

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner

v.

PLEXXIKON INC.,
Patent Owner

Case IPR No.: *To be Assigned*

DECLARATION OF PHIL S. BARAN, PH.D.

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Declaration of Phil S. Baran, Ph.D. (Ex.1002)

TABLE OF CONTENTS

TABLE OF CONTENTS	1
I. EXECUTIVE SUMMARY	2
II. QUALIFICATIONS	3
III. THE '640 PATENT	5
IV. PERSON OF ORDINARY SKILL IN THE ART	8
V. LEGAL PRINCIPLES	9
A. Priority Benefit Requires Written Description and Enablement	9
B. Anticipation.....	12
VI. THE CHALLENGED CLAIMS ARE NOT ENTITLED TO THE BENEFIT OF P2 OR ANY EARLIER APPLICATION	13
A. P2 Fails To Provide Written Description Support For The Challenged Claims	13
1. P2 Does Not Provide Blaze Marks from Which The POSITA Would Arrive at the Claimed Genus	14
2. P2 Specifically Fails to Provide Written Description for the Claimed Genus With Regard to the L ₁ Substituent.....	29
3. P2 Specifically Fails to Provide Written Description for the Claimed Genus With Regard to the R ¹ Substituent.	40
4. P2 Also Fails to Provide Written Description for the Challenged Composition and Method Claims.....	48
B. P2 Fails to Enable the POSITA to Make and Use the Full Scope of the Challenged Claims Without Undue Experimentation	49

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

1.	P2 Does Not Enable a POSITA to Make the Full Scope of Claimed Compounds for Which L ₁ is a Bond.....	50
2.	P2 Would Not Enable a POSITA to Use the Full Scope of Claimed Compounds For Which L ₁ Is a Bond.....	64
VII.	THE CHALLENGED CLAIMS ARE ANTICIPATED BY U.S. PATENT NO. 7,994,185 UNDER 35 U.S.C. § 102(B)	69
	APPENDIX A: THE CHALLENGED CLAIMS ARE ANTICIPATED BY THE '185 PATENT	1

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

EXHIBITS CITED IN THIS DECLARATION

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.
1003		Curriculum Vitae 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
1008		P4 Prosecution History, April 3, 2015 Office Action
1009		P4 Prosecution History, August 3, 2015 Amendment and Reply
1010		P4 Prosecution History, September 3, 2015 Office Action
1011		P4 Prosecution History, Examiner's Summary of January 15, 2016 Interview
1012		P4 Prosecution History, Statement of Substance of Interview
1013		P4 Prosecution History, April 18, 2016 Notice of Abandonment

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

1014		P5 Prosecution History, February 19, 2016 Preliminary Amendment
1015		P5 Prosecution History, April 18, 2016 Office Action
1016		P5 Prosecution History, July 20, 2016 Amendment and Response
1017		P5 Prosecution History, September 2, 2016 Notice of Allowance
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)
1019	Düfert	Düfert et al., “Suzuki-Miyaura Cross-Coupling of Unprotected, Nitrogen-Rich Heterocycles: Substrate Scope and Mechanistic Investigation,” 135 J. AM. CHEM. SOC. 12877-12885 (Aug. 2013)
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

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

		(Aug. 2010)
1024	Cox	Paul A. Cox et al., “Protodeboronation of heteroaromatic, vinyl and cyclopropyl boronic acids: pH-rate profiles, auto-catalysis and disproportionation,” 138(29) <i>J. Am. Chem. Soc.</i> 9145-57, 9152 (2016)
1024	Suzuki Nobel Lecture	Akira Suzuki, “Cross-Coupling Reactions of Organoboranes: An Easy Way to Construct C-C Bonds (Nobel Lecture), 50 <i>ANGEW. CHEM INT. ED.</i> 6723-6737, 6734 (2011)
1025	Li and Gribble	Li and Gribble (Eds.), <i>PALLADIUM IN HETEROCYCLIC CHEMISTRY: A GUIDE FOR THE SYNTHETIC CHEMIST</i> (2d ed. 2006).

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

1. I, Phil S. Baran, Ph.D., hereby declare as follows:

2. I have been retained by McDermott Will & Emery, LLP, the legal representative of Novartis Pharmaceuticals Corporation (Petitioner), as an expert witness for the above-captioned *Inter Partes* Review (“IPR”) of U.S. Patent No. 9,469,640 (“the ’640 patent”) (Ex. 1001). I have also been retained as an expert with respect to a related petition for Post-Grant Review of U.S. Patent No. 9,844,539 (“the ’539 patent”), in connection with which I am submitting a separate declaration. I further understand that the ’640 and ’539 patents have been asserted against Novartis Pharmaceuticals Corporation in *Plexxikon Inc. v. Novartis Pharmaceuticals Corporation*, Civil Action No. 4:17-cv-04405-HSG (EDL), filed August 3, 2017, in the United States District Court for the Northern District of California.

3. I am being compensated for my time in connection with this IPR at my standard rate, which is \$750/hour. My compensation is in no way tied to the opinions expressed herein or to the outcome of this or any other proceeding.

4. I understand that Petitioner requests IPR of claims 1, 2, 4-6, 9, 11, and 12 (“the Challenged Claims”) of the ’640 patent.

5. Based on my education and academic experience, which is evident from my Curriculum Vitae attached as Ex. 1003, and further discussed below, I am

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

a technical expert in synthetic organic chemistry and thus able to testify with respect to the scientific teachings of the '640 patent from the viewpoint of a person of ordinary skill in the art ("POSITA") at all relevant times.

6. In preparing this declaration, I have reviewed several references, which are listed above, and I have further relied upon my experience in the art of synthetic organic chemistry and considered the general knowledge in the art at the times discussed herein. I reserve my right to amend, supplement, or alter my analysis or opinions in view of any new information later presented to me.

I. EXECUTIVE SUMMARY

7. My opinions regarding the Challenged Claims of the '640 patent are summarized in the following paragraphs:

8. Based on my understanding of the law as communicated to me by counsel, at least U.S. Application No. 12/669,450 (PCT/US2008/070124) ("P2") does not satisfy the written description and enablement requirements of 35 U.S.C. § 112 for the Challenged Claims as required to receive the benefit of priority under 35 U.S.C. § 120.

9. Based on my understanding of the law as communicated to me by counsel, the earliest possible priority date of the Challenged Claims is the filing

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

date of the next continuation application, U.S. Application No. 13/866,353 (“P3”), which I am advised is April 19, 2013.

10. Based on my understanding of the law as communicated to me by counsel, each of the Challenged Claims is anticipated under pre-AIA 35 U.S.C. §§ 102(a), 102(b) and 102(e) by U.S. Patent No. 7,994,185 (“the ’185 patent”) (alternatively, under AIA 35 U.S.C. § 102(a)(1) and (2)), which was first published on December 3, 2009 under U.S. Patent Application Publication No. US2009/0298815 and issued on August 9, 2011, and which discloses compounds falling within the scope of each of the Challenged Claims as well as compositions and methods of treatment involving said compounds.

II. QUALIFICATIONS

11. My qualifications and credentials are fully set forth in my Curriculum Vitae, attached herein as Ex. 1003.

12. I graduated from New York University in 1997 with a B.S. with Honors in Chemistry. After college, I obtained a Ph.D. in Chemistry in 2001 from The Scripps Research Institute (“Scripps”), where I worked under Professor K.C. Nicolaou. After that, I did an NIH Postdoctoral Fellowship at Harvard University from 2001-2003, where I worked under Professor E.J. Corey.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

13. I started teaching at Scripps in June, 2003 as an Assistant Professor of Chemistry. In July, 2006, I earned tenure at Scripps and became an Associate Professor of Chemistry. I was promoted to Professor of Chemistry in June, 2008. Since January, 2013, I have held the Darlene Shiley Chair in Chemistry at Scripps. I have also been a Member of the Skaggs Institute for Chemical Biology since April 2009.

14. My work has been recognized by leaders in industry and the academy. For example, between 2005 and 2006, I won the Pfizer Award for Creativity in Organic Synthesis, the Eli Lilly Young Investigator Award, the AstraZeneca Excellence in Chemistry Award, the DuPont Young Professor Award, the Roche Excellence in Chemistry Award, the Amgen Young Investigator Award, and the GlaxoSmithKline Chemistry Scholar Award. I have also taught short courses in heterocyclic chemistry at Celgene and Genentech. More recently, I was named a Fellow of the American Association for the Advancement of Science in 2012, a MacArthur Fellow in 2013, a Fellow of the Royal Society of Chemistry in 2013 (in the same year, I also won the Royal Society of Chemistry Synthetic Organic Chemistry Award), and Member of The National Academy of Sciences in 2017.

15. I have published over 200 peer-reviewed articles relating to synthetic chemistry. I either hold or have applied for five United States patents. I have

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

authored 6 book chapters and am an author of the book *The Portable Chemist's Consultant: A Survival Guide for Discovery, Process, and Radiolabeling*.

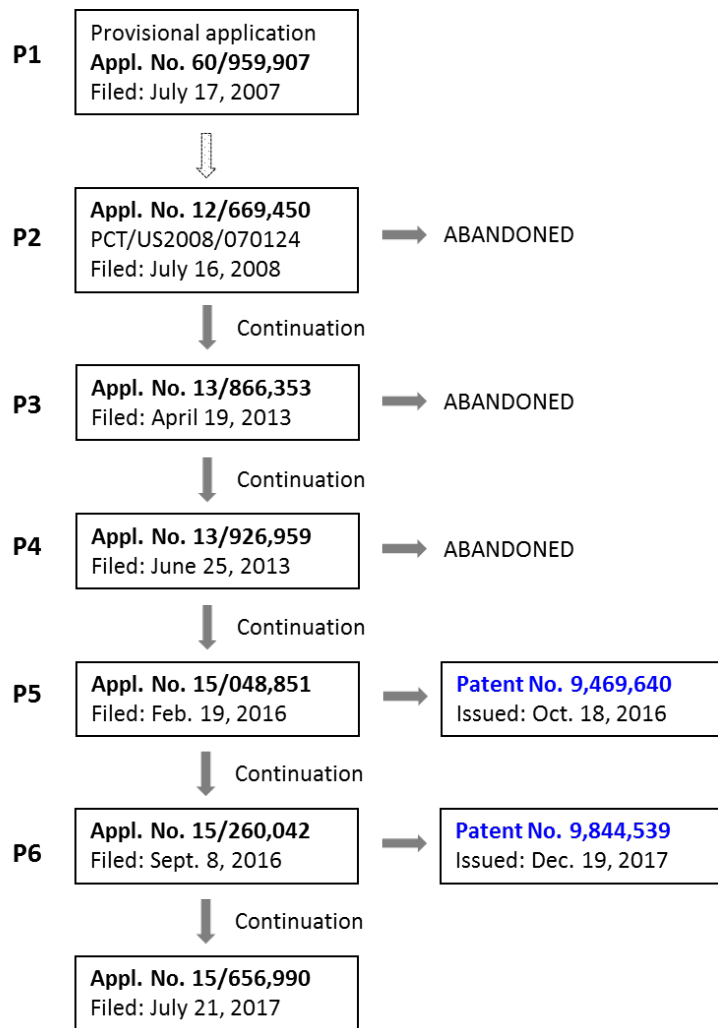
III. THE '640 PATENT

16. The '640 patent, entitled "Compound and Methods for Kinase Modulation, and Indications Therefor," issued on October 18, 2016. It is directed to "[c]ompounds active on protein kinases" "as well as methods of using such compounds to treat diseases and conditions associated with aberrant activity of protein kinases." ('640 patent, Abstract).

17. I am advised that the chain of priority of the '640 patent is shown in the Figure 1 below:

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

Figure 1 Priority Chain of '640 Patent

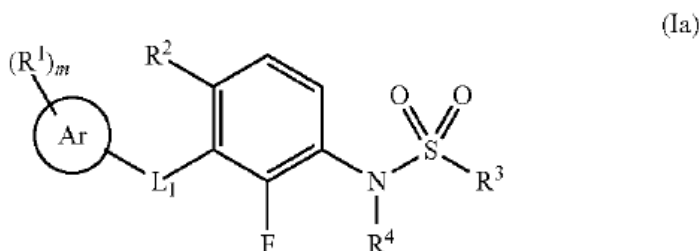


18. I am advised that the above-listed patents or patent applications have virtually identical specifications, differing only in the description of the genealogical chains of priority. Applications P2-P6 include all of the content of provisional application P1, as well as added matter that is not found in P1. Throughout this declaration, I will refer to the various applications by the numbers in the above figure (e.g., “P2” for U.S. Application No. 12/669,450).

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

19. The '640 patent has 12 claims. I am advised by counsel in this case that the Challenged Claims are claims 1, 2, 4-6, 9, 11, and 12. The Challenged Claims recite as follows:

1. A compound of formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein:

L₁ is a bond or -N(H)C(O)-;

each R¹ is optionally substituted lower alkyl or optionally substituted heteroaryl;

R² is hydrogen or halogen;

R⁴ is hydrogen;

R³ 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 R² is hydrogen.
4. The compound of claim 1, wherein R³ is optionally substituted phenyl.
5. The compound of claim 1, wherein R³ 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.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

6. The compound of claim 1, wherein R³ 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.

20. Challenged Claims 1, 2 and 4-6 are directed to compounds and can be referred to collectively as the “Challenged Compound Claims.” Claim 9 is directed to compositions including a compound of claim 1 and other material and can be referred to as the “Challenged Composition Claim.” Finally, claims 11 and 12 are directed to methods of treatment and can be referred to collectively as the “Challenged Method Claims.”

IV. PERSON OF ORDINARY SKILL IN THE ART

21. I understand that when reviewing patent claims to assess the technical subject matter described in therein, one must consider the scientific teachings of the patent specification from the viewpoint of the person of ordinary skill in the art (“POSITA”) at the time of the alleged invention.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

22. I consider myself knowledgeable about the capabilities and understandings of the POSITA in the relevant time period. I define a POSITA with respect to the '640 patent as one who 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.

V. LEGAL PRINCIPLES

A. Priority Benefit Requires Written Description and Enablement

23. In forming my opinions and conclusions, I have been informed by counsel that in order to claim the benefit of an earlier-filed priority 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. I have further been advised by counsel that 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.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

24. I have also been informed by counsel that the written description requirement of 35 U.S.C. § 112 mandates that the specification contain a written description of the invention that must clearly allow the POSITA 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 the POSITA that the inventor had possession of the claimed subject matter as of the filing date. I further understand that the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.

25. I am advised by counsel that where a claim recites a specific combination of variables, the specification must direct the POSITA to that specific combination; a general disclosure that encompasses the specific combination is not sufficient to satisfy the written description requirement. I further understand that, in the context of patent claims on chemical compounds, 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. I understand that, analogizing the disclosure to a forest (a large genus of trees), and the claim to a few trees (a sub-genus of the forest), the written description must provide “blaze

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

marks” directing the POSITA to the claimed invention out of the broader disclosure.

26. I am further informed by counsel that, when the claimed invention is a genus or subgenus, in order to show possession of the invention 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. The representative species must reflect the variance in the genus.

27. I have also been informed by counsel that the enablement requirement of 35 U.S.C. §112 mandates that the specification of a patent must teach the POSITA how to make and use the full scope of the claimed subject matter without undue experimentation. I understand that whether experimentation is undue is a conclusion reached by weighing many factual considerations, including (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.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

28. I have further been informed by counsel that 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. I further have been informed by counsel that 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.

B. Anticipation

29. I have been informed by counsel that a patent claim is invalid if it is anticipated by prior art. Specifically, I understand that 35 U.S.C. § 102 provides that “[a] person shall be entitled to a patent unless – (a) the invention was . . . patented . . . in this or a foreign country before the invention thereof by the applicant for patent, or (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, or (e) the invention was disclosed in . . . a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent.” I further understand that prior art anticipates claimed subject matter if it discloses every limitation of the claimed invention, either explicitly or inherently. I further understand that the disclosure of a species in the

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

prior art may anticipate a later-claimed genus if the species meets all of the limitations of (i.e. falls within) the genus. I am informed that, in order to anticipate, the prior art disclosure must be enabling for what it teaches.

VI. THE CHALLENGED CLAIMS ARE NOT ENTITLED TO THE BENEFIT OF P2 OR ANY EARLIER APPLICATION

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

30. It is my opinion that 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.

31. 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, and a small number of specific examples that fall within the scope of some (but not all) 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.

32. 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.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

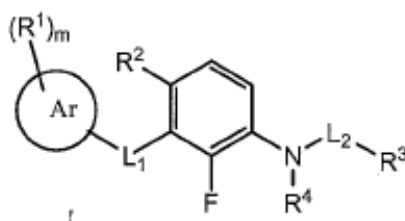
33. Nor does P2 set forth a representative number of species to support the full scope of the formulas of the Challenged Claims.

34. 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. Thus, based on my understanding of the law as given to me by counsel, none of the Challenged Claims is entitled to the benefit of the filing date of P2 or any earlier application.

1. P2 Does Not Provide Blaze Marks from Which The POSITA Would Arrive at the Claimed Genus

35. P2 discloses Formula I, which encompasses a broad genus of compounds. P2 provides the following disclosure of Formula I:

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



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

Ar is optionally substituted heteroaryl;

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

R¹ 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, -NO₂, -CN, -O-R⁵, -N(R⁵)-R⁶, -C(X)-N(R⁵)-R⁶, -C(X)-R⁷, -S(O)₂-N(R⁵)-R⁶, -S(O)_n-R⁷, -O-C(X)-R⁷, -C(X)-O-R⁵, -C(NH)-N(R⁸)-R⁹, -N(R⁵)-C(X)-R⁷, -N(R⁵)-S(O)₂-R⁷, -N(R⁵)-C(X)-N(R⁵)-R⁶, and -N(R⁵)-S(O)₂-N(R⁵)-R⁶;

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

n is 0, 1 or 2;

R² is hydrogen, lower alkyl or halogen;

L₂ is selected from the group consisting of -S(O)₂-, -C(X)-, -C(X)-N(R¹⁰)-, and -S(O)₂-N(R¹⁰)-;

R³ is optionally substituted lower alkyl, optionally substituted C₃₋₆ cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

L₁ is selected from the group consisting of a bond, -N(R¹¹)-, -O-, -S-, -C(X)-, -C(R¹²R¹³)-X-, -X-C(R¹²R¹³)-, -C(R¹²R¹³)-N(R¹¹)-, -N(R¹¹)-C(R¹²R¹³)-, -O-C(X)-, -C(X)-O-, -C(X)-N(R¹¹)-, -N(R¹¹)-C(X)-, -S(O)-, -S(O)₂-, -S(O)₂-N(R¹¹)-, -N(R¹¹)-S(O)₂-, -C(NH)-N(R¹¹)-, -N(R¹¹)-C(NH)-, -N(R¹¹)-C(X)-N(R¹¹)-, and -N(R¹¹)-S(O)₂-N(R¹¹)-;

X is O or S;

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

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, -NH₂, 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 -NR¹⁴R¹⁵;

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 C₃₋₆ alkenyl, optionally substituted C₃₋₆ 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 C₃₋₆ alkenyl, optionally substituted C₃₋₆ 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,

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

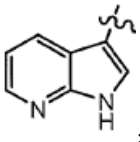
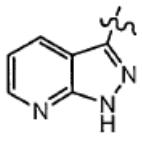
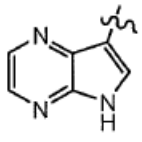
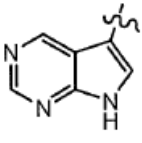
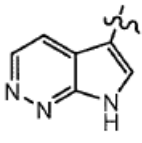

lower alkylthio, mono-alkylamino, di-alkylamino, and -NR¹⁴R¹⁵, wherein the alkyl chain(s) of lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or

R¹² and R¹³ 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

R¹⁴ and R¹⁵ 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, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio, provided, however, that when L₁ is a bond, -NR¹¹-, -O-, -S-, -C(X)-, -S(O)-, or -S(O)₂, Ar is not 1H-pyrrolo[2,3-b]pyridine-3-yl,

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

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 L₁.

P2 at 1-3.

36. P2 expressly defines certain of the terms used in the options for the Formula I variables themselves. *See, e.g.*, P2 at 47-61. As an example, Formula I's definition of R¹ 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

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

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, -NH₂, -NO₂, -CN, -C(O)-OH, -C(S)-OH, -C(O)-NH₂, -C(S)-NH₂, -S(O)₂-NH₂, -N(H)-C(O)-NH₂, -N(H)-C(S)-NH₂, -N(H)-S(O)₂-NH₂, -C(NH)-NH₂, -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)-NH₂, -N(R^o)-C(S)-NH₂, -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-NH₂, -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 bicyclic 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, -NH₂, -NO₂, -CN, -C(O)-OH, -C(S)-OH, -C(O)-NH₂, -C(S)-NH₂, -S(O)₂-NH₂, -N(H)-C(O)-NH₂,

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

-N(H)-C(S)-NH₂, -N(H)-S(O)₂-NH₂, -C(NH)-NH₂, -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)-NH₂,
-N(R^o)-C(S)-NH₂, -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-NH₂,
-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.

37. As reflected in the passages reproduced above, P2 encompasses an enormous number of possible R¹ groups that meet the definition of “lower alkyl” and “heteroaryl.” Moreover, there can be multiple different R¹ groups, and both the lower alkyl and heteroaryl groups can be optionally substituted with a wide variety of substituents. Thus, the definitions for “lower alkyl” and “heteroaryl” alone cover an enormous number – indeed, trillions – of different options.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

38. I note that 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.

39. 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 $-\text{SO}_2-$

Formula Ib: L_2 is $-\text{SO}_2-$, L_1 is $-\text{AN}(\text{R}^{11})-$, wherein A is $-\text{C}(\text{O})-$ or $-\text{C}(\text{R}^{12}\text{R}^{13})-$

Formula Ic: L_2 is $-\text{SO}_2-$, L_1 is a bond

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

Formula Ie: L_1 is a bond

Formula If: L_2 is $-\text{SO}_2-$, L_1 is $-\text{C}(\text{X})-\text{N}(\text{R}^{11})-$, $-\text{C}(\text{R}^{12}\text{R}^{13})-\text{X}-$, $-\text{X}-\text{C}(\text{R}^{12}\text{R}^{13})-$, $-\text{C}(\text{R}^{12}\text{R}^{13})-\text{N}(\text{R}^{11})-$, or $-\text{N}(\text{R}^{11})-\text{C}(\text{R}^{12}\text{R}^{13})-$

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

Formula Ih: L_2 is $-\text{SO}_2-$, L_1 is $-\text{NR}^{11}\text{A}-$, wherein A is $-\text{C}(\text{O})-$ or $-\text{C}(\text{R}^{12}\text{R}^{13})-$

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

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.

40. 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.* at 3-13.

41. For Formulas Ia-Ij, P2 discusses “some embodiments” with preferences for Ar, R^1 , R^2 , R^3 , R^4 , R^{11} , R^{12} and R^{13} . *Id.* at 3-21.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

42. 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 allegedly be synthesized. P2 at 74-79.

43. I note 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 . P2 does provide that “preferably any R^1 is independently R^{16} .” P2 at 15-17. However, R^{16} also encompasses an enormous number of compounds:

R^{16} at each occurrence is independently selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)-OH, -S(O)₂-NH₂, -C(O)-NH₂, -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, -NH₂, -CN, -NO₂, -C(O)-OH, -S(O)₂-NH₂, -C(O)-NH₂, -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} ,

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

-C(O)-O-R¹⁸, -C(O)-N(R¹⁹)-R¹⁸, -S(O)₂-N(R¹⁹)-R¹⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

P2 at 15-16.

44. P2 further narrows the preferences for R¹⁶, but even the narrowed list encompasses an enormous number of compounds:

any R¹ is bound to Ar at any available NH or CH, preferably any R¹ is independently R¹⁶, as defined in paragraph [0040], preferably wherein R¹⁶ at each occurrence is independently selected from the group consisting of halogen, -OH, -NH₂, -CN, lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and -NR²⁰R²¹, 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, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, or cycloalkylamino[.]

P2 at 17. (The same text is repeated for different formulas at pages 18, 19, and 20). Accordingly, even these “narrowed” formulas and “embodiments” each encompasses billions of compounds.

45. Within the extremely broad disclosures of the subgenera in P2, the specific combinations of variables set forth in the formulas of the Challenged

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

Claims are never disclosed, i.e., none of the subgenera in P2 corresponds to the subgenera of any of the Challenged Claims, and accordingly Formulas Ia-Ij do not provide blaze marks pointing one of ordinary skill to the formulas of the Challenged Claims.

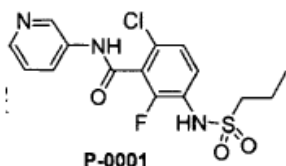
46. The examples included in P2 do not overcome this deficiency. Although P2 encompasses an enormous number of compounds, P2 specifically describes only 120 different compounds (P-0001 to P-0120), along with methods of their synthesis. P2 at 21-27, 79-110. None of compounds P-0001 to P-0120 falls within the scope of Compound Claims 2 and 4-6. 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).¹

47. The structures of P-0001, P-0007, and P-0012 are shown below:

¹ These compounds also fall within the scope of claims 9, 11 and 12 (which all depend from claim 1 of the '640 patent).

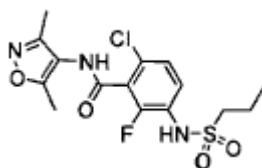
***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

P-0001



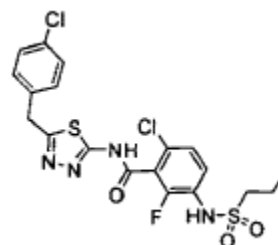
P2 at 91.

P-0007



P2 at 90.

P-0012



P2 at 91.

48. 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 for the lack of diversity with respect to the claimed variables. 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. But R^1 in each of the three species is methyl or chlorophenylsubstituted methyl. In addition, 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. 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. But R^3 in each of the three species is a propyl group. 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 $-N(H)C(O)-$.

49. This lack of diversity is reflected in the chart below:

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

Group	Claimed Genus	P-0001	P-0007	P-0012
m	“0, 1, 2, 3, 4, or 5”	0	2	1
R¹	“optionally substituted lower alkyl or optionally substituted heteroaryl”	None	methyl, methyl	chlorophenyl- substituted methyl
R²	“hydrogen or halogen”	chloro	chloro	chloro
R³	“optionally substituted lower alkyl or optionally substituted aryl”	propyl	propyl	propyl
L₁	“a bond or –N(H)C(O)–”	N(H)C(O)	N(H)C(O)	N(H)C(O)

50. Put another way, although P-0001, P-0007 and P-0012 fall within the scope of claim 1, they do not have many of the variables that are included within the scope of the Challenged Claims. For example, none has L₁ as a bond; R¹ as heteroaryl or substituted heteroaryl; R² as hydrogen; R³ as substituted lower alkyl, aryl or substituted aryl; or *m* as 3, 4, or 5. Thus, there are no representative species that fall within the scope of the Challenged Claims and have any of these particular aspects of the claims (L₁ as a bond; R¹ as heteroaryl or substituted heteroaryl; R² as hydrogen; R³ as substituted lower alkyl, aryl or substituted aryl; or *m* as 3, 4, or 5).

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

51. Therefore, it is my opinion that these examples do not constitute a sufficient number of representative species to support the breadth of the Challenged Claims.

2. P2 Specifically Fails to Provide Written Description for the Claimed Genus With Regard to the L₁ Substituent.

52. Each of the Challenged Claims provides that L₁ is either “a bond or –N(H)C(O)–.” It is my opinion that P2 does not guide one of ordinary skill to focus on either of these two options for L₁, particularly in combination with each of the other specific substituents in the Challenged Claims, including R¹.

53. The generic formulas Ia through Ij provide lists of options for L₁ that include both “a bond” and “–N(H)C(O)–,” but none describes a subgenus where L₁ is limited to “a bond or –N(H)C(O)–.” For example, P2 provides that in Formula I, L₁ is selected from a group consisting of 21 options (many of which contain sub-options):

L₁ is selected from the group consisting of a bond, –N(R¹¹)–, –O–, –S–, –C(X)–, –C(R¹²R¹³)–X–, –X–C(R¹²R¹³)–, –C(R¹²R¹³)–N(R¹¹)–, –N(R¹¹)–C(R¹²R¹³)–, –O–C(X)–, –C(X)–O–, –C(X)–N(R¹¹)–, –N(R¹¹)–C(X)–, –S(O)–, –S(O)₂–, –S(O)₂–N(R¹¹)–, –N(R¹¹)–S(O)₂–, –C(NH)–N(R¹¹)–, –N(R¹¹)–C(NH)–, –N(R¹¹)–C(X)–N(R¹¹)–, and –N(R¹¹)–S(O)₂–N(R¹¹)–;

P2 at 2.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

54. 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)²; 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.

55. 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 $-N(H)C(O)-$ ”. P2 at 4-21.

56. 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 on the compound to the specific options in the Challenged Claims.

57. P2’s prophetic schemes 1-3 similarly do not support a preference for L_1 as “a bond or $-N(H)C(O)-$.” Prophetic scheme 1 discloses the synthesis of compounds of Formula Ib or Id where L_1 is $-C(O)N(R^{11})-$. (P2 at 74-75). Prophetic scheme 2 discloses the synthesis of compounds of Formula 1c or 1e

² In Formulas Ib and Id, the A of $-AN(R^{11})-$ is attached to the inner phenyl ring; in formulas Ih and Ii, the A is attached to the aryl ring (Ar).

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

where L_1 is a bond.³ (P2 at pages 75-77). And prophetic scheme 3 discloses the synthesis of compounds of Formula I where L_1 is $-\text{CH}_2\text{NR}^{11}-$ (P2 at 77-79).

58. 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. P2 at 74-79.

59. Thus, none of the prophetic schemes provides any blaze marks directing the POSITA 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.

60. P2's synthetic schemes 4-16, which were actually conducted, produce compounds where L_1 is $-\text{N(H)C(O)}-$ (Schemes 4-10 and 14-16, P2 at 79-92, 98-101), $-\text{NHCH}_2-$ (Schemes 11-12, P2 at 92-95), and $-\text{OCH}_2-$ (Scheme 13, P2 at pages 95-98). These 16 schemes set forth the synthesis of the 120 disclosed compounds (P-0001 through P-0120). P2 at 79-110. Of these 120 compounds,

³ Scheme 2 discloses a reaction known as a Suzuki coupling to prepare the compounds of Formulas Ia and Ic, where L_1 is a bond. As discussed below, this disclosure is non-enabling with respect to a large proportion of the claimed genus.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

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 $-C(R^{12}R^{13})X-$. None has L_1 as a bond.

61. The activity data reported in P2 similarly fails to express a preference for L_1 being “a bond or $-N(H)C(O)-$.”

62. P2 reports in Tables 2a-2p representative compounds with activity toward different kinases. P2 at 110-12. Tables 2a-2p, taken together, list 20 compounds: P-0001, P-0002, P-0004, P-0005, P-0006, P-0008, P-0009, P-0010, P-0011, P-0012, P-0013, P-0015, P-0016, P-0017, P-0018, P-0020, P-0021, P-0025, P-0026, and P-0027. 16 of the 20 compounds included in Tables 2a-2p (P-0001, P-0002, P-0004, P-0005, P-0006, P-0008, P-0009, P-0010, P-0011, P-0012, P-0013, P-0015, P-0016, P-0017, P-0018 and P-0027) have L_1 as $-N(H)C(O)-$, three have L_1 as $-NHCH_2-$ (P-0021, P-0022 and P-0025), and one has L_1 as $-OCH_2-$ (P-0026). None has a L_1 as a bond.

63. 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. Similarly, P2 does not provide a preference for a subgenus with this combination of L_1 groups. If anything, P2 provides a preference for a subgenus where L_1 is limited to $-N(H)C(O)-$, as this is the most common substituent in the synthetic examples and compounds reported to have

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

activity. 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. 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.

64. 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.

65. As a result, it is my opinion that the Challenged Claims lack written description support as required by 35 U.S.C. § 112, 1st paragraph, and accordingly, are not entitled to benefit of P2 or any earlier application under 35 U.S.C. § 120.

66. My opinion that the Challenged Claims are not adequately described in the specification of P2 is further confirmed by the U.S. Patent Examiner's comments during prosecution of applications P3 and P4.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

67. For example, during prosecution of P3, the Examiner rejected claims to compounds where L₁ 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).

68. 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).

69. The Examiner also made clear that by filing P3 with claims where L₁ was a bond, the applicants had improperly added new matter that was not in the prior specifications, i.e., P1 and P2.

70. 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).

71. Rather than comply with the Examiner’s request, the applicants abandoned the application. (Ex. 1007).

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

72. Similar comments about the lack of written description for compounds where L₁ is a bond were made by the Examiner during prosecution of P4:

A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. All disclosed compounds have a linker moiety between the phenyl and the Ar. i.e., L1 in formula I is not a bond. The [P4] application provide[s] no convincing evidence, or rationale that the biological activity of disclosed compounds would have been retained if the L1 in formula I is a bond instead of those linking moieties.

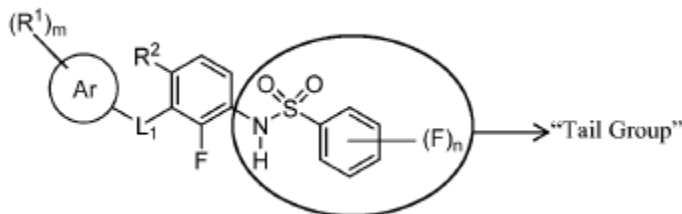
(Ex. 1008 at 6).

73. In response, the applicants amended the then-pending claims, including by limiting R³ 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).

74. 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. (*Id.* at 6-8 (citing Liu et al., *Nature Chem.*

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

Bio. 2(7):358-364 (2006) at 360; Tsai et al., *PNAS* 105(8):3041-46 (2008) at 3043 (citing Wan et al., *Cell* 111(6):855-67 (2004))).



75. 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.

76. The Examiner responded to these arguments by maintaining the § 112 written description rejection and maintaining that “[t]he application provide[s] no convincing evidence or rationale that the biological activity of disclosed compounds would have been retained if the L_1 in Formula I is a bond instead of [the] linking moieties.” (Ex. 1010 at 1-6).

77. 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

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

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 substituent rather than the L₁ substituent. (*Id.* at 9).

78. 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.

79. On February 19, 2016, the applicants filed a “Statement of Substance of Interview” indicating that compounds where L₁ 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 L₁ substituents for compounds of general Formulas I or Ia ([0007],

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.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

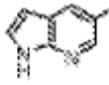
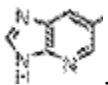
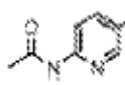
[0009]), or Ie [0021], or a general scheme for synthesis of these compounds (Scheme 2).

80. After the interview, the applicants abandoned the P4 application. (Ex. 1013).

81. 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. 1014 at 5).

82. The Examiner again rejected these claims for lack of written description support, stating:

All disclosed compounds have a linker moiety between the phenyl and the

Ar. Wherein the Ar is , , or . [sic] The application provide[s] no convincing evidence, or rationale that the biological activity of disclosed compounds would have been retained if the L_1 and Ar in formula I vary with the scope herein defined.

(Ex. 1015 at 2, 5-6).

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

83. After an interview with the Examiner, the applicants responded by making various amendments to the claims, including narrowing the scope of L₁ to a bond or –N(H)C(O)–. (Ex. 1016 at 2).

84. 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 applicants stated that support for L₁ as a bond “can be found throughout the specification, including but not limited to paragraphs [0007], [0009], [0011] and [0012]” as well as “Scheme 2 [which] provides exemplary methods of making compounds where L₁ is a bond.” (*Id.* at 6).

85. The Examiner indicated that the amendments were sufficient to overcome the rejections, but never explained why. (Ex. 1017 at 2).

86. Thus, while the Examiner ultimately did allow claims where L₁ is a bond, no meaningful reasons were provided to explain the change in position or basis for this allowance.

87. Even if there was support for L₁ as a bond, there are no blaze marks that would lead the POSITA to the claimed options for L₁: “a bond or –N(H)C(O)–.” Moreover, even if there was support for L₁ as a bond, it is my understanding from counsel that that narrow issue is not the proper question when assessing

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

written description. I am advised by counsel that 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) that appears in the Challenged Claims, was disclosed in P2. As discussed herein, that disclosure was not made.

3. P2 Specifically Fails to Provide Written Description for the Claimed Genus With Regard to the R^1 Substituent.

88. Each of the Challenged Claims provides that each R^1 is “optionally substituted lower alkyl or optionally substituted heteroaryl”. (Claims 1, 2, 4-6, 9-12). As noted above, the definitions of the terms “lower alkyl” and “heteroaryl” (the options for R^1) cover an enormous number – indeed, millions of millions – of different options. P2 fails to set forth a description of the specific options for R^1 that are recited in the Challenged Claims.

89. The generic formulas Ia through Ij provide lists of options for R^1 that include both “optionally substituted lower alkyl” and “optionally substituted heteroaryl” as two of many options. However, P2 does not describe a subgenus limited to the specific combination of “optionally substituted lower alkyl or optionally substituted heteroaryl.”

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

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

R¹ 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, -NO₂, -CN, -O-R⁵, -N(R⁵)-R⁶, -C(X)-N(R⁵)-R⁶, -C(X)-R⁷, -S(O)₂-N(R⁵)-R⁶, -S(O)_n-R⁷, -O-C(X)-R⁷, -C(X)-O-R⁵, -C(NH)-N(R⁸)-R⁹, -N(R⁵)-C(X)-R⁷, -N(R⁵)-S(O)₂-R⁷, -N(R⁵)-C(X)-N(R⁵)-R⁶, and -N(R⁵)-S(O)₂-N(R⁵)-R⁶;

(P2 at 2 (Formula I), 3-12 (Formulas Ia-Ij, which provide that R¹ is as defined for Formula I)).

91. P2 states that compounds of Formula I can have 0 to 5 R¹ groups, because *m*, i.e., the number of R¹ groups, can be 0, 1, 2, 3, 4 or 5. (P2 at 2).⁵

⁵ None of the applications, including P2, is enabling with respect to compounds where *m*=5 because it is impossible for there to be five R¹ groups. In particular, in a six-membered Ar group in which one carbon atom is attached to L₁, five atoms remain, but only four can carry R¹ groups because the required nitrogen atom does not generally form additional bonds outside the heterocycle. A five-membered Ar group, by the same token, can carry only three R¹ groups.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

92. The only specific discussion of R¹ 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 through Ie (P1) or Formulas I and Ia through Ij (P2). In connection with these embodiments, P2 states:

any R¹ is bound to Ar at any available NH or CH, preferably any R¹ is independently R¹⁶, wherein R¹⁶ at each occurrence is independently selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)-OH, -S(O)₂-NH₂, -C(O)-NH₂, -O-R¹⁷, -S-R¹⁷, -N(R¹⁹)-R¹⁷, -N(R¹⁹)-C(O)-R¹⁷, -N(R¹⁹)-S(O)₂-R¹⁷, -S(O)₂-R¹⁷, -C(O)-R¹⁷, -C(O)-O-R¹⁷, -C(O)-N(R¹⁹)-R¹⁷, -S(O)₂-N(R¹⁹)-R¹⁷, 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 R¹⁶**, or as substituents of lower alkyl, **are optionally substituted** with one or more substituents selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)-OH, -S(O)₂-NH₂, -C(O)-NH₂, -O-R¹⁸, -S-R¹⁸, -N(R¹⁹)-R¹⁸, -N(R¹⁹)-C(O)-R¹⁸, -N(R¹⁹)-S(O)₂-R¹⁸, -S(O)₂-R¹⁸, -C(O)-R¹⁸, -C(O)-O-R¹⁸, -C(O)-N(R¹⁹)-R¹⁸, -S(O)₂-N(R¹⁹)-R¹⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

(P2 at 15-16 (emphasis added)).

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

93. Each of R¹⁷, R¹⁸ and R¹⁹ is also defined. (P2 at 16). Like the Formula I definition of R¹, R¹⁶ includes both optionally substituted lower alkyl and optionally substituted heteroaryl amongst a long list of options.

94. In subsequent embodiments discussed in the specification, R¹⁶ is further stated to be preferably selected from the group consisting of:

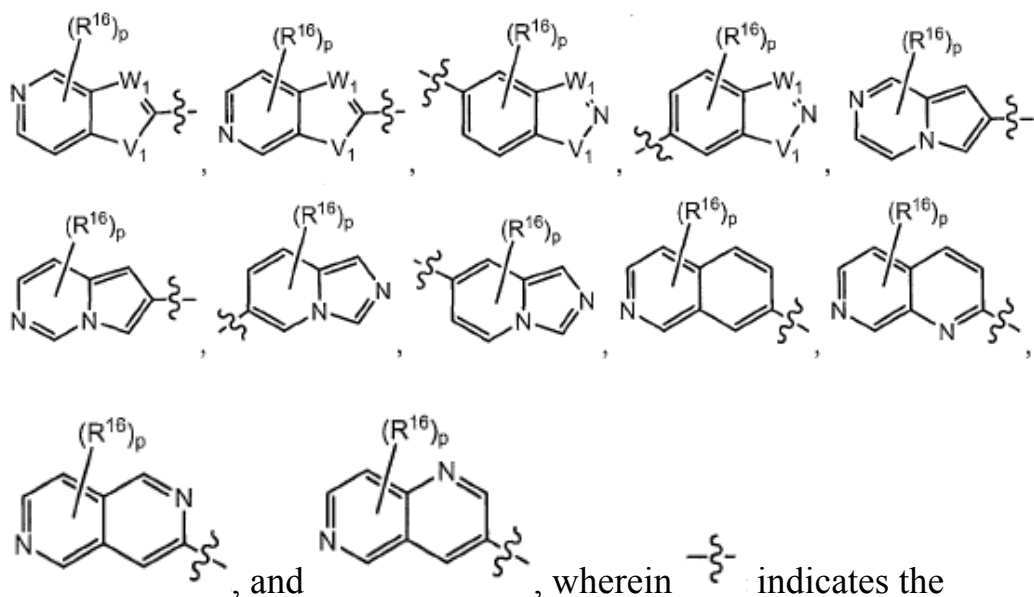
halogen, -OH, -NH₂, -CN, **lower alkyl**, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and-NR²⁰R²¹, **wherein lower alkyl** and the alkyl chain(s) of lower alkoxy, lower alkylthio, mono-alkylamino or di-alkylamino **are optionally substituted** with one or more, preferably 1, 2, or 3 substituents selected from the group consisting of fluoro, -OH, -NH₂, 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 R¹ includes optionally substituted lower alkyl groups among other options; however it does not include heteroaryl or optionally substituted heteroaryl.

95. There is also one passage in P2 that purports to set forth a list of optionally substituted heteroaryl R¹ groups to use in connection with compounds of Formulas Ic or Ie:

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

[0045] In some embodiments of compounds of Formula 1e or 1e, further to any of the above embodiments of Formula 1e or 1e, R¹ is selected from the group consisting of



attachment point of the Ar ring to the phenyl ring of Formula 1c or 1e, and wherein:

W₁ is N or CH;

V₁ is O, S, or NH;

p is 0, 1, 2 or 3; and

R¹⁶, substituting at any available CH or NH, is as defined in

paragraph **[0040]**, preferably wherein R¹⁶ at each occurrence is independently selected from the group consisting of halogen, -OH, -NH₂, -CN, lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and -NR²⁰R²¹, wherein lower alkyl and the alkyl chain(s) of lower alkoxy, lower alkylthio, monoalkylamino or di-alkylamino are optionally substituted with one or more, preferably 1, 2, or 3 substituents selected

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, monoalkylamino, di-alkylamino, or cycloalkylamino, wherein R²⁰ and R²¹ are as defined in paragraph [0041].

(P2 at 19-20). However, it appears that there is a typographical error and the reference to R¹ should instead be to Ar for at least three reasons: (i) the preceding paragraphs disclose embodiments that have certain specified Ar groups; (ii) the list of potential options is limited to heterocyclic aryl (i.e., Ar) groups; and (iii) each of the heterocyclic aryl groups has an optional R¹⁶ substituent, which as just discussed, is stated to be as defined as in paragraph [0040] of P2, and that paragraph provides that “any R¹ is independently R¹⁶.”

96. In the prophetic synthetic schemes, R¹ is defined as in Formula I, and therefore each R¹ is selected from a list of 23 options (many of which include sub-options). (P2 at 74-79). R¹ is not limited to “optionally substituted lower alkyl or optionally substituted heteroaryl.”

97. Of the 120 compounds generated using P2’s synthetic schemes 4-16, only three have an R¹ that is “optionally substituted lower alkyl” (P-0007 and P-

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

0019,⁶ which both have a methyl, i.e., a 1-carbon lower alkyl; and P-0012, which has an aryl-substituted methyl, i.e., a substituted 1-carbon lower alkyl). (P2 at 90, 92). None of the 120 compounds has an R¹ that is “optionally substituted heteroaryl.”

98. Reported activity data also fails to support a preference for R¹ as “optionally substituted alkyl or optionally substituted heteroaryl.” P2 reports in Tables 2a-2p representative compounds with activity toward different kinases. P2 at 110-12. Of the compounds included in Tables 2a-2p (P-0001, P-0002, P-0004, P-0005, P-0006, P-0008, P-0009, P-00010, P-0011, P-0012, P-0013, P-0015, P-0016, P-0017, P-0018, P-0020, P-0021, P-0025, P-0026, P-0027), only one (P-0012) has an R¹ that is “optionally substituted lower alkyl.” None has “optionally substituted heteroaryl.”⁷ Therefore, the compounds reported to have activity in P2 do not support the selection of the claimed R¹ groups.

⁶ P-0019 falls outside the scope of the Challenged Claims as it does not have L₁ as a bond or –N(H)C(O)–.

⁷ Seven of the compounds included in P2’s Tables 2a-2p have no R¹ group (P-0001, P-0013, P-0018, P-0021, P-0025, P-0026, and P-0027).

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

99. In summary, P2 does not describe a subgenus where R¹ 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. Similarly, P2 does not set forth a preference for these specific R¹ groups, or a subgenus that is limited to these R¹ groups.

100. P2 also fails to disclose a sufficient number of representative species to support the claimed R¹ groups. Although P2 encompasses an enormous number of compounds (a number so large it is effectively incalculable), P2 describes three species that have an R¹ that is “optionally substituted lower alkyl” (P-0007, P-0012, and P-0019), and two of those examples (P-0007 and P-0012) fall within the scope of claim 1. Not a single example falls within the scope of the remaining Challenged Compound Claims. And not a single example has an R¹ that is “optionally substituted heteroaryl.” Additionally, only one of the compounds that were reported to have activity in the assays reported in P2 has an R¹ that includes an optionally substituted lower alkyl, and none has an optionally substituted heteroaryl.

101. Based on the foregoing, a person of ordinary skill in the art would conclude that as of the filing date of P2, the applicants did not possess the

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

subgenera of the Challenged Claims. As a result, the Challenged Claims are not entitled to the benefit of P2 or any earlier application under 35 U.S.C. § 120.

4. P2 Also Fails to Provide Written Description for the Challenged Composition and Method Claims.

102. Challenged Composition Claim 9 and Method Claims 11 and 12 are each dependent claims that depend from 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, 1st paragraph, and are not entitled to the benefit of P1 or P2 under 35 U.S.C. § 120.

103. 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. These three indications appear in a laundry list of diseases and conditions that can be treated with any of the extremely large number of compounds of Formula I, including head injury, heart failure, dementia, diabetes, and asthma. (*See, e.g.*, P2 at 34-47).

104. Absent any data suggesting that compounds with L₁ 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. Thus, these claims lack written description support for this additional reason, and are not entitled to the benefit of P1 or P2 under 35 U.S.C. § 120.

B. P2 Fails to Enable the POSITA to Make and Use the Full Scope of the Challenged Claims Without Undue Experimentation

105. As described above, the Challenged Claims are directed to subgenera of compounds with individual variables L_1 , R^1 , R^2 , R^3 , R^4 , m , and Ar, which are so broad as to be effectively incalculable. Each of the subgenera provides that L_1 is either a bond or $-N(H)C(O)-$. As described below, it is my opinion that P2 does not enable a POSITA 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.

106. Moreover, as further discussed below, it is also my opinion that P2 fails to disclose how to **use** such compounds where L_1 is a bond, as P2 provides no data for any compounds where L_1 is a bond to show activity on kinase proteins and a POSITA would not have believed such compounds where L_1 is a bond would have such activity. Accordingly, it is my opinion that P2 does not meet the enablement requirement 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 for this reason as well.

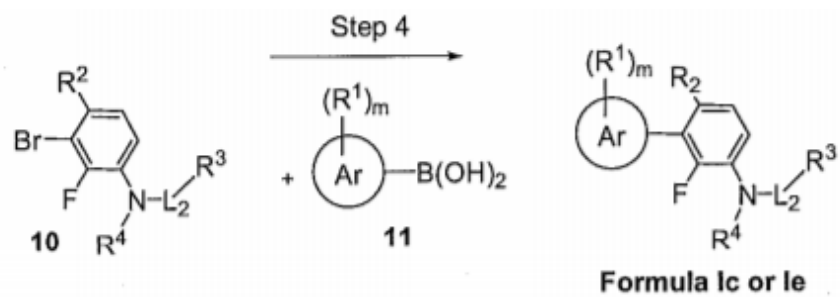
Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

1. P2 Does Not Enable a POSITA to Make the Full Scope of Claimed Compounds for Which L₁ is a Bond.

107. P2 provides virtually no direction or guidance to teach a skilled person how to make the *trillions* of claimed compounds wherein L₁ is a bond. P2 does not provide a single example of a compound wherein L₁ is a bond. All 120 of the examples in the specification of P2 have a chemical moiety such as an amide, reverse amide, -CH₂NH-, or -CH₂O-, at position L₁. (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 L₁ position.

108. Example 2 provides a prophetic general scheme for making theoretical compounds according to Formulae Ic and Ie, for which L₁ is a bond (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 L₁ is a bond.

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



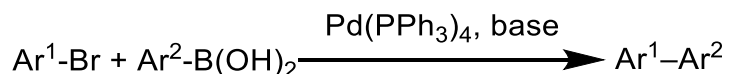
***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

(P2 at 76). P2 describes “Step 4” in general terms:

A mixture of compound 10, an appropriate boronic acid 11 (Ar, m and R¹ 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 1c (L₂ is S(O)₂) or 1d [sic] is purified by chromatography.

(*Id.* at 77).

110. The reaction described to form the L₁ bond in Step 4 is known as a Suzuki coupling.⁸ The general conditions described in P2 reflect the original conditions described by Suzuki in 1978 for the general reaction scheme shown below:



⁸ Some references refer to the reaction as a “Suzuki-Miyaura coupling.”

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

111. Suzuki reactions are widely used in the pharmaceutical industry. 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 originally described in 1978 and as taught in Step 4 of P2 – to form compounds comprising large portions of the claimed genera where L_1 is a bond.

112. Much of this difficulty stems from the fact that Suzuki reactions were originally developed to link aryl, as opposed to heteroaryl, moieties. 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. Many heteroaryl moieties described by the claims remain difficult or impossible to use in Suzuki reactions even to this day.

113. 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). Martin at 1465.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

114. 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. Düfert at 12877.

115. 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 R¹ groups in compound 11) or bromine (i.e., one F and one R² group in compound 10) moiety. Those substituents create steric hindrance which would inhibit the cross-coupling. Martin at 1464.

116. 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. 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. *See* 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. Jedinák at 157.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

117. 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. *See* Elizabeth Tyrrell and Phillip Brookes, “The Synthesis and Applications of Heterocyclic Boronic Acids,” 2003(4) Synthesis 469-483, 469 (“Despite their synthetic utility and known biological activities heterocyclic boronic acids feature less frequently often due to difficulties in their synthesis.”). The disclosure in P2 does not teach a POSITA how to obtain the requisite boronic acid starting materials. P2 is completely silent about the availability of compound 11 and does not describe any method of preparing it.

118. 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. 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 R¹ 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.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

119. P2 provides no information on the availability of compound 11 and does not describe any method of preparing it. 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. 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. Most remain commercially unavailable even to this day. 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. Indeed, 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.

120. 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. P2 does not provide any useful guidance in this regard.

121. For example, 4-thiazolyl boronic acids are well-documented to fail in Suzuki reactions. *See* Hämmerle at 8052. Such boronic acids are very unstable

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

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. See Paul A. Cox et al., “Protodeboronation of heteroaromatic, vinyl and cyclopropyl boronic acids: pH-rate profiles, auto-catalysis and disproportionation,” 138(29) *J. Am. Chem. Soc.* 9145-57, 9152 (2016) (“Thiazolyl and pyrazolyl boronic acids . . . also undergo rapid protodeboronation.”). The very high likelihood of failure affects all 4-thiazolyl boronic acids, including trillions of possible R¹ combinations falling within the scope of the Challenged Claims.

122. 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. 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. Suzuki Nobel Lecture at 6734; Li and Gribble at, *e.g.*, 7-10, 352-54, 388-89, 414-17. Certainly, 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 R¹, R², and Ar moieties.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

123. 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. Based on teachings in the art concerning Suzuki coupling reactions, a POSITA reading the specification would not expect those conditions to be effective to make the claimed compounds. Moreover, P2 provides no information guiding a POSITA on any other particular reaction conditions that would be effective for performing the Suzuki reaction to obtain the claimed compounds.

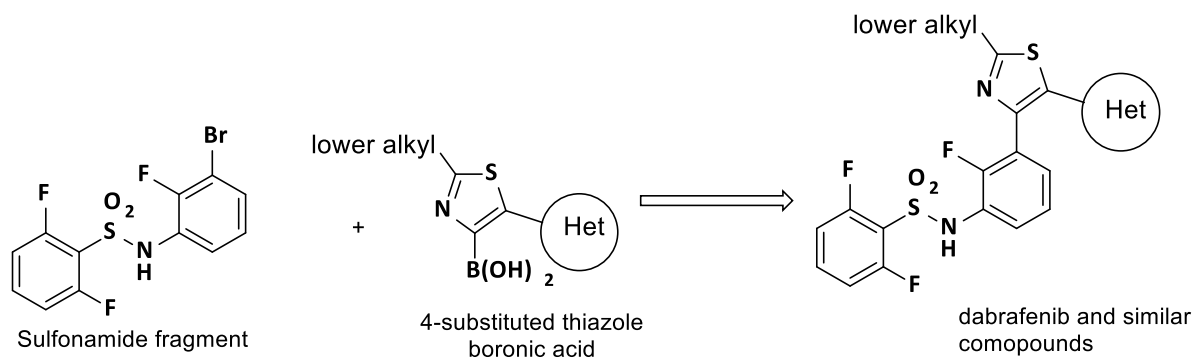
124. For example, the palladium catalyst described in P2 is the most primitive catalyst available for running Suzuki reactions. It has very low reactivity, and would be very unlikely to successfully catalyze a Suzuki reaction to generate the claimed compounds, which have nitrogen-containing heteroaryl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

125. 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. 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.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

126. Finally, depending on the Ar and R¹ 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.

127. 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. Step 4 of Example 2, specified for the formation of dabrafenib and similar compounds, is shown below:



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

128. 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 L₁ in dabrafenib. '185 patent at Scheme 1 (col. 69-70). There are at least three reasons why it would be nearly impossible to perform this step using a Suzuki reaction.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

129. First, thiazole-based boronic acid reagents are extremely difficult to prepare and are well-documented to fail in Suzuki reactions. 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.*

130. As noted, in the specific case of the 4-thiazolyl boronic acid shown above, the heteroaryl R¹ group increases the likelihood of protodeboronation and therefore makes the likelihood that the Suzuki coupling would fail even higher. This particular group affects the Suzuki reaction both because of its *ortho*- position relative to the boronic acid and because of its electrochemical properties. Many other potential R¹ groups share similar electrochemical properties that increase the likelihood of the Suzuki coupling's failure, and *any* R¹ group in the *ortho*- position increases the difficulty of forming the boronic acid and using it in the Suzuki coupling.

131. Second, the sulfonamide fragment is difficult or impossible to use in a Suzuki coupling because *ortho*-fluoro arenes⁹ bearing an acidic substituent are problematic aryl bromide substrates for Suzuki coupling. The *ortho*-fluoro moiety

⁹ As used here, “*ortho*” is relative to the bromine substituent of the sulfonamide fragment.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

prescribed by the Challenged Claims increases the likelihood of failure of the Suzuki coupling. Although dabrafenib has hydrogen at the R² position, sulfonamide fragments having an additional halogen in the second *ortho*- position (i.e. the R² position) would be even more difficult to use in the Suzuki coupling.

132. 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.¹⁰ 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.

133. Third, as noted, 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. 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

¹⁰ In addition to the steric hindrance of a second halogen at the R² position, a strongly electrophilic halogen like fluorine would increase the acidity of the sulfonamide and magnify the difficulty it presents for the Suzuki reaction.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

period. 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 R¹, R², and Ar moieties. Finally, depending on the Ar and R¹ 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.

134. Although I have described the problems with using the Suzuki coupling with respect to 4-thiazolyl boronic acids, many other kinds of heteroaryl rings that meet the Challenged Claims' criteria for Ar would also pose great difficulty in both forming a boronic acid and using it in the Suzuki coupling. *See, e.g.,* Kinzel at Abstract. Moreover, the enormous diversity permitted at the R¹ position, the potential for a halogen at the R² 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.

135. 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 R¹ and R² positions). This trial-and-error process would be

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

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. And for many such compounds, as discussed above, this process would never succeed, no matter how much experimentation was performed. The amount of experimentation required to make the full scope of the Challenged Claims cannot be overestimated.

136. 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. This type of experimentation was not, and is not to this day, routine. These difficulties were well understood in the art and are still the subject of active and ongoing research.

137. 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.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

138. 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. 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. 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. And a POSITA 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.

139. Thus, it is my opinion that P2 fails to enable the person of ordinary skill to make the full scope of the Challenged Claims without undue experimentation. The breadth of the claims is enormous (Factor 8). As described above, using Suzuki reactions to make compounds where L_1 is a bond can be highly unpredictable (Factor 7). 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

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

for how to make the full scope of the trillions of claimed compounds where L₁ is a bond (Factor 2). As described above, 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).

140. Accordingly, based on my understanding of the law, it is my opinion that 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.

2. P2 Would Not Enable a POSITA to Use the Full Scope of Claimed Compounds For Which L₁ Is a Bond.

141. In addition, I understand from counsel that 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. I further understand that showing utility for only part of a genus is not sufficient to meet the utility requirement when a person of ordinary skill would not reasonably believe the entire genus would have the stated utility based on the disclosure.

142. It is my opinion that P2 fails to meet this requirement for each of the Challenged Claims. As discussed above, P2 includes tables that list representative compounds with activity inhibiting different kinases. (P2 at 110-12). All of the

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

compounds listed in these tables have a chemical moiety in the L₁ position. P2 does not include in these tables any compound where L₁ is a bond (let alone compounds that also have the other substituents required by the Challenged Claims). Nor is activity data (in any assay) for such compounds presented anywhere in P2. Thus, P2 contains no working examples and no direction or guidance to show a POSITA reading the specification that compounds in which L₁ is a bond might work as kinase inhibitors, or for any other pharmacological purpose.

143. Given the absence of **any** data for compounds where L₁ is a bond, a person of ordinary skill would not have believed that compounds for which L₁ 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 L₁ is N(H)C(O)).

144. 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. 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. Indeed, it is well known that the nitrogen

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

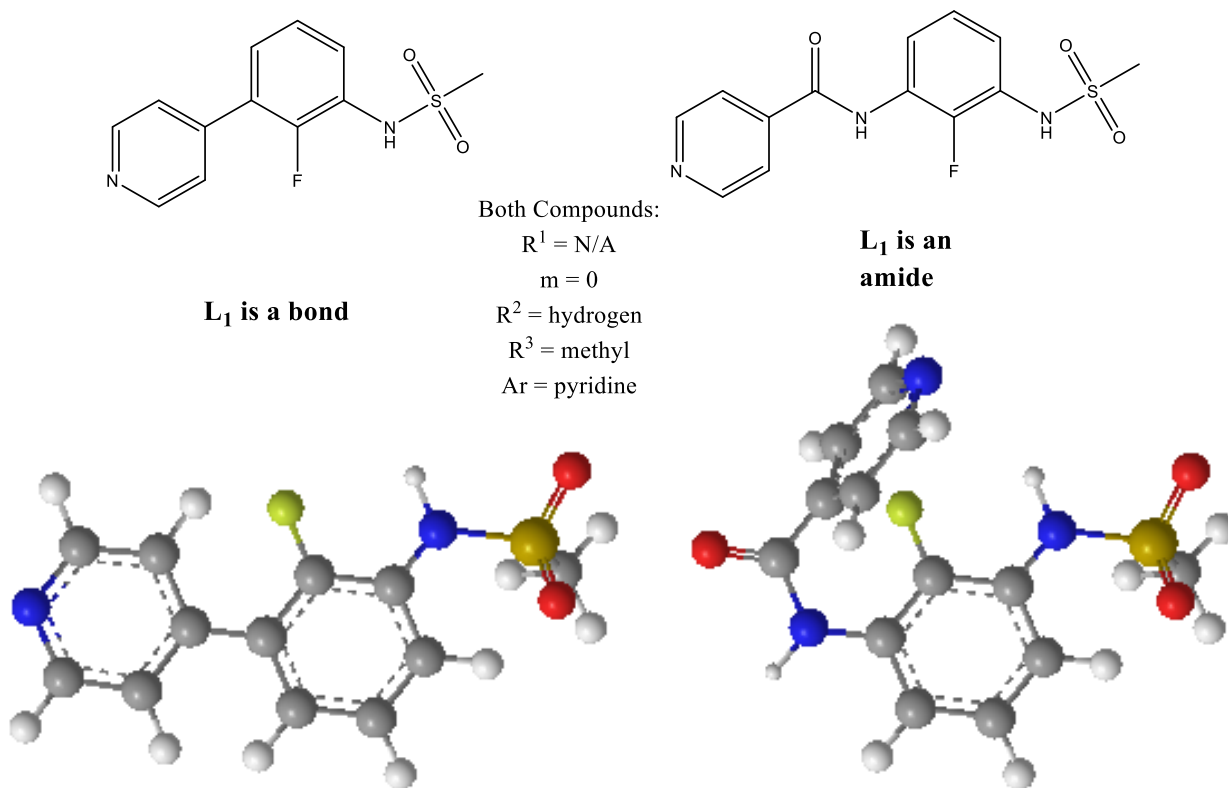
or oxygen atoms of an amide can form hydrogen bonds with amino acid. In contrast, a bond would not be able to make those hydrogen bonds. Accordingly, a POSITA would have no way of knowing whether or to what extent replacing an amide linker with a bond in the compounds of the Challenged Claims would prevent the compound from interacting with, binding to, and/or inhibiting the kinase.

145. 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. 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. Replacement of the amide with a bond would make the compound less soluble in water or other aqueous solvents.

146. 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. The amide linker

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

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:



147. It is well-known that 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. 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 POSITA would expect the two compounds to interact with the kinase differently and therefore to exhibit different kinase inhibition behavior. Thus, P2's disclosure of kinase inhibition data

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

with respect to amide-linked compounds would not enable a POSITA to even guess at how a compound in which L₁ is a bond would behave.

148. Moreover, although the Challenged Claims embrace a large genus of substituents at the R³ position ('640 patent, claim 1 ("R³ is optionally substituted lower alkyl or optionally substituted aryl")), each of the compounds disclosed as having activity has a propyl group at the R³ position. The type and substitution pattern of the group at the R³ position may affect the solubility of the claimed compounds as well as their interaction with the kinase. Because P2 does not provide any disclosure of activity for compounds with, e.g., aryl groups or groups having hydrophilic substituents¹¹ at R³ and also fails to disclose a structure-function relationship for substituents at that position, P2 does not enable a POSITA to use the full scope of the Challenged Claims.

149. In sum, P2 provides, at best, merely an invitation to test the compounds of the Challenged Claims where L₁ is a bond (approximately half of the compounds covered by the claims) to determine whether they have the asserted

¹¹ 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.

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

pharmacological activity on protein kinases. Based on my understanding of the law as given to me by counsel, this is insufficient to meet the utility standard of 35 U.S.C. § 101 and thus the “how-to-use” enablement requirement of 35 U.S.C. § 112. For this reason as well, it is my opinion that the Challenged Claims are not disclosed in P2 in the manner mandated by the enablement requirement.

150. For all of the reasons set out above, based on the law as I understand it from counsel, it is my opinion that the Challenged Claims are not disclosed in P2 in a manner mandated by the enablement requirement, and thus that the Challenged Claims are not entitled to the benefit of P2 or any earlier application under 35 U.S.C. § 120.

VII. THE CHALLENGED CLAIMS ARE ANTICIPATED BY U.S. PATENT NO. 7,994,185 UNDER 35 U.S.C. § 102(b)

151. U.S. Patent No. 7,994,185 (“the ’185 patent”), entitled “Benzene Sulfonamide Thiazole and Oxazole Compounds,” issued in August 9, 2011. Because the Challenged Claims are not entitled to the benefit of P1 or P2 under 35 U.S.C. § 120, the earliest possible priority date for those claims is the filing date of P3: April 19, 2013.¹² August 9, 2011 is more than one year before April 19, 2013.

¹² I have not been asked to analyze whether P3 meets the written description and enablement requirements with respect to the Challenged Claims. However, I am

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

Thus, the '185 patent is prior art to the Challenged Claims under 35 U.S.C. § 102(b).

152. The '185 patent discloses a species that falls within the scope of each of the Challenged Compound Claims. Specifically, Example 58 of the '185 patent discloses dabrafenib. ('185 patent, col. 177-182). Dabrafenib is specifically claimed in at least claims 1 and 6 of the '185 patent. (*Id.* at col. 406). Example 58 of the '185 patent presents three synthetic schemes to prepare dabrafenib (Examples 58a, 58b, and 58c), and two additional synthetic schemes to prepare the methanesulfonate (i.e. mesylate) salt of dabrafenib (Examples 58d and 58e). (*Id.* at col. 177-182).

153. During the prosecution of P3, the Examiner acknowledged that dabrafenib is disclosed in the '185 patent. (P3 Prosecution History, October 4, 2015 Office Action at 11-12).

154. Dabrafenib falls within the scope of each of the Challenged Compound Claims as shown in the attached claim chart. *See* Appendix A.

advised by counsel that the disclosure of P3 is the same as that of P2 and, therefore, in my view it would therefore fail to meet the requirements of 35 U.S.C. § 112 with respect to the Challenged Claims for all the reasons discussed above.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

155. Based on the foregoing, it is my opinion that the '185 patent anticipates the Challenged Compound Claims of the '640 patent.

156. The '185 patent further anticipates the Challenged Composition Claim (claim 9).¹³ The '185 patent states that the compound of Example 58 may be provided in a pharmaceutical composition: “In one embodiment, the pharmaceutical composition further comprises one or more of pharmaceutically acceptable carriers, diluents or excipients. In one aspect, the present invention provides a pharmaceutical composition comprising any of [0066] N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide . . . or a pharmaceutically acceptable salt thereof [i.e., the compound of Example 58].” ('185 patent at columns 12, 60).

157. The '185 patent also anticipates the Challenged Method Claims (claims 11 and 12).¹⁴ The '185 patent discloses method of treating colorectal

¹³ Claim 9 recites “[a] pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.”

¹⁴ Claim 11 recites “[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.”

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

cancer, melanoma and thyroid cancer using dabrafenib: “In another aspect, there is provided a method for treating cholangiocarcinoma, colorectal cancer, melanoma or thyroid cancer in a human in need thereof, comprising administering to the human, a therapeutically effective amount of [0093] N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide [i.e., the compound of Example 58] . . . or a pharmaceutically acceptable salt thereof.” (’185 patent at columns 14, 51-53). It further 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).” (’185 patent, col. 58:43-47).

158. The ’185 patent also reports that the compounds of Example 58 were tested for their ability to: (i) inhibit B-Raf activity in a B-Raf Accelerated MEK ATPase assay; (ii) inhibit growth of human colon tumor cells (Colo205); and (iii) inhibit growth of human melanoma cancer cells (SK-MEL-28), and that the

Claim 12 recites “[t]he method of claim 11, wherein the melanoma is melanoma having a mutation encoding a V600E amino acid substitution.”

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

compounds of Example 58 had activity in all three assays. ('185 patent at columns 389-410). Additional experiments in 22 cancer cell lines encoding B-Raf V600E mutations showed that 16 cells lines were sensitive to the compound ($gIC_{50} < 100$ nM), 2 had an intermediate response ($gIC_{50} \geq 100$ nM and < 1000 nM), and 4 were not sensitive ($gIC_{50} \geq 1000$ nM). ('185 patent at columns 401-402).

159. The compound of Example 58a was tested in three *in vivo* experiments which used the A375P F11s cell line—a melanoma cell line that encodes a B-Raf V600E mutation. ('185 patent at columns 402-04). The first experiment measured dose-dependent tumor inhibition using A377P F11s tumor cells that were implanted into mice after administration of the compound of Example 58. Partial regression (as defined in the '815 publication and '185 patent) was reported at doses of 100 and 300 mg/kg bid or qd. ('185 patent at columns 402-403).

160. The second experiment looked at pharmacodynamic effects against A375P F11s in a xenograft mouse model, and specifically inhibition of pERK (pERK/tERK), which is stated to be a good pharmacodynamic marker for BRAF inhibition. The compound of Example 58 was one of ten compounds that inhibited pERK (pERK/tERK) by 30% or more.

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

161. The third experiment examined efficacy against A377P F11s tumor cells that were implanted into mice. Of the eight compounds tested (one of which was the compound of Example 58), six caused tumor regression or stable disease (as defined in the '815 publication and '185 patent) as compared to animals treated with vehicle. ('185 patent at columns 403-404).

162. Thus, based on the disclosure of the '185 patent as a whole, including the examples presented above, it is my opinion that the '185 patent anticipates method claims 11 and 12.

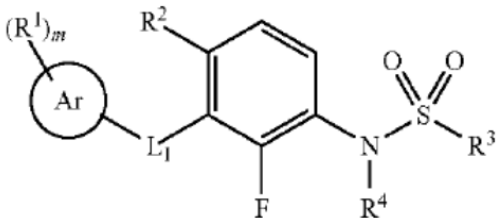
163. I declare under penalty of perjury under the laws of the United States that the foregoing is true and accurate to the best of my knowledge.

Dated:
_6/15/2018_____

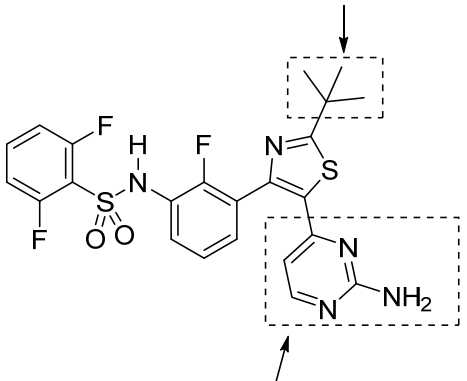
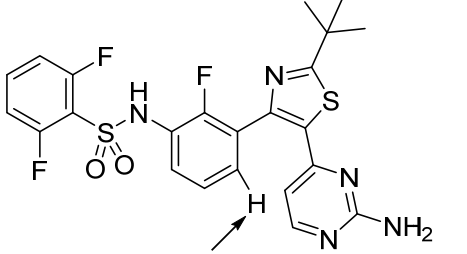
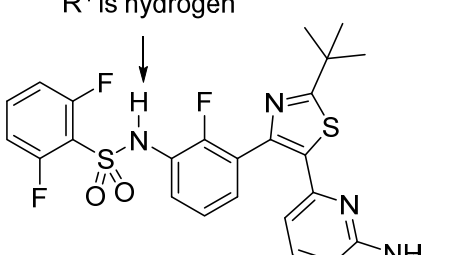
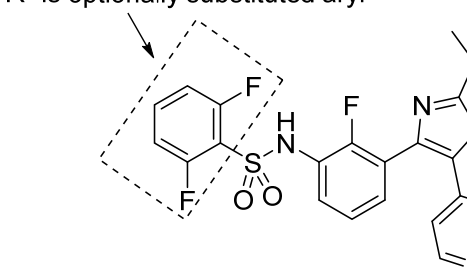


Dr. Phil S. Baran

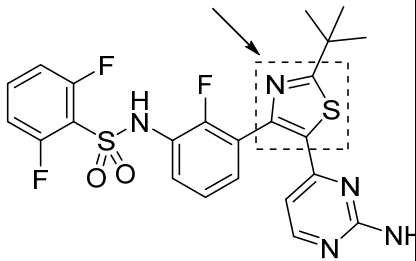
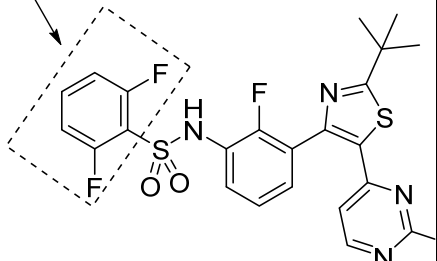
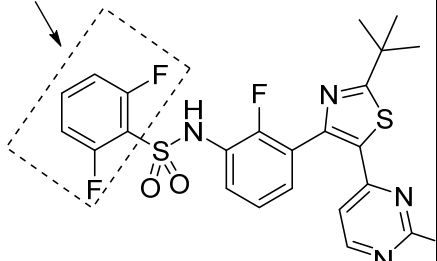
**APPENDIX A: THE CHALLENGED CLAIMS ARE ANTICIPATED BY
THE '185 PATENT**

Claim 1	Prior Art Disclosure
<p>Element [A]</p> <p>A compound of formula (Ia):</p> <div style="text-align: center;">  <p>(Ia)</p> </div> <p>or a pharmaceutically acceptable salt thereof, wherein:</p>	<p>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.</p> <p>One of the compounds that is specifically described is the compound of Example 58 (shown below), N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide, which today is commonly known as dabrafenib. '185 patent at columns 177-182.</p>
<p>Element [B]</p> <p>L₁ is a bond or —N(H)C(O)—;</p>	

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

<p>Element [C]</p> <p>each R¹ is optionally substituted lower alkyl or optionally substituted heteroaryl;</p>	<p>R¹ is optionally substituted lower alkyl</p>  <p>R¹ is optionally substituted heteroaryl</p>
<p>Element [D]</p> <p>R² is hydrogen or halogen;</p>	 <p>R² is hydrogen</p>
<p>Element [E]</p> <p>R⁴ is hydrogen;</p>	<p>R⁴ is hydrogen</p> 
<p>Element [F]</p> <p>R³ is optionally substituted lower alkyl or optionally substituted aryl;</p>	<p>R³ is optionally substituted aryl</p> 
<p>Element [G]</p> <p>m is 0, 1, 2, 3, 4, or 5; and</p>	<p>See Element [C], m is 2.</p>

Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)

<p>Element [H]</p> <p>Ar is a monocyclic heteroaryl containing 5 to 6 atoms wherein at least one atom is nitrogen.</p>	<p>Ar is a monocyclic heteroaryl containing 5 atoms wherein at least one atom is nitrogen</p> 
<p>Claim 2</p>	<p>Prior Art Disclosure</p>
<p>The compound of claim 1, wherein R² is hydrogen</p>	<p>See Claim 1, Element [D] above</p>
<p>Claim 4</p>	<p>Prior Art Disclosure</p>
<p>The compound of claim 1, wherein R³ is optionally substituted phenyl.</p>	<p>R³ is optionally substituted phenyl</p> 
<p>Claim 5</p>	<p>Prior Art Disclosure</p>
<p>The compound of claim 1, wherein R³ 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.</p>	<p>R³ is phenyl substituted with 2 fluoro</p> 
<p>Claim 6</p>	<p>Prior Art Disclosure</p>
<p>The compound of claim 1, wherein R³ is phenyl substituted with one or more fluoro.</p>	<p>See Claim 5</p>
<p>Claim 9</p>	<p>Prior Art Disclosure</p>
<p>A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or</p>	<p>The '185 patent states that the compound of Example 58 may be provided in a pharmaceutical</p>

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

excipient.	composition: “In one embodiment, the pharmaceutical composition further comprises one or more of pharmaceutically acceptable carriers, diluents or excipients. In one aspect, the present invention provides a pharmaceutical composition comprising any of [0066] N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide . . . or a pharmaceutically acceptable salt thereof [i.e., the compound of Example 58].” ’185 patent at column 12, lines 43-58.
Claim 11	Prior Art Disclosure
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.	<p>The ’185 patent states that “In another aspect, there is provided a method for treating cholangiocarcinoma, colorectal cancer, melanoma or thyroid cancer in a human in need thereof, comprising administering to the human, a therapeutically effective amount of N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide [i.e., the compound of Example 58] . . . or a pharmaceutically acceptable salt thereof.” ’185 patent at column 14, lines 29-43.</p> <p>The ’185 patent also reports that the compounds of Example 58 were tested for their ability to: (i)</p>

***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

	<p>inhibit B-Raf activity in a B-Raf Accelerated MEK ATPase assay; (ii) inhibit growth of human colon tumor cells (Colo205); and (iii) inhibit growth of human melanoma cancer cells (SK-MEL-28), and that the compounds of Example 58 had activity in all three assays. '185 patent at columns 389-410. Additional experiments in 22 cancer cell lines encoding B-Raf V600E mutations showed that 16 cells lines were sensitive to the compound (gIC₅₀<100 nM), 2 had an intermediate response (gIC₅₀≥100 nM and <1000 nM, and 4 were not sensitive (gIC₅₀≥1000 nM). '185 patent at columns 401-402.</p> <p>And the compound of Example 58a was tested in three <i>in vivo</i> experiments which used the A375P F11s cell line—a melanoma cell line that encodes a B-Raf V600E mutation. '185 patent at columns 402-04 and see lines 25-27 at column 403 for characterization of A375P F11s cell line.</p> <p>The first experiment measured dose-dependent tumor inhibition using A377P F11s tumor cells that were implanted into mice after administration of the compound of Example 58; partial regression (as defined in the '185 patent) was</p>
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***Inter Partes Review of U.S. Patent No. 9, 469,640
Declaration of Phil S. Baran, Ph.D. (Ex.1002)***

	<p>reported at doses of 100 and 300 mg/kg bid or qd. <i>Id.</i> at columns 402-403 beginning at line 34 of column 403.</p> <p>The second experiment looked at pharmacodynamic effects against A375P F11s in a xenograft mouse model, and specifically inhibition of pERK (pERK/tERK), which is stated to be a good pharmacodynamic marker for BRAF inhibition; the compound of Example 58 was one of ten compounds that inhibited pERK (pERK/tERK) by 30% or more. <i>Id.</i> at columns 403-404 beginning at line 15 of column 403.</p> <p>The third experiment examined efficacy against A377P F11s tumor cells that were implanted into mice; of the eight compounds tested (one of which was the compound of Example 58), six caused tumor regression or stable disease (as defined in the '815 publication and '185 patent) as compared to animals treated with vehicle. <i>Id.</i> at columns 403-404.</p>
Claim 12	Prior Art Disclosure
The method of claim 11, wherein the melanoma is melanoma having a mutation encoding a V600E amino acid substitution.	See claim 11 above and also claim 15 of the '185 patent.

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