg. Examples of ranges are from 40 mg to 50 mg, from 25 mg to 40 mg, from 25 mg to 50 mg, from 20 mg to 40 mg, from 20 mg to 50 mg, from 10 mg to 25 mg, from 10 mg to 20 mg, from 5 mg to 25 mg, from 5 mg to 20 mg, and from 5 mg to 10 mg. In one embodiment, a dose of 10 mg, 20 mg, 40 mg, and 50 mg is administered once a day. In one embodiment a dose of 5 mg, 10 mg, 20 mg, 40 mg, and 50 mg is administered twice a day.

Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for ruxolitinib.

For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

In another embodiment, the invention provides a method of inhibiting one or more of Janus Associated Kinases (JAKs) JAK1 and JAK2 in a cell, comprising contacting a cell with one or more compounds of Formula I or Formula A herein, or a pharmaceutically acceptable salt thereof.

According to another embodiment, the invention provides a method of treating a disease that is beneficially treated by ruxolitinib in a subject in need thereof, comprising the step of administering to the subject an effective amount of a compound or a composition of this invention. In one embodiment the subject is a patient in need of such treatment. Such diseases are well known in the art and are disclosed in, but not limited to the following patent: U.S. Pat. No. 7,598,257. Such diseases include, but are not limited to, diseases involving the immune system including, for example, organ transplant rejection (e.g., allograft refection and graft versus host dis-

ease); autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, autoimmune thyroid disorders; allergic conditions such as asthma, food allergies, atopic dermatitis and rhinitis; viral diseases such as Epstein Barr virus (EBV), hepatitis B, hepatitis C, HIV, HTLV 1, varicella-zoster virus (VZV) and human papilloma virus (HPV); skin disorders such as psoriasis (for example, psoriasis vulgaris), atopic dermatitis, skin rash, skin irritation, skin sensitization (e.g., contact dermatitis or allergic contact dermatitis; cancer, including those characterized by solid tumors (e.g., prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, melanoma), hematological cancers (e.g., lymphoma, leukemia such as acute lymphoblastic leukemia, or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (examples of which include Sezary syndrome and mycosis fungoides; myeloproliferative disorders (MPDs) such as polycythemia vera (PV), essential thrombocythemia (ET), myeloid metaplasia with myelofibrosis (MMM), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD); inflammation and inflammatory diseases, such as inflammatory diseases of the eye (e.g., iritis, uveitis, scleritis, conjunctivitis, or related disease), inflammatory diseases of the respiratory tract (e.g., the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis or the lower respiratory tract including bronchitis, chronic obstructive pulmonary disease, and the like), inflammatory myopathy such as myocarditis; systemic inflammatory response syndrome (SIRS) and septic shock; ischemia reperfusion injuries or a disease or condition related to an inflammatory ischemic event such as stroke or cardiac arrest; anorexia; cachexia; fatigue such as that resulting from or associated with cancer; restenosis; sclerodermitis; fibrosis; conditions associated with hypoxia or astrogliosis such as, for example diabetic retinopathy, cancer or neurodegeneration; gout; increased prostate size due to, e.g., benign prostatic hypertrophy or benign prostatic hyperplasia.

In one particular embodiment, the method of this invention is used to treat a disease or condition selected from myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis, essential thrombocythemia or a combination thereof; pancreatic cancer; prostate cancer; breast cancer; leukemia, non-Hodgkin's lymphoma; multiple myeloma;psoriasis and a combination thereof in a subject in need thereof.

In another particular embodiment, the method of this invention is used to treat a disease or condition selected from myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in a subject in need thereof.

Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the subject in need thereof one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with ruxolitinib. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention and a second therapeutic agent.

In particular, the combination therapies of this invention include co-administering a compound of Formula I or Formula A and a second therapeutic agent to a subject in need thereof for treatment of the following conditions (with the particular second therapeutic agent indicated in parentheses following the indication: myelofibrosis (lenalidomide or panobinostat); pancreatic cancer (capecitabine); and breast cancer (exemestane).

The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

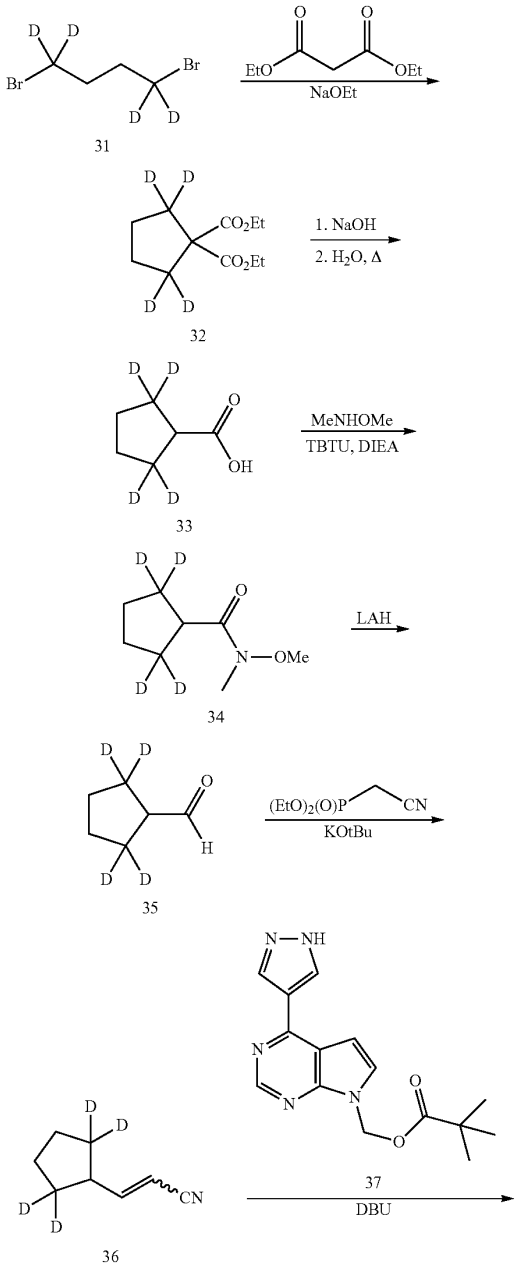
In yet another aspect, the invention provides the use of a compound of Formula I or Formula A alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I or Formula A for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

EXAMPLES

Example 1

Synthesis of (R)-3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-(2,2,5,5-d_4-cyclopentyl) propanenitrile (Compound 107)

Scheme 3. Preparation of Compound 107



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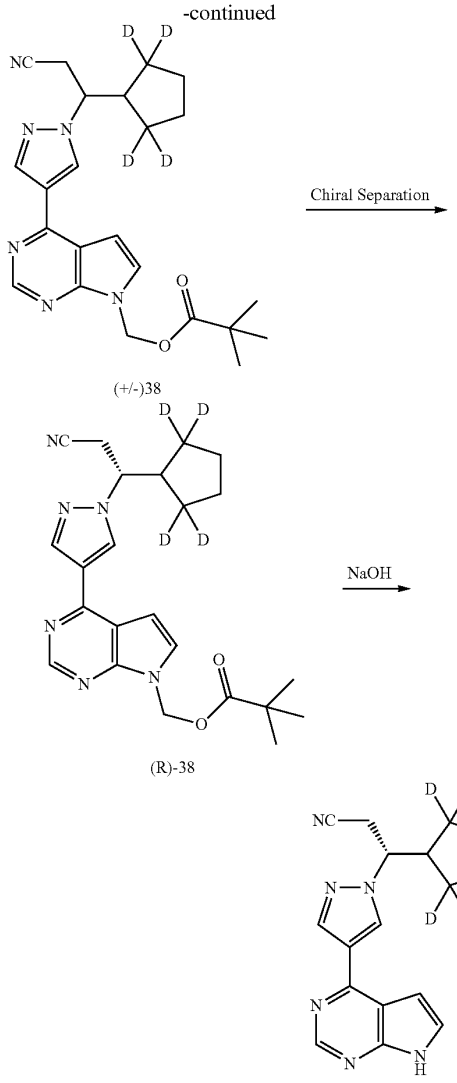


Step 1. Diethyl 2,2,5,5-d_4-cyclopentane-1,1-dicarboxylate (32). To a solution of diethyl malonate (6.57 mL, 43.3 mmol) in ethanol (40 mL) was added a 21 wt % solution of sodium ethoxide in ethanol (32.3 mL, 86.6 mmol) followed by 1,1,4,4-tetradeutero-1,4-dibromobutane (31, 5.53 mL, 45.5 mmol, CDN Isotopes, 98 atom % D). The resulting solution was stirred at reflux for two hours then cooled to room temperature and diluted with excess water. The majority of the ethanol was then removed via distillation and the resulting aqueous solution was extracted with ethyl acetate (3×75 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 32 as a yellow oil which was carried forward without purification. (9.45 g, 100%).

Step 2. 2,2,5,5-d_4-Cyclopentane-1-carboxylic acid (33). To a solution of 32 (9.45 g, 43.3 mmol) in ethanol (20 mL) was added a 5M solution of sodium hydroxide (20 mL). Additional water (15 mL) was then added and the reaction stirred at reflux for three hours. Upon cooling to room tem-

perature, the reaction was diluted with excess water and the majority of ethanol was removed via distillation. The aqueous solution was rendered acidic (pH<2) with 1N HCl and subsequently extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light orange solid was transfered to a pressure flask and water (140 mL) was added. The pressure flask was sealed and the reaction stirred at 160° C. for 15 hours then was cooled to room temperature. The reaction was diluted with 1N HCl and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 33 (4.37 g, 86%) as an amber oil which was used without purification.

Step 3. 2,2,5,5-d_4-N-Methoxy-N-methylcyclopentanecarboxamide (34). To a solution of 33 (4.37 g, 37.0 mmol) in acetonitrile (60 mL) at 0° C. was added N,O-dimethylhydroxylamine hydrochloride (4.33 g, 44.4 mmol), TBTU (12.5 g, 38.9 mmol) and N,N-diisopropylethylamine (19.0 mL, 111 mmol). The reaction stirred at room temperature for 15 hours, then was diluted with 1N HCl and extracted with ethyl acetate (3×50 mL) The organic layers were combined, washed with sat. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The reulting product was purified by column chromatography (SiO_2, 0-50% ethyl acetate/hexanes) to afford 34 (2.22 g, 37%) as a clear oil. MS (ESI) 162.3 [$(M+H)^+$].

Step 4. 2,2,5,5-d_4-Cyclopentane-1-carboxaldehyde (35). To a solution of 34 (2.22 g, 13.8 mmol) in THF (50 mL) at 0° C. was added dropwise a 1M solution of $LiAlH_4$ in THF (24.8 mL, 24.8 mmol). The reaction stirred at 0° C. for one hour then was quenched by sequential dropwise addition of water (940 μL), 15% NaOH (940 μL) and water (2.82 mL). The quenched reaction stirred at room temperature for 30 minutes then was filtered through Celite® and concentarted under reduced pressure. The resulting oil was diluted with 1N HCl and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 35 (850 mg, 60%) as a clear oil which was used without purification.

Step 5. 3-(2,2,5,5-d_4-cyclopentyl)acrylonitrile (36). To a 1M solution of potassium tert-butoxide in THF (8.74 mL, 8.74 mmol) at 0° C. was added dropwise a solution of diethyl cyanomethylphosphonate (1.48 mL, 9.15 mmol) in THF (12 mL). The reaction was warmed to room temperature, stirred for 15 minutes, then cooled to 0° C. Aldehyde 35 (850 mg, 8.32 mmol) was then added dropwise as a solution in THF (3 mL). The reaction was stirred at room temperature for 48 hours then diluted with excess water and extracted with diethyl ether (1×50 mL) and ethyl acetate (3×50 mL) The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 36 (1.17 g, >100%) as a light orange oil which was used without purification.

Step 6. (+/−)-(4-(1-(2-Cyano-1-(2,2,5,5-d_4-cyclopentyl) ethyl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl) methyl pivalate ((+/−)38). To a solution of 37 (400 mg, 1.34 mmol, preparation described in Lin, Q. et al. *Org. Lett.*, 2009, 11, 1999-2002) in acetonitrile (10 mL) was added 36 (418 mg, 3.34 mmol) followed by DBU (421 μL, 2.81 mmol). The reaction stirred at room temperature for 15 hours then was concentrated under reduced vacuum. The resulting crude mixture was diluted with water and extracted with ethyl acetate (3×50 mL). The organic layers were combined, washed with 1N HCl, dried (Na_2SO_4), filtered and concentrated underreduced pressure. Purification via normal phase column chromatography (SiO_2, 0-60% ethyl acetate/hexanes) followed by reverse phase column chromatography (C18, 5-70% acetonitrile/water containing 0.1% formic acid) afforded (+/−)38 (68 mg, 12%) as a white foam. 1H NMR (DMSO-d_6, 400 MHz) δ 8.84 (s, 1H), 8.79 (s, 1H), 8.40 (s, 1H), 7.74 (d, J=3.8 Hz, 1H), 7.12 (d, J=3.8 Hz, 1H), 6.24 (s, 2H), 4.54 (td, J=9.7, 4.3 Hz, 1H), 3.30-3.15 (m, 2H), 2.39 (d, J=9.8 Hz, 1H), 1.68-1.36 (m, 4H), 1.08 (s, 9H); MS (ESI) 425.3 [$(M+H)^+$].

Step 7. (R)-(4-(1-(2-cyano-1-(2,2,5,5-tetradeuterocyclopentyl)ethyl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate ((R)-38). Racemic compound (+/−) 38 (62 mg) was dissolved in acetonitrile at a concentration of 30 mg/mL and subjected to chiral separation by preparative HPLC on a Daicel ChiralPak AD column (20×250 mm, 10 μm) with 500 μL of (+/−)38 solution per injection using an isocratic method: 30% isopropanol (+0.1% diethylamine)/ 70% hexane (+0.1% diethylamine) at a flow rate of 17 mL/min. Under these conditions baseline separation was achieved with (S)-38 eluting at 15.0 minutes and (R)-38 eluting at 20.2 minutes.

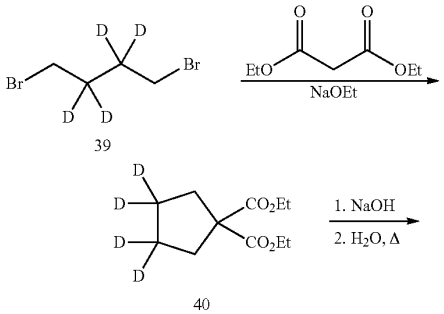
Fractions containing each enantiomer were pooled and concentrated yielding 28 mg of (S)-38 as a colorless film and 29 mg of (R)-38 as a colorless film.

Step 8. (R)-3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-(2,2,5,5-tetradeuterocyclopentyl)propanenitrile (Compound 107). Compound (R)-38 (28 mg, 0.066 mmol, 1 equiv) was dissolved in methanol (1 mL) in a 20 mL scintillation vial. Sodium hydroxide (0.13 mL of a 1 M solution, 0.13 mmol, 2 equiv) was added and the reaction was stirred at room temperature for 18 hours. The reaction was diluted with water (10 mL) and brine (20 mL). The aqueous mixture was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and evaporated. The crude material was purified using an Analogix automated chromatography system eluting with 0 to 6% methanol in dichloromethane. Product fractions were pooled and evaporated yielding compound 107 as a white foam. The chiral purity was found to be>99% ee (Chiralpak OD 4.6×250 mm, 10 um, 70% (hexane+0.1% diethylamine)+30% (isopropanol+0.1% diethylamine), 1 mL/min, 254 nm retention time=8.85 min).

Example 2

Synthesis of (R)-3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-(3,3,4,4-d_4-cyclopentyl) propanenitrile (Compound 103)

Scheme 4. Preparation of Compound 103



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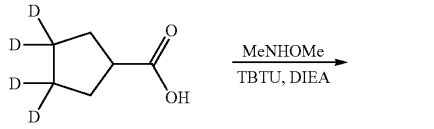

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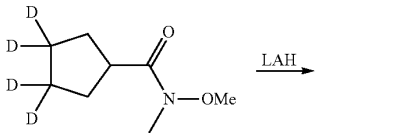

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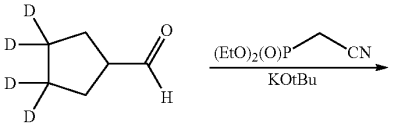

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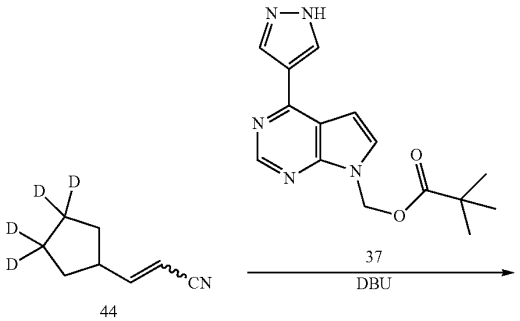

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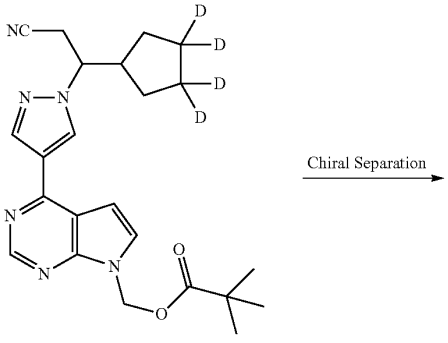
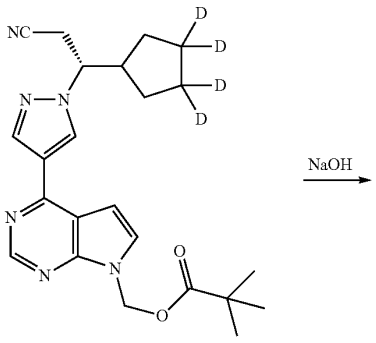


(+/-)45



(R)-45

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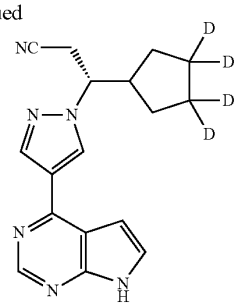


Compound 103

Step 1. Diethyl 3,3,4,4-d_4-cyclopentane-1,1-dicarboxylate (40). To a solution of diethyl malonate (3.25 mL, 21.4 mmol) in ethanol (20 mL) was added a 21 wt % solution of sodium ethoxide in ethanol (16.0 mL, 42.8 mmol) followed by 2,2,3,3-tetradeutero-1,4-dibromobutane (39, 4.95 g, 22.5 mmol, CDN Isotopes, 98 atom % D). The resulting solution was stirred at reflux for two hours then cooled to room temperature and diluted with excess water. The majority of the ethanol was then removed via distillation and the resulting aqueous solution was extracted with ethyl acetate (3×75 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 40 as a yellow oil which was carried forward without purification. (4.67 g, 100%).

Step 2. 3,3,4,4-d_4-Cyclopentane-1-carboxylic acid (41). To a solution of 40 (4.67 g, 21.4 mmol) in ethanol (10 mL) was added a 5M solution of sodium hydroxide (10 mL). Additional water (10 mL) was then added and the reaction stirred at reflux for three hours. Upon cooling to room temperature, the reaction was diluted with excess water and the majority of ethanol was removed via distillation. The aqueous solution was rendered acidic (pH<2) with 1N HCl and subsequently extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light orange solid was transfered to a pressure flask and water (70 mL) was added. The pressure flask was sealed and the reaction stirred at 160° C. for 15 hours then was cooled to room temperature. The reaction was diluted with 1N HCl and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 41 (1.93 g, 76%) as an amber oil which was used without purification.

Step 3. 3,3,4,4-d_4-N-Methoxy-N-methylcyclopentanecarboxamide (42). To a solution of 41 (1.93 g, 16.3 mmol) in acetonitrile (30 mL) at 0° C. was added N,O-dimethylhydroxylamine hydrochloride (1.91 g, 19.6 mmol), TBTU (5.50 g, 17.1 mmol) and N,N-diisopropylethylamine (8.52 mL, 48.9 mmol). The reaction stirred at room temperature for 15 hours, then was diluted with 1N HCl and extracted with ethyl acetate (3×50 mL). The organic layers were combined, washed with sat. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The reulting product was purified by column chromatography (SiO_2, 0-40% acetone/hexanes) to afford 42 (1.47 g, 56%) as a clear oil. MS (ESI) 162.3 [$(M+H)^+$].

Step 4. 3,3,4,4-d_4-Cyclopentane-1-carboxaldehyde (43). To a soultion of 42 (1.47 g, 9.12 mmol) in THF (35 mL) at 0° C. was added dropwise a 1M solution of $LiAlH_4$ in THF (16.4 mL, 16.4 mmol). The reaction stirred at room temperature for one hour then was quenched at 0° C. by sequential dropwise

addition of water (623 μL), 15% NaOH (623 μL) and water (1.87 mL). The quenched reaction stirred at room temperature for 30 minutes then was filtered through Celite® and concentarted under reduced pressure. The resulting oil was diluted with 1N HCl and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 43 (767 mg, 82%) as a clear oil which was used without purification.

Step 5. 3-(3,3,4,4-d_4-Cyclopentyl)acrylonitrile (44). To a solution of diethyl cyanomethylphosphonate (0.607 mL, 3.75 mmol) in THF (10 mL) at 0° C. was added dropwise a 1M solution of potassium tert-butoxide in THF (3.75 mL, 3.75 mmol). The reaction stirred at 0° C. for 1 hour. Aldehyde 43 (767 mg, 7.51 mmol) was then added dropwise as a solution in THF (3 mL). The reaction was stirred at room temperature for 15 hours then diluted with excess 1:1 water/brine and extracted with MTBE (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (100 ml) and washed with $NaHSO_3$ (3×25 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 44 (537 mg, 57%) as a light orange oil which was used without purification.

Step 6. (+/−)-(4-(1-(2-Cyano-1-(3,3,4,4-d_4-cyclopentyl) ethyl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl) methyl pivalate ((+/−)45). To a solution of 37 (514 mg, 1.72 mmol, preparation described in Lin, Q. et al. *Org. Lett.,* 2009, 11, 1999-2002) in acetonitrile (15 mL) was added 44 (537 mg, 4.29 mmol) followed by DBU (540 μL, 3.61 mmol). The reaction stirred at room temperature for 15 hours then was concentrated under reduced vacuum. The resulting crude mixture was diluted with water and extracted with ethyl acetate (3×50 mL). The organic layers were combined, washed with 1N HCl, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification via normal phase column chromatography (SiO_2, 0-60% ethyl acetate/hexanes) afforded (+/−) 45 (368 mg, 50%) as a white foam. 1H NMR (DMSO-d_6, 400 MHz) δ 8 8.84 (s, 1H), 8.79 (s, 1H), 8.40 (s, 1H), 7.75 (d, J=3.7 Hz, 1H), 7.12 (d, J=3.7 Hz, 1H), 6.24 (s, 2H), 4.53 (td, J=9.7, 4.2 Hz, 1H), 3.32-3.14 (m, 2H), 2.41 (q, J=8.7 Hz, 1H), 1.79 (dd, J=12.6, 7.6 Hz, 1H), 1.36-1.11 (m, 3H), 1.08 (s, 9H); MS (ESI) 425.2 [$(M+H)^+$].

Step 7. (R)-(4-(1-(2-Cyano-1-(3,3,4,4-d_4-cyclopentyp-ethyl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl) methyl pivalate ((R)-45). Racemic compound (+/−)45 (151 mg) was dissolved in acetonitrile at a concentration of 30 mg/mL and subjected to chiral separation by preparative HPLC on a Daicel ChiralPak AD column (20×250 mm, 10 μm) with 1000 μL of (+/−)45 solution per injection using an isocratic method: 30% isopropanol (+0.1% diethylamine)/ 70% hexane (+0.1% diethylamine) at a flow rate of 17 mL/min. Under these conditions baseline separation was achieved with (S)-45 eluting at 15.5 minutes and (R)-45 eluting at 20.7 minutes.

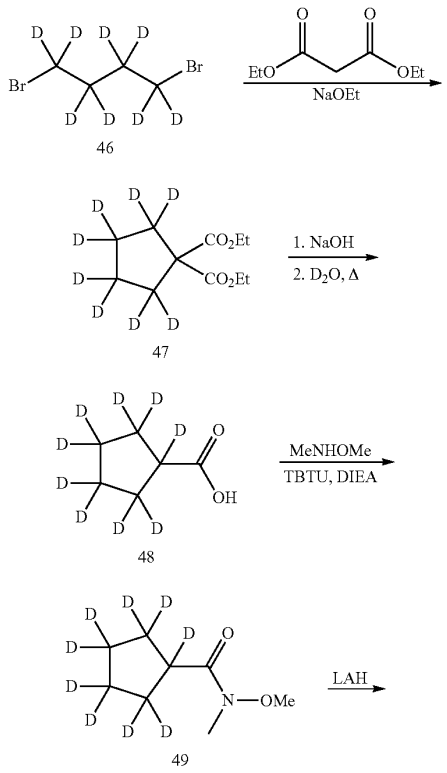
Fractions containing each enantiomer were pooled separately and concentrated to give g 51 mg of (S)-45 as a colorless film and 53 mg of (R)-45 as a colorless film.

Step 8. (R)-3-(4-(7H-Pyrrolo [2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-(3,3,4,4-d_4-cyclopentyl)propanenitrile (Compound 103). (R)-45 (53 mg, 0.13 mmol, 1 equiv) was dissolved in methanol (2 mL) in a 20 mL scintillation vial. Sodium hydroxide (0.25 mL of a 1 M solution, 0.25 mmol, 2 equiv) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (10 mL) and brine (20 mL). The aqueous mixture was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated. The crude material was purified using an Analogix automated chromatography system eluting with 0 to 6% methanol in dichloromethane. Product fractions were pooled and evaporated to give Compound 103 as a white foam in ~90% purity with the incompletely deprotected hydroxymethyl intermediate as the main impurity. Further chromatography failed to further improve the purity. The 90% pure material was dissolved in THF (2 mL) and treated with several drops of 10% aqueous sodium hydroxide at 40° C. for 8 hours resulting in complete conversion to Compound 103. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to a white foam. The foam was dissolved in minimal acetonitrile, diluted with water, and lyophilized to give Compound 103 (14 mg, 35% yield) as a white solid. The chiral purity was found to be>99% ee (Chiralpak OD 4.6×250 mm, 10 um, 70% (hexane+0.1% diethylamine)+30% (isopropanol+0.1% diethylamine), 1 mL/min, 254 nm retention time=7.56 min).

Example 3

Synthesis of (R)-3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-(cyclopentyl-d_9)propanenitrile (Compound 127)

Scheme 5. Preparation of Compound 127



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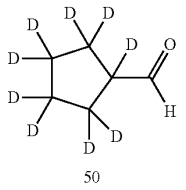

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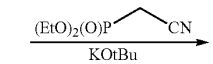

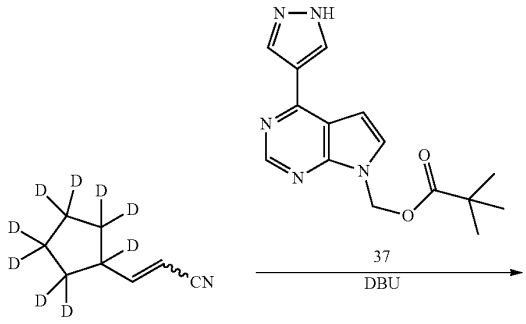

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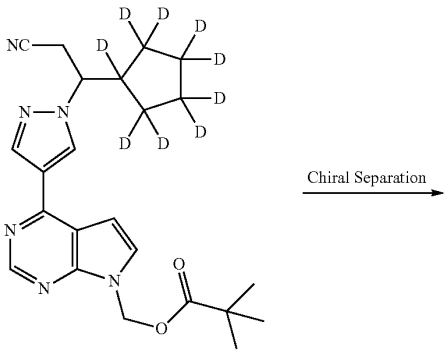
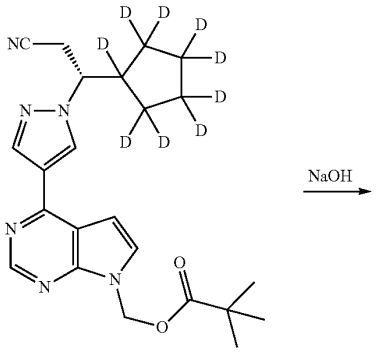


(+/-)52



(R)-52

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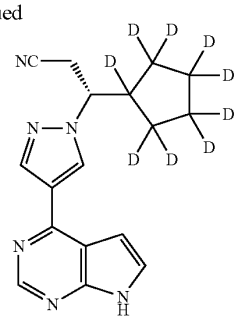


Compound 127

Step 1. Diethyl 2,2,3,3,4,4,5,5-d_8-Cyclopentane-1,1-dicarboxylate (47). To a solution of diethyl malonate (6.24 mL, 41.1 mmol) in ethanol (40 mL) was added a 21 wt % solution of sodium ethoxide in ethanol (30.7 mL, 82 2 mmol) followed by 1,1,2,2,3,3,4,4-octadeutero-1,4-dibromobutane (46, 9.67 g, 43.2 mmol, CDN Isotopes, 98 atom % D). The resulting solution was stirred at reflux for two hours then cooled to room temperature and diluted with excess water. The majority of the ethanol was then removed via distillation and the resulting aqueous solution was extracted with ethyl acetate (3×75 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 47 as a yellow oil (9.12 g, 100%) which was carried forward without purification.

Step 2. Perdeuterocyclopentane-1-carboxylic acid (48). To a solution of 47 (9.12 g, 41.1 mmol) in ethanol (20 mL) was added a 5M solution of sodium hydroxide (20 mL). Additional water (15 mL) was then added and the reaction stirred at reflux for three hours. Upon cooling to room temperature, the reaction was diluted with excess water and the majority of ethanol was removed via distillation. The aqueous solution was rendered acidic (pH<2) with 1N HCl and subsequently extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light orange solid was transfered to a pressure flask and D_2O (120 mL) was added. The pressure flask was sealed and the reaction stirred at 160° C. for 15 hours then was cooled to room temperature. The reaction was diluted with 1N HCl and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 48 (4.58 g, 90%) as a yellow oil which was used without purification.

Step 3. N-Methoxy-N-methyl(cyclopentane-d_9)carboxamide (49). To a solution of 48 (4.58 g, 37.2 mmol) in acetonitrile (60 mL) at 0° C. was added N,O-dimethylhydroxylamine hydrochloride (4.35 g, 44.6 mmol), TBTU (12.5 g, 39 1 mmol) and N,N-diisopropylethylamine (19.4 mL, 112 mmol). The reaction stirred at room temperature for 15 hours, then was diluted with 1N HCl and extracted with ethyl acetate (3×50 mL). The organic layers were combined, washed with sat. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The reulting product was purified by column chromatography (SiO_2, 0-50% ethyl acetate/hexanes) to afford 49 (3.41 g, 55%) as a clear oil. MS (ESI) 167.2 [(M+H)$^+$].

Step 4. Perdeuterocyclopentane-1-carboxaldehyde (50). To a solution of 49 (3.41 g, 20.5 mmol) in THF (80 mL) at 0° C. was added dropwise a 1M solution of $LiAlH_4$ in THF (37.0 mL, 37.0 mmol). The reaction stirred at room temperature for

one hour then was quenched at 0° C. by sequential dropwise addition of D_2O (1.41 mL), 15% NaOD/D_2O (1.41 mL) and D_2O (4.23 mL). The quenched reaction stirred at room temperature for 30 minutes then was filtered through Celite® and concentrated under reduced pressure. The resulting oil was diluted with 1N DCl/D_2O and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 50 (1.79 g, 82%) as a clear oil which was used without purification.

Step 5. 3-(Perdeuterocyclopentyl)acrylonitrile (51). To a solution of diethyl cyanomethylphosphonate (1.35 mL, 8.34 mmol) in THF (25 mL) at 0° C. was added dropwise a 1M solution of potassium tert-butoxide in THF (8.34 mL, 8.34 mmol). The reaction stirred at 0° C. for 1 hour. Aldehyde 50 (1.79 g, 16.7 mmol) was then added dropwise as a solution in THF (5 mL). The reaction was stirred at room temperature for 15 hours then diluted with excess 1:1 water/brine and extracted with MTBE (3×50 mL) The organic layers were combined, dried (Na_2SO_4), filtered and concentrated underreduced pressure. The organic layers were combined, dried (Na_2SO_4), filtered and concentrated underreduced pressure to afford 51 (1.61 g, 74%) as a light orange oil which was used without purification.

Step 6. (+/−)-(4-(1-(2-Cyano-1-(cyclopentyl-d_9)ethyl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate ((+/−)52). To a solution of 37 (619 mg, 2.07 mmol, preparation described in Lin, Q. et al. *Org. Lett.,* 2009, 11, 1999-2002) in acetonitrile (15 mL) was added 51 (673 mg, 5.17 mmol) followed by DBU (650 μL, 4.35 mmol). The reaction stirred at room temperature for 15 hours then was concentrated under reduced vacuum. The resulting crude mixture was diluted with water and extracted with ethyl acetate (3×50 mL) The organic layers were combined, washed with 1N HCl, dried (Na_2SO_4), filtered and concentrated underreduced pressure. Purification via normal phase column chromatography (SiO_2, 0-60% ethyl acetate/hexanes) afforded (+/−)52 (447 mg, 50%) as a white foam. 1H NMR (DMSO-d_6, 400 MHz) δ 8.84 (s, 1H), 8.79 (s, 1H), 8.39 (s, 1H), 7.75 (d, J=3.7 Hz, 1H), 7.12 (d, J=3.7 Hz, 1H), 6.24 (s, 2H), 4.53 (dd, J=9.6, 4.2 Hz, 1H), 3.32-3.13 (m, 2H), 1.08 (s, 9H); MS (ESI) 430.3[(M+H)$^+$].

Step 7. (R)-(4-(1-(2-Cyano-1-(cyclopentyl-d_9)ethyl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate ((R)-52). Racemic compound (+/−)52 (162 mg) was dissolved in acetonitrile at a concentration of 30 mg/mL and subjected to chiral separation by preparative HPLC on a Daicel ChiralPak AD column (20×250 mm, 10 μm) with 1000 μL of (+/−)52 solution per injection using an isocratic method: 30% isopropanol (+0.1% diethylamine)/70% hexane (+0.1% diethylamine) at a flow rate of 17 mL/min. Under these conditions baseline separation was achieved with (S)-52 eluting at 15.4 minutes and (R)-52 eluting at 20.5 minutes.

Fractions containing each enantiomer were pooled separately and concentrated to give 61 mg of (S)-52 as a colorless film and 63 mg of (R)-52 as a colorless film.

Step 8. (R)-3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-(cyclopentyl-d_9)propanenitrile (Compound 127). (R)-52 (60 mg, 0.14 mmol, 1 equiv) was dissolved in methanol (2 mL) in a 20 mL scintillation vial. Sodium hydroxide (0.28 mL of a 1 M solution, 0.28 mmol, 2 equiv) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (10 mL) and brine (20 mL). The aqueous mixture was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated. The crude material was purified using an Analogix automated chromatography system eluting with 0 to 6% methanol in dichloromethane. Product fractions were pooled and evaporated to give Compound 127 (34 mg) as a white foam in ~90% purity with the incompletely deprotected hydroxymethyl intermediate as the main impurity. Further chromatography failed to further improve the purity. The 90% pure material was dissolved in THF (2 mL) and treated with several drops of 10% aqueous sodium hydroxide at 40° C. for 8 hours resulting in complete conversion to Compound 127. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to a white foam. The foam was dissolved in minimal acetonitrile, diluted with water, and lyophilized to give Compound 127 (19 mg, 42% yield) as a white solid. The chiral purity was found to be>99% ee (Chiralpak OD 4.6×250 mm, 10 um, 70% (hexane+0.1% diethylamine)+30% (isopropanol+0.1% diethylamine), 1 mL/min, 254 nm retention time=7.55 min).

Example 4

Evaluation of Metabolic Stability in CYP3A4 Supersomes™

Evaluation of Metabolic Stability of Compounds 103, 107 and 127 in Human CYP3A4 Supersomes™.

SUPERSOMES™ Assay. 10 mM stock solutions of test compounds, Compounds 103, 107, 127 and ruxolitinib, were prepared in DMSO. The 10 mM stock solutions were diluted to 15.6 μM in acetonitrile (ACN). Human CYP3A4 supersomes™ (1000 pmol/mL, purchased from BD Gentest™ Products and Services) were diluted to 62.5 pmol/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted supersomes were added to wells of a 96-well polypropylene plate in triplicate. A 10 μL aliquot of the 15.6 μM test compound was added to the supersomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 50 pmol/mL CYP3A4 supersomes™, 0.25 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures were incubated at 37° C., and 50 μL aliquots were removed at 0, 5, 10, 20, and 30 minutes and added to 96-well plates which contained 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates were stored at 4° C. for 20 minutes after which 100 mL of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Biosystems API 4000 mass spectrometer.

Data analysis: The in vitro half-lives ($t_{1/2}$ values) for test compounds were calculated from the slopes of the linear regression of LN (% parent remaining) vs incubation time relationship:

$$\text{in vitro } t_{1/2} = 0.693/k$$

k=−[slope of linear regression of % parent remaining (ln) vs incubation time].

The results of this experiment are shown in Table 3 and FIG. **1**. As shown in Table 3, the half-life of ruxolitinib was calculated to be 14.5 minutes. In contrast, each of Compounds 103, 107 and 127 were more stable in the supersomes with calculated half-lives of 16.9, 17.9 and 32.0 minutes respectively. This respresents a 17% increase in $t_{1/2}$ for com-

pound 103, a 23% increase in $t_{1/2}$ for compound 107, and a 121% increase in $t_{1/2}$ for compound 127.

TABLE 3

Metabolic Stability of Compounds 103, 107 and 127 versus Ruxolitinib in Human CYP3A4 Supersomes ™

	$t_{1/2}$ (minutes)		
Compound	Experiment 1	Experiment 2	Ave ± SD
Ruxolitinib	14.5	14.5	14.5 ± 00
Compound 103	17.5	16.3	16.9 ± 0.9 (17%*)
Compound 107	18.4	17.0	17.9 ± 1.0 (23%*)
Compound 127	31.4	32.1	32.0 ± 0.5 (121%*)

*% Δ = [(deuterated species) − (nondeuterated species)](100)/(nondeuterated species)

Example 5

Evaluation of Metabolic Stability in Human Liver Microsomes

Microsomal Assay: Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, Kans.). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

Determination of Metabolic Stability: 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5-50 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37° C., and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4° C. for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for the non-deuterated counterpart of the compound of Formula I or Formula A and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

Data analysis: The in vitro $t_{1/2}$s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

$$\text{in vitro } t_{1/2} = 0.693/k$$

k=−[slope of linear regression of % parent remaining (ln) vs incubation time]

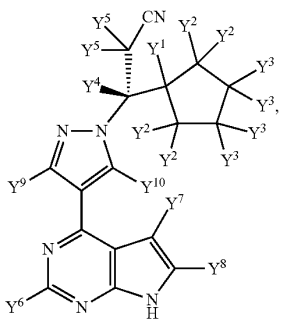
Data analysis is performed using Microsoft Excel Software.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

What is claimed is:

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9 and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

2. The compound of claim **1**, in which Y^4 is hydrogen and each Y^5 is hydrogen.

3. The compound of claim **1**, in which each Y^2 is deuterium and each Y^3 is hydrogen.

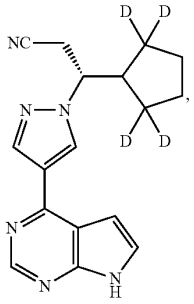
4. The compound of claim **1**, in which each Y^2 is hydrogen and each Y^3 is deuterium.

5. The compound of claim **1**, in which each Y^2 is deuterium and each Y^3 is deuterium.

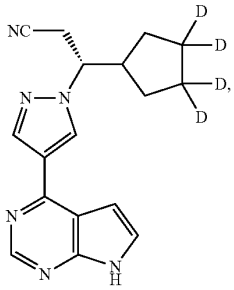
6. The compound of claim **1**, in which Y^6, Y^7 and Y^8 are each hydrogen.

7. The compound of claim **1**, in which the compound is selected from the group consisting of:

Compound 107

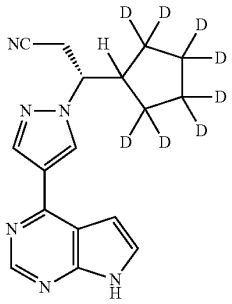


Compound 103



and

Compound 111

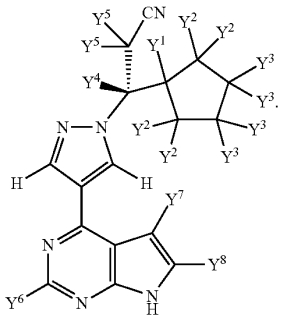


or a pharmaceutically acceptable salt of any of the foregoing.

8. A pharmaceutical composition comprising the compound of claim **1**, and a pharmaceutically acceptable carrier.

9. A compound of Formula I:

Formula I



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7 and Y^8 are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

10. The compound of claim **9**, in which Y^4 is hydrogen and each Y^5 is hydrogen.

11. The compound of claim **9**, in which each Y^2 is deuterium and each Y^3 is hydrogen.

12. The compound of claim **9**, in which each Y^2 is hydrogen and each Y^3 is deuterium.

13. The compound of claim **9**, in which each Y^2 is deuterium and each Y^3 is deuterium.

14. The compound of claim **9**, in which Y^6, Y^7 and Y^8 are each hydrogen.

15. A pharmaceutical composition comprising the compound of claim **9**, and a pharmaceutically acceptable carrier.

* * * * *

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because, excluding the parts of the document exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b), it contains 13,822 words.

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared using Microsoft Word for Office 365 in 14-point Times New Roman, a proportionally spaced typeface.

June 27, 2022

/s/ *William M. Jay*
William M. Jay

CERTIFICATE OF SERVICE

I hereby certify that on June 27, 2022, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit using the Court's CM/ECF system. Counsel for all parties to the case are registered CM/ECF users and will be served by the CM/ECF system.

June 27, 2022

/s/ *William M. Jay*
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