UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner

v.

PLEXXIKON INC.,
Patent Owner

Case No.: IPR2018-01287

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,469,640

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Exhibit No.	Special Designation (if applicable)	Description
1001	'640 patent	Wu et al., U.S. Patent No. 9,469,640 B2, "Compounds and Methods for Kinase Modulation, and Indications Therefor" (Oct. 18, 2016).
1002	Baran Dec.	Declaration of Phil S. Baran, Ph.D.
1004	P2	U.S. Application No. 12/669,450 (filed July 16, 2008)
1005		P3 Prosecution History, October 4, 2013 Office Action
1006	'185 patent	Tara R. Rheault, U.S. Patent No. 7,994,185, "Benzene Sulfonamide Thiazole and Oxazole Compounds," (Aug. 9, 2011)
1007		P3 Prosecution History, June 5, 2014 Notice of Abandonment
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1018	Martin	Martin et al., "Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands," 41 (11) ACCOUNTS OF CHEMICAL RESEARCH 1461-1473 (Nov. 2008)
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1020	Kinzel	Kinzel et al., "A New Palladium Precatalyst Allows for the Fast Suzuki-Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids" 132(40) J. AM. CHEM. SOC. 14073-75 (Oct. 2010)
1021	Jedinák	Jedinák et al., "The Suzuki−Miyaura Cross-Coupling Reaction of Halogenated Aminopyrazoles: Method Development, Scope, and Mechanism of Dehalogenation Side Reaction," 82 J. ORG. CHEM. 157-169 (Dec. 2016)
1022	Tyrrell	Elizabeth Tyrrell and Phillip Brookes, "The Synthesis and Applications of Heterocyclic Boronic Acids," 2003(4) Synthesis 469-483
1023	Hämmerle	Hämmerle et al., "A guideline for the arylation of positions 4 and 5 of thiazole via Pd-catalyzed cross-coupling reactions," 66 TETRAHEDRON 8051-8059 (Aug. 2010)

1024	Cox	Paul A. Cox et al., "Protodeboronation of heteroaromatic, vinyl and cyclopropyl boronic acids: pH-rate profiles, auto-catalysis and dispropotionation," 138(29) *J. Am. Chem. Soc.* 9145-57, 9152 (2016)
1025	Suzuki Nobel Lecture	Akira Suzuki, "Cross-Coupling Reactions of Organoboranes: An Easy Way to Construct C-C Bonds (Nobel Lecture), 50 ANGEW. CHEM INT. ED. 6723-6737, 6734 (2011)
1026	Li and Gribble	Li and Gribble (Eds.), PALLADIUM IN HETEROCYCLIC CHEMISTRY: A GUIDE FOR THE SYNTHETIC CHEMIST (2d ed. 2006).

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R Part 42, Petitioner respectfully requests that the Board institute an *inter partes* review of claims 1, 2, 4-6, 9, 11, and 12 (the "Challenged Claims") of U.S. Patent No. 9,469,640 ("the '640 patent," Ex. 1001) and determine that each of the Challenged Claims should be canceled as unpatentable.

I. INTRODUCTION

The '640 patent, entitled "Compounds and Methods for Kinase Modulation, and Indications Therefor," issued on October 18, 2016. The patent is assigned to Plexxikon Inc. ("Plexxikon"). The '640 patent claims priority to U.S. Application No. 12/669,450 (PCT/US2008/070124) ("P2"), filed on July 16, 2008, through a series of three continuation applications (all abandoned), and claims earliest priority to provisional application No. 60/959,907 ("P1"), filed July 17, 2007.

The Challenged Claims are not entitled to the benefit of the July 16, 2008 filing date of P2 or the earlier provisional application because P2 does not satisfy the written description and enablement requirements of 35 U.S.C. § 112 (pre-AIA) as required for benefit under 35 U.S.C. § 120.[1] Ex. 1002, Declaration of Phil S. Baran, Ph.D. ("Baran Dec.") ¶ 8. Specifically, P2 discloses enormous genera of chemical compounds which cover an effectively incalculable number of

[1] The pre-AIA versions of the Patent Act are used in this Petition; however, the conclusions would be the same under the AIA versions.

compounds, but provides no "blaze marks" to direct a person of ordinary skill to the subgenera of the Challenged Claims. Moreover, while the subgenera of the Challenged Claims cover trillions of compounds, there are only three examples in P2 that fall within the scope of the claims, and none where L_1 is a bond, which constitute approximately half of the compounds covered by the claims. P2 thus fails to meet the written description requirement of § 112. P2 also fails to meet the enablement requirement of § 112 because it does not enable a person of ordinary skill to make the full scope of claimed compounds wherein L_1 is a bond, nor does it meet the how-to-use/utility prong of the enablement requirement because it does not disclose any data showing that claimed compounds wherein L_1 is a bond achieve the desired results of the invention, *viz*. activity on protein kinases.

Because the Challenged Claims are not entitled to the priority date of P2 or any earlier application, the earliest possible priority date is April 19, 2013, the filing date of the next continuation application, U.S. Application No. 13/866,353 ("P3").[2] As a result, each of the Challenged Claims is anticipated under 35 U.S.C. § 102(b) (pre-AIA) by U.S. Patent No. 7,994,185 ("the '185 patent"), which issued

[2] None of the applications in the chain of continuations leading to the '640 patent satisfies the § 112 requirements – including P3 – but for purposes of the instant Petition it is only necessary to show that the Challenged Claims are not entitled to the benefit of P2 or any earlier application.

on August 9, 2011. The '185 patent discloses and claims specific compounds falling within the scope of each of the Challenged Claims, including dabrafenib, the active ingredient of a commercial pharmaceutical product sold by Petitioner. Plexxikon has accused dabrafenib of infringing the Challenged Claims in pending district court litigation in the Northern District of California. As set out below, each of the Challenged Claims should be cancelled as anticipated by the '185 patent.

The Examiner made a comparable rejection during prosecution of P3. P3 was filed on April 19, 2013, and sought to claim priority to its parent application, P2. The Examiner determined that the claims of P3 were not entitled to the priority date of the parent application, on grounds that the parent application "fails to provide adequate support or enablement" in the manner provided by 35 U.S.C. § 112. Ex. 1005 at 3. Because P3 was only entitled to its actual filing date of April 19, 2013, the Examiner found the claims invalid based (*inter alia*) on the '185 patent. *Id*. at 11-13. Rather than address the rejection, Plexxikon abandoned the P3 application. Inexplicably, the Examiner did not apply this same analysis during prosecution of the '640 patent. The Examiner's failure to apply this analysis and to find the claims of the '640 patent to be unpatentable was a mistake that should be corrected by the Board.

As shown below, there is a very strong likelihood (and certainly at least a reasonable likelihood) that Petitioner will prevail in establishing that all of the Challenged Claims of the ’640 patent should be canceled. Petitioner thus asks the Board to grant *inter partes* review and determine that the Challenged Claims of the ’640 patent are, in fact, unpatentable.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-In-Interest

Novartis Pharmaceuticals Corporation (“NPC”) is the real party-in-interest.

B. Related Matters

The ’640 patent is asserted in *Plexxikon Inc. v. Novartis Pharmaceuticals Corporation*, Civil Action No. 4:17-cv-04405 HSG (EDL) (N.D. Ca. filed Aug. 3, 2017).

A petition for Post-Grant Review of U.S. Patent No. 9,844,539 (“the ’539 patent) is being filed concurrently with the instant Petition. The ’539 patent is in the same patent family as the ’640 patent and is also asserted in the above-referenced district court action.

Additionally, U.S. Application No. 15/656,990 (filed July 21, 2017) is currently pending before the Office and claims priority to the application that issued as the ’640 patent.

C. Lead and Back-Up Counsel

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D. Service Information

Documents may be delivered by hand to the addresses of lead and back-up counsel, listed above. Petitioner consents to electronic service by e-mail at the above-listed e-mail addresses of Lead and Back-Up Counsel.

III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

The required fee is being paid through the Patent Review Processing System. No excess claim fees are required. The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 500417.

IV. REQUIREMENTS FOR PETITION UNDER 37 C.F.R § 42.104

A. Grounds for Standing

Petitioner certifies that the ’640 patent is available for *inter partes* review and that: (1) Petitioner does not own the ’640 patent; (2) Petitioner is the real party-in-interest and has not filed a civil action challenging the validity of a claim in the ’640 patent prior to the filing of this Petition; (3) this Petition has been filed

less than one year after the date on which Petitioner, the real party-in-interest, or a privy of Petitioner, was served with a complaint alleging infringement of the '640 patent; and (4) neither Petitioner as the real party-in-interest nor any privy of Petitioner is estopped from challenging the claims on the grounds identified in this Petition.

B. Identification of Challenge and Relief Requested

Petitioner requests *inter partes* review and cancellation of claims 1, 2, 4-6, 9, 11, and 12 of the '640 patent on the grounds that they are anticipated under 35 U.S.C. § 102(b) by the '185 patent.

C. Claim Construction

Petitioner believes each of the claim terms should be given their plain and ordinary meaning and does not propose any specific constructions for any of the claim terms.

D. Level Of Skill In The Art

A person of ordinary skill in the art would have a Ph.D. or equivalent degree in organic or medicinal chemistry, and 2-3 years of post-graduate experience working in medicinal chemistry, synthetic organic chemistry, and/or kinase chemistry, including in the development of potential drug candidates. A person of ordinary skill in the art would also include a person who has a Bachelor's or Master's degree in organic chemistry or medicinal chemistry if such a person had

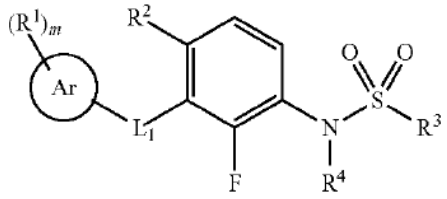
more years of experience in medicinal chemistry and/or the development of potential drug candidates. Baran Dec. ¶ 22.

V. THE '640 PATENT

A. The Challenged Claims

The '640 patent has a total of 12 claims. Petitioner challenges claims 1, 2, 4-6, 9, 11 and 12. Claims 1, 2, and 4-6 are compound claims ("Compound Claims"). Claim 9 is a composition claim ("Composition Claim"). Claims 11 and 12 are method claims ("Method Claims"). Each Challenged Claim is reproduced below:

1. A compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is a bond or —N(H)C(O)—;

each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl;

R^2 is hydrogen or halogen;

R^4 is hydrogen;

R^3 is optionally substituted lower alkyl or optionally substituted aryl;

m is 0, 1, 2, 3, 4, or 5; and

Ar is a monocyclic heteroaryl containing 5 to 6 atoms wherein at least one atom is nitrogen.

2. The compound of claim **1**, wherein R^2 is hydrogen.

4. The compound of claim **1**, wherein R^3 is optionally substituted phenyl.

5. The compound of claim **1**, wherein R^3 is phenyl substituted with one or more substituents selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio.

6. The compound of claim **1**, wherein R^3 is phenyl substituted with one or more fluoro.

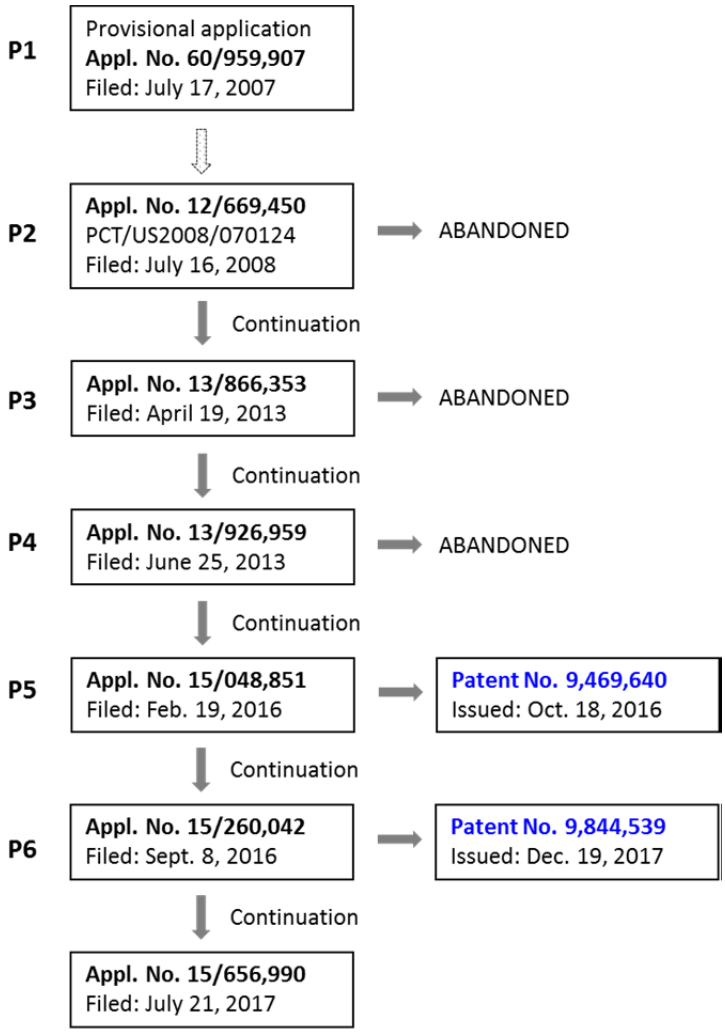
9. A pharmaceutical composition comprising a compound of claim **1** and a pharmaceutically acceptable carrier or excipient.

11. A method for treating a subject suffering from melanoma, thyroid cancer or colorectal cancer, said method comprising administering to the subject an effective amount of a compound of claim **1**.

12. The method of claim **11**, wherein the melanoma is melanoma having a mutation encoding a V600E amino acid substitution.

B. The '640 Patent Family

The series of patent applications that led to the '640 patent is depicted below. The relevant applications have been identified using the designations P1 through P5.



VI. THERE IS A REASONABLE LIKELIHOOD THAT PETITIONER WILL PREVAIL

A. Claims 1, 2, 4-6, 9, 11, and 12 Are Anticipated By The '185 Patent

As discussed below, the Challenged Claims are not entitled to claim the priority date of P2 or any earlier application. Thus, the earliest possible priority date is the filing date of P3, April 19, 2013. As a result, all of the Challenged

Claims are anticipated by the '185 patent, which issued on August 9, 2011. Ex. 1006, front page.

1. The Challenged Claims Lack Written Description And Enablement Support In P2 Under 35 U.S.C. § 112 And Thus Are Not Entitled To The Benefit Of P2 Or Any Earlier Application Under 35 U.S.C. § 120

a. The Standard For Claiming Benefit To An Earlier-Filed Application.

In order to claim the benefit of an earlier-filed application under 35 U.S.C. § 120, the earlier-filed application must meet the written description and enablement requirements of 35 U.S.C. § 112. 35 U.S.C. § 120; *Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 906 (Fed. Cir. Feb. 1, 2018); *In re NTP, Inc.*, 654 F.3d 1268, 1277 (Fed. Cir. 2011). Moreover, "if any application in the priority chain fails to make the requisite disclosure of subject matter, the later filed application is not entitled to the benefit of the filing date of applications preceding the break in the priority chain." *Hollmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012). Here, the Challenged Claims are not entitled to the benefit of the filing date of P2 or any earlier application because they fail to meet the § 112 requirements.

b. The Standard For Written Description, 35 U.S.C. § 112 (Pre-AIA)

35 U.S.C. § 112 (pre-AIA) provides that "[t]he specification shall contain a written description of the invention." "[T]he description must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is

claimed. In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (citations and quotations omitted).

Where a claim recites a specific combination of variables, the specification must direct the person of ordinary skill to that specific combination; a general disclosure that encompasses the specific combination is not sufficient to satisfy the written description requirement. As the Court explained in *In re Ruschig*, 379 F.2d 990, 995-96 (C.C.P.A. 1967):

> It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail or in finding one's way through the woods where the trails have disappeared — or have not yet been made, which is more like the case here — to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees.

Where the claimed invention is not "specifically named or mentioned in any manner [in the application as filed], one is left to selection from the myriads of possibilities encompassed by the broad disclosure, with no guide indicating or directing that this particular selection should be made rather than any of the many others which could also be made." *Id.* at 995; *see also Purdue Pharma L.P. v.*

Faulding Inc., 230 F.3d 1320, 1326-27 (Fed. Cir. 2000) ("[O]ne cannot disclose a forest in the original application, and then later pick a tree out of the forest and say 'here is my invention'. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.").

This analysis has been applied to claims that cover subgenera. A claim to a particular subgenus is not adequately supported where the specification discloses only a broader genus and fails to sufficiently describe the subgenus. As the Federal Circuit explained in *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570-71 (Fed. Cir. 1996):

> In finding that Wattanasin's disclosure failed to sufficiently describe the proposed sub-genus, the Board again recognized that the compounds of the [subgenus] were not Wattanasin's preferred, and that his application contained no blazemarks as to what compounds, other than those disclosed as preferred, might be of special interest. In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses. *See, e.g.*, [*In re Ruschig*,] 379 F.2d at 994, 154 U.S.P.Q. (BNA) at 122 ("Specific claims to single compounds require reasonably specific supporting disclosure and while . . . *naming* [each species] is not essential, something more than the disclosure of a class of 1000, or 100, or even 48 compounds is required.").

* * *

> [J]ust because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a "laundry list" disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not "reasonably lead" those skilled in the art to any particular species.

Fujikawa, 93 F.3d at 1570-71. Thus, when a specification discloses a large genus or broad definitions for a series of variables, it is not permissible to work backward with the claims in hand "to derive written description support from an amalgam of disclosures plucked selectively from the [] application." *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (holding patent invalid for lack of written description because although specification separately disclosed three individual claim limitations, it did not disclose a compound that had at once all three limitations).

In addition, to show possession of an invention to a genus or subgenus, the specification must set forth "either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can visualize or recognize members of the genus." *Ariad*, 598 F.3d at 1351. Moreover, those representative species must reflect the variance in that genus. *See AbbVie Deutschland GmbH & Co., KG v.*

Janssen Biotech, Inc., 759 F.3d 1285, 1300 (Fed. Cir. 2014) (the disclosure must adequately reflect the structural diversity of the claimed genus, either through the disclosure of sufficient species that are "representative of the full variety or scope of the genus," or by the establishment of "a reasonable structure-function correlation"); *Carnegie Mellon Univ. v. Hoffman-La Roche Inc*., 541 F.3d 1115, 1126 (Fed. Cir. 2008) ("To satisfy the written description requirement in the case of a chemical or biotechnological genus, more than a statement of the genus is normally required. One must show that one has possession, as described in the application, of sufficient species to show that he or she invented and disclosed the totality of the genus."); *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (disclosure of two chemical species was insufficient to support claims to 21 chemical species).

c. P2 Fails To Provide Written Description Support For The Challenged Claims

(i) Overview

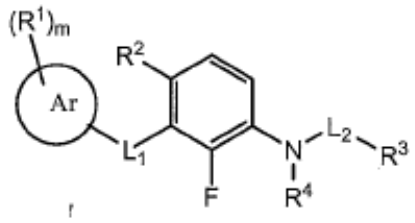
The '640 patent is a quintessential case of a patentee disclosing a "forest" in P2 and later claiming a "tree," without providing in P2 any "blaze marks" identifying that tree. *In re Ruschig*, 379 F.2d at 994-95; *Purdue Pharma*, 230 F.3d at 1326-27.

Simply put, there is no disclosure in P2 that would lead one of ordinary skill to conclude that the applicants had possession of any of the subgenera in the

Challenged Claims as of the filing date of that application. Baran Dec. ¶ 30. While P2 includes formulas with the individual variables L_1, R^1, R^2, R^3, R^4, *m*, and Ar, which encompass the substituents claimed in each of the Challenged Claims, there are no blaze marks directing one of ordinary skill in the art to the specific combinations of substituents recited in the formulas of the Challenged Claims. Baran Dec. ¶ 31. Thus, P2 does not guide one of ordinary skill to pick and choose the particular claimed options for each of the variables L_1, R^1, R^2, R^3, R^4, *m*, and Ar, or the combination of those variables, from the broad genera disclosed in P2 to arrive at the subject matter of the Challenged Claims. Baran Dec. ¶ 32. Nor does P2 set forth a representative number of species to support the full scope of the formulas of the Challenged Claims. Baran Dec. ¶ 33. Accordingly, P2 does not provide evidence that the inventors were in possession of the subject matter of the Challenged Claims as of the filing date of that applications. Baran Dec. ¶ 34. Thus, none of the Challenged Claims is entitled to the benefit of the filing date of P2 or any earlier application. *Id.*

More specifically, P2 discloses Formula I, which encompasses a broad genus of compounds. Baran Dec. ¶ 35. P2 provides the following disclosure of Formula I:

> **[0004]** In some embodiments, compounds have the structure according to Formula I:



Formula I

or a salt, a prodrug, a tautomer or an isomer thereof, wherein:

Ar is optionally substituted heteroaryl;

R^1 at each occurrence is independently selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-NO_2$, -CN, $-O-R^5$, $-N(R^5)-R^6$, $-C(X)-N(R^5)-R^6$, $-C(X)-R^7$, $-S(O)_2-N(R^5)-R^6$, $-S(O)_n-R^7$, $-O-C(X)-R^7$, $-C(X)-O-R^5$, $-C(NH)-N(R^8)-R^9$, $-N(R^5)-C(X)-R^7$, $-N(R^5)-S(O)_2-R^7$, $-N(R^5)-C(X)-N(R^5)-R^6$, and $-N(R^5)-S(O)_2-N(R^5)-R^6$;

m is 0, 1, 2, 3, 4 or 5;

n is 0, 1or 2;

R^2 is hydrogen, lower alkyl or halogen;

L_2 is selected from the group consisting of $-S(O)_2-$, -C(X)-, $-C(X)-N(R^{10})-$, and $-S(O)_2-N(R^{10})-$;

R^3 is optionally substituted lower alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

L_1 is selected from the group consisting of a bond, $-N(R^{11})-$, -O-, -S-, -C(X)-, $-C(R^{12}R^{13})-X-$, $-X-C(R^{12}R^{13})-$, $-C(R^{12}R^{13})-N(R^{11})-$,

$-N(R^{11})-C(R^{12}R^{13})-$, -O-C(X)-, -C(X)-O-, $-C(X)-N(R^{11})-$, $-N(R^{11})-C(X)-$, -S(O)-, $-S(O)_2-$, $-S(O)_2-N(R^{11})-$, $-N(R^{11})-S(O)_2-$, $-C(NH)-N(R^{11})-$, $-N(R^{11})-C(NH)-$, $-N(R^{11})-C(X)-N(R^{11})-$, and $-N(R^{11})-S(O)_2-N(R^{11})-$;

X is O or S;

R^4, R^{10} and each R^{11} are independently hydrogen or lower alkyl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, fluoro substituted mono-alkylamino, di-alkylamino, fluoro substituted di-alkylamino, and $-NR^{14}R^{15}$;

R^5, R^6, R^8, and R^9 at each occurrence are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, optionally substituted C_{3-6} alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^8 and R^9 combine with the nitrogen to which they are attached to form a 5-7 membered optionally substituted nitrogen containing heterocycloalkyl or a 5 or 7 membered optionally substituted nitrogen containing heteroaryl;

R^7 at each occurrence is independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, optionally substituted C_{3-6} alkynyl, optionally substituted cycloalkyl, optionally substituted

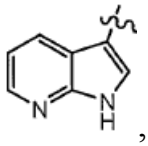
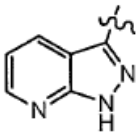
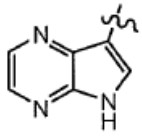
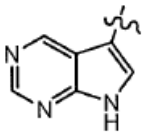
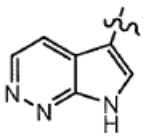
heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, fluoro, -OH, -NH2, lower alkyl, lower alkoxy, lower alklylthio, mono-allcylamino, di-alkylamino, and -$NR^{14}R^{15}$, wherein the alkyl chain(s) oflower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH2, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or

R^{12} and R^{13} combine with the carbon to which they are attached to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH2, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; and

R^{14} and R^{15} at each occurrence independently combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl or 5-7 membered heterocycloalkyl substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH_2, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio,

provided, however, that when L_1 is a bond, -NR^{11}-, -O-, -S-, -C(X)-, -S(O)-, or -$S(O)_2$, Ar is not 1H-pyrrolo[2,3-b]pyridine-3-yl, 1H-pyrazolo[3,4-b]pyridine-3-yl, 5H-pyrrolo[2,3-b]pyrazine-7-yl, 7H-pyrrolo[2,3-d]pyrimidine-5-yl, or 7H-pyrrolo[2,3-c]pyridazine-5-yl,

i.e. is not  ,  ,  ,  , or  ,

wherein  indicates the attachment point to L_1.

P2 at 1-3.

P2 expressly defines certain of the terms used in the options for the Formula I variables themselves. P2 at 47-61. As an example, Formula I's definition of R^1 includes, from among a long list, "optionally substituted lower alkyl" and "optionally substituted heteroaryl." P2 at 2. P2's definitions of "lower alkyl" and "heteroaryl" are reproduced below:

> **[0084]** "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. The straight chain or branched alkyl group is chemically feasible and attached at any available point to produce a stable compound. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. An "optionally substituted lower alkyl" denotes lower alkyl that is optionally independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents,

attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of -F, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)-OH, -C(S)-OH, $-C(O)-NH_2$, $-C(S)-NH_2$, $-S(O)_2-NH_2$, $-N(H)-C(O)-NH_2$, $-N(H)-C(S)-NH_2$, $-N(H)-S(O)_2-NH_2$, $-C(NH)-NH_2$, $-O-R^o$, $-S-R^o$, $-O-C(O)-R^o$, $-O-C(S)-R^o$, $-C(O)-R^o$, $-C(S)-R^o$, $-C(O)-O-R^o$, $-C(S)-O-R^o$, $-S(O)-R^o$, $-S(O)_2-R^o$, $-C(O)-N(H)-R^o$, $-C(S)-N(H)-R^o$, $-C(O)-N(R^o)-R^o$, $-C(S)-N(R^o)-R^o$, $-S(O)_2-N(H)-R^o$, $-S(O)_2-N(R^o)-R^o$, $-C(NH)-N(H)-R^o$, $-C(NH)-N(R^p)-R^c$, $-N(H)-C(O)-R^o$, $-N(H)-C(S)-R^o$, $-N(R^o)-C(O)-R^o$, $-N(R^o)-C(S)-R^o$, $-N(H)-S(O)_2-R^o$, $-N(R^o)-S(O)_2-R^o$, $-N(H)-C(O)-N(H)-R^o$, $-N(H)-C(S)-N(H)-R^o$, $-N(R^o)-C(O)-NH_2$, $-N(R^o)-C(S)-NH_2$, $-N(R^o)-C(O)-N(H)-R^o$, $-N(R^o)-C(S)-N(H)-R^o$, $-N(H)-C(O)-N(R^o)-R^o$, $-N(H)-C(S)-N(R^o)-R^o$, $-N(R^o)-C(O)-N(R^o)-R^o$, $-N(R^o)-C(S)-N(R^o)-R^o$, $-N(H)-S(O)_2-N(H)-R^o$, $-N(R^o)-S(O)_2-NH_2$, $-N(R^o)-S(O)_2-N(H)-R^o$, $-N(H)-S(O)_2-N(R^o)-R^o$, $-N(R^o)-S(O)_2-N(R^o)-R^o$, $-N(H)-R^o$, $-N(R^o)-R^o$, $-R^e$, $-R^f$, and $-R^g$. Furthermore, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formula I, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkyl" denotes a lower alkyl group substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

P2 at 48.

[0090] "Heteroaryl" alone or in combination refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bi cyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, and indolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein at least one heteroatom is N. In some instances, for example when R groups of a nitrogen combine with the nitrogen to form a 5 or 7 membered nitrogen containing heteroaryl, any heteroatoms in such 5 or 7 membered heteroaryl are N. An "optionally substituted heteroaryl" is a heteroaryl that is optionally independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of halogen, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)-OH, -C(S)-OH, $-C(O)-NH_2$, $-C(S)-NH_2$, $-S(O)_2-NH_2$, $-N(H)-C(O)-NH_2$, $-N(H)-C(S)-NH_2$, $-N(H)-S(O)_2-NH_2$, $-C(NH)-NH_2$, $-O-R^o$, $-S-R^o$, $-O-C(O)-R^o$, $-O-C(S)-R^o$, $-C(O)-R^o$, $-C(S)-R^o$, $-C(O)-O-R^o$, -C(S)-O-

> R^o, -S(O)-R^o, -$S(O)_2$-R^o, -C(O)-N(H)-R^o, -C(S)-N(H)-R^o, -C(O)-$N(R^o)$-R^o, -C(S)-$N(R^o)$-R^o, -$S(O)_2$-N(H)-R^o, -$S(O)_2$-$N(R^o)$-R^o, -C(NH)-N(H)-R^o, -C(NH)-$N(R^p)$-R^c, -N(H)-C(O)-R^o, -N(H)-C(S)-R^o, -$N(R^o)$-C(O)-R^o, -$N(R^o)$-C(S)-R^o, -N(H)-$S(O)_2$-R^o,-$N(R^o)$-$S(O)_2$-R^o, -N(H)-C(O)-N(H)-R^o, -N(H)-C(S)-N(H)-R^o, -$N(R^o)$-C(O)-NH_2, -$N(R^o)$-C(S)-NH_2, -$N(R^o)$-C(O)-N(H)-R^o, -$N(R^o)$-C(S)-N(H)-R^o, -N(H)-C(O)-$N(R^o)$-R^o, -N(H)-C(S)-$N(R^o)$-R^o,-$N(R^o)$-C(O)-$N(R^o)$-R^o, -$N(R^o)$-C(S)-$N(R^o)$-R^o, -N(H)-$S(O)_2$-N(H)-R^o, -$N(R^o)$-$S(O)_2$-NH_2, -$N(R^o)$-$S(O)_2$-N(H)-R^o, -N(H)-$S(O)_2$-$N(R^o)$-R^o, -$N(R^o)$-$S(O)_2$-$N(R^o)$-R^o, -N(H)-R^o, -$N(R^o)$-R^o, -R^d, -R^e, -R^f, and -R^g. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

P2 at 51-52.

As reflected in the passages reproduced above, P2 encompasses an enormous number of possible R^1 groups that meet the definition of "optionally substituted lower alkyl" and "optionally substituted heteroaryl." Baran Dec. ¶ 37. Moreover, there can be multiple different R^1 groups, and both the lower alkyl and heteroaryl groups can be optionally substituted with a wide variety of substituents. *Id.* Thus, the definitions for "optionally substituted lower alkyl" and "optionally substituted heteroaryl" alone cover an enormous number – indeed, trillions – of different options. *Id.*

Notably, R^1 is not Formula I's only variable. Formula I includes eight different variables (L_1, L_2, R^1, R^2, R^3, R^4, *m*, and Ar), each of which is defined in

turn by a list of different variables. When the trillions of different permutations are factored in, Formula I encompasses a genus that is so large it is effectively incalculable. Baran Dec. ¶ 38.

P2 discloses subgenera (Formulas Ia to Ij) that narrow one or more of L_1, L_2 and R^3, as shown below:

Formula Ia: L_2 is $–SO_2–$

Formula Ib: L_2 is $–SO_2–$, L_1 is $–AN(R^{11})–$, wherein A is –C(O)– or $–C(R^{12}R^{13})–$

Formula Ic: L_2 is $–SO_2–$, L_1 is a bond

Formula Id: L_1 is $–ANR^{11}–$, wherein A is –C(O)– or $–C(R^{12}R^{13})–$

Formula Ie: L_1 is a bond

Formula If: L_2 is $–SO_2–$, L_1 is $–C(X)\text{-}N(R^{11})–$, $–C(R^{12}R^{13})\text{-}X–$, $–X\text{-}C(R^{12}R^{13})–$, $–C(R^{12}R^{13})\text{-}N(R^{11})–$, or $–N(R^{11})\text{-}C(R^{12}R^{13})–$

Formula Ig: L_1 is $–C(X)\text{-}N(R^{11})–$, $–C(R^{12}R^{13})\text{-}X–$, $–X\text{-}C(R^{12}R^{13})–$, $–C(R^{12}R^{13})\text{-}N(R^{11})–$, or $–N(R^{11})\text{-}C(R^{12}R^{13})\text{-}$

Formula Ih: L_2 is –SO2–, L_1 is $–NR^{11}A–$, wherein A is –C(O)– or $–C(R^{12}R^{13})–$

Formula Ii: L_1 is $–NR^{11}A–$, wherein A is –C(O)– or $–C(R^{12}R^{13})–$

Formula Ij: L_2 is $–SO_2–$, R^3 is selected from the group consisting of mono-alkylamino, di-alkylamino, optionally substituted lower alkyl,

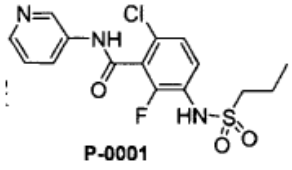
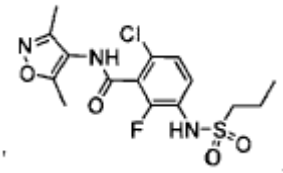
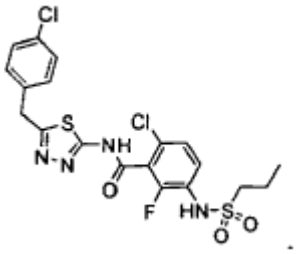
> optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl, wherein the alkyl chain(s) of mono-alkylamino or di-alkylamino are independently optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH2, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino.

P2 at 3-13. In each of Formulas Ia-Ij, the variables *m,* Ar, R^1, R^2, R^4, R^{11}, R^{12} and R^3, L_1, and L_2 (to the extent R^3, L_1 and L_2 are not expressly defined), are as defined for Formula I. *Id*. For Formulas Ia-Ij, P2 discusses "some embodiments" with preferences for Ar, R^2, R^3, R^4, R^{11}, R^{12} and R^{13}. P2 at 3-21. P2 also provides three prophetic synthetic schemes by which certain compounds of Formulas Ib, Ic, Id, Ie and Formula I (where L_1 is CH_2NHR^{11}) can be synthesized. P2 at 74-79; Baran Dec. ¶ 42. It is notable that in P2, none of Formulas Ia to Ij, the embodiments discussed in connection with those formulas, or the prophetic schemes, provides any limitations for R^1. Baran Dec. ¶ 43. P2 does provide that "preferably any R^1 is independently R^{16}." P2 at 15-17. But R^{16} also encompasses an enormous number of compounds. *Id.* (quoting P2 at 15-16). P2 further narrows the preferences for R^{16}, but even the narrowed list encompasses an enormous number of compounds.

Baran Dec. ¶ 44 (quoting P2 at 17, 18, 19, 20). Accordingly, even these "narrowed" formulas and "embodiments" each encompasses billions of compounds. *Id.*

Within the extremely broad disclosures of the subgenera in P2, the specific combinations of variables set forth in the formulas of the Challenged Claims are never disclosed, *i.e.*, none of the subgenera in P2 corresponds to the subgenera of any of the Challenged Claims. Accordingly, Formulas Ia-Ij do not provide blaze marks pointing one of ordinary skill to the formulas of the Challenged Claims. Baran Dec. ¶ 45.

The examples included in P2 do not overcome this deficiency. Baran Dec. ¶ 46. Although P2 encompasses an enormous number of compounds, P2 specifically describes only 120 different compounds (P-0001 to P-0120), along with methods of their synthesis. *Id.* (citing P2 at 21-27, 79-110). None of compounds P-0001 to P-0120 falls within the scope of Compound Claims 2 and 4-6. *Id.* Only three of these 120 compounds (depicted below) fall within the scope of any of the formulas of the Challenged Compound Claims, and even then, these compounds fall within the scope of only claim 1 (P-0001, P-0007 and P-0012). *Id.*

P-0001	**P-0007**	**P-0012**
		
P2 at 91.	P2 at 90.	P2 at 91.

The lack of sufficient representative species is reflected not only in the limited number of species disclosed (three species for genus claims covering trillions of compounds), but also in the lack of diversity with respect to the claimed variables. Baran Dec. ¶¶ 48-49. For example, the claims recite that R^1 can be an optionally substituted lower alkyl or optionally substituted heteroaryl, which can include trillions of permutations. *Id.* But R^1 in each of the three species is methyl or chlorophenylsubstituted methyl. *Id.* Also, the claims recite that R^2 is either hydrogen or halogen, but R^2 in each of the three species is chloro, a particular species of halogen. *Id.* Similarly, the claims recite that R^3 is either an optionally substituted lower alkyl or an optionally substituted aryl, which also can include trillions of permutations. *Id.* But R^3 in each of the three species is a propyl group. *Id.* Further, the claims recite that L_1 is either –N(H)C(O)– or a bond, but L_1 in each of the three species is –N(H)C(O)–. *Id.*

Put another way, although P-0001, P-0007 and P-0012 fall within the scope of claim 1,[3] they do not have many of the variables that are included within the scope of the Challenged Claims. Baran Dec. ¶ 50. For example, none has L_1 as a bond; R^1 as heteroaryl or substituted heteroaryl; R^2 as hydrogen; R^3 as substituted lower alkyl, aryl or substituted aryl; or *m* as 3, 4, or 5. *Id.* Thus, there are no representative species that fall within the scope of the Challenged Claims and have any of these structural features of the claims. *Id.* These three examples, therefore, do not constitute a sufficient number of representative species to show possession of the breadth of the Challenged Claims. Baran Dec. ¶ 51.

(ii) The L_1 And R^1 Substituents Of The Challenged Claims

There are no blaze marks in P2 that point one of ordinary skill to the specific combination of claimed L_1 and R^1 substituents.

(a) The L_1 Substituent

The Challenged Claims provide that L_1 is either "a bond or –N(H)C(O)–." Baran Dec. ¶ 52. P2 does not guide one of ordinary skill to focus on either of these two options for L_1, particularly in combination with each of the other specific substituents in the Challenged Claims, including R^1. *Id.*

[3] P-0001, P-0007, and P-0012 also fall within the scope of claims 9-12, which are dependent from claim 1 but do not further limit the subgenus of claim 1.

Generic formulas: In the generic formulas, P2 provides lists of options for L_1 that include both "a bond" and "–N(H)C(O)–," but none describes a subgenus where L_1 is limited to "a bond or –N(H)C(O)–." Baran Dec. ¶ 53. For example, P2 provides that in Formula I, L_1 is selected from a group consisting of 21 options (many of which contain sub-options):

> L_1 is selected from the group consisting of a bond, -N(R^{11})-, -O-, -S-, -C(X)-, -C($R^{12}R^{13}$)-X-, -X-C($R^{12}R^{13}$)-, -C($R^{12}R^{13}$)-N(R^{11})-, -N(R^{11})-C($R^{12}R^{13}$)-, -O-C(X)-, -C(X)-O-, -C(X)-N(R^{11})-, -N(R^{11})-C(X)-, -S(O)-, -S$(O)_2$-, -S$(O)_2$-N(R^{11})-, -N(R^{11})-S$(O)_2$-, -C(NH)-N(R^{11})-, -N(R^{11})-C(NH)-, -N(R^{11})-C(X)-N(R^{11})-, and-N(R^{11})-S$(O)_2$-N(R^{11})-;

P2 at 2. P2 also discloses generic Formulas Ia-Ij, where L_1 is defined as in Formula I (Formulas Ia, Ij); L_1 is –AN(R^{11})–, wherein A is –C(O)– or –C($R^{12}R^{13}$)– (Formulas Ib, Id, Ih and Ii); L_1 is a bond (Formulas Ic, Ie); L_1 is selected from a list of 5 options, none of which is "a bond" and many of which contain sub-options (Formulas If, Ig). P2 at 4-12.

In "some embodiments" of Formula I, Ia, Ib, and Id, lists of options for L_1 are specifically presented, including –N(H)C(O)–; however, none of those lists includes the specific combination "a bond or –N(H)C(O)–". Baran Dec. ¶ 55 (citing P2 at 4-21).

The generic subformulas in which L_1 is a bond and the subembodiments of the generic subformulas where L_1 is –N(H)C(O)– do not limit the other substituents to the specific options in the Challenged Claims. Baran Dec. ¶ 56.

Prophetic schemes: The schemes included in P2 similarly do not support a preference for L_1 as "a bond or –N(H)C(O)–." Baran Dec. ¶ 57. Prophetic schemes 1-3 disclose syntheses of compounds of Formula Ib or Id where A is –C(O)– (i.e. L_1 is –C(O)N(R^{11})–); compounds of Formula Ic or Ie where L_1 is a bond; or compounds of Formula I where L_1 is –CH_2NR^{11}–. *Id.* (citing P2 at 74-75 (Scheme 1), 75-77 (Scheme 2), 77-79 (Scheme 3)). In each of these schemes, the variables R^1, R^2, R^3, R^4, *m* and Ar are as defined for Formula I and are not limited to the specific combination of variables in the Challenged Claims. Baran Dec. ¶ 58 (citing P2 at 74-79). Thus, none of these schemes provides any blaze marks directing one of ordinary skill to select any specific combination of R^1, R^2, R^3, R^4, *m* or Ar groups in connection with the L_1 groups in the prophetic schemes, let alone the specific combinations of those substituents in the Challenged Claims. Baran Dec. ¶ 59.

Synthetic schemes/example compounds: P2's synthetic schemes 4-16, which were actually conducted, produce compounds where L_1 is –N(H)C(O)– (Schemes 4-10 and 14-16), –$NHCH_2$– (Schemes 11-12), and –OCH_2– (Scheme 13). Baran Dec. ¶ 60 (citing P2 at 79-101). These 16 schemes set forth the

synthesis of the 120 disclosed compounds (P-0001 through P-0120). *Id.* (citing P2 at 79-110). Of these 120 compounds, 107 have L_1 as –N(H)C(O)–, 6 have L_1 as –$N(R^{11})C(R^{12}R^{13})$–, and 7 have L_1 as –$C(R^{12}R^{13})X$–. *Id.* None has L_1 as a bond. *Id.*

Activity data: P2 reports in Tables 2a-2p representative compounds with activity toward different kinases. Baran Dec. ¶ 62 (citing P2 at 110-12). Tables 2a-2p, taken together, list 20 compounds. *Id.* 16 of the 20 compounds included in Tables 2a-2p have L_1 as –N(H)C(O)–, three have L_1 as –$NHCH_2$–, and one has L_1 as –OCH_2–. *Id.* None has L_1 as a bond. *Id.*

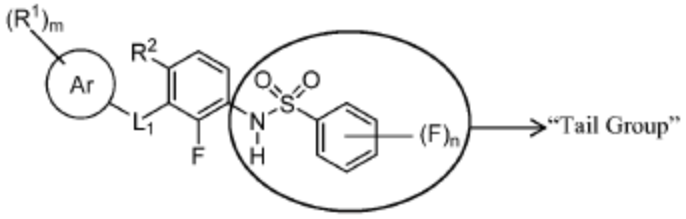
In summary, P2 does not describe a subgenus where L_1 is "a bond or –N(H)C(O)–" let alone a subgenus that also sets forth the other variables in the formulas of the Challenged Claims. Baran Dec. ¶ 63. Similarly, P2 does not provide a preference for a subgenus with this combination of L_1 groups. *Id.* While generic Formulas Ic and Ie (and related Scheme 2) are limited to compounds where L_1 is a bond, P2, viewed as a whole, does not direct one of ordinary skill to focus on these compounds or indicate a preference for these compounds, as none of the examples (P-0001 to P-0120) describes a compound where L_1 is a bond, and no compound with L_1 as a bond was reported to have biological activity. *Id.* Moreover, Formulas Ic and Ie do not limit the other substituents (R^1, R^2, R^3, R^4, *m*, and Ar) to those in the Challenged Claims. *Id.*

The absence in P2 of any subgenus that corresponds to the scope of L_1 in the Challenged Claims, and the absence in P2 of any representative species where L_1 is a bond, would have suggested to a person of ordinary skill that as of the filing date of P2, the applicants did not possess the subgenera of the Challenged Claims. Baran Dec. ¶ 64. As a result, the Challenged Claims lack written description support as required by 35 U.S.C. § 112 ¶1, and accordingly, are not entitled to benefit of P2 or any earlier application under 35 U.S.C. § 120. Baran Dec. ¶ 65.

The conclusion that the Challenged Claims lack written description support for L_1 is consistent with the U.S. Patent Examiner's comments during prosecution of P3 and P4. Baran Dec. ¶ 66. For example, during prosecution of P3, the Examiner rejected claims to compounds where L_1 was a bond, stating that "[P2] fails to provide adequate support [*i.e.*, written description] or enablement in the manner provided by 35 U.S.C. § 112(a) or pre-AIA 35 U.S.C. 112, first paragraph." Ex. 1005 at 3. The Examiner further stated that "[n]o compound within the claimed scope has been produced or disclosed" and "[a]ll disclosed compounds have a linker moiety between the phenyl and the Ar. i.e., L1 in formula I is not a bond. The application provide[s] no convincing evidence, or rationale that the biological activity of [the] disclosed compounds would have been retained if the L1 in formula I is a bond instead of those linking moieties." *Id.* at 7, 8. The Examiner also made clear that by filing P3 with claims where L_1 was a bond, the

applicants had improperly added new matter that was not in the prior specifications, *i.e.*, P1 and P2. *Id*. The Examiner required the applicants to amend the specification to incorporate this new matter and to revise the relationship between P3 and P2 to clarify that the application was a continuation-in-part, rather than a continuation. *Id.* at 3-4. Rather than comply with the Examiner's request, the applicants abandoned the application. Ex. 1007.

Similar comments about the lack of written description for compounds where L_1 is a bond were made by the Examiner during prosecution of P4. Ex. 1008 at 6. In response the applicants amended the then-pending claims, including by limiting R^3 to phenyl groups with one or two fluoro substituents, limiting Ar to nitrogen-containing heteroaryl groups, and canceling the then-pending method of treatment claims. Ex. 1009 at 2-4. The applicants also cited prior art allegedly showing that the "tail group" of the claimed compounds (the applicants' figure is reproduced below) was known to interact with certain kinases. Ex. 1009 at 6-8 (internal citations omitted).



The applicants never specifically explained how the cited art (which discusses compounds that differ in structure from the claimed compounds,

including because they do not have a feature analogous to the claimed compounds where L_1 is a bond), addressed the lack of adequate written description in the specification, or established a credible utility or enablement for the specifically claimed compounds.

The Examiner responded to these arguments by maintaining the § 112 written description rejection. Ex. 1010 at 1-6. The Examiner also specifically discussed the applicants' arguments and prior art, but noted they were "unpersuasive as to the rejections set forth above" and the arguments concerning the known correlation between structure and function and references were not "probative" as to the full scope of the claims. In this rejection, the Examiner focused on the breadth of the Ar substituents rather than the L_1 substituent. *Id.* at 9.

After the rejection, the applicant initiated an interview with the Examiner. The interview summary indicates that "[i]t is agreed that the application has support for L1 as amide or a bond, and Ar as bicyclic nitrogen-containing heteroaryl with the proviso in the claims."[4] Ex. 1011. The Examiner provided no further explanation as to how this agreement was reached. On February 19, 2016,

[4] Compounds for which "Ar [is a] *bicyclic* nitrogen-containing heteroaryl" (emphasis added) do not fall within the scope of the Challenged Claims, all of which required that "Ar is a *monocyclic* heteroaryl . . . ." '640 patent, claim 1.

the applicants filed a "Statement of Substance of Interview" indicating that compounds where L_1 is a bond have support "through the specification, including but not limited to paragraphs [0007], [0009], and [0021]. Further, Scheme 2 provides exemplary methods of making compounds where L1 is a bond." Ex. 1012 at 2. But these paragraphs provide only a list of possible L_1 substituents for compounds of general Formulas I or Ia ([0007], [0009]), or Ie [0021], or a general scheme for synthesis of these compounds (Scheme 2). Baran Dec. ¶ 79. After the interview, the applicants abandoned the P4 application. Ex. 1013.

Nevertheless, during prosecution of P5, the applicants again added claims to compounds of formula Ia that included those where L_1 is a bond, citing as evidence paragraphs [0007], [0009] and [0010] (none of which is limited to L_1 as a bond and -N(H)C(O)-). Ex. 1013 at 5. The Examiner again rejected these claims for lack of written description support. Ex. 1015 at 2, 5-6. After an interview with the Examiner, the applicants responded by making various amendments to the claims, including narrowing the scope of L_1 to a bond or –N(H)C(O)–. Ex. 1016 at 2. The applicants further noted that "the Office agreed that the application provides support for L1 as amide or a bond … as discussed below and during the prosecution of the parent application [P4]." *Id.* at 5. The Examiner indicated that the amendments were sufficient to overcome the rejections, but never explained why. Ex. 1017 at 2. Thus, while the Examiner ultimately did allow claims where

L_1 is a bond, no meaningful reasons were provided to explain the change in position or basis for this allowance.

In addition, even if there was support for L_1 as a bond in P2, that narrow issue is not the proper question to consider when assessing written description. The proper question is whether the entire claimed subject matter, including each specific selection of each of the variables (L_1, R^1, R^2, R^3, R^4, *m*, and Ar) in combination as they appear in the Challenged Claims, was disclosed in P2. *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d at 1349 (explaining that the written description analysis requires "[t]aking each claim . . . as an integrated whole rather than as a collection of independent limitations"). That disclosure was not made.

(b) The R^1 Substituent

The Challenged Claims provide that "each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl." P2 does not guide one of ordinary skill to focus on any of these options for R^1, particularly in combination with the other specific substituents in the Challenged Claims, including L_1. Accordingly, P2 fails to show that the inventors were in possession of the compounds of the Challenged Claims. *See* Baran Dec. ¶ 88.

Generic formulas: In the generic formulas, P2 provides lists of options for R^1 that include both "optionally substituted lower alkyl" and "optionally

substituted heteroaryl" as two of many options; however none of these applications describes a subgenus that has this specific combination of substituents. Baran Dec. ¶ 89.

P2 provides that in each of Formulas I and Ia-Ij, R^1 is selected from a group consisting of 23 options (many of which contain sub-options):

> R^1 at each occurence is independently selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-NO_2$, -CN, $-O-R^5$, $-N(R^5)-R^6$, $-C(X)-N(R^5)-R^6$, $-C(X)-R^7$, $-S(O)_2-N(R^5)-R^6$, $-S(O)_n-R^7$, $-O-C(X)-R^7$, $-C(X)-O-R^5$, $-C(NH)-N(R^8)-R^9$, $-N(R^5)-C(X)-R^7$, $-N(R^5)-S(O)_2-R^7$, $-N(R^5)-C(X)-N(R^5)-R^6$, and $-N(R^5)-S(O)_2-N(R^5)-R^6$;

P2 at 2 (Formula I), 3-12 (Formulas Ia-Ij, which provide that R^1 is as defined for Formula I). P2 states that compounds of Formula I can have 0 to 5 R^1 groups, because *m*, *i.e.*, the number of R^1 groups, can be 0, 1, 2, 3, 4 or 5. P2 at 2.

The only specific discussion of R^1 groups in connection with these formulas appears in the discussion of Ar groups that can be used in "some embodiments" of compounds of Formulas I and Ia-Ij. Baran Dec. ¶ 92. In connection with these embodiments, P2 states:

any R^1 is bound to Ar at any available NH or CH, preferably any R^1 is independently R^{16}, wherein R^{16} at each occurrence is independently selected from the group consisting of -OH, -NH_2, -CN, -$N0_2$, -C(O)-OH, -$S(O)_2$-NH_2, -C(O)-NH_2, -O-R^{17}, -S-R^{17}, -N(R^{19})-R^{17}, -N(R^{19})-C(O)-R^{17}, -N(R^{19})-$S(O)_2$-R^{17}, -$S(O)_2$-R^{17}, -C(O)-R^{17}, -C(O)-O-R^{17}, -C(O)-N(R^{19})-R^{17}, -$S(O)_2$-N(R^{19})-R^{17}, halogen, **lower alkyl**, cycloalkyl, heterocycloalkyl, aryl and **heteroaryl**, **wherein lower alkyl is optionally substituted** with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, monoalkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and **heteroaryl** as R^{16} , or as substituents of lower alkyl, **are optionally substituted** with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -C(O)-OH, -$S(O)_2$-NH_2, -C(O)-NH_2, -O-R^{18}, -S-R^{18}, -N(R^{19})-R^{18}, -N(R^{19})-C(O)-R^{18}, -N(R^{19})-$S(O)_2$-R^{18}, -$S(O)_2$-R^{18}, -C(O)-R^{18}, -C(O)-O-R^{18}, -C(O)-N(R^{19})-R^{18}, -$S(O)_2$-NR^{19})-R^{18}, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

P2 at 15-16 (emphasis added). Each of R^{17}, R^{18} and R^{19} is also defined. P2 at 16. Like the Formula I definition of R^1, R^{16} includes both optionally substituted lower alkyl and optionally substituted heteroaryl amongst a long list of options. *Id.*

In subsequent embodiments discussed in the specification, R^{16} is further stated to be preferably selected from the group consisting of:

> halogen, -OH, -NH_2, -CN, **lower alkyl**, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and-$NR^{20}R^{21}$, **wherein lower alkyl** and the alkyl chain(s) of lower alkoxy, lower alkylthio, mono-alkylamino or di-alkylamino **are optionally substituted** with one or more, preferably 1, 2, or 3 substituents selected from the group consisting of fluoro, -OH, -NH_2, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, or cycloalkylamino.

P2 at 17, 18, 19 (emphasis added). This list of preferences for R^1 includes optionally substituted lower alkyl groups; however it does not include heteroaryl or optionally substituted heteroaryl.

Prophetic schemes: In the prophetic synthetic schemes, R^1 is defined as in Formula I, and therefore each R^1 is selected from a list of 23 options (many of which include sub-options). Baran Dec. ¶ 96 (citing P2 at 74-79). R^1 is not limited to "optionally substituted lower alkyl or optionally substituted heteroaryl." *Id.*

Synthetic schemes/example compounds: Of the 120 compounds generated using P2's synthetic schemes 4-16, three have an R^1 that is "optionally substituted lower alkyl." Baran Dec. ¶ 97 (citing P2 at 90, 92). None of the 120 compounds has an R^1 that is "optionally substituted heteroaryl." *Id.*

Activity data: P2 reports in Tables 2a-2p representative compounds with activity toward different kinases. Baran Dec. ¶ 98 (citing P2 at 110-12). Of the compounds included in Tables 2a-2p, only one (P-0012) has an R^1 that is

"optionally substituted lower alkyl." *Id.* None has "optionally substituted heteroaryl." *Id.* Therefore, the compounds reported to have activity in P2 do not support the selection of the claimed R^1 groups. *Id.*

In summary, P2 does not describe a subgenus where R^1 is "optionally substituted lower alkyl or optionally substituted heteroaryl," let alone describe a subgenus that also sets forth the other variables in the Challenged Claims. Baran Dec. ¶ 99. Similarly, P2 does not set forth a preference for these specific R^1 groups, or a subgenus that is limited to these R^1 groups. *Id.* P2 also fails to disclose a sufficient number of representative species to support the claimed R^1 groups. Baran Dec. ¶ 100. Although the Challenged Claims encompass trillions of compounds, P2 describes only three species that have an R^1 that is "optionally substituted lower alkyl" (P-0007, P-0012, and P-0019), and only two of those examples (P-0007 and P-0012) fall within the scope of claim 1. *Id.* Not a single example falls within the scope of the remaining Challenged Compound Claims. *Id.* And not a single example has an R^1 that is "optionally substituted heteroaryl." *Id.* Additionally, only one of the compounds that were reported to have activity in the assays reported in P2 has an R^1 that includes an optionally substituted lower alkyl, and none has an optionally substituted heteroaryl. *Id.*

The absence in P2 of any preference for the R^1 groups recited in the Challenged Claims (along with the lack of preference for compounds with all of

the other substituents of the Challenged Claims) would have suggested to a person of ordinary skill that, as of the filing date of P2, the applicants did not possess the subgenera of the Challenged Claims. *See* Baran Dec. at ¶ 101. As a result, the Challenged Claims lack written description support as required by 35 U.S.C. § 112 ¶1, and accordingly, are not entitled to the benefit of P2 or any earlier application under 35 U.S.C. § 120. *Id.*

(c) The Challenged Composition and Method Claims

Challenged Composition Claim 9 and Method Claims 11 and 12 are each dependent claims that depend from claim 1 but do not further limit the compounds claimed in claim 1. Because P2 does not describe the specific subgenus of claim 1 (as set forth above), claims 9, 11 and 12 are invalid under 35 U.S.C. § 112 ¶1 and are not entitled to the benefit of P2 or any earlier application under 35 U.S.C. § 120. Baran Dec. ¶ 102.

In addition, with respect to the Method Claims (claims 11 and 12), there are no blaze marks in the specification to direct one of ordinary skill to use the specific compounds of claim 1 for the three particular indications recited in the Method Claims: melanoma, thyroid cancer and colorectal cancer. Baran Dec. ¶ 103. These three indications appear in a laundry list of diseases including head injury, heart failure, dementia, diabetes and asthma. *Id.* (citing P2 at 34-47). Moreover, given the absence of any data suggesting that compounds with L_1 as a bond may have

activity against any particular disease or condition, there is no reason one of ordinary skill would reasonably expect that the inventors had possession of methods of using such compounds to treat melanoma, thyroid cancer and colorectal cancer. Baran Dec. ¶ 104. Thus, these claims lack written description support for this additional reason. *Id.*

d. The Challenged Claims Are Not Entitled To The Benefit Of P2 Under 35 U.S.C. § 120 Because They Fail To Meet The Enablement Requirement Under 35 U.S.C. § 112

As described above, the Challenged Claims are directed to broad subgenera of compounds. Baran Dec. ¶ 105. Each of the subgenera provides that L_1 is either a bond or –N(H)C(O)–. *Id.* P2 does not enable a person of ordinary skill to *make* the full scope of compounds in these claims where L_1 is a bond, which constitute approximately half of the compounds covered by the claims.

Moreover, P2 fails to disclose how to *use* such compounds where L_1 is a bond, as P2 provides no data showing that any of the claimed compounds where L_1 is a bond has activity on kinase proteins and a person of ordinary skill would not have believed such compounds where L_1 is a bond would have such activity. Baran Dec. ¶ 106. Accordingly, P2 does not meet the enablement requirement of 35 U.S.C. § 112 and thus the Challenged Claims are not entitled to the benefit of P2 or any earlier application under 35 U.S.C. § 120 for this reason as well. *Id.*

(i) The Standard For Enablement, 35 U.S.C. § 112 (Pre-AIA)

35 U.S.C. § 112 requires that a patent disclosure must contain sufficient information to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.*

In addition, the "how-to-use" prong of the enablement requirement under 35 U.S.C. § 112 incorporates as a matter of law the requirement under 35 U.S.C. § 101 that the specification disclose a practical utility for the invention. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005). The "how-to-use" prong is not satisfied "'when there is a complete absence of data supporting

the statements which set forth the desired results of the claimed invention.'" *Id*. (quoting *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999)); s*ee also Brenner v. Manson*, 383 U.S. 519, 535 (1966) ("Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing"). Moreover, showing utility for only part of a genus is not sufficient to meet the utility requirement when an artisan would not reasonably believe the entire genus would have the stated utility based on the limited disclosure. *In re Fouche*, 439 F.2d 1237, 1242-43 (C.C.P.A. 1971).

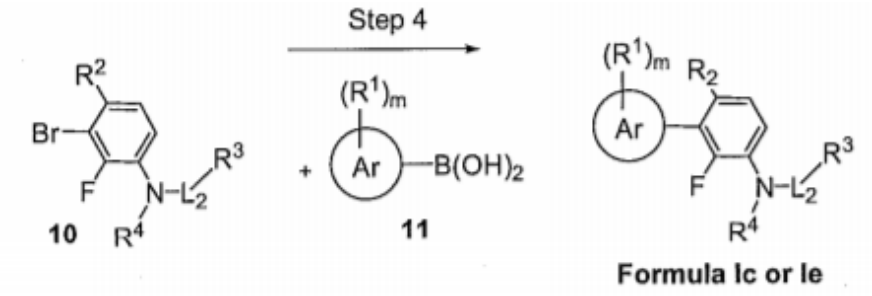
(ii) P2 Does Not Enable a Person of Ordinary Skill to Make the Full Scope of Claimed Compounds for Which L_1 is a Bond.

P2 provides virtually no direction or guidance to teach a skilled person how to make the trillions of claimed compounds wherein L_1 is a bond. Baran Dec. ¶ 107. P2 does not provide a single example of a compound wherein L_1 is a bond. *Id.* All 120 of the examples in the specification of P2 have a chemical moiety such as an amide, $–CH_2NH–$, or $–CH_2O–$, at L_1. *Id.* (citing P2 at 79-110). The three examples in the specification that fall within the scope of claim 1 (but not within any of the other Challenged Compound Claims) each have an amide at the L_1 position. *Id.*

Example 2 provides a prophetic general scheme for making theoretical compounds according to Formulae Ic and Ie, for which L_1 is a bond. Baran Dec. ¶

108 (citing P2 at 75-77). But no compounds were actually synthesized according to this scheme, and the specification provides no indication that the scheme would be feasible across the full scope of the claimed genera where L_1 is a bond. *Id.*

Step 4 of the general scheme of Example 2 is reproduced below:

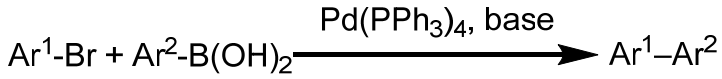


Baran Dec. ¶ 109 (citing P2 at 76). P2 describes "Step 4" in general terms:

> A mixture of compound 10, an appropriate boronic acid 11 (Ar, m and R^1 as defined in paragraph [0004]), and a catalyst (e.g. tetrakis(triphenylphosphine)palladium) in a mixture of base (e.g. aqueous solution of potassium carbonate) and an appropriate organic solvent (e.g. acetonitrile) is heated in an oil bath or is irradiated in a microwave system at over 100°C for an appropriate time depending on starting materials. The reaction mixture is poured into water and then extracted with an appropriate organic solvent (e.g. dichloromethane or ethyl acetate). The organic solvents are then combined. The desired compound of Formula Ic (L_2 is $S(O)_2$) or 1d [sic] is purified by chromatography.

Id. (quoting P2 at 77).

The reaction described to form the L_1 bond in Step 4 is known as a Suzuki coupling.[5] Baran Dec. ¶ 110. The general conditions described in P2 reflect the original conditions described by Suzuki in 1978 for the general reaction scheme shown below:



Id.

Suzuki reactions are widely used in the pharmaceutical industry. Baran Dec. ¶ 111. However, given the particular structure and variables of the claimed genera and the enormous number of potential moieties for each of the different variables, it would be extremely difficult or even impossible to use a Suzuki reaction – especially as taught in Step 4 of P2 – to form compounds comprising large portions of the claimed genera where L_1 is a bond. *Id.*

Much of this difficulty stems from the fact that Suzuki reactions were originally developed to link aryl, as opposed to heteroaryl, moieties. Baran Dec. ¶ 112. Although Suzuki reactions typically work quite well when linking aryl moieties, the Challenged Claims required the linkage of an aryl group with a heteroaryl moiety at the Ar position, specifically a 5- or 6-member heteroaryl wherein at least one atom is nitrogen. *Id.* Many heteroaryl moieties described by

[5] Some references refer to the reaction as a "Suzuki-Miyaura coupling."

the claims remain difficult or impossible to use in Suzuki reactions even to this day. *Id.*

As noted in the literature, cross-coupling reactions, such as the Suzuki reaction, with heteroaryl reactants, such as the Ar defined above, have proven significantly more challenging than those with all-carbon reactants (e.g., an aryl). Baran Dec. ¶ 113 (citing Martin at 1465).[6] For example, it was reported in August 2013 that many standard protocols for Suzuki reactions fail in the presence of reactants bearing a free-NH group. Baran Dec. ¶ 114 (citing Düfert at 12877). Moreover, the Challenged Claims comprise a large portion of compounds which, under Step 4 of Example 2, would require a cross-coupling of compounds 10 and 11, each of which possesses two substituents next to the boron (i.e., two R^1 groups in compound 11) or bromine (i.e., one F and one R^2 group in compound 10)

[6] Martin was published four months after the filing date of P2. Later-dated references which describe the difficulty, impossibility or unpredictability of performing certain types of chemical reactions are relevant to establishing the difficulty, impossibility or unpredictability of performing such reactions as of the filing date. *See* MPEP 2164.05(a) ("If individuals with skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing.") (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)).

moiety. Baran Dec. ¶ 115. Those substituents create steric hindrance which would inhibit the cross-coupling. *Id.* (citing Martin at 1464).

The Challenged Claims also comprise a large portion of compounds which, under Step 4 of Example 2, would require a cross-coupling involving a five-membered 2-heteroaromatic boronic acid or pyridinyl boronic acid as compound 10. Baran Dec. ¶ 116. As reported in 2010, five-membered 2-heteroaromatic boronic acids were unstable, and substantial efforts were required to identify unique palladium catalyst(s) for the Suzuki reaction to occur. *Id.* (citing Kinzel). Another paper published in 2016 indicated that the 2-heteroaryl and pyridinyl boronic acids remained problematic with respect to Suzuki couplings because of their instability and/or poor reactivity leading to undesired side reactions such as protodeboronation and oxidative coupling. *Id.* (citing Jedinák at 157).

In addition, it was exceedingly difficult – if not impossible – to obtain the boronic acid starting materials that were required to make the compounds of the Challenged Claims. Baran Dec. ¶ 117 (citing Tyrrell at 469). The disclosure in P2 does not teach a POSITA how to obtain the requisite boronic acid starting materials. *Id.* P2 is completely silent about the availability of compound 11 and does not describe any method of preparing it. *Id.*

It was well known in the art that the stability of boronic acid reagents like compound 11 varies widely and is highly unpredictable, and many such boronic

acid reagents are, therefore, unstable and cannot be used, even if they could be made. Baran Dec. ¶ 118. The success of preparing and using any single boronic acid compound, let alone the full scope of millions or trillions of boronic acid compounds – especially when R^1 is an optionally substituted heteroaryl – depends on the nature of the corresponding starting material and reaction conditions, which is highly unpredictable to the POSITA and requires a large quantity of experimentation. *Id.* The ability to prepare boronic acids is important because only a very small subset of the boronic acids necessary to make the full scope of the Challenged Claims were commercially available during the relevant time period. Baran Dec. ¶ 119. Substituted 5 or 6-membered heteroaryl boronic acid, (i.e., when m is 1 or above, especially when m is 2 or above, and one R^1 is an optionally substituted heteroaryl) were not commercially available during the relevant time-period. *Id.* Most remain commercially unavailable even to this day. *Id.* Hence, Scheme 2 of P2 requires the POSITA to synthesize millions if not trillions of boronic acids from scratch in order to make the full scope of the claimed genera. *Id.* It was well known in the field that such boronic acid reagents were extremely challenging to procure and use, and even now, researchers are still actively trying to address these unsolved problems. *Id.*

Even assuming that the necessary boronic acid starting materials were readily available (and they generally were *not*), performance of the Suzuki reaction

step itself would have been highly unpredictable. Baran Dec. ¶ 120. P2 does not provide any useful guidance in this regard. *Id.* For example, 4-thiazolyl boronic acids are well-documented to fail in Suzuki reactions. Baran Dec. ¶ 121 (citing Hämmerle at 8052). Such boronic acids are very unstable and are subject to a phenomenon called protodeboronation, in which the boronic acid moiety is cleaved from the thiazole before the Suzuki coupling can take place. *Id.* (citing Cox at 9152). The very high likelihood of failure affects all 4-thiazolyl boronic acids, including trillions of possible R^1 combinations falling within the scope of the Challenged Claims. *Id.* Indeed, to the extent that Suzuki coupling with intermediates such as those described above is possible at all, it requires careful and laborious trial-and-error optimization of reaction conditions such as the solvent, the particular base, the particular catalyst, and any protection/deprotection steps that may be required. Baran Dec. ¶ 122.

The Suzuki reaction has long been understood to be highly sensitive to reaction conditions: its success or failure is unpredictable and depends on the identity and nature of compounds 10 and 11, the base, the catalyst, and the solvent used. *Id*. (citing Suzuki Nobel Lecture at 6734; Li and Gribble at, *e.g.*, 7-10, 352-54, 388-89, 414-17). Moreover, the reaction conditions, base, catalyst, and solvent that work for any one pair of reactants may not work for any other pair depending on the exact nature of the R^1, R^2, and Ar moieties. *Id.*

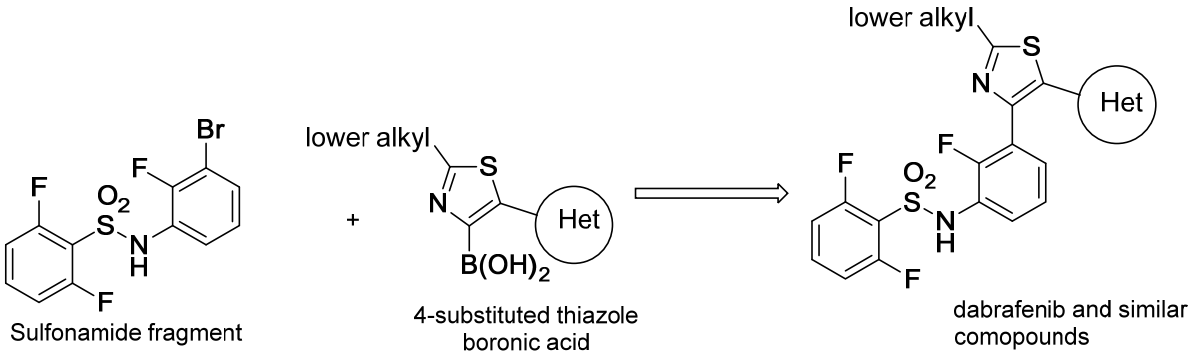
P2 does not teach that the 1978 reaction conditions set forth in Step 4 would work to perform the Suzuki reaction to obtain the claimed compounds. Baran Dec. ¶ 123. Based on teachings in the art concerning Suzuki coupling reactions, a person of ordinary skill reading the specification would not expect those conditions to be effective to make the claimed compounds. *Id.* Moreover, P2 provides no information guiding a person of ordinary skill on any other particular reaction conditions that would be effective for performing the Suzuki reaction to obtain the claimed compounds. *Id.*

For example, the palladium catalyst described in P2 is the most primitive catalyst available for running Suzuki reactions. Baran Dec. ¶124. It has very low reactivity, and would be unlikely to successfully catalyze a Suzuki reaction to generate the claimed compounds, which have nitrogen-containing heteroaryl moieties. *Id.* Even using newer, more sophisticated catalysts that were developed after the disclosure in P2, such reactions would be very difficult. *Id.*

In addition, P2 teaches use of potassium carbonate base, but this base would not work well in a Suzuki coupling using certain heteroaryl boronic acid reagents due to documented protodeboronation. Baran Dec. ¶ 125. P2 also teaches use of an acetonitrile solvent, but this solvent might not work well in a Suzuki coupling using heteroaryl boronic acid reagents because acetonitrile is miscible with water and therefore could further favor a protodeboronation pathway. *Id.* Finally,

depending on the Ar and R^1 groups, protection and deprotection steps may be required; P2 never mentions such steps nor provides any guidance for when they might be required or how to perform them. Baran Dec. ¶ 126.

To give but one illustrative example of the above, dabrafenib and similar compounds are examples of compounds that would be extremely difficult or even impossible to form using the Suzuki reaction scheme taught in P2. Baran Dec. ¶ 127. Step 4 of Example 2, specified for the formation of dabrafenib and similar compounds, is shown below:



both lower alkly and Het (i.e., heteroaryl) can be substituted or unsubstituted

Id. This reaction is nearly impossible to perform using the teachings of P2, as reflected in the fact that GSK did not use a Suzuki reaction to form the carbon-carbon bond at L_1 in dabrafenib. Baran Dec. ¶ 138; '185 patent at Scheme 1 (col. 69-70). There are at least three reasons for this.

First, thiazole-based boronic acid reagents are extremely difficult to prepare and are well-documented to fail in Suzuki reactions. Baran Dec. ¶ 129 (citing

Hämmerle at 8052). Moreover, 4-thiazolyl boronic acids are notorious for being the most difficult out of all possible thiazole isomers in this regard. *Id*. As noted, in the specific case of the 4-thiazolyl boronic acid shown above, the heteroaryl R^1 group increases the likelihood of protodeboronation and therefore makes the likelihood that the Suzuki coupling would fail even higher. Baran Dec. ¶ 130. This particular group affects the Suzuki reaction both because of its *ortho*- position relative to the boronic acid and because of its electrochemical properties. *Id.* Many other potential R^1 groups share similar electrochemical properties that increase the likelihood of the Suzuki coupling's failure, and *any* R^1 group in the *ortho*- position increases the difficulty of forming the boronic acid and using it in the Suzuki coupling. *Id.*

Second, the sulfonamide fragment is difficult or impossible to use in a Suzuki coupling because ortho-fluoro arenes bearing an acidic substituent are problematic aryl bromide substrates for Suzuki coupling. Baran Dec. ¶ 131. The ortho-fluoro moiety prescribed by the Challenged Claims increases the likelihood of failure of the Suzuki coupling. *Id.* Although dabrafenib has hydrogen at the R^2 position, sulfonamide fragments having an additional halogen in the second *ortho*-position (i.e. the R^2 position) would be even more difficult to use in the Suzuki coupling. *Id.* Moreover, the sulfonamide moiety, an acidic substituent from the phenyl ring that is also prescribed by the Challenged Claims, further increases the

likelihood that a Suzuki coupling would fail. Baran Dec. ¶ 132. Because the sulfonamide and at least one ortho-fluoro moiety are prescribed by Formula Ia, these issues would affect the entire genus of the Challenged Claims. *Id.*

Third, as noted, to the extent Suzuki coupling with intermediates such as those described above is possible at all, it requires careful and laborious trial-and-error optimization of reaction conditions such as the solvent, the particular base, the particular catalyst, and any protection/deprotection steps that may be required. Baran Dec. ¶ 133. Many of the catalysts that are in use today were either unavailable or not known to be useful in Suzuki reactions during the relevant time period. *Id.* Moreover, the reaction conditions, base, and catalyst that work for any one pair of intermediates may not work for any other pair depending on the exact nature of the R^1, R^2, and Ar moieties. *Id.* Finally, depending on the Ar and R^1 groups, protection and deprotection steps may be required. *Id.* P2 never mentions such steps nor provides any guidance for when they might be required or how to perform them. *Id.*

The problems with using the Suzuki coupling with respect to 4-thiazolyl boronic acids also affect many other kinds of heteroaryl rings that meet the Challenged Claims' criteria for Ar and would also pose great difficulty in both forming a boronic acid and using it in the Suzuki coupling. Baran Dec. ¶ 134 (citing Kinzel at Abstract). Moreover, the enormous diversity permitted at the R^1

position, the potential for a halogen at the R^2 position, and the presence of the sulfonamide group on the phenyl ring would make any Suzuki reaction much less likely to work, even if an ideal non-heteroaryl aromatic group were employed instead of the heteroaryl moiety required by Ar in the claims. *Id.* Indeed, the diverse properties of each kind of heteroaryl would require from-the-ground-up optimization of reactions conditions and selection of bases and catalysts for each different Ar group (even excluding differences caused by diversity at the R^1 and R^2 positions). Baran Dec. ¶ 135. This trial-and-error process would be enormously time-consuming, laborious, and unpredictable – and it would have to be performed for each of the trillions of compounds falling within the scope of the Challenged Claims. *Id.* And for many such compounds, as discussed above, this process would never succeed, no matter how much experimentation was performed. *Id.* The amount of experimentation required to make the full scope of the Challenged Claims cannot be overestimated. *Id.*

Because viable Suzuki reaction conditions would need to be determined for each of the millions (or trillions) of boronic acid reagents, the person of ordinary skill would have had to undergo massive amounts of laborious and time-consuming experimentation that would have been highly unpredictable and that likely would not have worked. Baran Dec. ¶ 136. This type of experimentation was not, and is not to this day, routine. *Id.* These difficulties were well understood

in the art and are still the subject of active and ongoing research. *Id.* In other words, confronted with a myriad of combinations of reaction conditions that might be employed in an attempt to make Compound 11 and to conduct the Suzuki reaction, without knowing if Compound 11 can be made and/or whether Suzuki reaction will occur at all, the person of ordinary skill would have had to engage in a massive program of unguided trial-and-error experimentation. Baran Dec. ¶ 137.

In sum, a POSITA would not be able to use the Suzuki coupling to form the full scope of the compounds in the claimed genera for which L_1 is a bond. Baran Dec. ¶ 138. P2 suggests a very generic Suzuki coupling but fails to provide any guidance or examples of how to use the Suzuki coupling to form any actual compound of the claims. *Id.* Moreover, despite the high level of diversity among intermediates that would be starting materials in the Suzuki coupling, P2 fails to provide any guidance for how to select reaction conditions, bases, or catalysts, or how to determine the necessity of or perform protection/deprotection steps. *Id.* And a person of ordinary skill would have fully expected that the Suzuki reaction would actually be impossible for a very large number of compounds for which L_1 is a bond falling within the scope of the Challenged Claims. *Id.*

Thus, P2 fails to enable the person of ordinary skill to make the full scope of the Challenged Claims without undue experimentation. Baran Dec. ¶ 139. The breadth of the claims is enormous (Factor 8). *Id.* As described above, using

Suzuki reactions to make compounds where L_1 is a bond can be highly unpredictable (Factor 7). *Id.* While the relative skill of those in the art is fairly high (Factor 6), there are no working examples in P2 for compounds where L_1 is a bond (Factor 3), and the disclosure of the prophetic general scheme for using a Suzuki reaction using the original 1978 conditions provides little or no guidance for how to make the full scope of the trillions of claimed compounds where L_1 is a bond (Factor 2). *Id.* Even today, large categories of the claimed compounds could not be made using a Suzuki reaction, and the quantity of experimentation that would be necessary to make those that could be made would be enormous (Factor 1). *Id.* Accordingly, P2 does not meet the enablement requirements of 35 U.S.C. § 112 and thus that the Challenged Claims are not entitled to the benefit of P2 under 35 U.S.C. § 120. Baran Dec. ¶ 140.

(iii) P2 Would Not Enable a Person of Ordinary Skill to Use the Full Scope of Claimed Compounds For Which L_1 Is a Bond.

As noted above, the "how-to-use" prong of the enablement requirement incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose a practical utility for the invention. *Rasmusson*, 413 F.3d at 1323. While the '640 patent asserts that the claimed compounds are "active on protein kinases" and are useful "to treat diseases and conditions associated with aberrant activity of protein kinases," '640 patent, Abstract, P2 presents no data

whatsoever that any of the claimed compounds where L_1 is a bond has such activity.

P2 includes tables that list representative compounds with activity inhibiting different kinases. Baran Dec. ¶ 142 (citing P2 at 110-12). These tables do not include any compound where L_1 is a bond (let alone compounds that also have the other substituents required by the Challenged Claims). *Id.* Nor is activity data (in any assay) for such compounds presented anywhere in P2. *Id.* Thus, P2 contains no working examples and no direction or guidance to show a person of ordinary skill reading the specification that compounds in which L_1 is a bond might work as kinase inhibitors, or for any other pharmacological purpose. *Id.* Given the absence of **any** data for compounds where L_1 is a bond, a person of ordinary skill would not have believed that compounds for which L_1 is a bond would have any pharmacological activity, much less that they would behave in a kinase inhibition assay in the same manner as a compound containing an amide linker (i.e. for which L_1 is N(H)C(O)). Baran Dec. ¶ 143. There are several reasons for this.

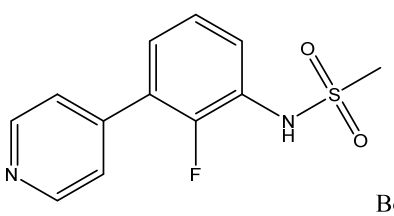
First, P2 does not explain whether and how the amide linker might relate to the function of compounds containing the linker, and whether a bond would be capable of carrying out the same function. Baran Dec. ¶ 144. For example, an amide linker contains nitrogen and oxygen atoms that may interact with amino acids of the kinase such that removing the amide would directly impact the overall

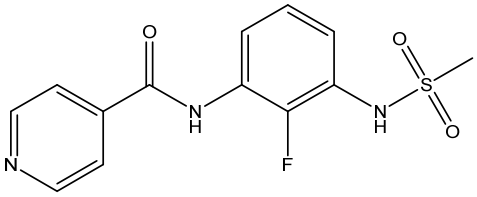
interaction between the compound and the kinase. *Id.* Indeed, it is well known that the nitrogen or oxygen atoms of an amide can form hydrogen bonds with amino acids. *Id.* In contrast, a bond would not be able to make those hydrogen bonds. *Id.* Accordingly, a POSITA would have no way of knowing whether or to what extent replacing an amide linker with a bond in the compounds of the Challenged Claims would prevent the compound from interacting with, binding to, and/or inhibiting the kinase. *Id.*

Second, as compared to compounds in which L_1 is a bond, the inclusion of an amide linker may alter the chemical properties of the molecule such as pH and solubility. Baran Dec. ¶ 145. For example, the carbonyl (C=O) moiety of the amide linker bears a partial negative charge on the oxygen atom and a partial positive charge on the carbon atom; the presence of such partial charges generally increases the ability of amide-containing compounds to interact with – and therefore increases the compounds' solubility in – water or other aqueous solvents. *Id.* Replacement of the amide with a bond would make the compound less soluble in water or other aqueous solvents. *Id.*

Third, as compared to compounds in which L_1 is a bond, the inclusion of an amide linker alters the position of the Ar-$(R^1)_m$ portion of the compounds relative to the sulfonamide-containing portion of the compounds. Baran Dec. ¶ 146. The

amide linker changes both the overall length and the three-dimensional shape of the compounds as shown in the 2-D (top) and 3-D (bottom) models below:

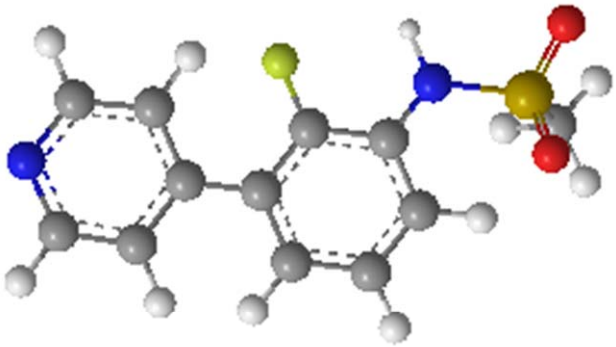


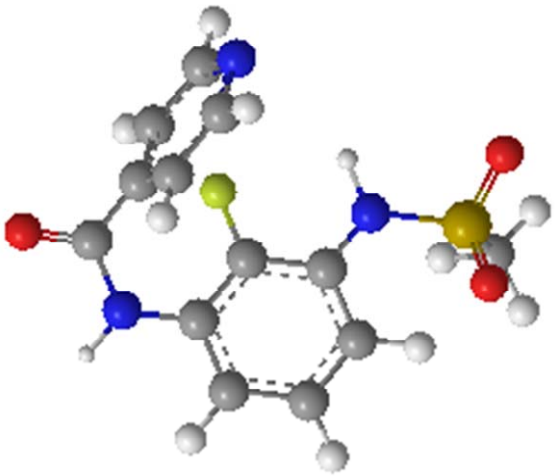


L_1 is a bond

Both Compounds:
R^1 = N/A
m = 0
R^2 = hydrogen
R^3 = methyl
Ar = pyridine

L_1 is an amide





Id. A kinase inhibitor's function depends on its ability to fit into the active site of the kinase in such a way that atoms found on the inhibitor can interact with particular amino acid residues of the kinase. Baran Dec. ¶ 147. Because an amide-linked compound would necessarily have a different size and shape from an otherwise-identical compound having L_1 as a bond, a person of ordinary skill would expect the two compounds to interact with the kinase differently and therefore to exhibit different kinase inhibition behavior. *Id.* Thus, P2's disclosure of kinase inhibition data with respect to amide-linked compounds would not enable

a person of ordinary skill to even guess at how a compound in which L_1 is a bond would behave. *Id.*

Moreover, although the Challenged Claims embrace a large genus of substituents at the R^3 position ('640 patent, claim 1 ("R^3 is optionally substituted lower alkyl or optionally substituted aryl"), each of the compounds disclosed as having activity has a propyl group at the R^3 position. Baran Dec. ¶ 148. The type and substitution pattern of the group at the R^3 position may affect the solubility of the claimed compounds as well as their interaction with the kinase. *Id.* Because P2 does not provide any disclosure of activity for compounds with, *e.g.*, aryl groups or groups having hydrophilic substituents[7] at R^3 and also fails to disclose a structure-function relationship for substituents at that position, P2 does not enable a person of ordinary skill to use the full scope of the Challenged Claims. *Id.*

In sum, P2 provides, at best, merely an invitation to test the compounds of the Challenged Claims where L_1 is a bond (approximately half of the compounds covered by the claims) to determine whether they have the asserted pharmacological activity on protein kinases. Baran Dec. ¶ 149. This is insufficient to meet the utility standard of 35 U.S.C. § 101 and thus the "how-to-use"

[7] Propyl is a hydrophobic group, but many of the substituents permitted by the specification are more hydrophilic. This qualitative difference is well known to affect the behavior of pharmaceutical compounds.

enablement requirement of 35 U.S.C. § 112. *See Brenner v. Manson,* 383 U.S. at 535 ("Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing"). Because there was no credible utility disclosed for approximately half the compounds covered by the chemical formulae in the Challenged Claims, P2 fails to meet the utility requirement under 35 U.S.C. § 101 and thereby fails to satisfy the how-to-use prong of the enablement requirement of 35 U.S.C. § 112.

For all of the reasons set out above, the Challenged Claims are not disclosed in P2 in a manner mandated by the enablement requirement and thus are not entitled to the benefit of the filing date of P2 or any earlier application under 35 U.S.C. § 120.

2. Because The Challenged Claims Are Not Entitled To Benefit Of P2, They Are Anticipated By The '185 Patent Under 35 U.S.C. § 102(b)

a. The Standard For Anticipation Under 35 U.S.C. § 102(b) (Pre-AIA)

35 U.S.C. § 102(b) (pre-AIA) provides that "[a] person shall be entitled to a patent unless – (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States . . . ." The prior art describes, *i.e.* anticipates, claimed subject matter if it "disclose[s]

every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

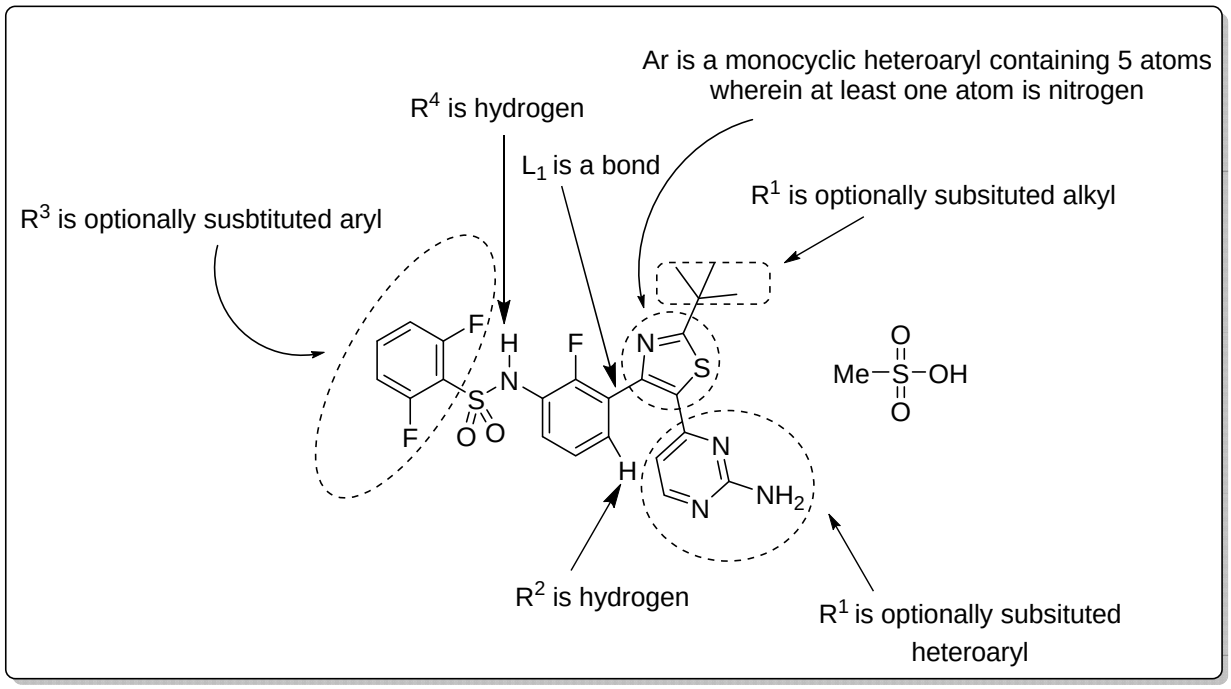
b. The Challenged Claims Are Anticipated By The '185 Patent

Because the Challenged Claims are not entitled to the benefit of the July 16, 2008 filing date of P2, their earliest possible priority date is April 19, 2013. As such, the Challenged Claims are anticipated under § 102(b) by the '185 patent, which issued on August 9, 2011, more than one year prior to the earliest possible priority date of the Challenged Claims.

Challenged Compound Claims: The '185 patent discloses thiazole sulfonamide and oxazole sulfonamide compounds, compositions containing those compounds, and methods for their use as pharmaceutical agents. '185 patent, Abstract. One of the compounds that is specifically described is the compound of Example 58 (shown below), which today is known as dabrafenib. Baran Dec. ¶¶ 152 (citing '185 patent at cols. 177-182), 153 (citing Ex. 1005 at 11-12). Dabrafenib is specifically claimed in at least claims 1 and 6 of the '185 patent. Baran Dec. ¶ 152.

Example 58 presents three synthetic schemes to prepare dabrafenib or polymorphs thereof (Examples 58a, 58b and 58c), and two additional synthetic schemes to prepare the methanesulfonate (or mesylate) salt of dabrafenib (Examples 58d and 58e). *Id.*

As shown below, the compound of Example 58, dabrafenib, falls within the scope of each of the Challenged Compound Claims. Baran Dec. ¶ 154, Appendix A.



Because dabrafenib falls within the scope of each of the Challenged Compound Claims, the '185 patent anticipates those claims. Baran Dec. ¶ 155; *In re Gosteli*, 872 F.2d at 1010.

Plexxikon has sued Novartis for infringement of the Challenged Claims based on "Novartis's importation, offer for sale, and sale of the drug dabrafenib," which "Novartis markets . . . under the trademark Tafinlar®." *Plexxikon Inc. v. Novartis Pharms. Corp.*, Case No. 4:17-cv-04405-HSG (EDL) (N.D. Cal.) Docket Entry 55 (Second Amended Complaint) at page 2. "That which infringes if later, anticipates if earlier." *Peters v. Active Mfg. Co.*, 129 U.S. 530, 537 (1889);

Upsher-Smith Labs v. Pamlab, L.L.C.., 412 F.3d 1319, 1322 (Fed. Cir. 2005). To the extent dabrafenib infringes the Challenged Compound claims (claims 1, 2, 4-6), the '185 patent anticipates those claims.

The '185 patent also anticipates the Challenged Composition Claim (claim 9). Baran Dec. ¶ 156. The '185 patent states that the compound of Example 58 may be provided in a pharmaceutical composition. *Id.* (citing '185 patent at columns 12, 60).

Finally, the'185 patent anticipates the Challenged Method Claims (claims 11 and 12). Baran Dec. ¶ 157. The '185 patent discloses "a method of treating a susceptible neoplasm in a mammal in need thereof, comprising the steps of: . . . (b) selecting a mammal having a neoplasm with a mutation encoding the V600E amino acid substitution in B-Raf; and (c) administering a therapeutically effective amount of a compound of the present invention to the mammal selected in step (b)." *Id.* (citing '185 patent, col. 58:43-47). Methods of treating colorectal cancer, melanoma and thyroid cancer using the compounds of Example 58 are also disclosed. *Id.* (citing '185 patent at columns 14, 51-53). The '185 patent also discloses test data on the activity of the compounds of Example 58 against pertinent cancers. Baran Dec. ¶¶ 158-61. Thus, based on the disclosure of the '185 patent as a whole, the'185 patent anticipates method claims 11 and 12. Baran Dec. ¶ 162, Appendix A.

VII. CONCLUSION

For the reasons discussed above, Petitioner requests that the Board institute an *inter partes* review and determine that claims 1, 2, 4-6, 9, 11 and 12 of the '640 patent be canceled as unpatentable.

Respectfully submitted,

Dated: June 18, 2018

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R.§ 42.24 (d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). According to the word processing program used to prepare this Petition, this Petition contains 13,949 words, excluding the parts of the petition exempted by 37 C.F.R. §42.24(a). This is less than the 14,000 word limit.

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on June 18, 2018, I caused to be served true and correct copies of the foregoing "PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 9,844,539" in addition to Exhibits 1001-1026 by Electronic Service (email and FTP) at the correspondence address of record for U.S. Patent No. 9,469,640, and additionally at other addresses known as likely to effect service, as follows:

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