

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BeiGene USA, Inc. and BeiGene, LTD.,
Petitioners

v.

Pharmacyclics LLC,
Patent Owner

PGR2024-00009
U.S. Patent No. 11,672,803

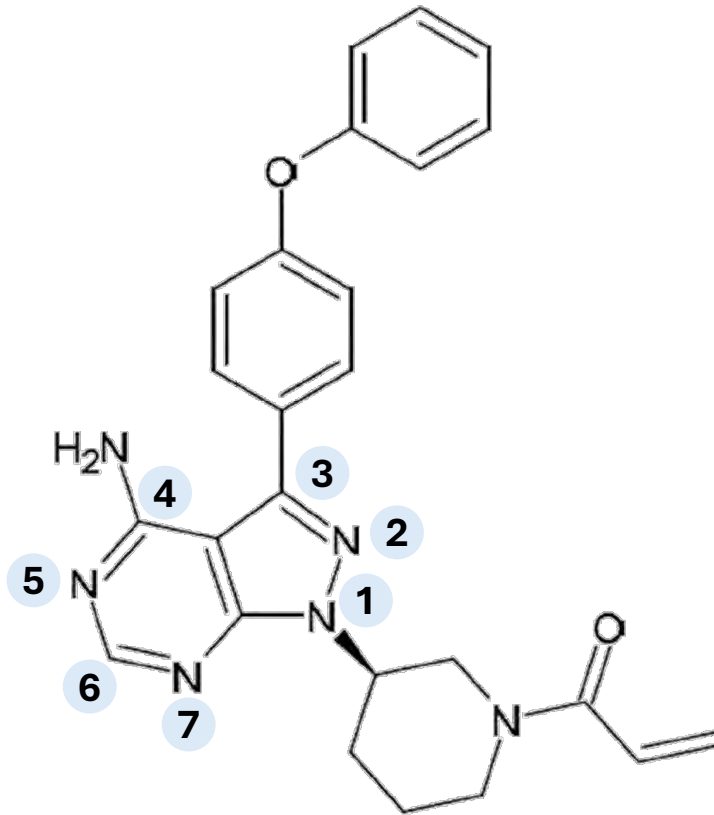
PETITIONERS' DEMONSTRATIVE EXHIBITS

United States Patent and Trademark Office
Before the Patent Trial and Appeal Board

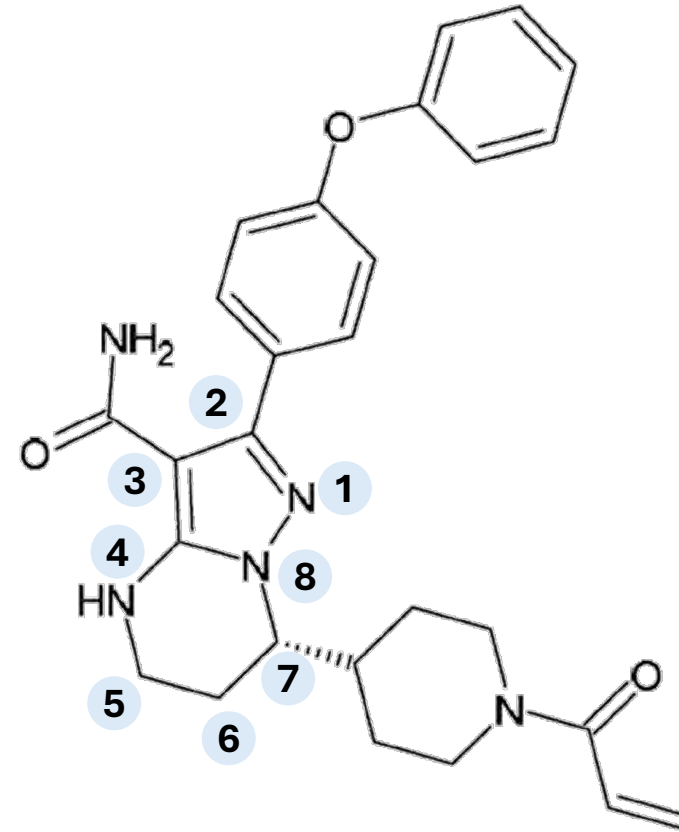
BeiGene USA, Inc. and BeiGene, LTD. v. Pharmacyclics LLC
Post Grant Review of U.S. Patent No. 11,672,803
Case No. PGR2024-00009

Petitioners' Demonstratives
Oral Hearing: January 30, 2025

IMBRUVICA (Ibrutinib) Versus BRUKINSA (Zanubrutinib)



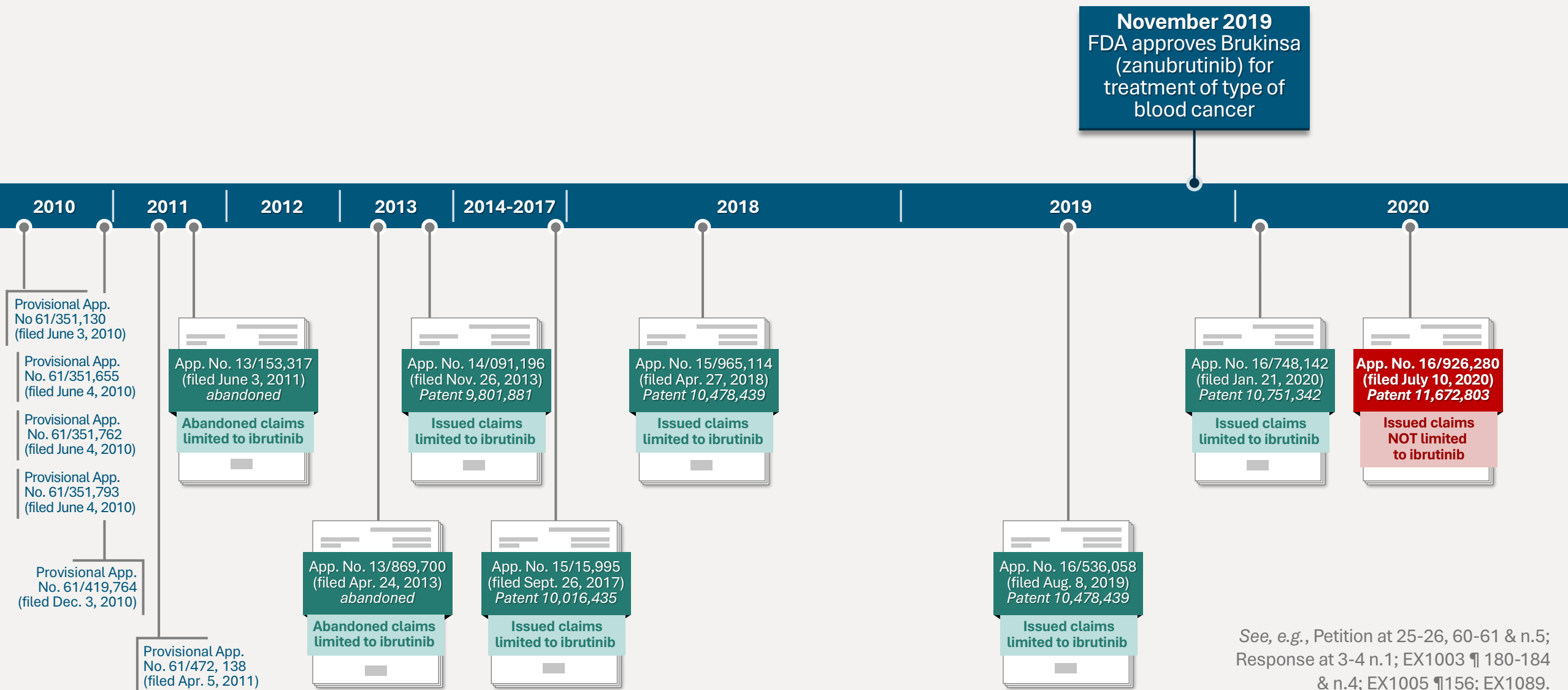
IMBRUVICA



BRUKINSA

Veal Decl. (EX1105) ¶ 58 (rotated and annotated).

Every Issued Claim Prior to the '803 Patent Was Limited to Ibrutinib



Idenix Pharms. LLC v. Gilead Scis. Inc.

941 F.3d 1149, 1164-65 (Fed. Cir. 2019)

“The written description requirement specifically defends against . . . attempts to cover any compound later actually invented and determined to fall within the claim’s functional boundaries.”

Instituted Grounds

Ground 1

Claims 1-8, 12, and 20 lack written description support, with an effective filing date no earlier than July 10, 2020

Ground 2

Claims 1-8, 12, and 20 are not enabled, with an effective filing date no earlier than July 10, 2020

Grounds 3 & 4

Claims 1-8, 12, and 20 are anticipated and/or obvious over Patent Owner's intervening Imbruvica publications (Byrd and/or Imbruvica Label)

See, e.g., Petition at 56; Institution Decision (Paper 9) at 42.

Petitioner Has Demonstrated Challenged Claims Are Invalid on All Four Grounds

Ground 1: Written Description

- No representative number of species
- No common structural features
- No blaze marks to claimed genus

Ground 2: Enablement

- The claims encompass large number of potential inhibitors
- Undue experimentation required to model and test potential inhibitors

Grounds 3 & 4

- Patent Owner concedes claims are anticipated/obvious if challenged claims are not entitled to priority date

See, e.g., Petition at 1-3; Reply at 1-2.

Patent Owner's Counterarguments Fail

Ground 1: Written Description

- Modeling potential inhibitors does not satisfy written description “visualization” requirement
- Modeling at most shows that certain other inhibitors might be obvious
- Modeling of specification and prior art Z' structures in fact shows no well-known structure-function relationship throughout full scope of the genus

Ground 2: Enablement

- Even adopting Patent Owner's assumptions, millions of compounds meet structural limitations, requiring years of modeling work just to predict full scope of genus
- No predictable way to identify working inhibitors based on scant guidance in specification and prior art

Ground 1: Lack of Written Description/Priority

Amgen Inc. v. Hoechst Marion Roussel, Inc.

314 F.3d 1313, 1330 (Fed. Cir. 2003)

“The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to ‘recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.’”

Ariad Pharms., Inc. v. Eli Lilly & Co.

598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (en banc)

“[C]laims to research plans . . . impose costs on downstream research, discouraging later invention. The goal is to get the right balance, and the written description doctrine does so by giving the incentive to actual invention and not ‘attempt[s] to preempt the future before it has arrived.’ . . . As this court has repeatedly stated, the purpose of the written description requirement is to ‘ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.’”

Two Bases Upon Which to Find Lack of Written Description/Priority

Basis 1

No Representative
Number of Species or
Common Structural
Features for Members
of the Claimed Genus

Basis 2

No Blaze Marks to
the Claimed Genus

Institution Decision

That said, the Federal Circuit explains that written description of a genus requires more than a “broad outline of a genus’s perimeter”:

[W]ritten description of a broad genus requires description of not only the outer limits of the genus but also of either a representative number of members of the genus or structural features common to the members of the genus, in either case with enough precision that a relevant artisan can visualize or recognize the members of the genus.

Regents of the Univ. of Minn. v. Gilead Sciences, Inc., 61 F.4th. 1350, 1356 (Fed. Cir. 2023). “For genus claims, . . . we have looked for blaze marks within the disclosure that guide attention to the claimed species or subgenus.” *Id.*

Institution Decision (Paper 9) at 13-14.

As Issued, Challenged Claims of the '803 Patent

All challenged claims are method claims to treat CLL or SLL with a genus of compounds that have certain structural features and meet certain functional limitations:

- irreversibly binding BTK
- therapeutically effective amount
- result in lymphocytosis

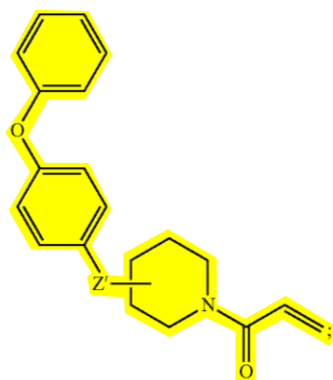
See, e.g., Petition at 28-29.

1. A method for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual comprising:

orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity;

wherein lymphocytosis is not considered progression of the CLL or SLL, and

wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms;

wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

wherein the irreversible inhibitor of Btk forms a covalent bond with Cys⁴⁸¹ of a Bruton's tyrosine kinase.

'803 Patent, Claim 1.

8. A method for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual comprising:

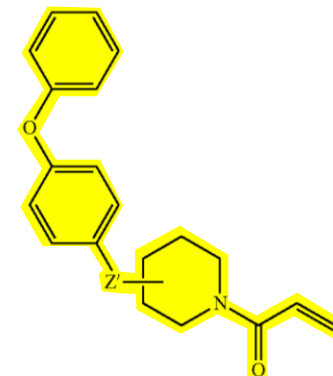
orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity;

wherein:

lymphocytosis is not considered progression of the CLL or SLL;

said administration of the therapeutically effective amount is an amount that results in >90% of the Btk active sites in the peripheral blood mononuclear cells of the individual being occupied by the irreversible inhibitor of Btk twenty-four hours following said administration; and

the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; and

wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom.

'803 Patent, Claim 8.

Specification Does Not Disclose a Representative Number of Species

Ariad Pharms., Inc. v. Eli Lilly & Co.
598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc)

“[A] sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus. . . . We explained that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.”

Patent Owner Does Not Assert That the '803 Patent Discloses a Representative Number of Species

Patent Owner Response

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C. The Specification Describes **Common Structural Features** for the Ibrutinib-Like iBTKIs Used In the Claimed Method.....39

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2. Phenoxyphenyl Structure Directs Selectivity and Potency in BTK Binding.....42

3. The Specification Describes the Claimed Z'-Scaffold Such That a POSA Could Visualize Ibrutinib-Like iBTKIs that Bind BTK.....43

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a. Zanubrutinib Mimics Adenine and Ibrutinib.....50

b. Petitioner Ignores the Full Context of the Ibrutinib-Like iBTKIs of the Claims54

c. Petitioner's Cited Evidence Contradicts Its Unpredictability Assertions57

d. Petitioner's Cited Cases Are Readily Distinguishable62

Response at i-ii (TOC).

Patent Owner Sur-Reply

B. The Fixed Features of the Claimed Ibrutinib-Like iBTKIs Correlate to the Claimed Function

The evidence demonstrates that the **structural features** of the claims *define* the genus of compounds that irreversibly inhibit BTK. §IV.A. A POSA would therefore understand how these features, drawn from ibrutinib, correlate with their ability to bind and irreversibly inhibit BTK and thus be useful in the claimed methods. POR 12-24.

Petitioner argues that because certain compounds falling within the scope of the claims have reported poor potency, the fixed features of the claims legally cannot qualify as common structural features. Reply 16. But “written description does not require a *perfect* correspondence” but a “more modest[]” “*correlation* between structure and function.” *Ajinomoto Co. v. Int’l Trade Comm’n*, 932 F.3d 1342, 1360 (Fed. Cir. 2019). Moreover, as Dr. Eck explained, and Dr. Veal’s own analysis demonstrates, because of the sophisticated structure-function relationship for the Z’-scaffold, modeling in 2011 would identify those compounds not expected to inhibit BTK. §§IV.D, VI.C.

Sur-Reply at 14.

Specification Does Not Disclose
Common Structural Features of
Members of the Claimed Genus

Ariad Pharms., Inc. v. Eli Lilly & Co.
598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc)

“[A] sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus. . . . We explained that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.”

Ariad Pharms., Inc. v. Eli Lilly & Co.

598 F.3d 1336, 1349-50 (Fed. Cir. 2010) (en banc)

“The [written description] problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. . . . We have also held that functional claim language can meet the written description requirement when the art has established a correlation between structure and function.”

AbbVie Deutschland GmbH v. Janssen Biotech, Inc.

759 F.3d 1285, 1299-1300 (Fed. Cir. 2014)

“[A]nalogizing the genus to a plot of land, if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus. . . . One describes a plot of land by its furthest coordinates, in effect drawing a perimeter fence around it. That may be akin to the function of patent claims to particularly point out and distinctly circumscribe the outer boundaries of a claimed invention.”

AbbVie Deutschland GmbH v. Janssen Biotech, Inc.

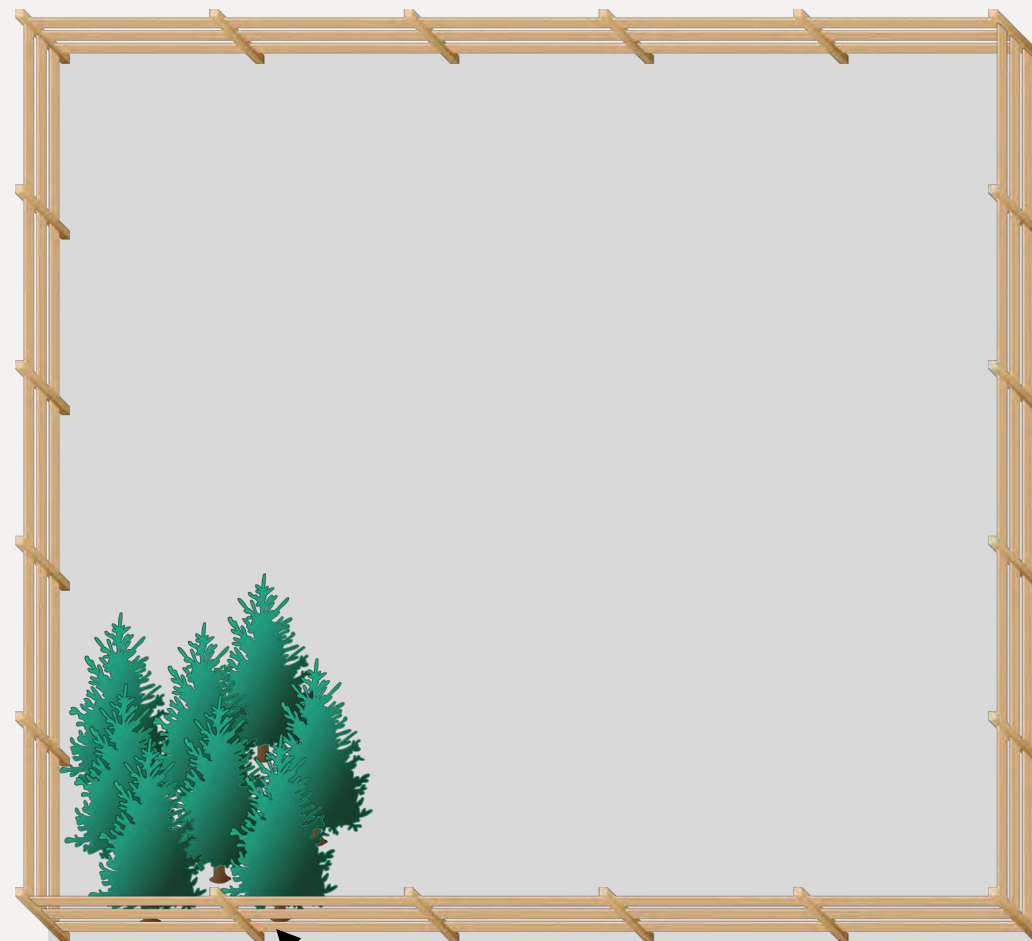
759 F.3d 1285, 1293 (Fed. Cir. 2014) (annotated)

	Stelara (accused product)	J695 (high affinity binder)	Joe-9 (low affinity binder)
Sequence Similarity	50%	90%	90%
CDR Length	Different	Identical	Identical
Epitope Binding Site	Side Binder	Bottom Binder	Bottom Binder
V _H Family	V _H 5	V _H 3	V _H 3
Light Chain Type	Kappa	Lambda	Lambda

Sufficient to Meet *Ariad* Test



NOT Sufficient to Meet *Ariad* Test

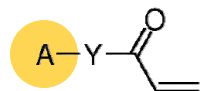


Boundaries as defined by the claim

See, e.g., *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299-1300 (Fed. Cir. 2014).

Patent Owner Concedes That Predecessor Genus Claims Were Invalid

34. (New) The method of claim 32, wherein the inhibitor of Btk has the structure:

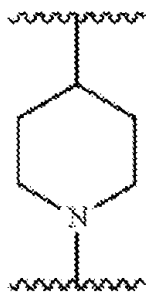


wherein:

A is a moiety that binds to the active site of Btk; and
Y is a substituted heterocycloalkylene.

35. (New) The method of claim 34, wherein Y is a piperidinylene.

36. (New) The method of claim 34, wherein Y is:



EX1002.426-27.

⁶ Recognizing the Petition's weakness, Petitioner now seeks to escape the estoppel consequences of a final written decision, requesting that if the Board finds the Challenged Claims described and enabled by the 2011 specification, then the Board should terminate the PGR. Reply 27 n.11. PGR is available only for a patent that "contains or contained **at any time**" a claim that has an effective filing date after March 16, 2013. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 293, §3(n)(1) (2011). As Petitioner pointed out, the '280 Application, from which the '803 Patent issued, presented claims that were rejected by the Examiner for lack of written description and enablement. Pet. 36-38. In response, the claims were narrowed to address the §112 rejections until the present claims were allowed. *Id.* 38-41. Because the Examiner found the specification did not disclose the prior, broader claims "in the manner provided by [§]112(a)," **those claims were not entitled to "the benefit of an earlier filing date."** 35 U.S.C. §100(i)(1)(B), 120. The effective filing date for those **rejected claims** would be "the actual filing date" of the '280 Application, July 10, 2020. 35 U.S.C. §100(i)(1)(A). **Therefore, the '803 Patent, while pending as the '280 Application, contained claims that had an effective filing date after March 16, 2013.** The pendency of such claims renders the patent PGR-eligible even though they did not issue. *Microsurgical Tech., Inc. v. Regents of Univ. of Colo.*, PGR2021-00026, Paper 12 at 13-24 (P.T.A.B. June 16, 2021). The Board has a complete record before it on which to make its determination and issue a final decision. Petitioner should be held to the consequences of having submitted a fatally flawed Petition.

Sur-Reply at 25 n.6.

But the Issued Claims Are Not Meaningfully Narrower: The Z' Structure Defines a Genus of Billions of Compounds

Dr. Hollis
Showalter
*Petitioner's
Expert*

142. The number of structural species encompassed by these Structural Limitations is at least in the billions (as explained below, due to the recursive nature of the permitted substitutions, it can actually be infinite). My conservative calculation is based on the following parameters defined by the claim language of these Structural Limitations and the construction of “optionally substituted fused heterocyclic ring system.” Specifically, the structural limitations prescribe four subgenera that allow for a large number of structurally distinct species. Further, the vast number of structural species arises from the diversity of the fused heterocyclic ring systems coupled with the diversity of substitution patterns for each ring system, which are affected by a variety of factors, including the aromaticity of the ring systems (*i.e.*, biaryl *v.* non-biaryl), substitution patterns (*i.e.*, type, number, and position of substitutions present on the ring system), and heteroatom patterns (*i.e.*, type, number, and position of heteroatoms in the ring system).

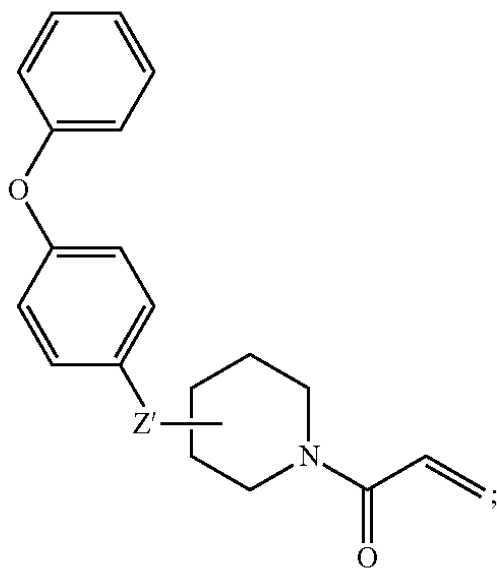
Showalter Decl. (EX1003) ¶¶ 141-178; see also Petition at 57-60, Reply at 4-5 (collecting cites); Showalter Reply Decl. (EX1105) ¶¶ 16-35; Veal Reply Decl. (EX1106) ¶¶ 227-30.

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q. I understand. That was my question about just the Z'-structure itself. So to be fair and to be clear, just looking at the Z'-structure itself, as described in that claim, you would agree that that alone, by itself, encompasses billions of possible structures?
- A. Again, considering it aside from the claim, I would agree that that could potentially encompass billions of structures according to Dr. Showalter's calculations.

Eck Dep. Tr. (EX1110) at 42:18-43:18; see also Reply at 4-5 (collecting cites); Showalter Reply Decl. (EX1105) ¶ 19; Veal Reply Decl. (EX1106) ¶¶ 185, 248, 254.

Claimed Z' Structures Encompass Cores With Varied Aromaticities



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

'803 Patent, Claim 1.

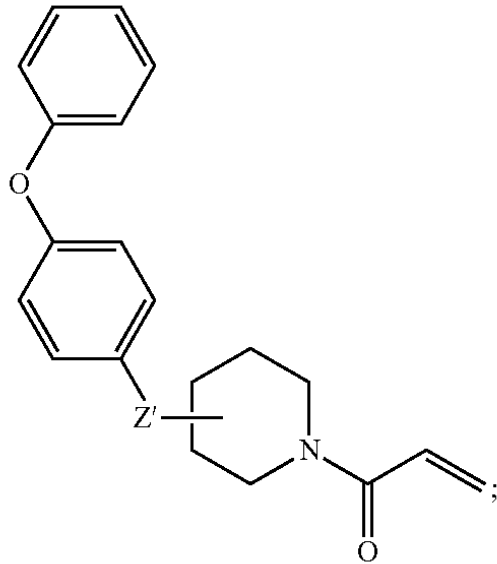
Petition

could be either aromatic or non-aromatic. EX1003, ¶144. The Structural Limitations are therefore directed to at least the following four structurally distinct and extremely broad subgenera defined by the aromaticity of the ring system of the Z'-structure:

- An aromatic 5-membered ring fused to an aromatic 6-membered ring (“biaryl”)
- An aromatic 5-membered ring fused to a non-aromatic 6-membered ring (“5-aro, 6-non-aro”)
- A non-aromatic 5-membered ring fused to an aromatic 6-membered ring (“5-non-aro, 6-aro”)
- A non-aromatic 5-membered ring fused to a non-aromatic 6-membered ring (“bi-non-aromatic”). *Id.*

Petition at 58; see also Showalter Decl. (EX1003) ¶¶ 143-147.

Claimed Z' Structures Encompass Cores With Varied Heteroatoms Patterns (Numbers, Identities, Locations)



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

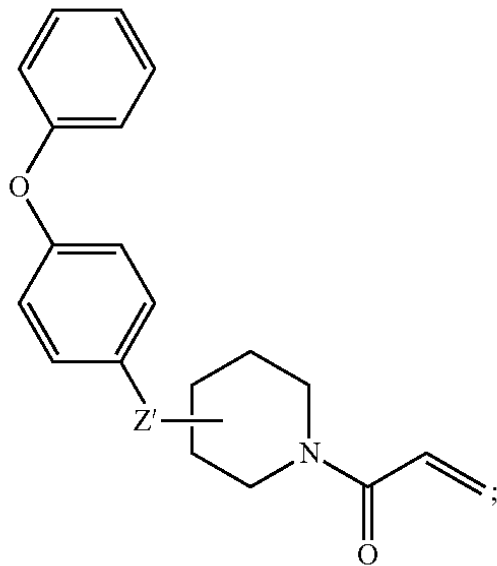
'803 Patent, Claim 1.

Petition

Second, within each of the four subgenera, there are at least hundreds of possible ring systems for the Z'-structures based on the following variables: (1) degree of saturation of the non-aromatic rings; (2) number and position of nitrogen heteroatoms; and (3) number, type, and position of other heteroatoms. EX1003, ¶¶148-158. Dr. Showalter's Declaration and Appendix A provide a non-exhaustive and conservative list of exemplary ring systems encompassed by the Structural Limitations. *Id.* The differences in the ring systems impact the BTKIs' claimed functions. *Supra* III.C-III.D.1; EX1003, ¶158.

Petition at 59; see also Showalter Decl. (EX1003) ¶¶ 148-158.

Claimed Z' Structures Encompass Cores With Varied Substituent Patterns (Identities and Locations)



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

'803 Patent, Claim 1.

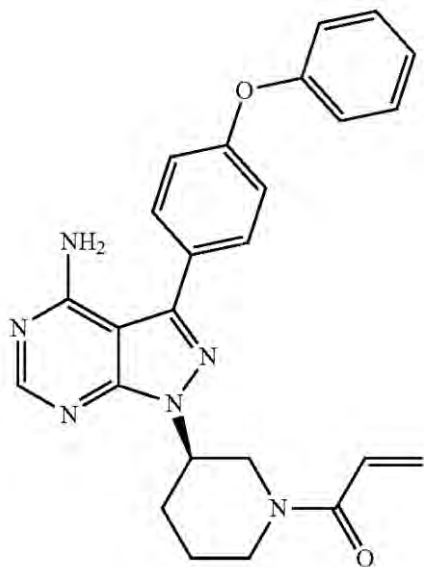
Petition

Third, each of the hundreds of ring systems can have optional substitutions selected from a list of 21 broad categories from the specification, each category including numerous possible substitutions. EX1003, ¶¶159-174. Each ring system provides a different number and location of positions available for substitution. EX1003, ¶¶167, 172-173.

Petition at 59; see also Showalter Decl. (EX1003) ¶¶ 159-174.

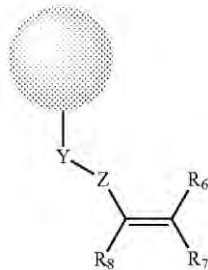
Specification Does Not Provide Common Features So That POSA Can Visualize or Recognize Genus of Z' Structures

Ibrutinib



'803 Patent at 65:10-25 (annotated.)

Formula (E)

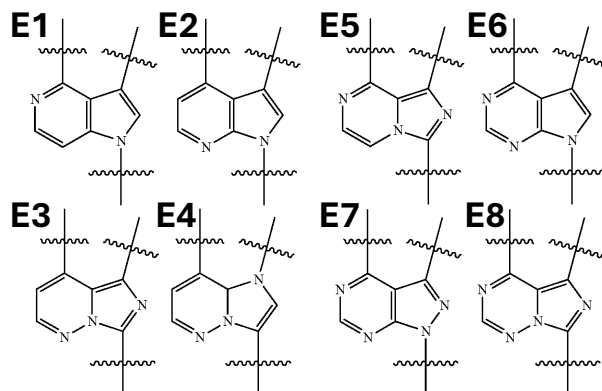


wherein:

wherein Y is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

'803 Patent at 62:1-17.

In some embodiments, Z is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

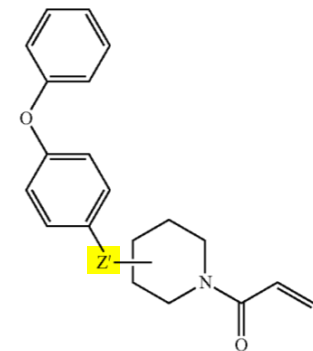
≠

1. A method for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual comprising:

orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity;

wherein lymphocytosis is not considered progression of the CLL or SLL, and

wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

wherein the irreversible inhibitor of Btk forms a covalent bond with Cys⁴⁸¹ of a Bruton's tyrosine kinase.

'803 Patent, Claim 1.

See, e.g., Petition at 65-71.

Claims Far Broader Than Specification Disclosure in Multiple Respects

	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
Substitution pattern	Amine substitution at C4 Linker/warhead at N1 Hydrophobic moiety at C3	Numerous different substituents at any position on 6:5 rings Linker/warhead at any position Hydrophobic moiety at any position	Amide substitution at C3 Linker/warhead at C7 Hydrophobic moiety at C2
Heteroatom pattern	One of eight patterns of heteroatom substitution: (1) N1, N5; (2) N1, N7; (3) N2, N7, N8; (4) N3, N7, N8; (5) N2, N5, N8; (6) N1, N5, N7; (7) N1, N2, N5, N7; (8) N2, N5, N7, N8.	2-4 N heteroatoms anywhere in 6:5 ring system with at least one N per ring Could have O and/or S heteroatoms	Three N heteroatoms at N1, N4, and N8
Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67.

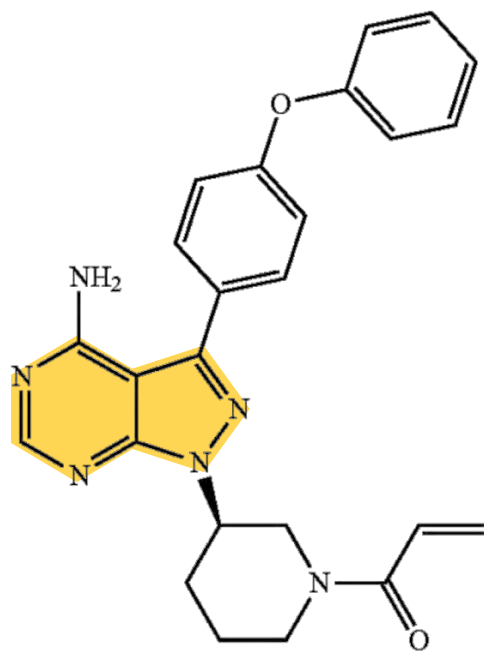
⁸ As stated, a POSA would disregard E4, and in any event, E4 is limited to its particular aromaticity and particular heteroatom/substitution patterns as shown in the chart. EX1003, ¶190, n.6, n.7; *see also id.*, ¶115, n.2, ¶¶190-191, ¶¶194-205.

Petition at 67 n.8.

See Petition at 65-71 (collecting cites); *see also, e.g.*, Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207.

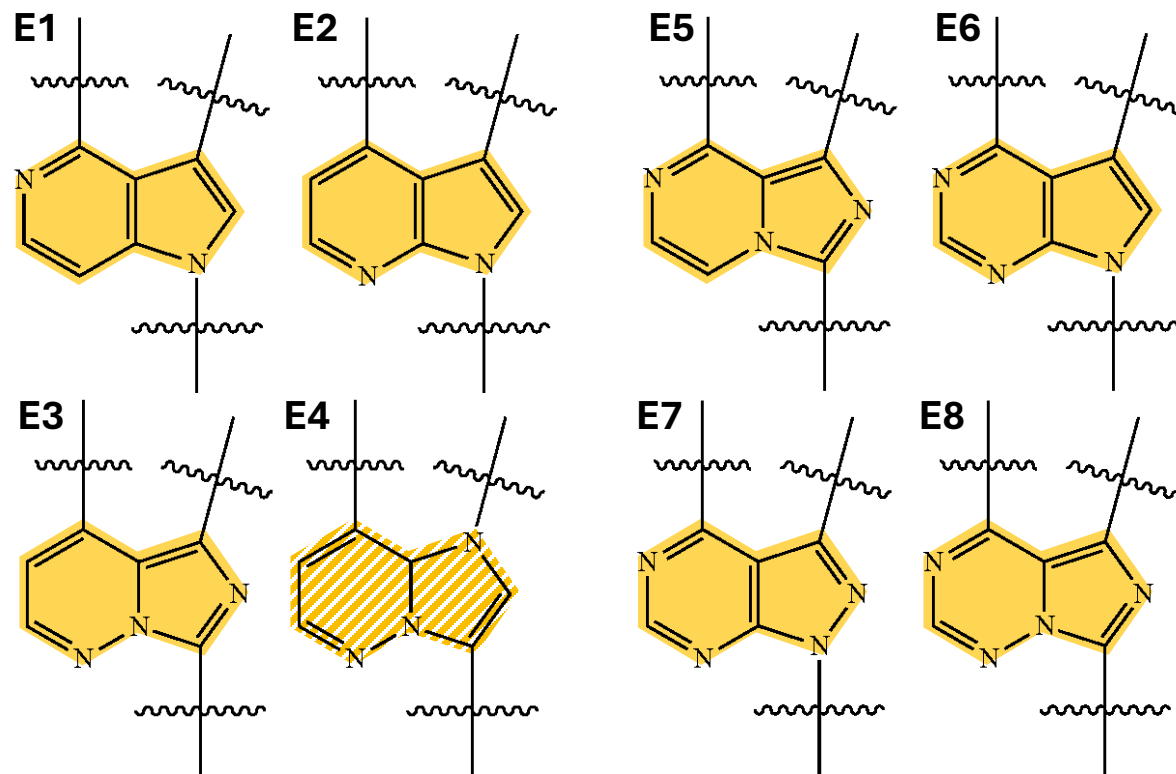
For Example, Formula E and Ibrutinib (E7) Provide Examples Only of Cores With Two Aromatic Rings for Z' Structures

Ibrutinib



'803 Patent at 65:10-25 (annotated).

In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

See Petition at 65-71 (collecting cites); see also, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207.

As Board Found in Institution Decision, POSA Would Understand E4 to Be a Mistake

Institution Decision

⁴ Although the Specification includes a non-biaryl moiety as an embodiment of the ball of Formula (E) (i.e., “E4”), Petitioner asserts that a POSA would disregard E4 as an error because the Specification identifies it as an example of a “biaryl moiety.” Pet. 67 n.8 (citing Ex. 1003 ¶¶ 115 n.2, 190–191, n.6). Patent Owner disagrees, arguing the Specification does not limit the use of “biaryl” to the explicit disclosure of the structures and the definition of “aryl” does not exclude structures that are partially non-aromatic. Prelim. Resp. 33–34 n.4. On this record, we find Petitioner has the better position, as the Specification prefaces the structures with “In some embodiments, [the ball] is a substituted fused biaryl moiety *selected from*” and we accept, at this stage of the proceeding, Dr. Showalter’s definition of “biaryl” as both the 5- and 6-membered rings are aromatic. Ex. 1001, 62:44–45; Ex. 1003 ¶ 41. That said, the parties are invited to address this issue further during trial.

Institution Decision (Paper 9) at 21 n.4.

Patent Owner's Expert Concedes That “Biaryl” Ordinarily Refers to Two Aromatic Rings

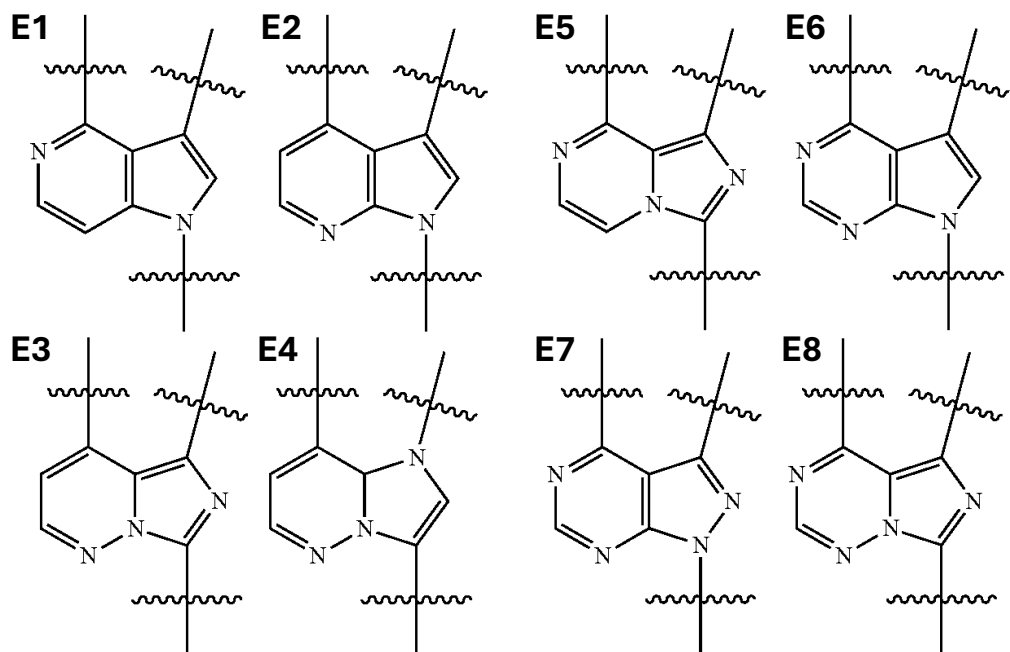
Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q.** I asked you a different question, though. What does “biaryl” mean to you outside of the context of this patent?
- A.** So outside of the context of this patent, you know, “biaryl”, if you break it down literally, suggests two aromatic rings.

Eck Dep. Tr. (EX1110) at 82:1-6; see also Petition at 67-88 n.8, Reply at 8-9 (collecting cites); Showalter Reply Decl. (EX1105) ¶¶ 40-43; Veal Reply Decl. (EX1106) ¶¶ 53, 213.

Claim 13 Demonstrates That E4 Was Intended to Have Two Aromatic Rings

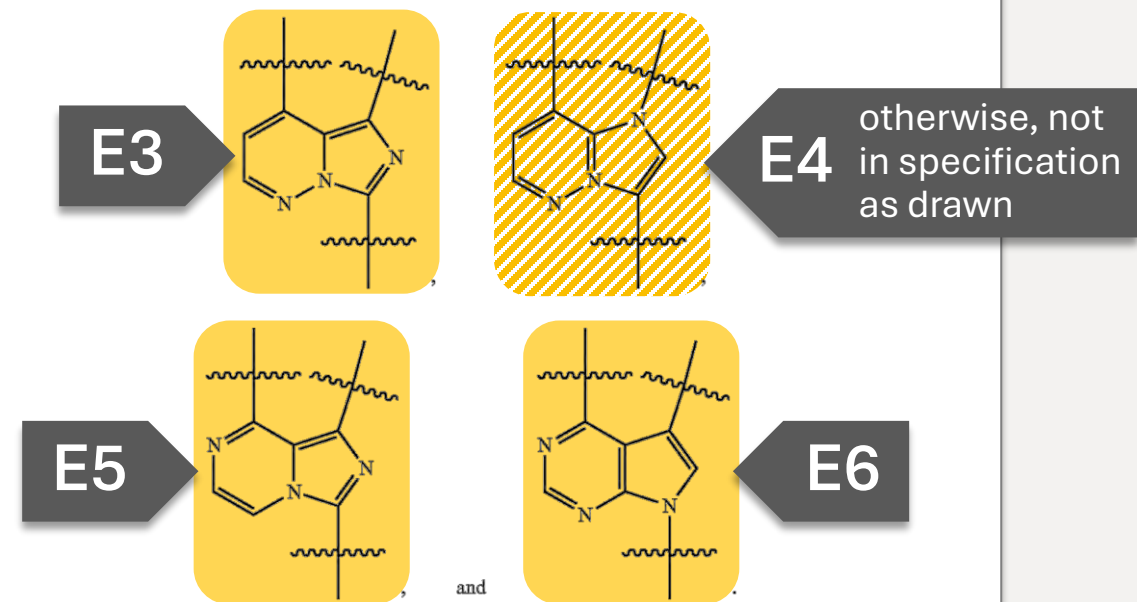
In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

12. The method of claim 1, wherein the fused heterocyclic ring system comprises 3 nitrogen heteroatoms.

13. The method of claim 12, wherein the fused heterocyclic ring system is selected from:



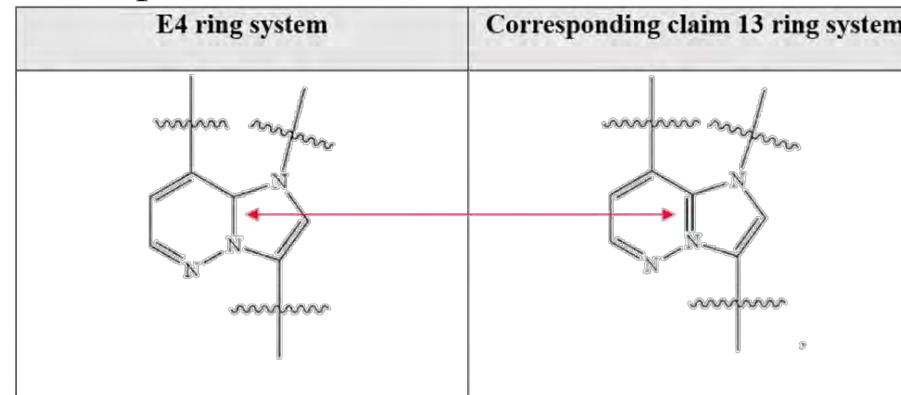
'803 Patent, Claims 12-13.

See Reply at 8-9 (collecting cites); Showalter Reply Decl. (EX1105) ¶¶ 40-43 & n.8; Veal Reply Decl. (EX1106) ¶¶ 53, 213.

Claim 13 Demonstrates That E4 Was Intended to Have Two Aromatic Rings

Showalter Reply Declaration

⁸ A POSA would still consider E4 a mistake regardless of the definition of biaryl based on claim 13. Three out of the four ring systems claimed in claim 13 other than the ring system depicted below can be found among the eight Formula E ring systems that comprise 3 N atoms.



The missing ring system is almost identical to E4 but, unlike E4, has a double bond off the bridgehead N. This structure has an error as the bridgehead N should have a positive charge. Because the corresponding structure in claim 13 appears nowhere in the specification and “biaryl” is used to describe the eight Formula E structures, a POSA reading the 803 Patent would conclude that the inventors were attempting to disclose in E4 and claim in claim 13 a biaryl ring system containing two heteroaryl rings and 3 N atoms, but failed to do so correctly.

Showalter Reply Decl. (EX1105) at 24 n.8.

See also Reply at 8-9 (collecting cites); Showalter Reply Decl. (EX1105) ¶¶ 40-43; Veal Reply Decl. (EX1106) ¶¶ 53, 213.

Claims Far Broader Than Specification Disclosure in Multiple Respects

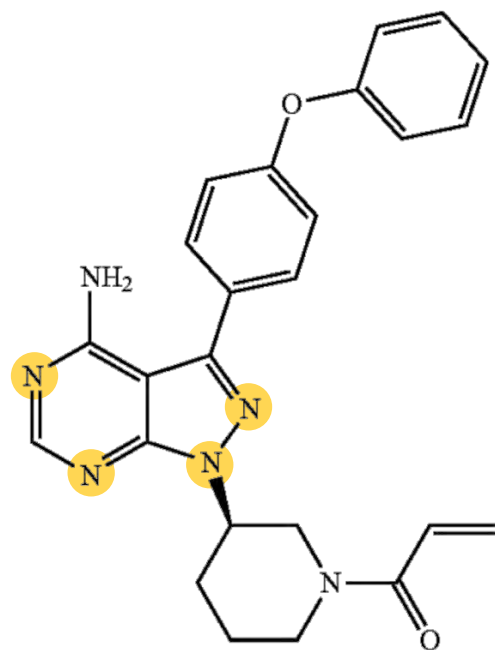
	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
Substitution pattern	Amine substitution at C4 Linker/warhead at N1 Hydrophobic moiety at C3	Numerous different substituents at any position on 6:5 rings Linker/warhead at any position Hydrophobic moiety at any position	Amide substitution at C3 Linker/warhead at C7 Hydrophobic moiety at C2
Heteroatom pattern	One of eight patterns of heteroatom substitution: (1) N1, N5; (2) N1, N7; (3) N2, N7, N8; (4) N3, N7, N8; (5) N2, N5, N8; (6) N1, N5, N7; (7) N1, N2, N5, N7; (8) N2, N5, N7, N8.	2-4 N heteroatoms anywhere in 6:5 ring system with at least one N per ring Could have O and/or S heteroatoms	Three N heteroatoms at N1, N4, and N8
Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67.

See Petition at 65-71 (collecting cites); see also, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207.

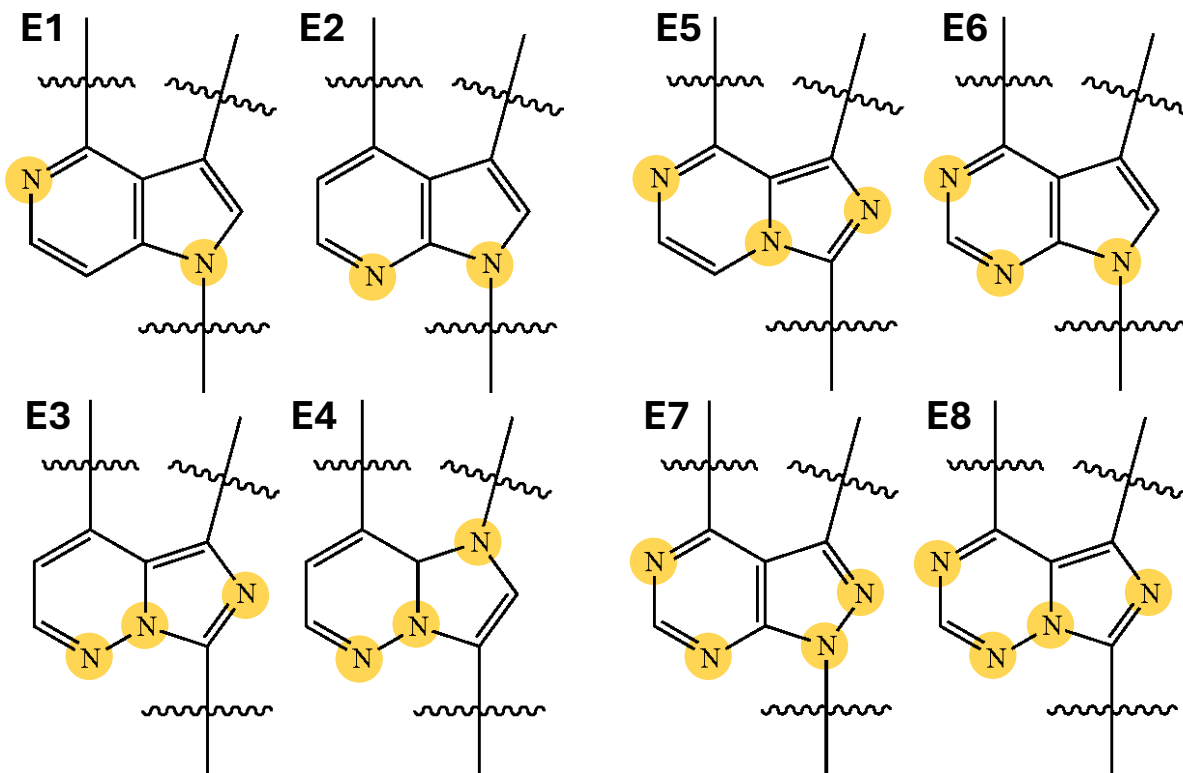
Formula E and Ibrutinib (E7) Provide Examples of Only Eight Specific Heteroatom Patterns

Ibrutinib



'803 Patent at 65:10-25 (annotated).

In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

See Petition at 65-71 (collecting cites); see also, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207.

Claims Far Broader Than Specification Disclosure in Multiple Respects

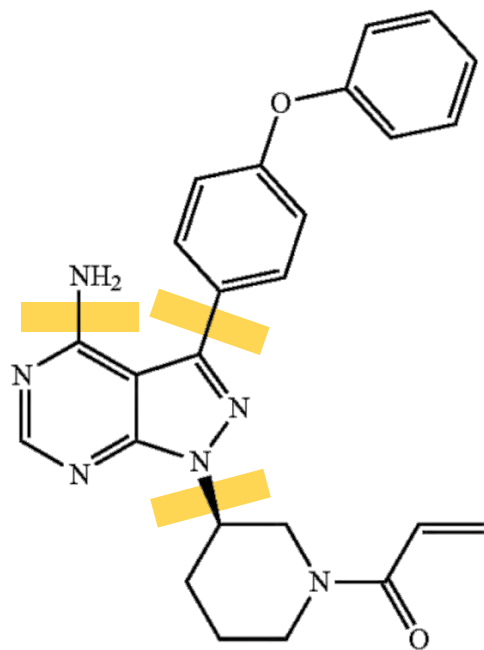
	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
Substitution pattern	Amine substitution at C4 Linker/warhead at N1 Hydrophobic moiety at C3	Numerous different substituents at any position on 6:5 rings Linker/warhead at any position Hydrophobic moiety at any position	Amide substitution at C3 Linker/warhead at C7 Hydrophobic moiety at C2
Heteroatom pattern	One of eight patterns of heteroatom substitution: (1) N1, N5; (2) N1, N7; (3) N2, N7, N8; (4) N3, N7, N8; (5) N2, N5, N8; (6) N1, N5, N7; (7) N1, N2, N5, N7; (8) N2, N5, N7, N8.	2-4 N heteroatoms anywhere in 6:5 ring system with at least one N per ring Could have O and/or S heteroatoms	Three N heteroatoms at N1, N4, and N8
Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67.

See Petition at 65-71 (collecting cites); see also, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207.

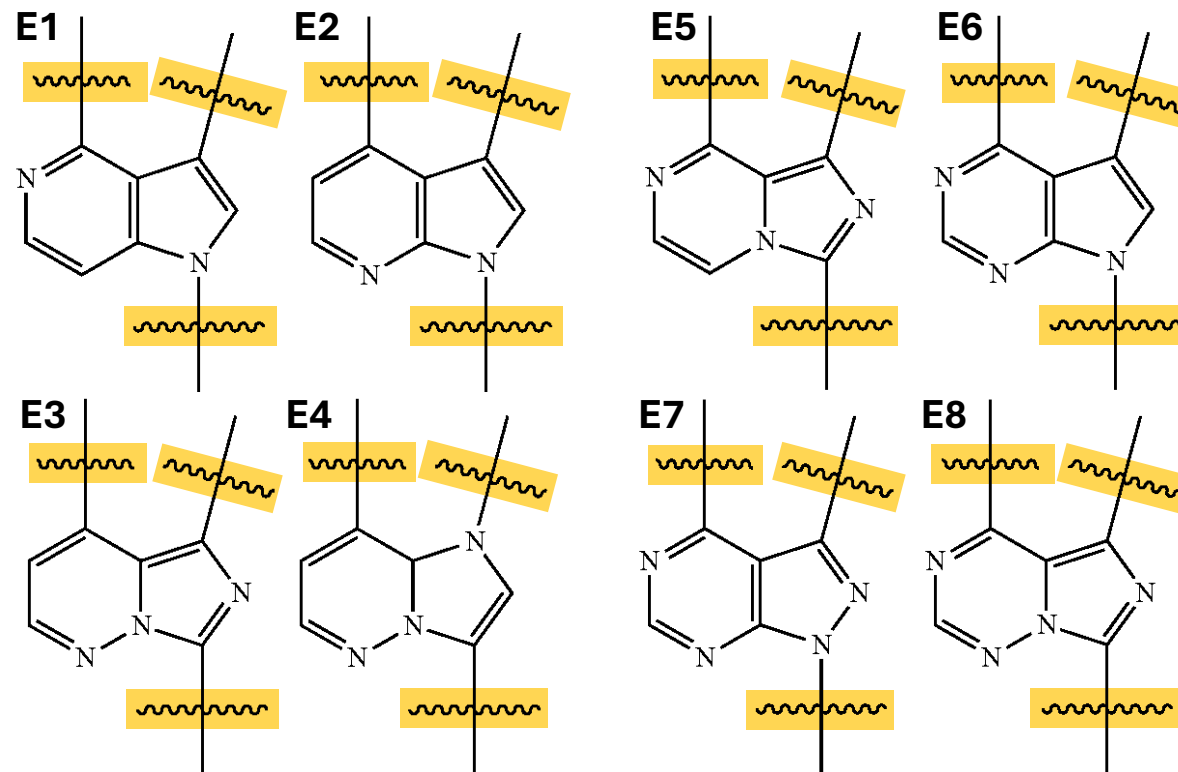
As Another Example, Formula E and Ibrutinib (E7) Provide Only One Specific Configuration for the Position of Substituents for Z' Structure

Ibrutinib



'803 Patent at 65:10-25 (annotated).

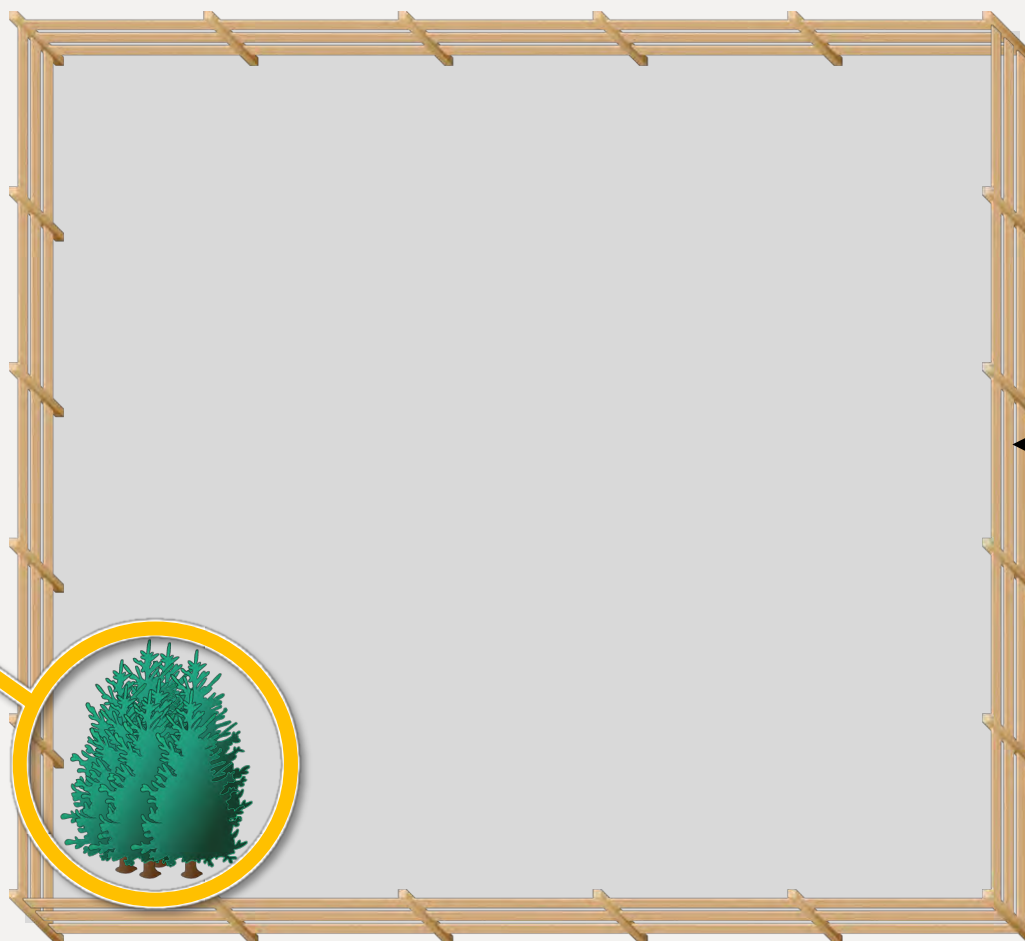
In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

See Petition at 65-71 (collecting cites); see also, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207.

**Examples with
two aromatic rings,
particular nitrogen
heteroatom
patterns, and single
substituent pattern**

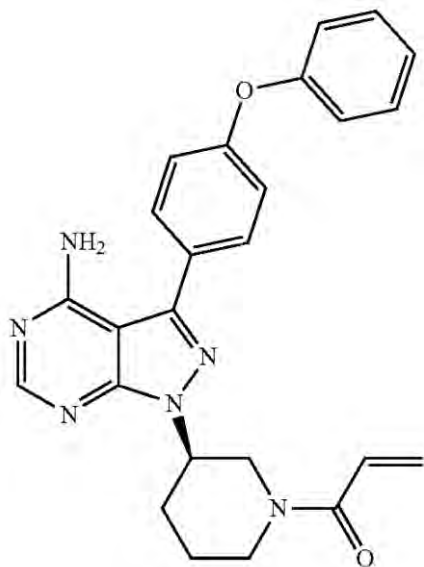


**Structural boundaries
as defined by the
claim, not limited to
two aromatic rings,
particular heteroatom
patterns, and single
substituent pattern**

See Petition at 65-71 (collecting cites); see *also*, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207.

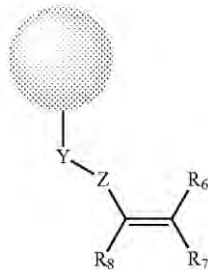
Specification Also Does Not Provide Common Features So That POSA Can Visualize or Recognize Which Subset of Z' Structures *Will Meet the Functional Limitations*

Ibrutinib



'803 Patent at 65:10-25.

Formula (E)

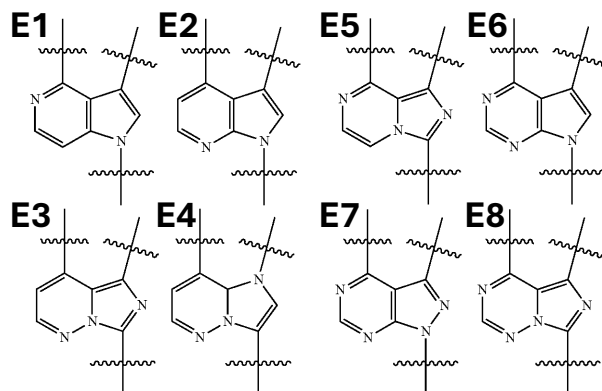


wherein:

wherein Y is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

'803 Patent at 62:1-17.

In some embodiments, Z is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

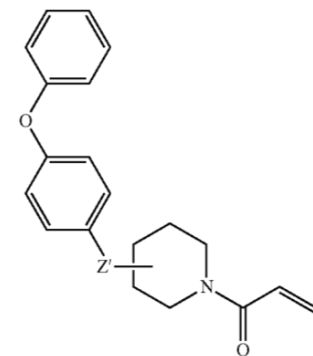
≠

1. A method for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual comprising:

orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity;

wherein lymphocytosis is not considered progression of the CLL or SLL, and

wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

wherein the irreversible inhibitor of Btk forms a covalent bond with Cys⁴⁸¹ of a Bruton's tyrosine kinase.

'803 Patent, Claim 1.

See, e.g., Petition at 71-80.

Idenix Pharms. LLC v. Gilead Scis. Inc.

941 F.3d 1149, 1164-65 (Fed. Cir. 2019)

“[The specification] provides lists or examples of supposedly effective nucleosides, but do[es] not explain what makes them effective, or why. As a result, a POSA is deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result. In the absence of that guidance, the listed examples and formulas cannot provide adequate written description support for undisclosed nucleosides that also happens to treat HCV.”

At First, Patent Owner Attempts to Imply That *All* Compounds Meeting the Claims' Structural Limitations Will Meet the Functional Ones

Patent Owner Response

² As used here, “ibrutinib-like iBTKIs” are iBTKIs having the structural features (based on ibrutinib) recited in the claims: fixed phenoxyphenyl and linker-warhead substituents attached to a central 5:6 heterocyclic scaffold with nitrogen heteroatoms.

Response at 4 n.2.

Patent Owner Response

A hallmark of the '803 Patent is its use of the structural features of ibrutinib to define the group of compounds for use in the claimed method. The express structural limitations and the structure-function relationship between those limitations and the claimed method distinguish this case from published decisions where generic functional claims were held invalid for lack of written description. Here, a POSA—armed with the specification and the knowledge of the binding mode for the compounds of the claims—would recognize the claims as limited to compounds expected to work in the recited method because of their common structural features with ibrutinib. Petitioner's development of zanubrutinib only confirms the structural features of the claims result in compounds that work in the method. The claims are more than adequately described in view of a POSA's understanding of the specification.

Response at 29.

The Z' Structure Defines a Genus of Billions of Compounds

Dr. Hollis Showalter
Petitioner's Expert

142. The number of structural species encompassed by these Structural Limitations is at least in the billions (as explained below, due to the recursive nature of the permitted substitutions, it can actually be infinite). My conservative calculation is based on the following parameters defined by the claim language of these Structural Limitations and the construction of “optionally substituted fused heterocyclic ring system.” Specifically, the structural limitations prescribe four subgenera that allow for a large number of structurally distinct species. Further, the vast number of structural species arises from the diversity of the fused heterocyclic ring systems coupled with the diversity of substitution patterns for each ring system, which are affected by a variety of factors, including the aromaticity of the ring systems (*i.e.*, biaryl *v.* non-biaryl), substitution patterns (*i.e.*, type, number, and position of substitutions present on the ring system), and heteroatom patterns (*i.e.*, type, number, and position of heteroatoms in the ring system).

Showalter Decl. (EX1003) ¶¶ 141-178; see also Petition at 57-60, Reply at 4-5 (collecting cites); Showalter Reply Decl. (EX1105) ¶¶ 16-35; Veal Reply Decl. (EX1106) ¶¶ 227-30.

Dr. Michael J. Eck
Patent Owner's Expert

- Q.** I understand. That was my question about just the Z'-structure itself. So to be fair and to be clear, just looking at the Z'-structure itself, as described in that claim, you would agree that that alone, by itself, encompasses billions of possible structures?
- A.** Again, considering it aside from the claim, I would agree that that could potentially encompass billions of structures according to Dr. Showalter's calculations.

Eck Dep. Tr. (EX1110) at 42:18-43:18; see also Reply at 4-5 (collecting cites); Showalter Reply Decl. (EX1105) ¶ 19; Veal Reply Decl. (EX1106) ¶¶ 185, 248, 254.

Patent Owner's Expert Conceded That Only a Subset of Z' Structures Will Form Compounds That Meet Additional Functional Requirements

Eck Declaration

151. First, as I have explained, in 2011, a POSA reading the '803 . . .

X.A.1.b. The need for the linker-warhead to be oriented generally towards Cys481 would limit the scope of acceptable Z'-scaffolds.

* * *

152. Second, as I have also explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the phenoxyphenyl group would need to be oriented to allow for binding within BTK's hydrophobic back pocket, which would limit the scope of acceptable Z'-scaffolds. *See supra* §§VI.D.2, VII.A.3, X.A.1.c. The

* * *

218. As I have explained, proper consideration of a POSA's knowledge about the kinase hinge region in June 2011 from the '803 Patent and art would limit the scope of acceptable compounds to those that have a Z'-scaffold that functions as a hinge-binding element and makes the necessary one to three H-bonds with the BTK hinge region. *See supra* §§VI.D.3, VII.A.4, X.A.2. Moreover, as discussed

Eck Declaration (EX2010) ¶¶ 151, 152, 218.

Dr. Michael J. Eck

Patent Owner's Expert

Q. Okay. What is the size of the genus of what you refer to as, "acceptable Z'-scaffolds"?

A. I have no idea. I haven't tried to do that calculation.

* * *

A. The answer is I wouldn't put a number on it. You know, I would say comfortably more than hundreds but beyond that, you know, without – yeah, just not – haven't done that analysis, haven't thought about how I would do that analysis precisely, and so I don't want to try to put a number on it.

Eck Dep. Tr. (EX1110) at 44:17-45:10.

Z' Structure Critically Impacts Whether the Claimed Compounds Will Meet the Functional Limitations

Petition

The Z'-structure of a BTKI plays a critical role in binding Btk because it controls the orientation of the BTKI relative to Btk and affects whether and how the hydrophobic moiety and warhead align with the correct regions of Btk. EX1003, ¶¶53-60. If the Z'-structure does not first orient the molecule in a particular manner to form favorable noncovalent interactions and project the linker and warhead in the correct orientation to Cys481, the molecule will not be able to make a covalent bond with Cys481. *Id.* The Z'-structure is not simply a space-filler; it dictates whether and how the molecule will inhibit Btk. *Id.*

Petition at 17; see also, e.g., Showalter Decl. (EX1003) ¶¶ 53-60.

Patent Owner Concedes Z' Structure Impacts Whether the Claimed Compounds Will Meet the Claims' Functional Limitations

Patent Owner Response

donor and acceptor. EX1052.002 (Fig. 2); EX2010 ¶¶62; EX2012 ¶¶24-25. For compounds with ibrutinib-like binding, as shown in Marcotte, the Z'-scaffold hydrogen bonds with the expected hinge residues and orients the phenoxyphenyl and linker-warhead components within BTK—projecting the phenoxyphenyl toward the back-pocket and projecting the linker-warhead toward Cys481. EX2001.0001-.0002; EX2010 ¶¶71, 111-112.

* * *

zanubrutinib. *See* Pet. 10-11. Aromaticity is again the wrong analysis. A POSA in 2011 would understand Z'-scaffolds need to properly orient the fixed structural components and form H-bonds with the hinge. EX2010 ¶¶168-171; EX2012 ¶¶25-28. Once the fixed and H-bonding components are properly placed, a POSA would

Response at 23, 52.

Instead of Identifying Common Structural Features of Z' Structures That Will Satisfy the Functional Limitations, Patent Owner Identifies More Functional Requirements

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q.** Can you identify structures that would be common to all of the species of Z'-scaffolds that would satisfy those requirements
- A.** So the claim species have many structural features in common. So as I've laid out in the declaration, it's very clear that there is a phenoxyphenyl that's required. It's very clear that there is a specific linker-warhead, the pepperidine (phonetic) with the attached acrylamide that's required.

With respect to the Z'-structure, it will be required that it be able to appropriately position the phenoxyphenyl to bind in the back pocket and simultaneously appropriately position the linker-warhead to react with Cys481. So Z's that are within the claim will have that structural feature. Additionally, they will have to sterically fit within the ADP binding site and form from one to three hydrogen bonds with the hinge.

Patent Owner Contends the POSA Could Visualize Members of Genus Satisfying All Functional Limitations By Modeling

Patent Owner Response

[structure]”). A POSA would use software with Marcotte’s data to visualize the structures within the claims to recognize the compounds that bind and inhibit BTK. EX2010 ¶¶111-118, 153.

* * *

with BTK’s hinge. EX2010 ¶¶71, 111-112, 153. Indeed, a POSA in 2011 would have been able to accurately dock zanubrutinib into the BTK active site to recognize it as an ibrutinib-like iBTKI. §IV.C.3; EX2010 ¶¶117-118. The robust structural

Response at 46-47, 65.

Modeling Only Serves As a Tool to Approximate If An Individual Potential Inhibitor, Already Drawn, Might Bind BTK

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q. Okay. So reading the patent, which of those eight would they – would be in the category of at least some that would be able to be used to make an ibrutinib-like BTK?
- A. So as I said, as we sit here, I haven't done that analysis. As we sit here today, I can't answer that question, but I can tell you that as a POSA or as a member of a POSA team, how I would approach that, right. So, you know, taking, for example, the structure in the lower left in Column 63, that looks to me as a POSA, like a promising structure for making a BTK-like inhibitor. I would propose an amine substitution in the first position that's indicated for, you know, for substitution. I would propose the phenoxyphenyl in the second and the linker-warhead of the claims in the third.

I would consult with my medicinal chemist colleague for an opinion as to whether he agreed that that would be good. I would carry out a docking exercise to assess how well it fit within the active site of BTK. And, yeah, and will thereby have visualized a new BTK inhibitor, ibrutinib-like. "New" in the sense of one that, you know, has been invented and described here, but probably not been synthesized and tested previously.

E.g., Eck Dep. Tr. (EX1110) at 72:6-73:5; see also, e.g., Reply 10-13 (collecting cites); Veal Reply Decl. (EX1106) ¶¶ 98, 107, 188-91, 244-252.

As *Juno* Demonstrates, That Is Not the Test for Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc.
10 F.4th 1330, 1334, 1336-40 (Fed. Cir. 2021)

- Claims directed to scFv antibodies capable of binding given targets
- Antibody binding assays were widely available
- Yet genus claim still invalid, as the specification “fail[ed] to disclose structural features common to scFvs capable of binding specific targets” and “fail[ed] to disclose a way to distinguish those scFvs capable of binding from scFvs *incapable* of binding those targets”—specifically because it “provide[d] no amino acid sequences or other distinguishing characteristics of the scFvs that bind”

See, e.g., Petition 71-80; Reply at 10-13, 15-21.

As *Idenix* Demonstrates, That Is Not the Test for Written Description

Idenix Pharms. LLC v. Gilead Scis. Inc.

941 F.3d 1149, 1153-55, 1159, 1164-65 (Fed. Cir. 2019)

- Claims directed to method of treating HCV by administering nucleoside compounds with some specified chemical and stereochemical structure (2'-methyl-up)
- 2'-methyl-up nucleosides could be “screened” for HCV efficacy
- Yet genus claim still invalid, as the specification “provide[d] no method of distinguishing effective from ineffective compounds for the compounds reaching beyond the formulas disclosed”

See, e.g., Petition 71-80; Reply at 10-13, 15-21.

As *AbbVie* Demonstrates, That Is Not the Test for Written Description

AbbVie Deutschland GmbH v. Janssen Biotech, Inc.

759 F.3d 1285, 1291-92, 1300-01 (Fed. Cir. 2014)

- Claims directed to human antibodies that bind to and neutralize the activity of IL-12 at a certain level
- Specification did demonstrate that an exemplary antibody “showed a significant increase in IL-12 binding and neutralizing activity”—demonstrating that assays were available
- Yet genus claim still invalid, as “the jury heard ample evidence that AbbVie’s patents only describe one type of structurally similar anti-bodies and that those antibodies are not representative of the full variety or scope of the genus,” necessitating a “trial and error approach to modify individual amino acids in order to improve the IL-12 binding affinity”

See, e.g., Petition 71-80; Reply at 10-13, 15-21.

Patent Owner's Modeling Argument Is at Most an Argument That Certain Other Compounds Might Be Obvious

Ariad Pharms., Inc. v. Eli Lilly & Co.
598 F.3d 1352 (Fed. Cir. 2010)

“[W]hile the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement.”

Lockwood v. Am. Airlines, Inc.
107 F.3d 1565, 1572 (Fed. Cir. 1997)

“The question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification. Rather, a prior application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.”

See, e.g., Reply at 6-8, 10-19; see also *Daichi Sankyo v. SeaGen*, PGR2021-00030, Paper 57 at 25 (Jan. 16, 2024).

Patent Owner Response

D. A POSA Would Know How to Use Ibrutinib and Available Modeling to Create Additional Ibrutinib-Like iBTKIs with Different Z'-Scaffolds

A POSA reading the ’803 Patent would leverage the known structure-function relationship for binding to the BTK hinge to select ibrutinib-like iBTKIs for use in the claimed methods. In particular, in 2011, a POSA would have known of widely available and widely used computational tools for docking candidate iBTKIs. *See, e.g.*, EX2035; EX2036; EX2041; EX2010 ¶¶115-118. In 2011, these tools were an integral part of kinase inhibitor design, used to visualize binding modes and prioritize compounds for synthesis and potential further preclinical development. EX2010 ¶115. This would have been particularly true for ibrutinib-like iBTKIs, where Marcotte revealed the binding mode for this class of inhibitors and the ’803 Patent provided functional and clinical data validating the mechanism. *Id.* ¶¶108-118.

Response at 25; see also Reply 3; EX1001.

Patent Owner's Modeling Argument Depends on Marcotte, Not Cited in the '803 Patent Specification

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q.** Do you mean that it may, it may not, you'd have to model or test it to figure that out; is that what you mean?
- A.** I think, as I said, that the POSA would use the standard tools of the trade and compose a structure positioned hydrogen bond donors, acceptors, model it in the structure of **Marcotte**, et al, and would be able to readily determine whether it was useful for that.
- Q.** Okay. And with respect to that scaffold structure you see on Page 53, where would a POSA attach the phenoxyphenyl group?
- A.** As we've discussed before, I would, you know, as we sit here today, I'm not equipped to do that, but my approach to it would be to work with other members of the POSA team, apply modeling tools.

E.g., Eck Dep. Tr. (EX1110) at 91:18-92:8; see also Reply at 3; EX1001.

Patent Owner's Expert Conceded Modeling Does Not Generate Structures to Test

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q. Okay. So reading the patent, which of those eight would they – would be in the category of at least some that would be able to be used to make an ibrutinib-like BTK?
- A. So as I said, as we sit here, I haven't done that analysis. As we sit here today, I can't answer that question, but I can tell you that as a POSA or as a member of a POSA team, how I would approach that, right. So, you know, taking, for example, the structure in the lower left in Column 63, that looks to me as a POSA, like a promising structure for making a BTK-like inhibitor. I would propose an amine substitution in the first position that's indicated for, you know, for substitution. I would propose the phenoxyphenyl in the second and the linker-warhead of the claims in the third.

I would consult with my medicinal chemist colleague for an opinion as to whether he agreed that that would be good. I would carry out a docking exercise to assess how well it fit within the active site of BTK. And, yeah, and will thereby have visualized a new BTK inhibitor, ibrutinib-like. "New" in the sense of one that, you know, has been invented and described here, but probably not been synthesized and tested previously.

E.g., Eck Dep. Tr. (EX1110) at 72:6-73:5; see also, e.g., Reply 10-13 (collecting cites); Veal Reply Decl. (EX1106) ¶¶ 98, 107, 188-91, 244-252.

Patent Owner's Expert Admitted It Would Take Him About an Hour to Model Each Potential Inhibitor

Dr. Michael J.
Eck
*Patent Owner's
Expert*

Q. According to you, visualizing the docking of a candidate BTKI could be accomplished in a matter of minutes, right?

A. That's correct.

Q. So you could take that scaffold structure and in a matter of minutes visualize whether it would be a candidate BTKI, right?

A. We're talking about two different things. So as I've – the section of my declaration that you're quoting from, I'm talking about taking a fully-formed inhibitor and docking it. Here, we are talking about taking a scaffold and elaborating it into a fully-formed inhibitor.

Q. How long would that take?

A. I mean, if I were in my office, at my work station, you know, I could in a matter of, you know, I think less than an hour, have a clear sense of where I would want to attach the phenoxyphenyl and the linker-warhead and the other substitutions that I might be interested in adding in order to achieve hydrogen bonds with the hinge. Others who are – you know – what am I trying to say? Yeah, I'm not particularly fast. I'm slow and deliberate. Others could probably do it even faster.

Eck Dep. Tr. (EX1110) at 94:1-95:1; see also, e.g., Veal Reply Decl. ¶ 247.

Patent Owner Contends That Modeling Was “Sophisticat[ed]” and “Precis[e]”

Patent Owner Response

Indeed, Petitioner itself used exactly this approach in the development of zanubrutinib. Using Marcotte’s structure, Petitioner predicted how a zanubrutinib analog would bind to BTK. As seen in Petitioner’s published figure below, the Marcotte structure (green structure, left panel) was used to dock the zanubrutinib analog (purple structure, middle panel). The docking revealed the precise alignment of these structures (overlay, right panel). EX2039.0003-.0004, Fig. 1; EX2010 ¶164. The predicted zanubrutinib binding mode was later confirmed in its crystal structure. EX1044.004, Fig. 2B; EX2010 ¶164. Such accurate binding mode predictions illustrate the sophistication and precision of virtual docking and modeling for useful ibrutinib-like iBTKIs based on Marcotte. EX2010 ¶¶108-118.

Response at 25-26.

Both Parties' Experts Agreed That Modeling Must Be Validated by Synthesis and Experimental Testing

Veal Reply Declaration

101. As described below, modeling in 2010/2011 (and even today) would not have accurately predicted whether a compound will irreversibly inhibit Btk. Therefore, experimental testing would have been required in order to determine whether any given structure will irreversibly inhibit Btk. The binding of a ligand or inhibitor to a protein target is a complex physicochemical process involving both enthalpic and entropic interactions, and covalent modification adds additional complexity. Even today, modeling necessarily uses multiple approximations to represent what can only accurately be measured by applying quantum mechanics to a large dynamic system consisting of the ligand, protein, solvent, counterion, and other potential cofactors. This is beyond the scope of computer capabilities even today. Thus, modeling and structure aided drug design is used to improve probabilities of success but has significant limitations and cannot replace experimental testing.

Veal Reply Decl. (EX1106) ¶ 101; see *also*, e.g., Reply at 11-12 (collecting cites).

David Scott

Patent Owner's Expert

- Q. If a modeler were to tell you that a candidate kinase inhibitor would inhibit the target based on their modeling, would you take them at their word?
- A. I would want to understand the work they had done and the information the model was based upon.
- Q. Would you do any additional testing to confirm that they were correct?
- A. I'm not sure I understand what you mean by testing.
- Q. Would you run an assay to confirm that the inhibitor actually inhibits the target?
- A. Oh, I see. Yes, it's valuable to validate predictions of modeling with data, and that's something that we would have done.

Scott Dep. Tr. (EX1117) at 40:18-41:13.

Petitioner's Expert Demonstrated That Modeling Is Not Predictive of BTK Inhibition

Reference	Compound	Glide Docking Score	Reported IC ₅₀ Value	Reported IC ₅₀ Value Source
	Ibrutinib*	-10.5	2.0 nM	EX2063.0002 (Fig. 3)
	Zanubrutinib*	-9.3	0.3 nM (S isomer); 11 nM (R isomer)	EX1053.005 (Table 6)
WO'289 (EX1108)	Compound 81	-9.7	5,900 nM	EX1108, [0642], Table II
WO'185 (EX1109)	Compound 9	-10.3	> 1000 nM < 100,000 nM	EX1109, [00348]

Veal Reply Decl. (EX1106) ¶¶ 99-104, 114-138 (annotated).

- More negative docking scores suggest tighter binding
- Compounds with an IC₅₀ value of >1000 nM are inactive
- None of Patent Owner's experts disagreed with these thresholds

See Veal Reply Decl. (EX1106) ¶¶ 97, 119; Showalter Reply Decl. (EX1105) ¶ 39.

AbbVie Deutschland GmbH v. Janssen Biotech, Inc.

759 F.3d 1285, 1299-1300 (Fed. Cir. 2014)

“With the *written description* of a genus, however, merely drawing a fence around a perceived genus is not a description of the genus. One needs to show that one has truly invented the genus, i.e., that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.”

Patent Owner Asserts That Z' Structures Are “Fungibl[e]”

Patent Owner Response

The specification’s Formula E recognizes the fungibility and predictability of substructures that bind to the highly conserved kinase hinge while maintaining the fixed linker-warhead and phenoxyphenyl groups of ibrutinib. EX1001, 61:66-63:21; EX2010 ¶¶60, 83-84. For the Z’-scaffold, Formula E invokes the kinase inhibitor

* * *

Here, as in *Invitrogen* and *Falko-Gunter*, in 2011, there was a “well known” or “sufficiently known correlation” between heterocyclic scaffold structure and hinge-binding function that would have been understood in view of the specification’s teaching. See §§II.C.3, IV.C.3; EX2010 ¶¶192-193. In view of a

Response at 23, 72.

See, e.g., Reply at 8-10.

Other Than Ibrutinib, Patent Owner's Expert Did Not Attempt to Model Any Known Prior Art Scaffolds With the Claimed Z' Structure

Veal Reply Declaration

2. Modeling/Docking of Specific Structures

a) Structures Modeled by Dr. Eck

105. Dr. Eck performed modeling using Glide docking within the Maestro (Schrödinger) modeling environment on ibrutinib, zanubrutinib, Compounds 20, 30, and 122 of the 446 Patent, and Compounds 7 and 8 of Zhang. *See* EX2010, ¶¶116-118, 184-185. Of these structures, the only one that was known as of 2011 is ibrutinib. In fact, PO admitted that “[i]n June 2011, there were no [BTKIs] approved by FDA; ibrutinib was the first approved [BTKI].” EX1078, ¶108.

Veal Reply Decl. (EX1106) ¶¶ 105-13, 139; *see also*, e.g., Eck Decl. (EX2010) ¶¶ 116-118, 185-85.

Patent Owner's Expert Did Not Model Even the E1 to E8 Cores From the Specification (Other Than Ibrutinib)

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q. So a POSA would read this patent, and you said would understand – that at least some of them would be able to be used to make an ibrutinib-like BTK inhibitor; which ones? You read the patent.
- A. I read the patent. I can take a minute to remind myself, for example, which one is, you know, is precisely ibrutinib.
- Q. You don't need to do that because we know that ibrutinib is ibrutinib.
- A. I think we can agree that a POSA would well understand that.
- Q. What about the other ones that are not ibrutinib?
- A. As I said, I haven't – I haven't gone through them one by one and done that analysis.

If Modeling Is Predictive, E2, E3, and E4 Show Lack of Correlation Between Structural and Functional Limitations of Claims

- At least 3 of 8 of the E1 to E8 cores, when modeled with ibrutinib’s substituents, do NOT bind
- Patent Owner did NOT provide evidence showing that these compounds would bind

141. Below is a table summarizing the most negative docking scores I obtained for various structures with non-biaryl cores (including Structure E4) and two biaryl cores disclosed in the specification (Structures E2 and E3). Notably, while the inventors of the 803 Patent suggested using BTKIs comprising the E2-E4 cores, modeling suggests that compounds comprising these Z'-scaffolds do not irreversibly inhibit Btk.

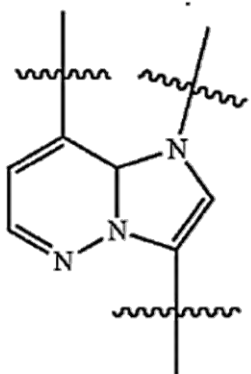
Reference	Compound	Fused Heterocyclic Ring System Subgenus	Glide Docking Score
803 Patent (EX1001)	Structure E2	Biaryl	-8.5
803 Patent (EX1001)	Structure E3	Biaryl	-8.6
803 Patent (EX1001)	Structure E4	5-non-aro, 6-non-aro	-7.4
820 Patent (EX2023)	Formula I scaffold	5-aro, 6-non-aro	-7.4
EX2055	PDB: 2QD9	5-aro, 6-non-aro	-7.5
EX2046	PDB: 5TR6/5TT7	5-non-aro, 6-aro	-6.9

Veal Reply Decl. (EX1106) ¶¶ 139-152.

If Modeling Is Predictive, It Suggests the E4 Core Is Not Expected to Bind BTK With Ibrutinib's Substituents

Veal Reply Declaration

150. Structure E4 comprises a non-biaryl core (*i.e.*, non-aromatic 5-membered and 6-membered rings), as shown below:



EX1001, 62:44-63:21

151. When modeling Structure E4 (which I believe to be an inaccurately drawn structure), I used the same substitution pattern as ibrutinib (*i.e.*, amine substitution at the C4 position of the 6-membered ring, linker-warhead substitution at the C1 position of the 5-membered ring, and phenoxyphenyl substitution at the N3 position of the 5-membered ring).

152. While Structure E4 properly oriented the phenoxyphenyl to bind Btk's back pocket, Structure E4 was not at all tolerated in the binding site of Btk, did not form any H-bonds to Btk's hinge region, and did not properly orient the linker-warhead to covalently bind Cys481 (even the best docking pose had the linker-warhead significantly displaced from the vicinity of Cys481). In my opinion, Structure E4 does not dock well at least in part because it does not have one of the aromatic nitrogens that is present in ibrutinib and forms a H-bond with Btk's hinge region. Moreover, the "butterfly" conformation of the structure due to its sp^3 hybridized carbon favoring a tetrahedral geometry leads to an unfavorable steric clash that displaces the ligand from the adenine binding region. Below is the docking pose of Structure E4 with attached substituents with the most negative Glide docking score (-7.4).

Veal Reply Decl. (EX1106) ¶¶ 150-152.

Patent Owner did not address the modeling of E4 in sur-reply.

As to E2 and E3, Patent Owner's Only Response Is That Petitioner's Expert Modeled One Compound With the E2 and E3 Cores

Patent Owner Sur-Reply

³ Petitioner asserts that “modeling suggests that no claimed compound comprising E2-E3 would covalently bind.” Reply 14 n.9. Dr. Veal’s opinion on these compounds was based on Dr. Eck’s “conclusion” that compounds having a heterocyclic ring that does not H-bond to BTK’s hinge would be inactive. EX2119, 218:18-224:22. Dr. Eck did not opine that E2-E3 could never be scaffolds in a BTKI but rather identified that particular compounds made **no** H-bonds to the hinge. *E.g.*, EX2010, ¶184. But these particular compounds lacked other structural features, such as the amine substituent, that form necessary H-bonds to support binding. EX2119, 220:20-221:20; EX1106, ¶¶142-149. Further, Dr. Veal modeled a single compound for both scaffolds, which does not support that **no compounds** with these scaffolds would covalently bond. *E.g.*, EX1106, ¶¶142-149.

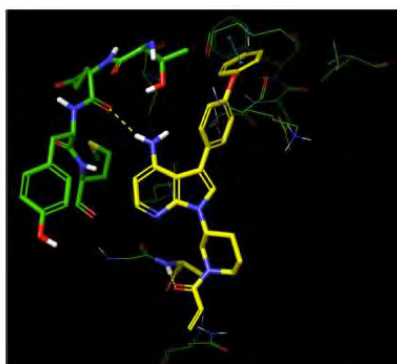
Sur-Reply at 13 n.3.

But Petitioner's Expert Modeled E2 and E3 With the Substitution Pattern Directed by Formula E and the Specification

Patent Owner Sur-Reply

³ Petitioner asserts that E2-E3 would covalently bond to the heterocyclic ring that is described in 218:18-224:22. Dr. Eckert, however, but rather identified the structure in EX2010, ¶184. But the structure is not the same as the amine substituent in EX2010, ¶220:20-221:20; EX1106, ¶184. For both scaffolds, which would covalently bond

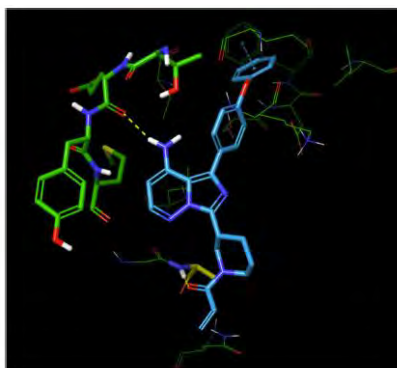
Veal Reply Declaration



EX1147.001

145. When modeling Structure E2, I used the same substitution pattern as ibrutinib (*i.e.*, amine substitution at the C4 position of the 6-membered ring, linker-warhead substitution at the N1 position of the 5-membered ring, and phenoxyphenyl substitution at the C3 position of the 5-membered ring).

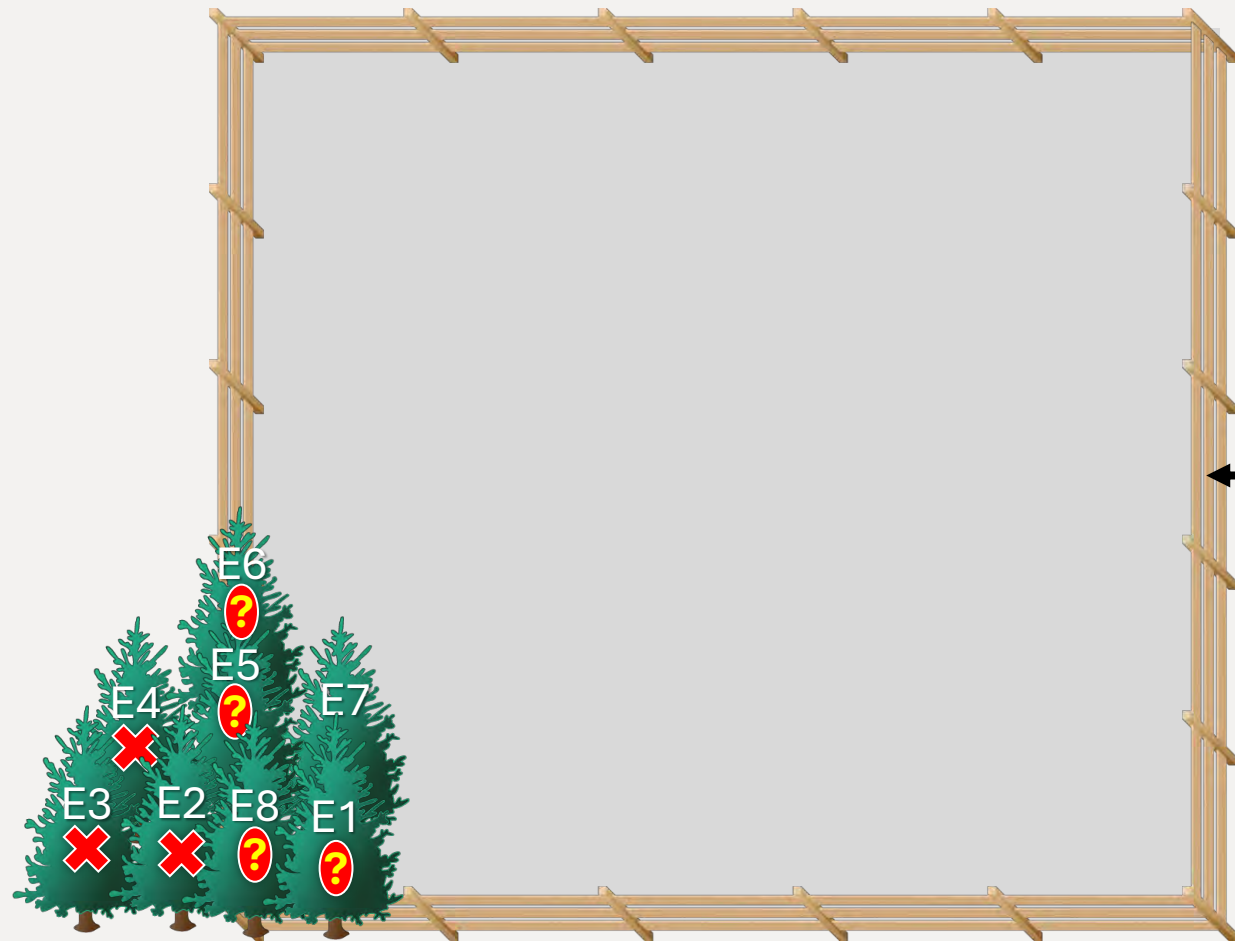
Veal Reply Decl. (EX1106) ¶ 145.



EX1148.001

148. When modeling Structure E3, I used the same substitution pattern as ibrutinib (*i.e.*, amine substitution at the C4 position of the 6-membered ring, linker-warhead substitution at the C1 position of the 5-membered ring, and phenoxyphenyl substitution at the C3 position of the 5-membered ring).

Veal Reply Decl. (EX1106) ¶ 148.



**Structural and
functional boundary,
as defined by the claim**

See Petition at 71-80, Reply at 8-9 (collecting cites); see *also*, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207; Veal Reply Decl. (EX1106) ¶¶ 139-152.

Patent Owner Asserts That the Prior Art Taught Partially Non-Aromatic Hinge Binding Elements

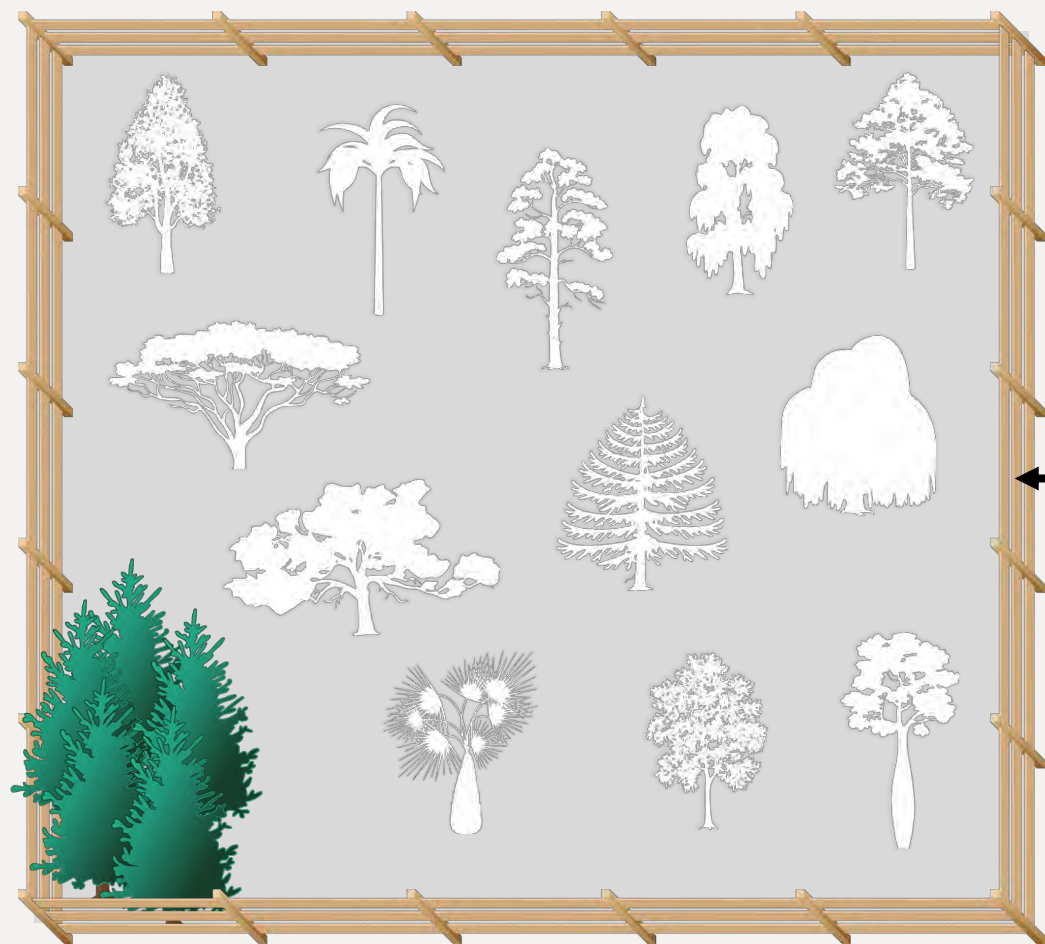
Patent Owner Response

EX2010 ¶¶168-171. A POSA would have been aware of numerous hinge-binding elements, including those with non-aromatic (i.e., partially saturated and non-planar) portions. *Id.* ¶¶168-175; EX1052.003, .012-.013 (partially saturated scaffolds 30, 31, 33, 37, 39); EX2028.0004, Fig. 5 (disclosing a “highly potent, novel inhibitor[]” with partially saturated scaffold); EX2023, 2:1-6 (kinase inhibitors with 5:6 heterocyclic scaffold having saturated 6-membered ring); EX2026, cls. 1, 10 (BTKIs with partially saturated hinge-binding scaffold); EX2055; EX2038.0001, Fig. 1; EX2053.

Response at 52.

Supp. 3d at 639, 645-46. Similarly, here there were numerous known heterocyclic scaffolds that bound to the “highly conserved” kinase hinge. EX2010 ¶¶83-89, 147-148; §II.C.3; EX1077.003-.004; EX2028.0002-.0004; EX1052.003-.018; EX2023, 2:1-6; EX1073.009, Tbl. 2 (BTKIs); EX2026, cls. 1 & 10, [0023], [0076] (BTKIs); EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1) (BTKIs). As taught in the specification’s Formula E, a POSA would understand heterocyclic scaffolds make predictable interactions with the kinase hinge. EX2010 ¶¶83-89, 147-148; EX1052.002; EX2028.0001-.0005. Further, a POSA would have access to

Response at 64-65.



**Structural and
functional boundary,
as defined by the claim**

See, e.g., Response at 52, 64-65.

But the Prior Art Patent Owner Relies on Disclose Cores That (1) Do Not Satisfy the Structural Limitations of Z', (2) Are Biaryl, or (3) Modeling Predicts Will Not Bind

Patent Owner Response

EX2010 ¶¶168-171. A POSA would have been aware of numerous hinge-binding elements, including those with non-aromatic (i.e., partially saturated and non-planar) portions. *Id.* ¶¶168-175; EX1052.003, .012-.013 (partially saturated scaffolds 30, 31, 33, 37, 39); EX2028.0004, Fig. 5 (disclosing a “highly potent, novel inhibitor[]” with partially saturated scaffold); EX2023, 2:1-6 (kinase inhibitors with 5:6 heterocyclic scaffold having saturated 6-membered ring); EX2026, cls. 1, 10 (BTKIs with partially saturated hinge-binding scaffold); EX2055; EX2038.0001, Fig. 1; EX2053.

Response at 52.

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Response at 64-65.



scaffold not a Z' structure



biaryl



modeling shows not expected to bind

See, e.g., Reply at 8-9 & n.4;
Veal Reply Decl. (EX1106) ¶¶ 63-68,
139-143, 153-161, 171, 195, 211, 214-220.

But the Prior Art Patent Owner Relies on Disclose Cores That (1) Do Not Satisfy the Structural Limitations of Z', (2) Are Biaryl, or (3) Modeling Predicts Will Not Bind

Patent Owner Response

EX2010 ¶¶168-171. A POSA would have been aware of numerous hinge-binding elements, including those with non-aromatic (i.e., partially saturated and non-planar) portions. *Id.* ¶¶168-175; EX1052.003-.012-.013 (partially saturated scaffolds 30, 31, 33, 37, 39); EX2028.0004, Fig. 5 (disclosing a “highly potent, novel inhibitor[]” with partially saturated scaffold); EX2023, 2.1-6 (kinase inhibitors with 5.6 heterocyclic scaffold having saturated 6-membered ring); EX2026, cls. 1, 10 (BTKIs with partially saturated hinge-binding scaffold); EX2055; EX2038.0001, Fig. 1; EX2053.

Response at 52.

Supp. 3d at 639, 645-46. Similarly, here there were numerous known heterocyclic scaffolds that bound to the “highly conserved” kinase hinge. EX2010 ¶¶83-89, 147-148; §II.C.3; EX1077.003-.004, EX2028.0002-.0004, EX1052.003-.018, EX2023, 2:1-6; EX1073.009, Tbl. 2 (BTKIs); EX2026, cls. 1 & 10, [0023], [0076] (BTKIs); EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1) (BTKIs). As taught in the specification’s Formula E, a POSA would understand heterocyclic scaffolds make predictable interactions with the kinase hinge. EX2010 ¶¶83-89, 147-148; EX1052.002; EX2028.0001-.0005. Further, a POSA would have access to

Response at 64-65.

-  scaffold not a Z' structure
-  biaryl
-  modeling shows not expected to bind
-  not BTK inhibitor

See, e.g., Reply at 8-9 & n.4; Veal Reply Decl. (EX1106) ¶¶ 63-68, 139-143, 153-161, 171, 195, 211, 214-220.

Petitioner’s Unrebutted Modeling Shows That None of the Prior Art Non-Biaryl Z’ Structures Patent Owner Cites Are Expected to Bind

Veal Reply Declaration

139. I performed modeling of various known biaryl and non-biaryl Z'-scaffolds that Dr. Eck alleges that a POSA could easily use to perform “scaffold swapping.” EX2010, ¶¶104, 171, 172, 174. Dr. Eck acknowledged that he did not

* * *

Reference	Compound	Fused Heterocyclic Ring System Subgenus	Glide Docking Score
803 Patent (EX1001)	Structure E2	Biaryl	-8.5
803 Patent (EX1001)	Structure E3	Biaryl	-8.6
803 Patent (EX1001)	Structure E4	5-non-aro, 6-non-aro	-7.4
820 Patent (EX2023)	Formula I scaffold	5-aro, 6-non-aro	-7.4
EX2055	PDB: 2QD9	5-aro, 6-non-aro	-7.5
EX2046	PDB: 5TR6/5TT7	5-non-aro, 6-aro	-6.9

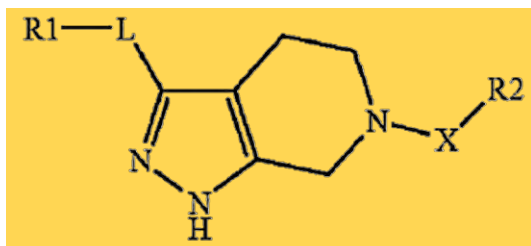
Veal Reply Decl. (EX1106) ¶¶ 139-161.

Formula I of EX2023 Would Not Lead a POSA to a Non-Biaryl Z' Structure

Veal Reply Declaration

(4) 820 Patent (EX2023), Formula I

153. Formula I of the 820 Patent comprises a non-biaryl Z'-scaffold (a non-aromatic 6-membered ring fused to an aromatic 5-membered ring), as shown below:



EX2023, 1:65-2:6

154. In my opinion, a POSA would recognize that the 5-membered ring (pyrazole group) would almost certainly be the hinge binder moiety on the scaffold and form H-bonds to Btk's hinge region with the pyrazole NH forming a H-bond to Glu475 C=O and the pyrazole N forming an H-bond to Met477 NH. Based on this concept, the phenoxyphenyl was attached to the 6-membered ring (piperidine) nitrogen and the linker-warhead was attached to the unsubstituted carbon of the

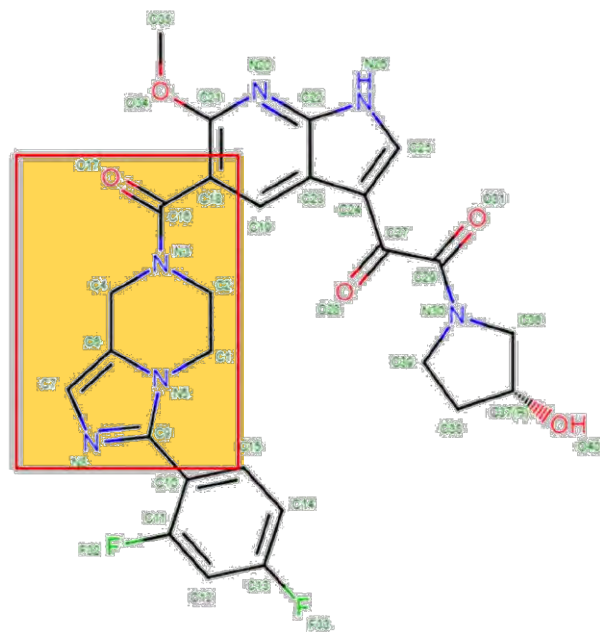
piperidine meta to the piperidine nitrogen. The chirality of the carbon was varied, and the warhead was incorporated both meta and para within the linker-warhead ring. The Glide docking poses that resulted from this approach were unfavorable for binding to Btk with the best Glide score being -7.4. The phenoxyphenyl docked correctly and the linker-warhead was able to position as well in the vicinity of Cys481. However, making these binding interactions significantly distorted the ability of the pyrazole to bind proximal to the hinge region and form appropriate H-bonds. Thus, it is my opinion that the 820 Patent (EX2023), Formula I structure does provide any guidance that would lead one to the zanubrutinib structure or any non-biaryl Z'-scaffold. Note that I also evaluated adding an NH2 group to the pyrazole (similarly to ibrutinib), but this resulted in a poorer docking score versus not adding the NH2 group.

Veal Reply Decl. (EX1106) ¶¶ 63-64, 139-143, 153-154, 211, 213; see also EX2023.

2QD9 of EX2055 Would Not Lead a POSA to a Non-Biaryl Z' Structure

Veal Reply Declaration

155. The structure of 2QD9 obtained from the PDB is shown below:



EX1153.003

EX1153 is the PDB entry for 2QD9, the inhibitor Patent Owner's expert contends is disclosed in EX2055.

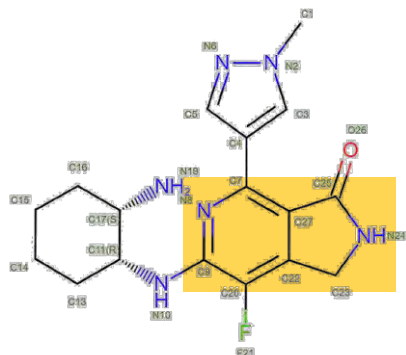
157. 2QD9 had a poor Glide docking score (-7.5) with no H-bonding to the hinge region of Btk. Below is the docking pose of the 2QD9 Z'-scaffold with the attached substituents with the most negative Glide docking score (-7.5). The phenoxyphenyl docked correctly and the linker-warhead was able to position in the vicinity of Cys481. However, similar to what was observed with the 5-membered ring in the 820 Patent (EX2023) Formula I structure, making these binding interactions prevented the acetyl group from binding proximal to the hinge region and forming an appropriate H-bond to the Met477 NH. Thus, it is my opinion that the 2QD9 structure does not provide any guidance that would lead one to the zanubrutinib structure or any non-biaryl Z'-scaffold. Note that adding an NH₂ group, in a position analogous to that of the NH₂ of ibrutinib, would require attaching it ortho the acetyl to a sp³ carbon, which would be expected to be both sterically unfavorable and result in a positively charge amine.

Veal Reply Decl. (EX1106) ¶¶ 139-143, 155-157, 213, 215; see also EX1153; EX2055.

5TR6/5TT7 of EX2046 (2016) Also Would Not Lead a POSA to a Non-Biaryl Z' Structure

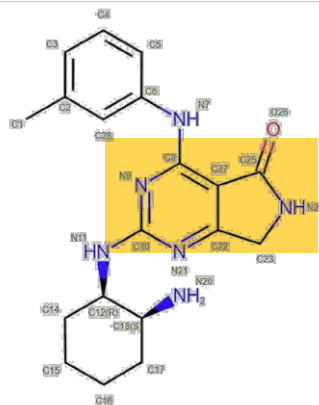
Veal Reply Declaration

158. The structure of 5TR6 obtained from the PDB is shown below:



EX1154.003

159. The structure of 5TT7 obtained from the PDB is shown below:

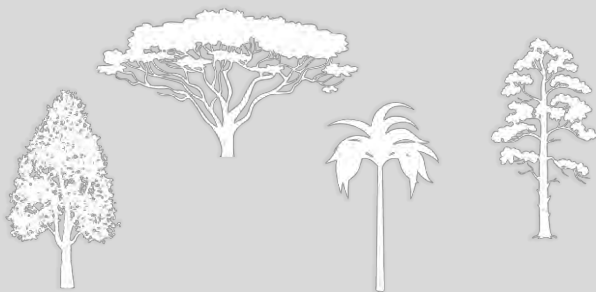


EX1155.003

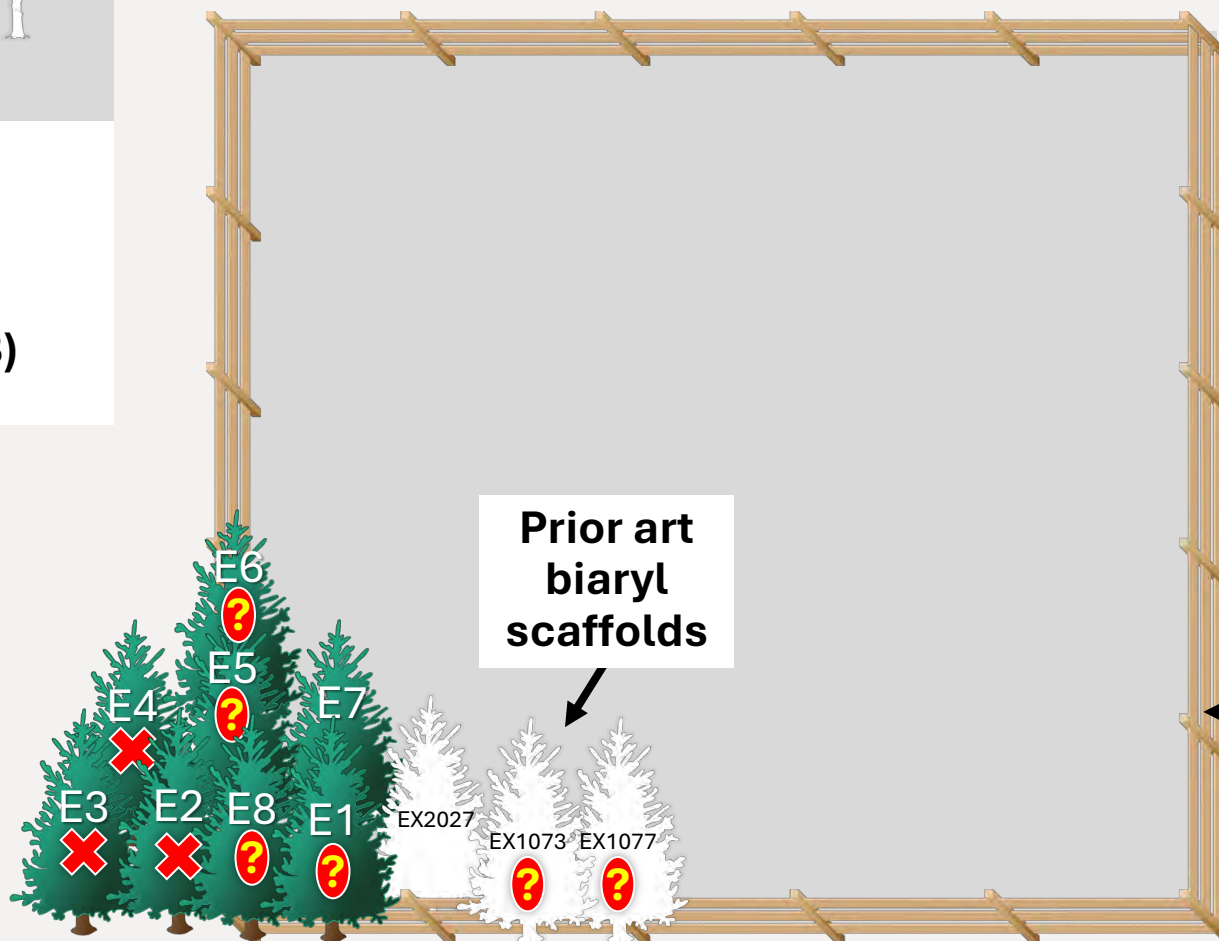
EX1154 and EX1155 are the PDB entries for 5TR6 and 5TT7, the inhibitors Patent Owner's expert contends are disclosed in EX2046.

161. While the unsubstituted aza-oxindole could dock without issue, once again the H-bonding to the hinge region of Btk was disrupted when the phenoxypheyl was added. Glide generally seemed to prioritize proper docking of the phenoxyphenyl over making correct H-bonding to the Btk hinge region. The results for the 5TR6 docking would not provide guidance on how to identify zanubrutinib or any non-biaryl Z'-scaffold. Below is the docking pose of the 5TR6/5TT7 Z'-scaffold with the attached substituents with the most negative Glide docking score (-6.9). Note that adding an NH₂ group, in a position analogous to that of the NH₂ of ibrutinib, would require attaching it to the sp³ carbon of the aza-oxindole ring, which would be expected to be both sterically unfavorable and result in a positively charged amine.

Veal Reply Decl. (EX1106) ¶¶ 139-143, 158-161, 220; see also EX1154; EX1155; EX2046.



Prior art scaffolds that are not Z' structures (e.g., EX2026, EX2038)



EX2023



EX2055

Prior art non-biaryl Z' structures; modeling predicts not expected to bind BTK

Structural and functional boundary, as defined by the claim

See Petition at 71-80, Reply at 8-9 & n.4 (collecting cites);
see also, e.g., Showalter Decl. (EX1003) ¶¶ 39-48, 98-117, 190-207;
Veal Reply Decl. (EX1106) ¶¶ 63-68, 139-161, 171, 195, 211, 214-220.

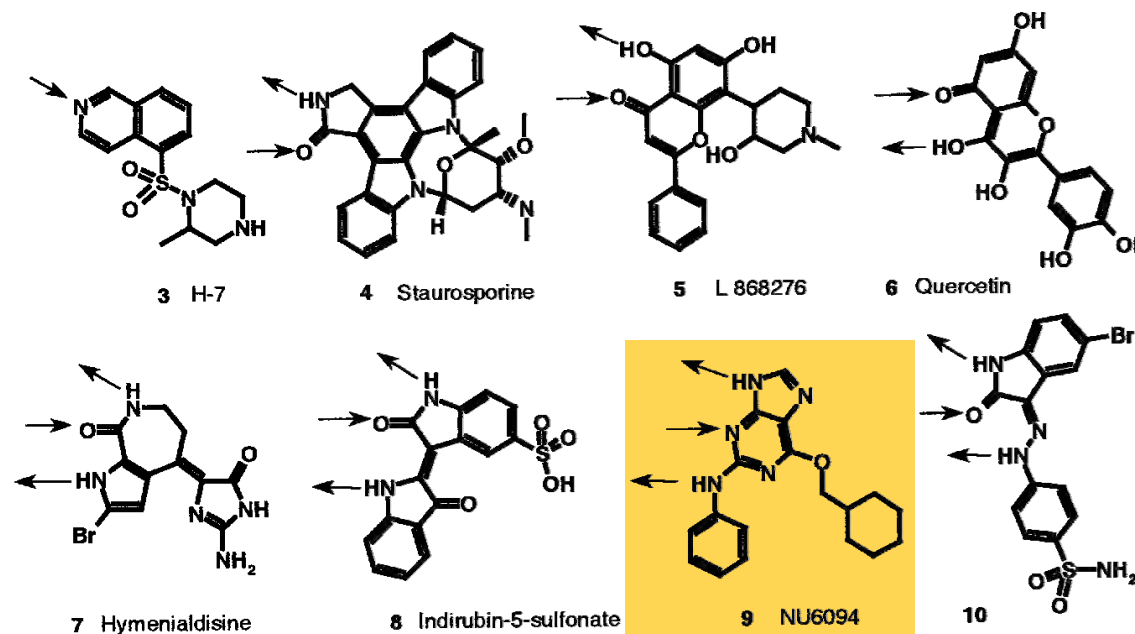
Patent Owner Points to Dr. Veal's Prior Art Publications, But Identifies No Non-Biaryl Molecules That Meet Claim's Structural Limitations, Let Alone Functional Ones

Patent Owner Sur-Reply

75:10-78:7. In his pre-2011 publications, Dr. Veal identifies partially and *fully* non-aromatic “[r]epresentative substructures” that “all have precedent as adenine mimetics for protein kinases” and “offer the potential to satisfactorily replace the two hydrogen bonds formed by ATP to the backbone groups of the kinase hinge region.” EX2120.0023, Fig. 16.5; EX2119, 62:3-18, 66:13-19, 112:12-21; EX2121.0026, Scheme 2.2. Thus, contrary to Petitioner’s litigation-driven attempt

Sur-Reply at 9.

The only structure within scope of Z' is *biaryl* (and not disclosed to be a BTK inhibitor)



Scheme 2.2 Arrows indicate the hydrogen bonding pattern of the inhibitor to the kinase backbone determined by X-ray crystallography.

EX2121.0026.

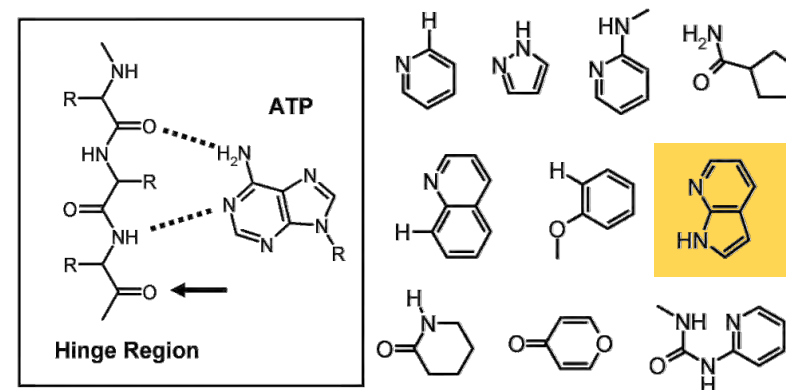
Patent Owner Points to Dr. Veal's Prior Art Publications, But Identifies No Non-Biaryl Molecules That Meet Claim's Structural Limitations, Let Alone Functional Ones

Patent Owner Sur-Reply

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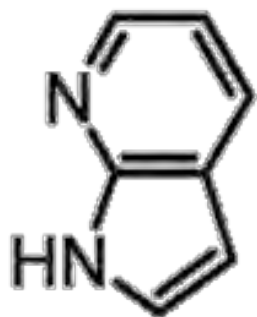


- Pyridine-like with ortho aromatic H
- Phenol / anisole with ortho H
- Pyrazole-like with free NH
- Azaindole
- 2-amino-pyridine-like
- Cyclic secondary amide
- Primary amide attached to ring
- Flavone-like
- Quinazoline-like (aromatic H at C8)
- Urea at 2-position of pyridine

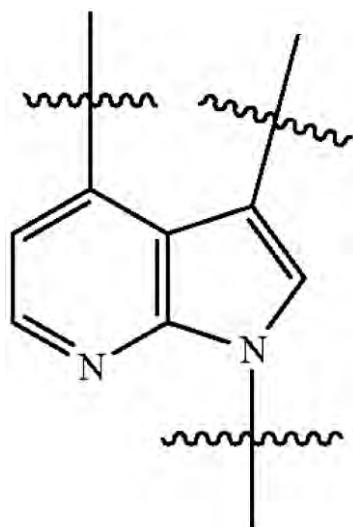
Figure 16.5. Representative substructures that can be used in developing screening libraries. The structures all have precedent as adenine mimetics for protein kinases. They offer the potential to satisfactorily replace the two hydrogen bonds formed by ATP to the backbone groups of the kinase hinge region. Sufficiently polar aromatic hydrogens may act as isosteres for the exocyclic N6 amino group of ATP. Note also that combining or substituting the various mimetics allows for targeting an additional backbone carbonyl group in the hinge region that is well positioned for hydrogen bonding.

EX2120.0023.

The Biaryl Core in EX2120 Is E2, Which Unrebutted Modeling Predicts Will Not Bind



EX2120.0023



'803 Patent at 62:47-57.

Veal Reply Declaration

Reference	Compound	Fused Heterocyclic Ring System Subgenus	Glide Docking Score
803 Patent (EX1001)	Structure E2	Biaryl	-8.5

146. Structure E2 properly oriented the linker-warhead and phenoxyphenyl to bind Cys481 and Btk's back pocket, respectively. Modeling suggests that Structure E2 is inactive, however, because it does not form any H-bonds to Btk's hinge region. Below is the docking pose of Structure E2 with attached substituents with the most negative Glide docking score (-8.5).

Veal Reply Decl. (EX1106) ¶¶ 141, 144-46.

Patent Owner Also Relies on Post-Priority References to Imply That the Prior Art Included “Varied Z’-Scaffolds”

Patent Owner Sur-Reply

lymphocytosis. POR 7-12, 31-34. The field includes examples of varied Z’-scaffolds appended to ibrutinib’s fixed features that chiefly achieve potent irreversible BTK inhibition, as the specification teaches. POR 60.

E.g., Sur-Reply at 6.

Patent Owner Reply

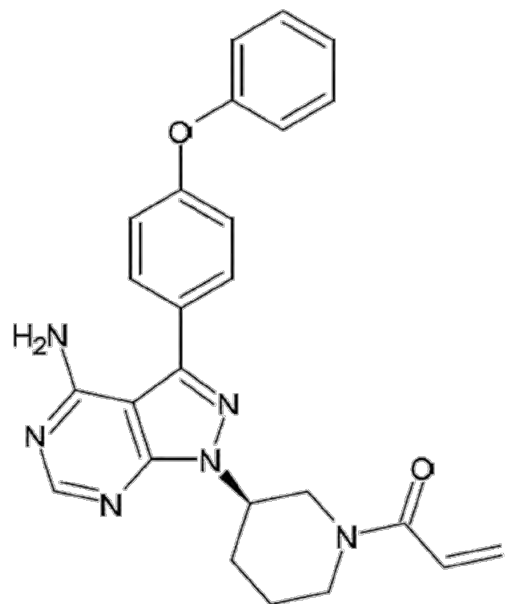
between the scaffold and residues located in the hinge region.” EX1003 ¶240. But as Marcotte later confirmed, Pan suggests ibrutinib’s linker-warhead engages Cys481 and irreversibly inhibits BTK. EX1060.001-002; EX2010 ¶160. Further, nothing in Honigberg reports anything about a “limited understanding of the structure-function relationship[]” of BTK inhibition with ibrutinib-like structures. EX1003 ¶240 (citing EX1055.004); EX2010 ¶¶160-161.

Fourth, Petitioner’s cited ’432 Publication, a 2020 patent publication describing BTK/ITK inhibitors, shows that structures falling within the genus of the claims are iBTKIs, with IC₅₀ ranging from 1-30 nM, which even Dr. Showalter admits a POSA would consider “highly potent.” EX1003 ¶76 (summarizing EX1036); EX2018, 131:17-132:8; EX2010 ¶159. Thus, these structures demonstrate the common structural features of the genus impart the claimed function.⁸

⁸ At deposition, Dr. Showalter attempted to identify “inactive” compounds within the claims that he failed to include in his declaration. EX2018, 12:11-15:12. These compounds further confirm the robust structure-function relationship for ibrutinib-like iBTKIs. Based on docking, a POSA would have recognized the compounds that would not appropriately orient within BTK’s active site, explaining their higher IC₅₀

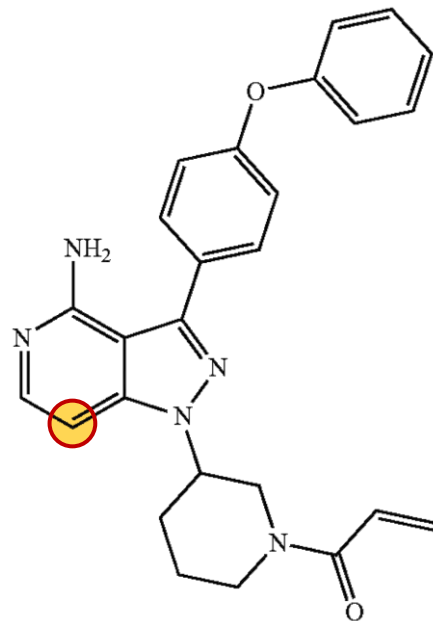
Response at 60.

But EX1036 (2020) Discloses Just One Core Beyond Ibrutinib's, and the Additional Core Is Biaryl



IMBRUVICA

Showalter Decl. (EX1003) ¶ 51.



EX1036.011-.083
(‘432 publication).

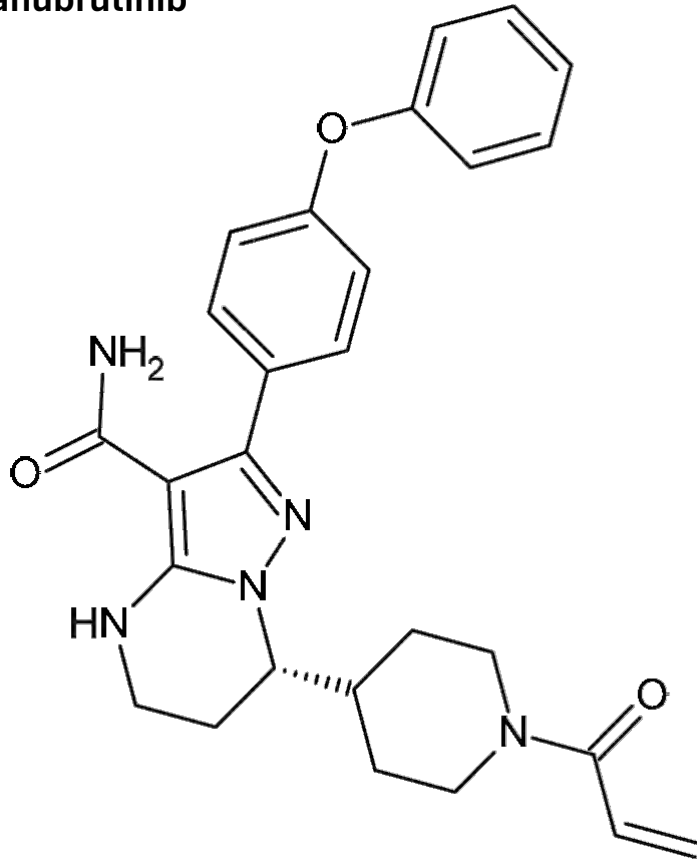
Veal Reply Declaration

nM. See EX2010, ¶159. Note that the structures in the 432 Publication have a Z'-scaffold that is closely related to the ibrutinib Z'-scaffold, differing by a single nitrogen to carbon change in which the NH2-pyrimidine of ibrutinib is modified to an NH2-pyridine. The 432 Publication was not published until May 2020 and therefore not available to a POSA in 2011. Further, the 432 Publication does not

E.g., Veal Reply Decl. (EX1106) ¶ 197.

Finally, Patent Owner Contends That Zanubrutinib Demonstrates the Feasibility of a Non-Biaryl Core

Zanubrutinib



Showalter Decl. (EX1103) ¶ 38.

Patent Owner Sur-Reply

limitations. *Id.* In this context, zanubrutinib reflects the interchangeability of Z'-scaffolds—despite different degrees of aromaticity and planarity. *Id.*

Sur-Reply at 15; see also *id.* at 14-16; Response at 50-54.

Idenix Pharms. LLC v. Gilead Scis. Inc.

941 F.3d 1149, 1165 (Fed. Cir. 2019)

“We are mindful of *Ariad*’s caution that written description does not require ‘a nucleotide-by-nucleotide recitation of the entire genus.’ . . . The purpose of that rule is to allow relatively few representative examples or formulas to support a claim on a structurally similar genus. . . . It does not extend to this case, where the specification lists tens or hundreds of thousands of possible nucleosides, substituent-by-substituent, with dozens of distinct stereochemical structures, and yet the compound in question is conspicuously absent.”

Patent Owner's Expert Concedes the Zanubrutinib Core Was Unknown in 2011 and Not Possessed by the Inventors of the '803 Patent

Dr. Michael J.
Eck
*Patent Owner's
Expert*

Q. You do agree that a POSA would not be able to find that scaffold structure for zanubrutinib anywhere in the prior art as of June 2011, correct?

A. You mean the specific scaffold structure of zanubrutinib?

Q. Yes.

A. That's correct. To my recollection, it's not drawn anywhere in the '803 patent.

Q. It's not drawn in the '803 patent, and it's not drawn anywhere in the prior art, right, that you know of?

A. That's correct. As far as I know, it's not drawn in the prior art.

* * *

Q. But you would agree that the inventors of the '803 patent did not possess that specific structure, correct?

A. That's correct.

Eck Dep. Tr. (EX1110) at 56:25-57:12, 58:7-10; see also, e.g., *id.* at 54:14-22, 110:17-22; EX1034; Reply at 17 (collecting cites).

Zanubrutinib, Unlike Ibrutinib, Does Not Have a Hinge-Binding Pattern Mimicking Adenine

Eck Declaration

Ligand	BTK Residue	
	GK+3 Met477 (NH, H-bond donor)	GK+1 Glu475 (C=O, H-bond acceptor)
Adenine	Ring N (H-bond acceptor)	-NH ₂ amine substituent (H-bond donor)
Ibrutinib	Ring N (H-bond acceptor)	-NH ₂ amine substituent (H-bond donor)
Zanubrutinib ⁹	-C=O of amide substituent (H-bond acceptor)	-NH ₂ of amide substituent (H-bond donor)

⁹ Zanubrutinib also makes a third H-bond to the third available H-bond interaction in the BTK hinge: H-bond acceptor of GK+3 residue Met477. *See* EX1053.005 (PDB: 6J6M). Based on the distance between the hydrogen bond donor and acceptor (3.34Å), this is likely a relatively weak hydrogen bond, but this nevertheless aligns with the understanding from the '803 Patent and state of the art regarding the standard one to three H-bonds formed with specific residues of the protein kinase hinge. *See supra* §§VI.D.3, VII.A.4; EX1077.003; EX2028.0001-0002; EX1052.020.

Eck Decl. (EX2010) ¶ 92 & n.9.

Veal Reply Declaration

207. Dr. Eck contends that a POSA would use the term “adenine mimic” to refer to “hinge binding scaffolds that mimic the interactions of the adenine portion of ATP” and zanubrutinib is an adenine mimic. EX2010, ¶¶167-169; *see also id.* ¶92. Dr. Eck appears to contend that zanubrutinib is an adenine mimic because it forms H-bonds with the same Btk residues as adenine, namely GK+3 Met477 and GK+1 Glu475. EX1110, 167:1-10. While zanubrutinib competes with ATP, as does any competitive inhibitor of any target kinase, zanubrutinib’s hinge-binding pattern does not mimic adenine’s hinge binding pattern. Compared to adenine (and ibrutinib), zanubrutinib forms distinct H-bonds to Btk using both a primary amide group and piperidine NH versus an NH₂-pyrimidine ring and its Z'-scaffold occupies a different space within the binding site. *See supra* Section VI.A.6.

Veal Reply Decl. (EX1106) ¶¶ 69-81, 207-213, 224; *see also, e.g.*, Showalter Decl. (EX1003) ¶¶ 61-67, 71; Showalter Dep. Tr. (EX2018) at 17:18-18:20, 112:12-113:20.

See, e.g., Petition at 9-15, 17-18 (collecting cites); Reply at 17-19 (collecting cites).

Patent Owner's Expert Could Not Identify Any Place in the Patent Where Non-Biaryl Cores Were Disclosed

Dr. Michael J. Eck

Patent Owner's Expert

Q. All right. So **aside from Formula E**, okay, which we've covered, I think exhaustively, **is there anything else in this patent that would have lead a POSA to the Z-scaffold structure in zanubrutinib?**

A. Yes, I think so.

* * *

A. Right here. Sorry. So throughout the patent, in looking to the specification and in taking into consideration what's known in the art, one can learn how to prepare inhibitors of the claims. So as specific examples, **we have the example of ibrutinib itself** that's present in many locations in the patent. I'm sure you can find it faster than I can, but a POSA would be able to understand how ibrutinib, precisely how ibrutinib binds in BTK.

They would read from the specification that 5:6 fused heterocycles were useful for conjoining and presenting in the desired orientation the phenoxyphenyl and the linker-warhead.

They would learn from the specification that it was possible to have variability in the orientation of attachment of the linker-warhead. So there are very rich teachings that a POSA familiar with the art of kinase inhibitor design and the rich structural information already available in the literature for BTK could have brought to bear in elaborating the structure of zanubrutinib.

Q. Do you have a column and line number for me anywhere in there beside Formula E?

A. **So the structure of ibrutinib is at Column 65, roughly lines 10 through 25.**

Q. Okay.

A. And in other places, there are linker-warhead structures depicted that show variability. So, for example, in Column 53, roughly lines 5 through 10. And while the scaffold ibrutinib per se is not exemplified –

Q. I think you meant “zanubrutinib.” You said “ibrutinib.”

A. Sorry. The scaffold of zanubrutinib per se is not exemplified in columns 62 and 63. The embodiments presented there show that there is variability in the 5:6 heterocycles that can be used in some embodiments of the claim. Again, the disclosure in the specification interpreted in light of the rich knowledge in the art and the powerful structural information is enabling in my opinion.

Eck Dep. Tr. (EX1110) at 102:18-105:8.

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Dr. Michael J. Eck

Patent Owner's Expert

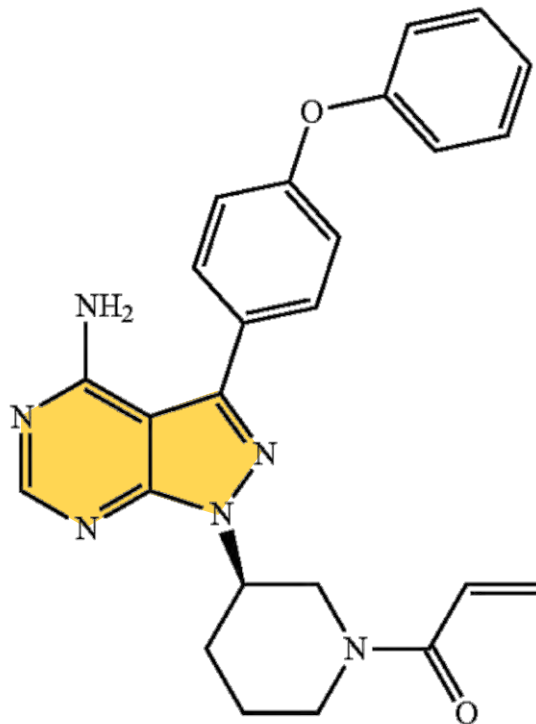
Q. All right. So aside from what you think exhaustively, have you ever lead a POSA

A. Yes, I think so.

A. Right here. Sorry. So in the specification and in the art, one can learn from specific examples, present in many locations faster than I can, but ibrutinib, precisely

They would read from the heterocycles were the desired orientation

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'803 Patent at 65:10-25.

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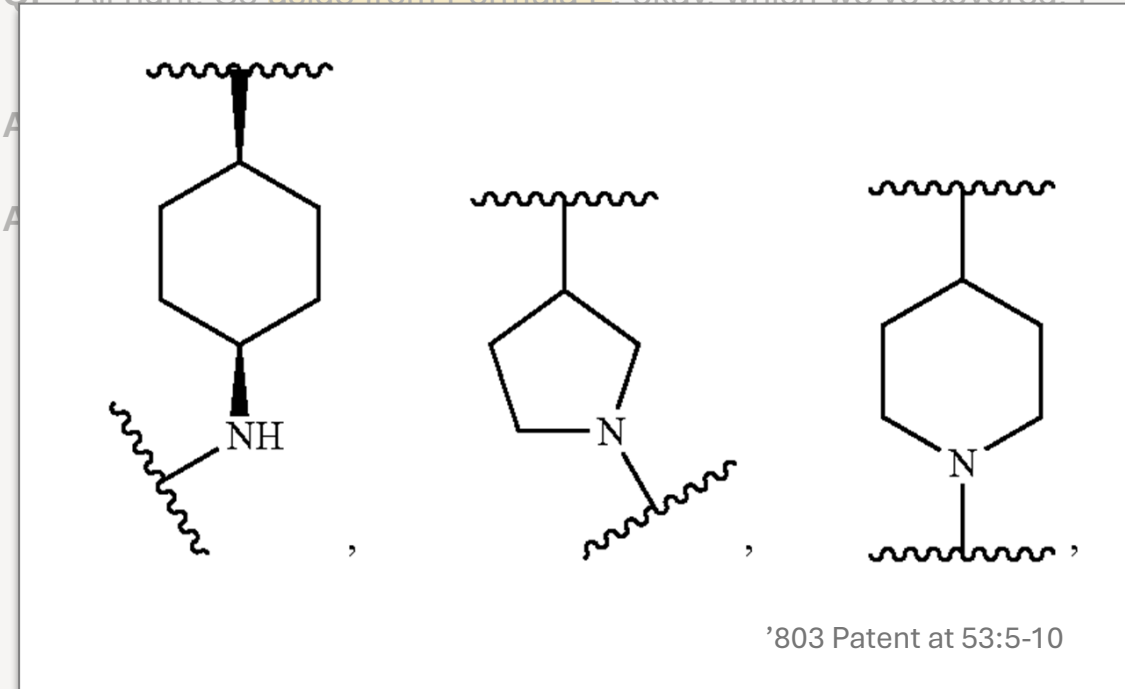
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Dr. Michael J. Eck

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Patent Owner's Expert

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A. Yes, I think so.

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A. Right here. Sorry. So throughout the patent, in looking to the specification and in taking into consideration what's known in the art, one can learn how to prepare inhibitors of the claims. So as specific examples, we have the example of ibrutinib itself that's present in many locations in the patent. I'm sure you can find it faster than I can, but a POSA would be able to understand how ibrutinib, precisely how ibrutinib binds in BTK.

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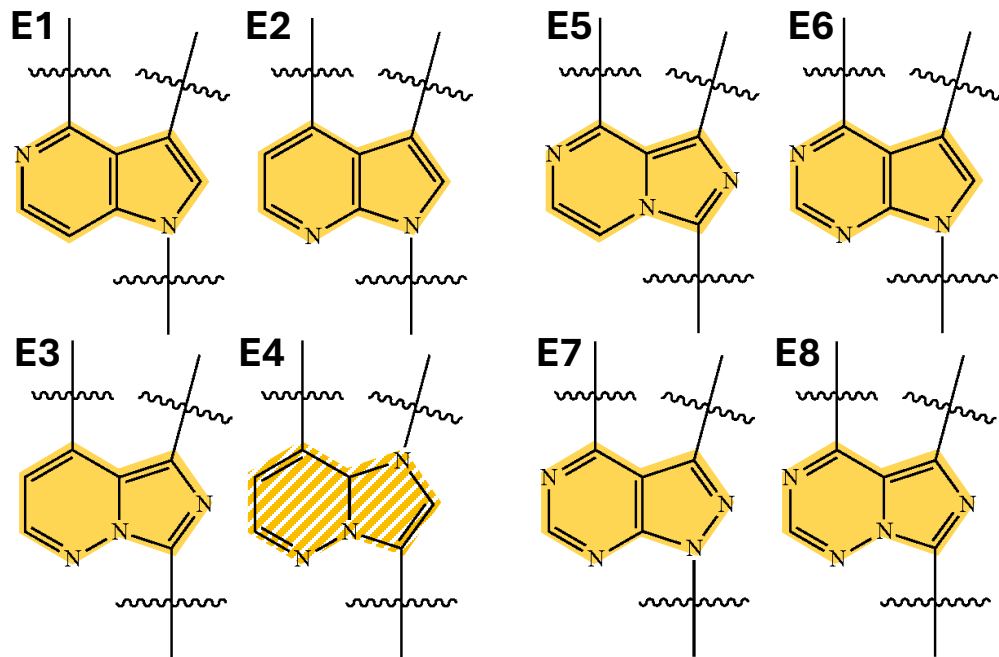
Eck Dep. Tr. (EX1110) at 102:18-105:8.

Patent Owner's Expert Could Not Identify Any Place in the Patent Where Non-Biaryl Cores Were Disclosed

Dr. Michael J. Eck

Patent Owner's Expert

In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

Q. Do you have a column and line number for me anywhere in there beside Formula E?

A. So the structure of ibrutinib is at Column 65, roughly lines 10 through 25.

Q. Okay.

A. And in other places, there are linker-warhead structures depicted that show variability. So, for example, in Column 53, roughly lines 5 through 10. And while the scaffold ibrutinib per se is not exemplified –

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Eck Dep. Tr. (EX1110) at 102:18-105:8.

The POSA Would Not Have Visualized Zanubrutinib From the Specification Without Hindsight

Veal Reply Declaration

106. It is clear that Dr. Eck modeled zanubrutinib based only on hindsight bias because the structure of zanubrutinib was not publicly disclosed until 2015 and a POSA would not have known of its structure or whether or how it binds Btk in 2011. EX1034; EX1110, 54:14-22, 56:25-57:12, 110:17-22. Dr. Eck acknowledged that the inventors of the 803 Patent did not possess the structure of zanubrutinib. EX1110, 58:7-10. Further, when Dr. Eck was asked if anything in the specification aside from Formula E would have directed a POSA to zanubrutinib's Z'-scaffold, Dr. Eck pointed to the structure of ibrutinib and linker-warhead structures. EX1110, 102:18-105:8 (citing EX1001, 53:5-10, 65:10-25). I have reviewed these disclosures in the specification, including those relating to Formula E, and disagree that this

would have directed a POSA to zanubrutinib's structure, particularly zanubrutinib's Z'-scaffold. *See supra* Section VI.A.6. Rather, the specification at most describes that ibrutinib, which comprises a biaryl Z'-scaffold that is a close adenine mimetic, irreversibly inhibits Btk. The structure of ibrutinib, however, is very different compared to zanubrutinib, which comprises a non-biaryl Z'-scaffold; the phenoxyphenyl and linker-warhead are attached to different positions on the Z'-scaffold and has an amide instead of amino substituent. *See supra* Section VI.A.6. Thus, in my opinion, neither the 803 Patent nor anything in the art would have directed a POSA to zanubrutinib's structure.

Veal Reply Decl. (EX1106) ¶ 106; see *also* Reply at 12-13, 17-19 (collecting cites).

The Absence of Prior Examples Beyond Ibrutinib Distinguishes This Case From *UroPep*

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330, 1339 n.3 (Fed. Cir. 2021)

“Juno also relies on *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629 (E.D. Tex. 2017), *aff’d*, 739 F. App’x 643 (Fed. Cir. 2018). In that case, there were hundreds of known PDE5 inhibitors, the type of compound at issue, and the patent identified the compounds by chemical name and structural drawings. . . . The compounds also shared a common physical structure to fit the active site of the PDE5 enzyme to inhibit its activity, and the evidence supported that a skilled artisan ‘could make modifications to increase potency and selectivity.’ . . . The ‘190 patent, in contrast, does not disclose any amino acid sequences or structures to distinguish scFvs that bind to selected targets from those that do not, and the modifications of the sequence can change the binding ability. Juno also does not dispute that very few CD19-specific scFvs were known as of the priority date.”

See also *Forte BioSciences v. Univ. of Mass.*, PGR2023-00014, Paper 45 at 20 (June 24, 2024).

- Patent owner has not identified any prior art non-biaryl compound that is within the scope of the genus
- The only way to distinguish between the Z’ structures that bind BTK and those that do not is experimentation

See, e.g., Institution Decision at 23-24; Reply at 20-21.

Falko-Gunter and *Invitrogen* Are Distinguishable for Same Reasons

Falko-Gunter Falkner v. Inglis

448 F.3d 1357, 1366-68 (Fed. Cir. 2006)

“Falkner argues, *inter alia*, that the Inglis specifications do not adequately describe the poxvirus invention, in light of *Eli Lilly*, because they do not describe the “essential regions” of any poxvirus,” but Court determined there was sufficient written description because “testimony of Inglis’ expert, Dr. Boursnell, established that the articles describing essential genes for poxvirus **were well-known in the art.**”

Invitrogen Corp. v. Clontech Lab’ys Inc.

429 F.3d 1052, 1072-73 (Fed. Cir. 2005)

Court determined there was sufficient written description because “at the time of the invention, the sequences of RT genes **were known** and members of the RT gene family **shared significant homologies** from one species of RT to another[]” and **the art “established a sufficiently known correlation”** between gene structure and function.

Patent Owner's Attempts to Show Fungibility for Cores With Different Substituents Are Also Unpersuasive

	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
Substitution pattern	Amine substitution at C4 Linker/warhead at N1 Hydrophobic moiety at C3	Numerous different substituents at any position on 6:5 rings Linker/warhead at any position Hydrophobic moiety at any position	Amide substitution at C3 Linker/warhead at C7 Hydrophobic moiety at C2
Heteroatom pattern	One of eight patterns of heteroatom substitution: (1) N1, N5; (2) N1, N7; (3) N2, N7, N8; (4) N3, N7, N8; (5) N2, N5, N8; (6) N1, N5, N7; (7) N1, N2, N5, N7; (8) N2, N5, N7, N8.	2-4 N heteroatoms anywhere in 6:5 ring system with at least one N per ring Could have O and/or S heteroatoms	Three N heteroatoms at N1, N4, and N8
Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67.

Patentee Concedes That Substituents Are “Necessary” “To Support Binding”

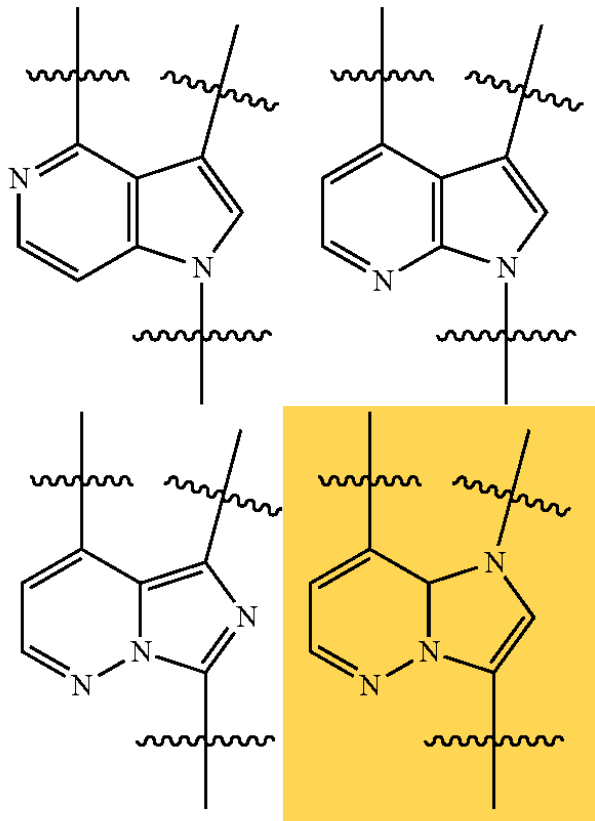
Patent Owner Sur-Reply

³ Petitioner asserts that “modeling suggests that no claimed compound comprising E2-E3 would covalently bind.” Reply 14 n.9. Dr. Veal’s opinion on these compounds was based on Dr. Eck’s “conclusion” that compounds having a heterocyclic ring that does not H-bond to BTK’s hinge would be inactive. EX2119, 218:18-224:22. Dr. Eck did not opine that E2-E3 could never be scaffolds in a BTKI but rather identified that particular compounds made **no** H-bonds to the hinge. *E.g.*, EX2010, ¶184. But these particular compounds lacked other structural features, such as the amine substituent, that form necessary H-bonds to support binding. EX2119, 220:20-221:20; EX1106, ¶¶142-149. Further, Dr. Veal modeled a single compound for both scaffolds, which does not support that **no compounds** with these scaffolds would covalently bond. *E.g.*, EX1106, ¶¶142-149.

Sur-Reply at 13 n.3.

But Starting From a Formula E Core, Patent Owner's Expert Could Not Visualize Structures With Different Substituent Positions

In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-66.

Dr. Michael J. Eck *Patent Owner's Expert*

- Q. Flip to column 62. Right there. For the figure on the bottom right, do you see that one?
- A. This one? (Pointing.)
- Q. Yes.
Could you draw what a POSA would do with respect to making an ibrutinib-like BTK using that scaffold based on reading the '803 patent?
- A. You know, off the cuff, I wouldn't – wouldn't draw something on this scaffold.
- Q. Why?
- A. I think, you know, sitting here today looking at it, not having thought about it or analyzed it previously, would have to apply tools to decide where to substitute it to make it mostly likely to adopt, you know, to properly position the phenoxyphenyl and other groups.

Eck Dep. Tr. (EX1110) at 75:25-76:15; see also *id.* at 92:2-8.

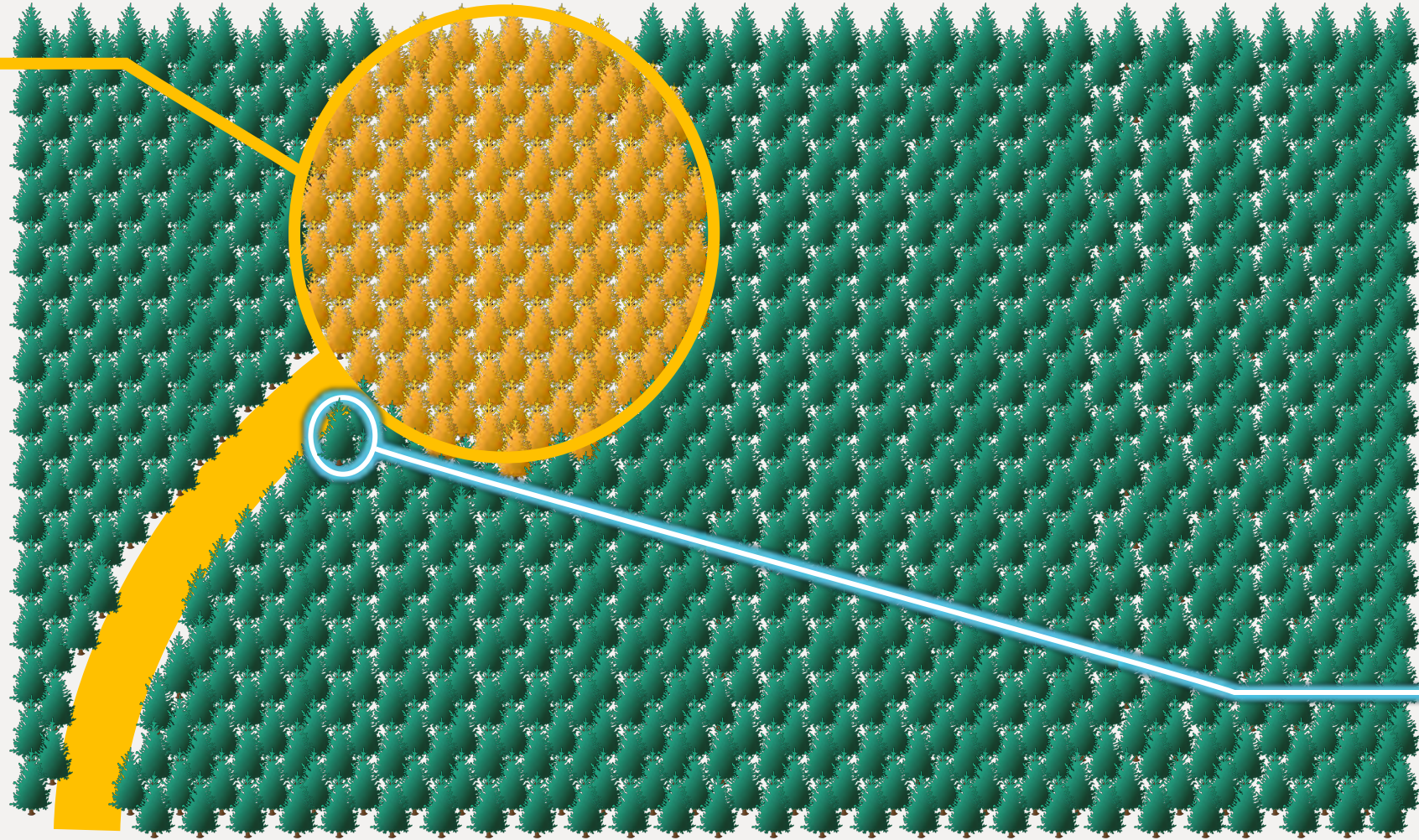
Specification Has
No Blaze Marks
to the Claimed Genus

Fujikawa v. Wattanasin

93 F.3d 1559, 1571 (Fed. Cir. 1996)

“As the Board pointed out, Fujikawa’s proposed sub-genus diverges from Wattanasin’s preferred elements at least with respect to position R. Although, in hindsight, the substitution of cyclopropyl for isopropyl might seem simple and foreseeable, Wattanasin’s disclosure provides no indication that position R would be a better candidate for substitution than any other. . . . Were we to extend *Ruschig*’s metaphor to this case, we would say that it is easy to bypass a tree in the forest, even one that lies close to the trail, unless the point at which one must leave the trail to find the tree is well marked. Wattanasin’s preferred embodiments do blaze a trail through the forest; one that runs close by Fujikawa’s proposed tree. His application, however, does not direct one to the proposed tree in particular, and does not teach the point at which one should leave the trail to find it. We therefore affirm the Board’s denial of Fujikawa’s motion.”

**Wattanasin's
preferred
embodiments**



**Fujikawa tree
without
sufficient blaze
marks**

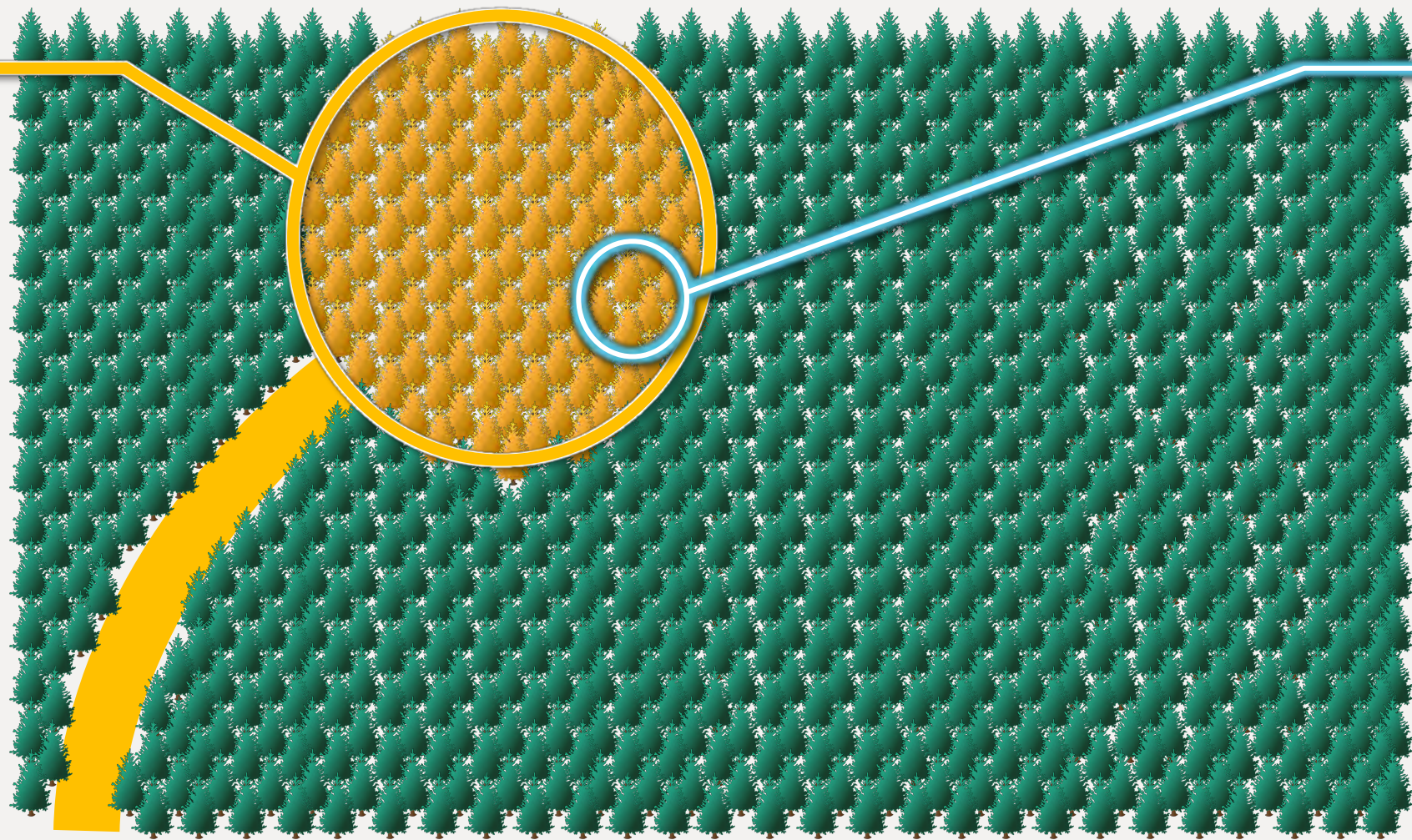
See Fujikawa v. Wattanasin, 93 F.3d 1559, 1571 (Fed. Cir. 1996); see also, e.g., Reply at 14.

Regents of the Univ. of Minnesota v. Gilead Scis., Inc.

61 F.4th 1350, 1358 (Fed. Cir. 2023)

“[T]he Board addressed the question whether one of skill in the art would have been able to visualize or recognize the members of the claimed genus by ‘search[ing] for blaze marks that guide a skilled artisan to the claimed subgenera.’ . . . Regarding whether common structural features must exist between a claim and a putative priority disclosure, those features must constitute the near-entirety of the structures being compared. But the structures here are so extensive and varied that the structures of P1 claim 47, which, through its multiple dependencies, encompasses a significantly larger genus than that claimed in the ’830 patent, are not sufficiently common to that of claim 1 of the ’830 patent to provide written description support.”

**Structures of P1
Claim 47**



**Gilead claim
without
sufficient
blaze marks**

See Regents of the Univ. of Minn. v. Gilead Scis., Inc., 61 F.4th 1350, 1358 (Fed. Cir. 2023); *see also*, e.g., Petition at 64, 69; Reply at 14.

The Only Specification Passages Patent Owner Points to Are Formula E and E1 to E8

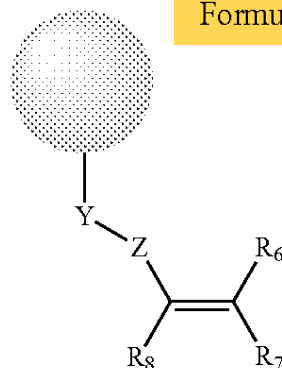
Patent Owner Sur-Reply

In **Formula E**, the specification teaches a genus of iBTKIs with a linker-warhead structure attached to a moiety that “binds to the active site” of BTK. EX1001, 61:65-62:17. As Petitioner’s experts admit, the active site is a well-conserved structure across kinases, *e.g.*, EX2018, 103:12-104:2, and a POSA would understand, when appended to the fixed phenoxyphenyl and linker-warhead of ibrutinib, diverse scaffolds would bind within the active site to form H-bonds to BTK’s hinge. §IV.C; EX1106, ¶44 n.4. The Patent further specifies “some embodiments” of this active-site-binding moiety, listing eight example scaffolds.³

EX1001, 62:44-63:21. As Petitioner’s expert admits, each of the disclosed embodiments has the structural features of the claims: 5:6 fused heterocyclic ring system with 2-4 nitrogen heteroatoms and one nitrogen heteroatom in each ring. EX2119, 179:1-180:21. As such, *Regents of the University of Minnesota v. Gilead Sciences*, 61 F.4th 1350, 1358 (Fed. Cir. 2023) is inapposite. There, the description included structures “so extensive and varied” that “encompass[ed] a significantly larger genus than that claimed.” *Id.* Here, the claimed genus **encompasses the described embodiments**, reciting common structural features that “constitute the near-entirety” of the claimed Z'-scaffolds. *Id.* A POSA reading the specification would recognize the ibrutinib-like iBTKIs included in the claims. POR 66-72.

Sur-Reply at 12-13.

Formula (E)

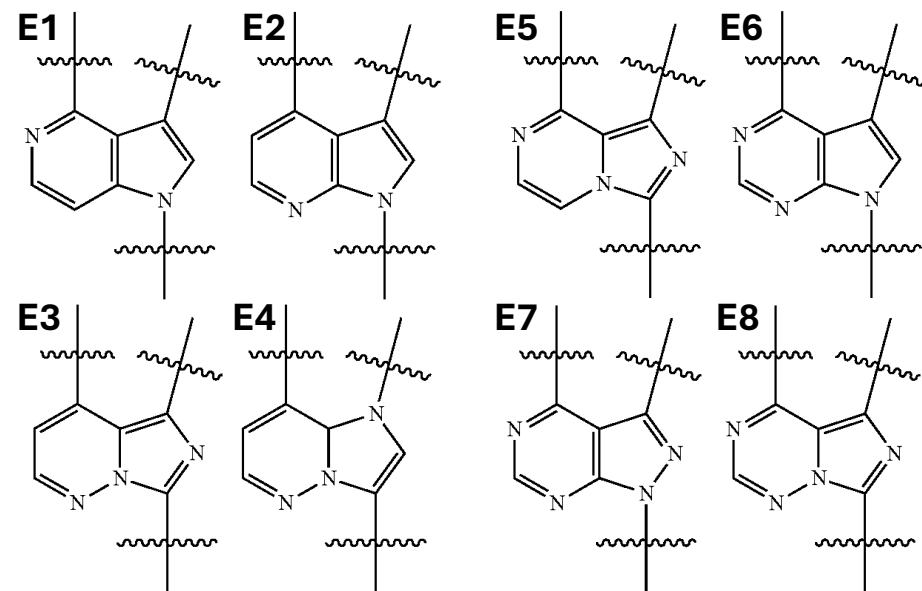


wherein:

wherein  is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

'803 Patent at 62:1-17.

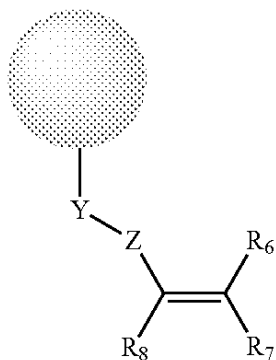
In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

The Formula E “Ball” Does Not Provide Sufficient Blaze Marks to the Claimed Subgenus

Formula (E)

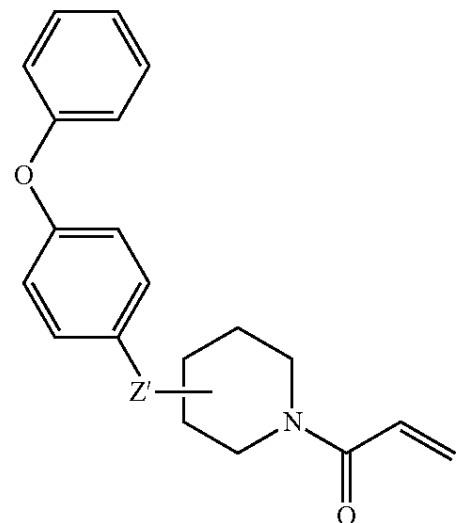


wherein:

wherein  is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

'803 Patent at 62:1-17.

wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



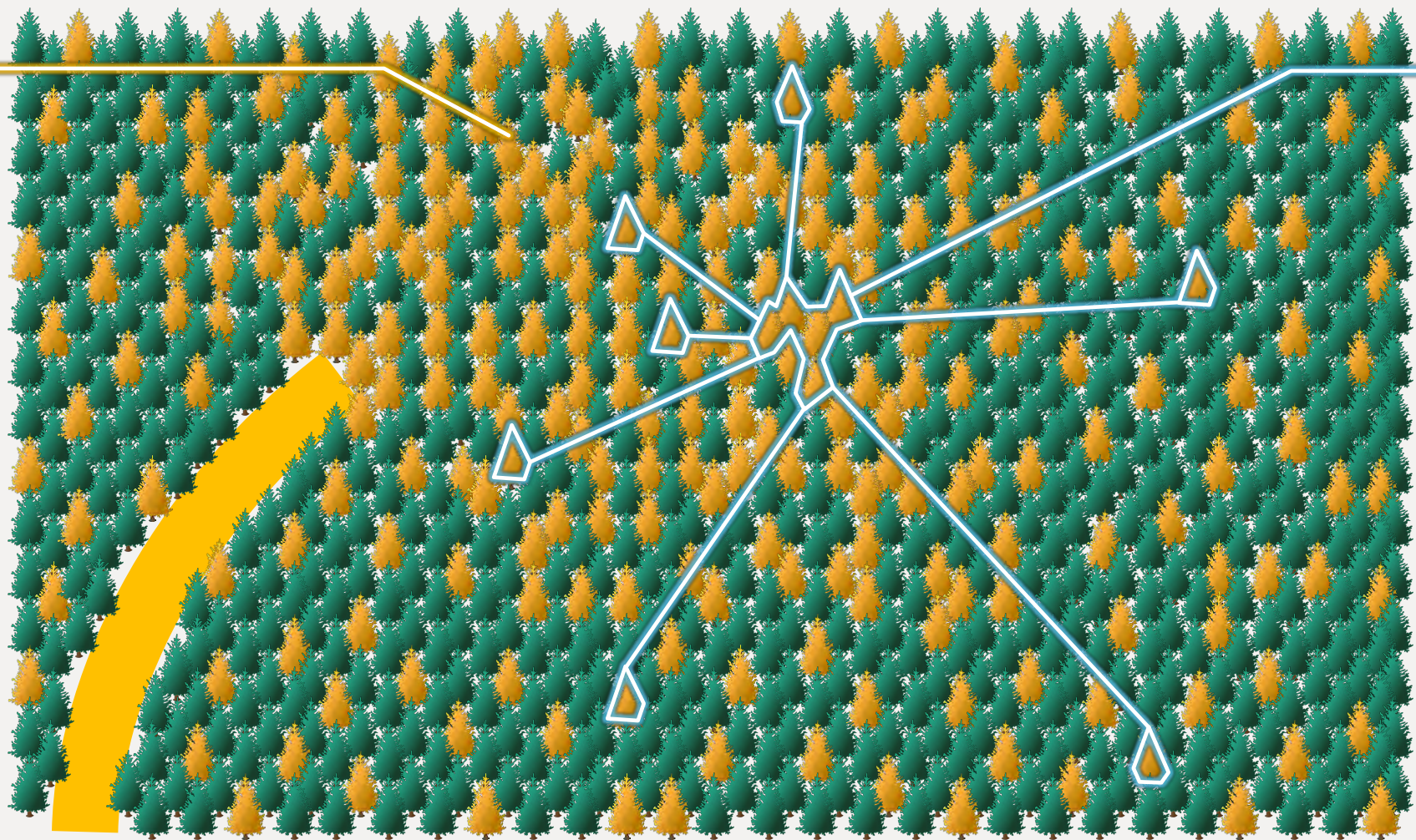
wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

'803 Patent, Claim 1.

The Formula E “Ball” Does Not Provide Sufficient Blaze Marks to the Claimed Subgenus

Formula E
“Ball”

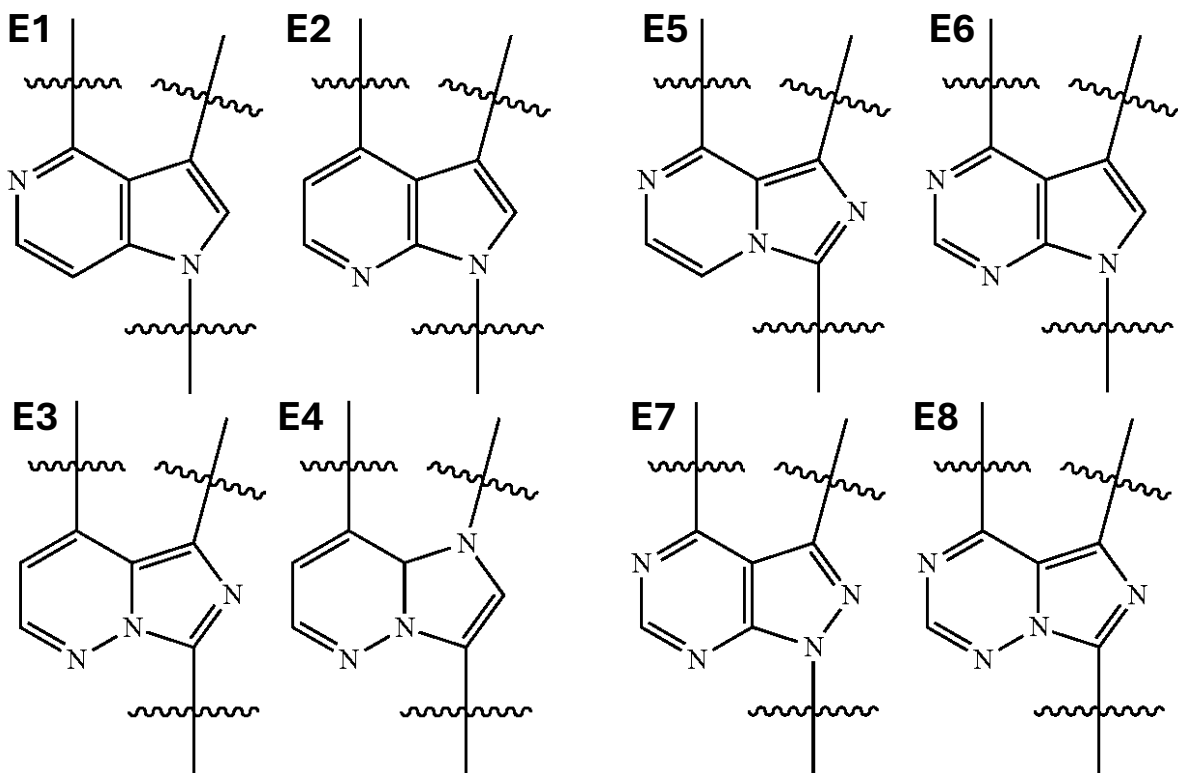
Challenged
claim(s)



See, e.g., Petition at 65-80; Reply at 13-15.

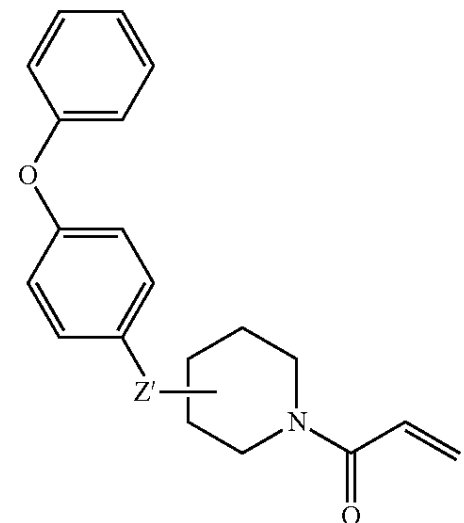
E1 to E8, Forming a Genus Narrower Than the Claimed Genus, Also Do Not Provide Sufficient Blaze Marks

In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

'803 Patent, Claim 1.

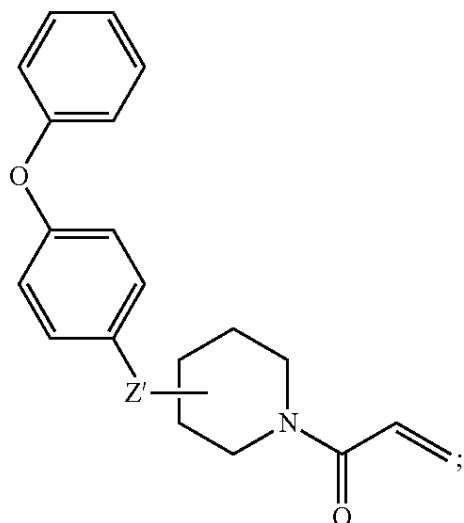
Patent Owner Does Not Identify Any Blaze Marks to Non-Biaryl Moieties

	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
Substitution pattern	Amine substitution at C4 Linker/warhead at N1 Hydrophobic moiety at C3	Numerous different substituents at any position on 6:5 rings Linker/warhead at any position Hydrophobic moiety at any position	Amide substitution at C3 Linker/warhead at C7 Hydrophobic moiety at C2
Heteroatom pattern	One of eight patterns of heteroatom substitution: (1) N1, N5; (2) N1, N7; (3) N2, N7, N8; (4) N3, N7, N8; (5) N2, N5, N8; (6) N1, N5, N7; (7) N1, N2, N5, N7; (8) N2, N5, N7, N8.	2-4 N heteroatoms anywhere in 6:5 ring system with at least one N per ring Could have O and/or S heteroatoms	Three N heteroatoms at N1, N4, and N8
Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67; see also Petition at 65-80, Reply at 13-15 (collecting cites).

Patent Owner Does Not Identify Any Blaze Marks to Non-Biaryl Moieties

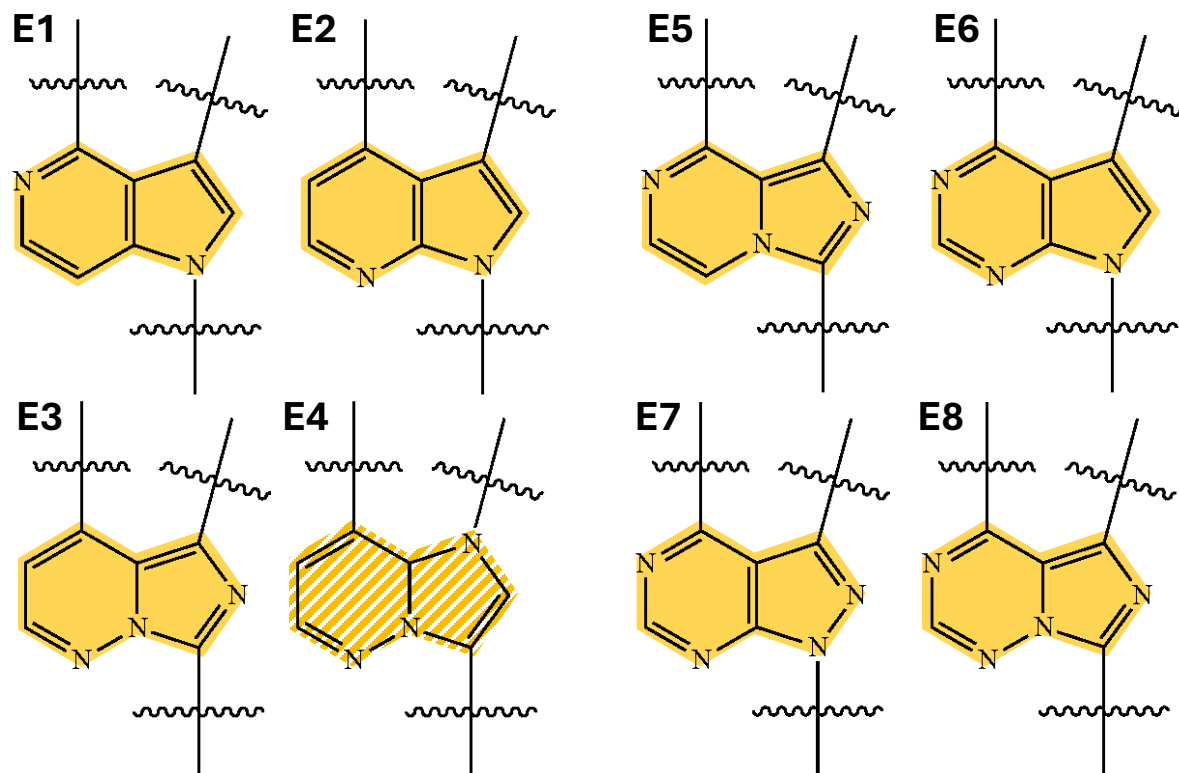
wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

'803 Patent, Claim 1.

In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

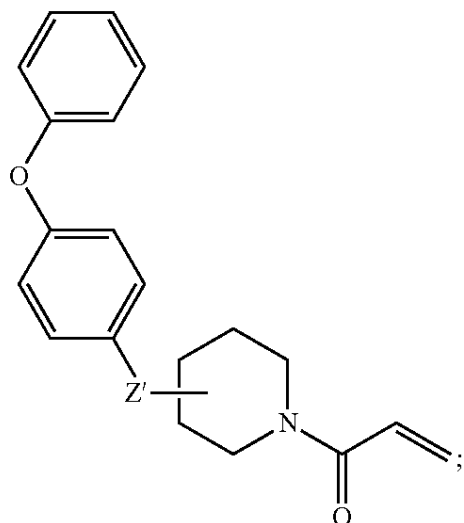
Patent Owner Does Not Identify Any Blaze Marks to Other Substituent Positions

	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
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Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67; see also Petition at 65-80, Reply at 13-15 (collecting cites).

Patent Owner Does Not Identify Any Blaze Marks to Other Substituent Positions

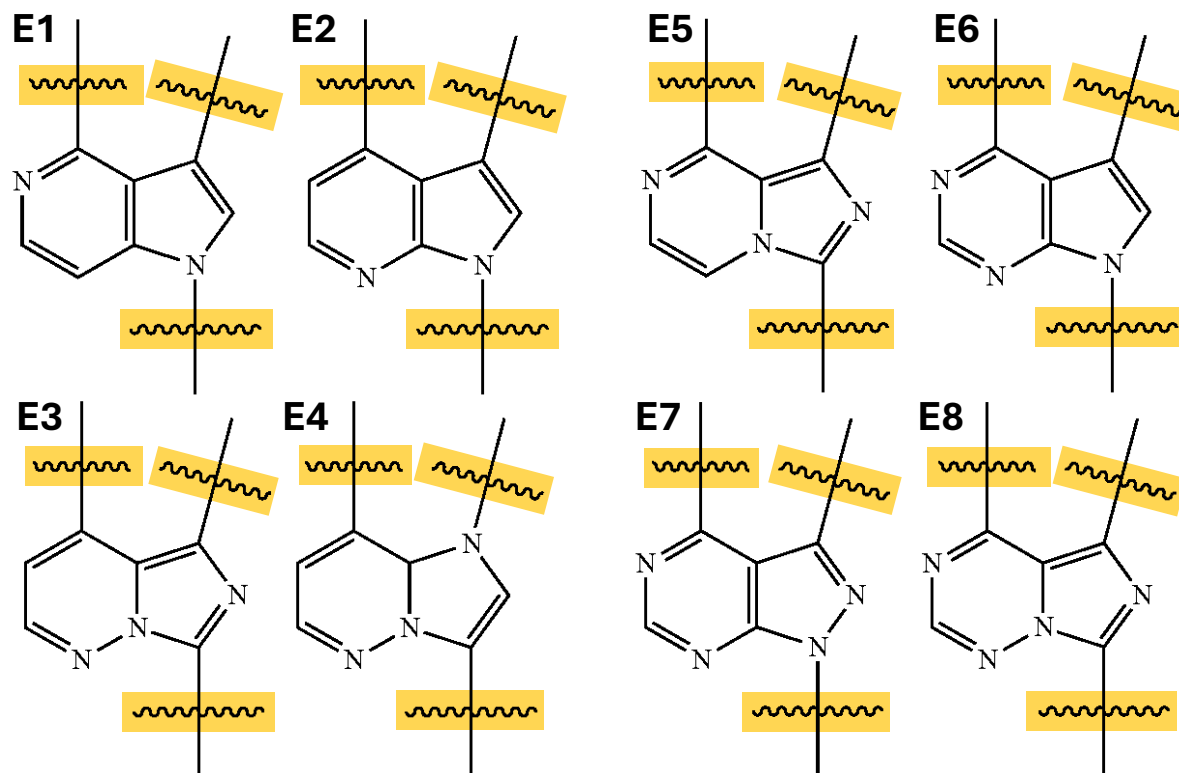
wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

'803 Patent, Claim 1.

In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

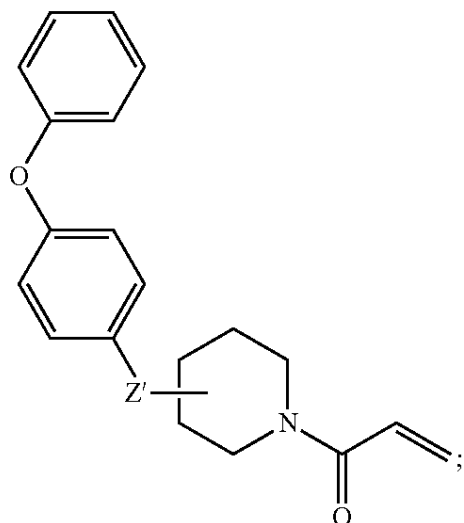
Patent Owner Does Not Identify Any Blaze Marks to Other Heteroatom Patterns

	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
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Heteroatom pattern	One of eight patterns of heteroatom substitution: (1) N1, N5; (2) N1, N7; (3) N2, N7, N8; (4) N3, N7, N8; (5) N2, N5, N8; (6) N1, N5, N7; (7) N1, N2, N5, N7; (8) N2, N5, N7, N8.	2-4 N heteroatoms anywhere in 6:5 ring system with at least one N per ring Could have O and/or S heteroatoms	Three N heteroatoms at N1, N4, and N8
Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67; see also Petition at 65-80, Reply at 13-15 (collecting cites).

Patent Owner Does Not Identify Any Blaze Marks to Other Heteroatom Patterns

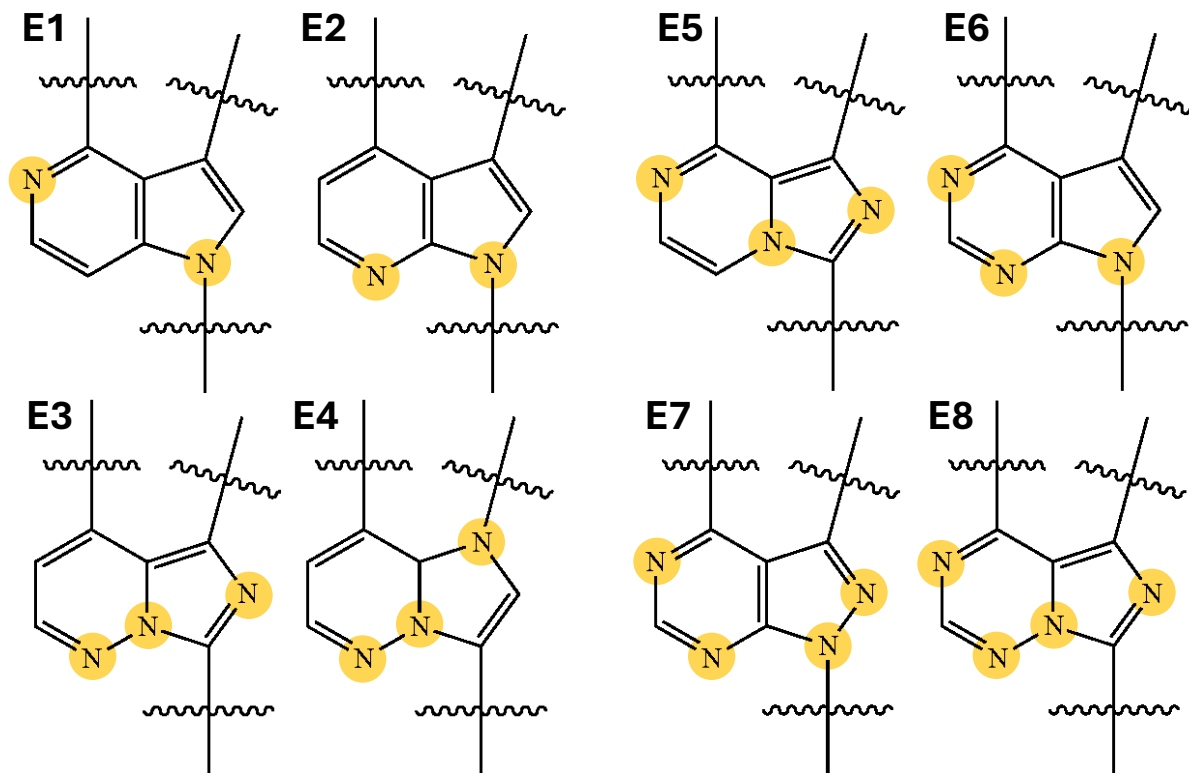
wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists of a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and

'803 Patent, Claim 1.

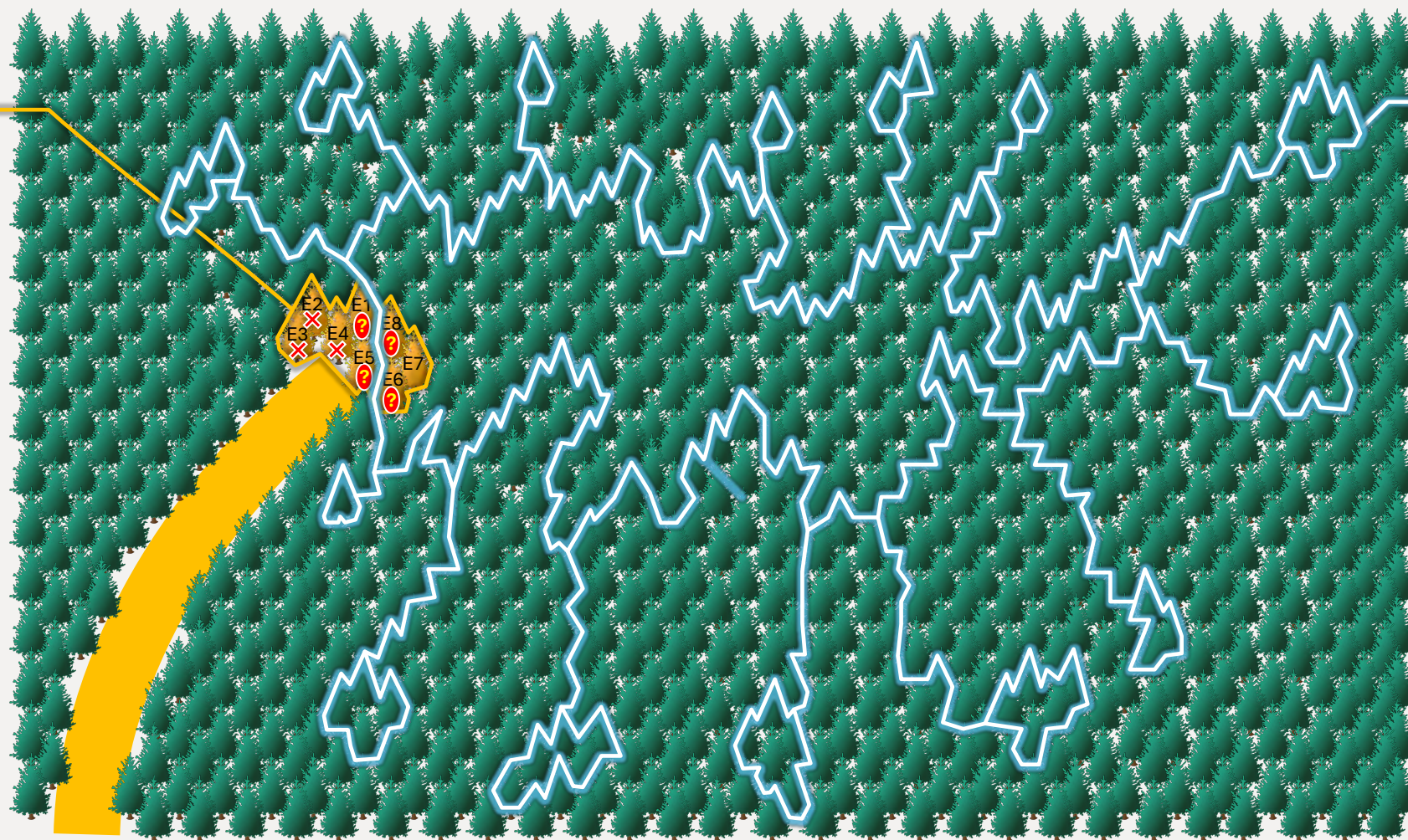
In some embodiments,  is a substituted fused biaryl moiety selected from



'803 Patent at 62:44-63:20 (annotated).

Patent Owner Does Not Identify Any Blaze Marks to Non-Biaryl Moieties, More Than Eight Heteroatom Patterns, or More Than One Substituent Pattern

E1 to E8



Challenged claim(s), not limited to two aromatic rings, particular heteroatom patterns, and single substituent pattern, and excluding at least E2 to E4

See, e.g., Petition at 65-80; Reply at 13-15; see also, e.g., Reply 8-9.

Patent Owner's Attempt to Distinguish *Gilead* Is Unpersuasive

Patent Owner Sur-Reply

In Formula E, the specification teaches a genus of iBTKIs with a linker-warhead structure attached to a moiety that “binds to the active site” of BTK. EX1001, 61:65-62:17. As Petitioner’s experts admit, the active site is a well-conserved structure across kinases, e.g., EX2018, 102:12-104:2, and a POSA would

larger genus than that claimed.” *Id.* Here, the claimed genus ***encompasses the described embodiments***, reciting common structural features that “constitute the near-entirety” of the claimed Z'-scaffolds. *Id.* A POSA reading the specification would recognize the ibrutinib-like iBTKIs included in the claims. POR 66-72.

larger genus than that claimed.” *Id.* Here, the claimed genus ***encompasses the described embodiments***, reciting common structural features that “constitute the near-entirety” of the claimed Z'-scaffolds. *Id.* A POSA reading the specification would recognize the ibrutinib-like iBTKIs included in the claims. POR 66-72.

Patent Owner Sur-Reply at 12-13

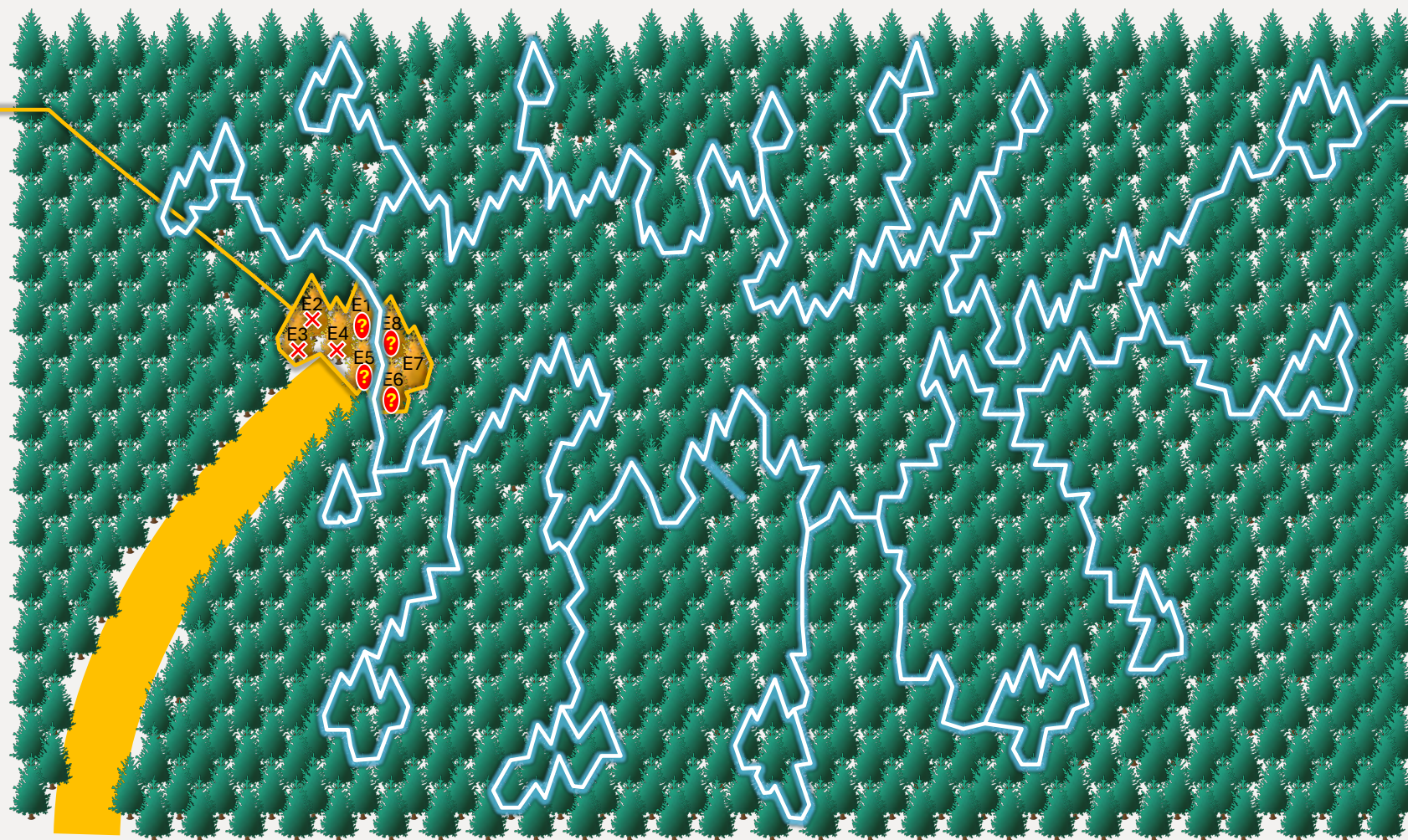
Regents of the Univ. of Minnesota v. Gilead Scis., Inc.

61 F.4th 1350, 1358 (Fed. Cir. 2023)

“[T]he Board addressed the question whether one of skill in the art would have been able to visualize or recognize the members of the claimed genus by ‘search[ing] for blaze marks that guide a skilled artisan to the claimed subgenera.’ . . . Regarding whether common structural features must exist between a claim and a putative priority disclosure, those features must constitute the near-entirety of the structures being compared. But the structures here are so extensive and varied that the structures of P1 claim 47, which, through its multiple dependencies, encompasses a significantly larger genus than that claimed in the ’830 patent, are not sufficiently common to that of claim 1 of the ’830 patent to provide written description support.”

That the Claimed Genus Here Encompasses (Some Of) the Embodiments Is Irrelevant for Blaze Mark Analysis; Were That Enough, Infinite Genuses Would Be Described

E1 to E8

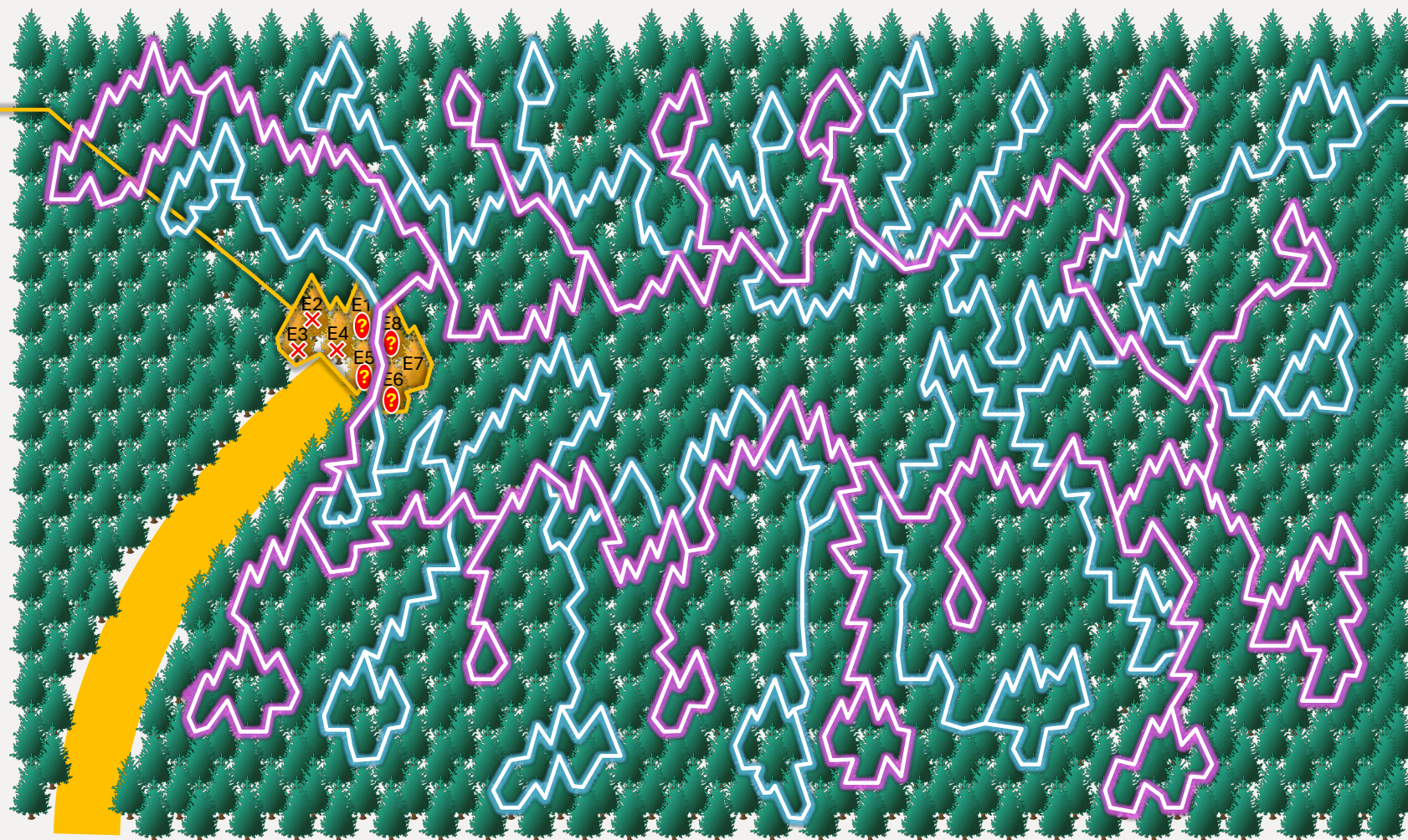


Challenged claim(s), not limited to two aromatic rings, particular heteroatom patterns, and single substituent pattern, and excluding at least E2 to E4

See, e.g., Petition at 65-80; Reply at 13-15; see also, e.g., Reply 8-9.

That the Claimed Genus Here Encompasses (Some Of) the Embodiments Is Irrelevant for Blaze Mark Analysis; Were That Enough, Infinite Genuses Would Be Described

E1 to E8

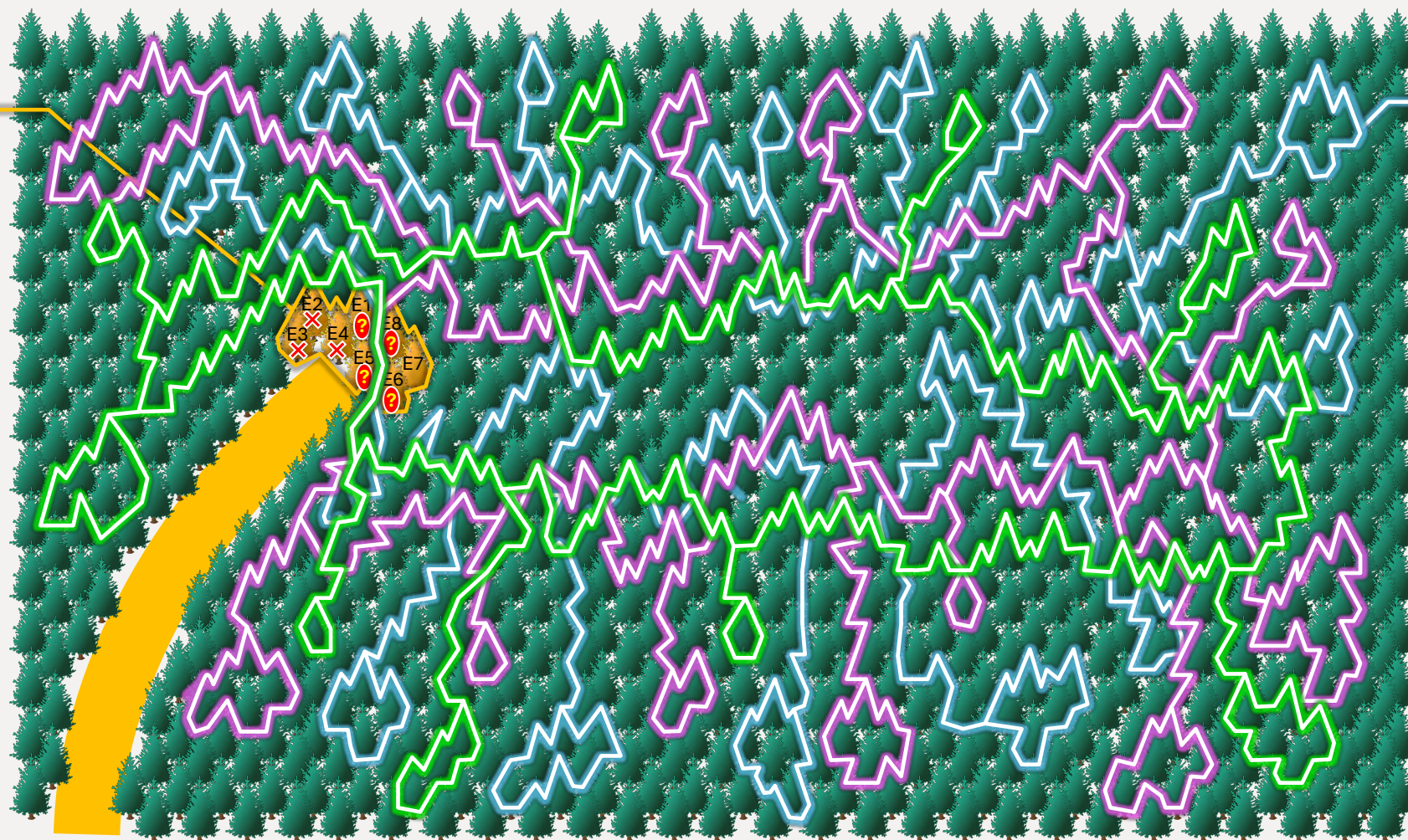


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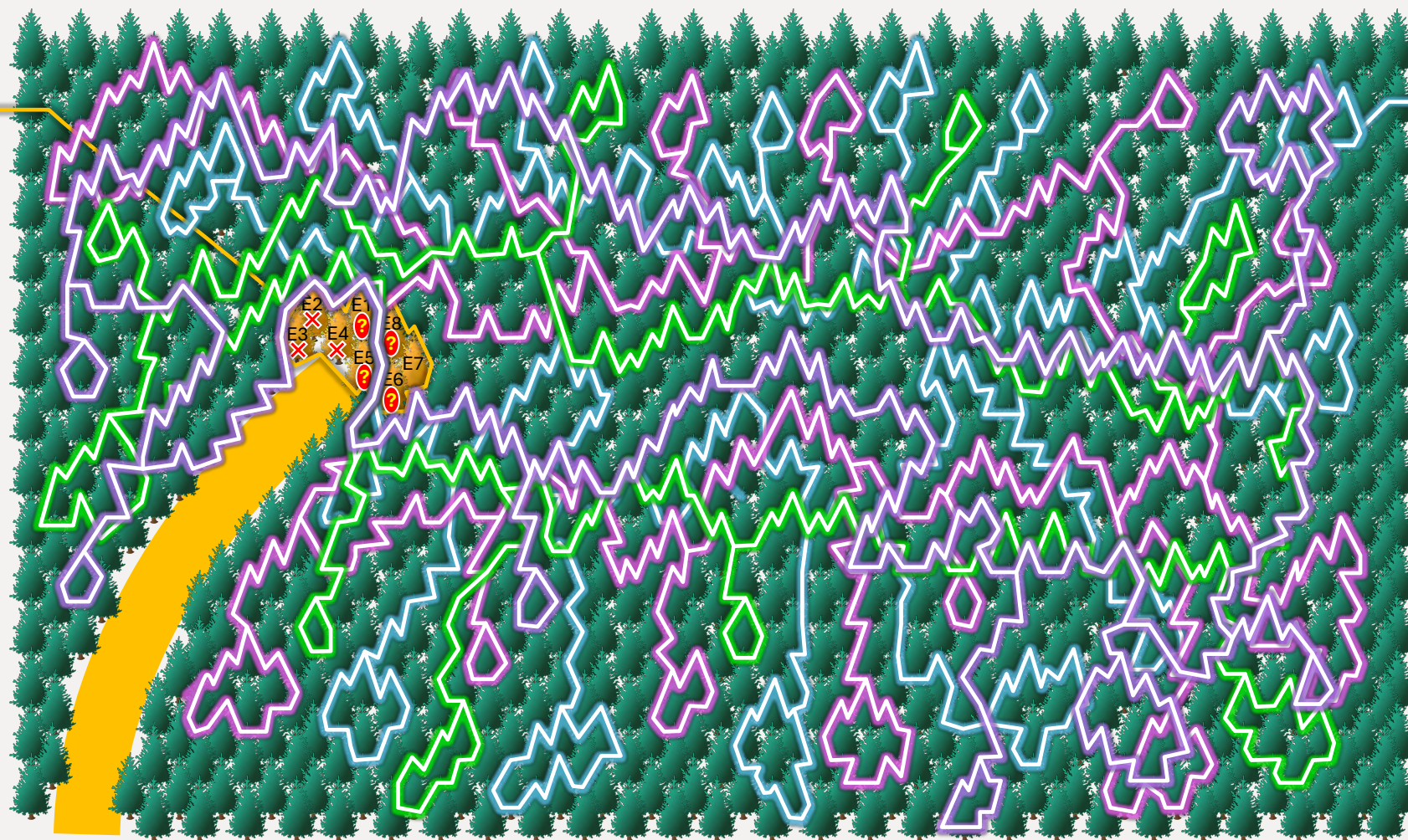


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E1 to E8

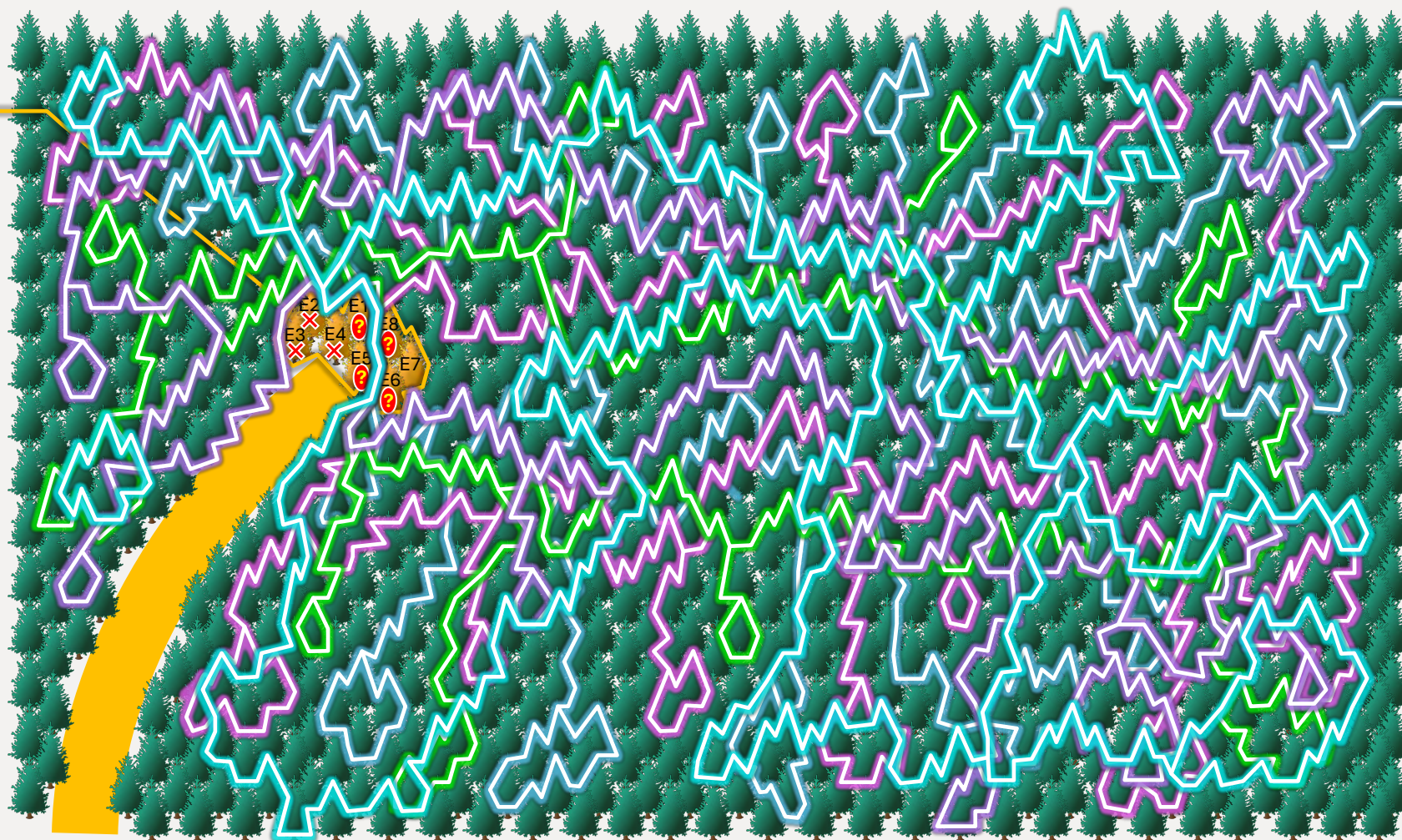


Challenged claim(s), not limited to two aromatic rings, particular heteroatom patterns, and single substituent pattern, and excluding at least E2 to E4

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That the Claimed Genus Here Encompasses (Some Of) the Embodiments Is Irrelevant for Blaze Mark Analysis; Were That Enough, Infinite Genuses Would Be Described

E1 to E8



Challenged claim(s), not limited to two aromatic rings, particular heteroatom patterns, and single substituent pattern, and excluding at least E2 to E4

See, e.g., Petition at 65-80; Reply at 13-15; *contra* Sur-Reply at 12-13; see also, e.g., Reply 8-9.

E1 to E8 Do Not Possess Common Structural Features That Constitute the Near Entirety of Claimed Compounds With Varied Z' Structures

	Specification	Challenged Claims	BRUKINSA
Heterocyclic ring system	Formula (E) ring systems - biaryl ⁸	Any combination of 6:5 aromatic, partially saturated, and unsaturated ring systems, including biaryl, 5-aro-6-non-aro, 5-non-aro-6-aro, and 5-non-aro-6-non-aro	5-aro-6-non-aro ring system
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Adenine-mimetic?	Only adenine-mimetics	Not limited to adenine-mimetics	No

Petition at 67.

Ground 2: Lack of Enablement/Priority

In re Wands

858 F.2d 731, 737 (Fed. Cir. 1988)

“[I]t is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation.”

“Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

Wands Factors (1) and (8): Quantity of Experimentation and Breadth of Claims

McRO, Inc. v. Bandai Namco Games Am. Inc.

959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020)

“In cases involving claims that state certain structural requirements and also require performance of some function (e.g., efficacy for a certain purpose), we have explained that undue experimentation can include undue experimentation in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that satisfy the functional requirement.”

Idenix Pharms. LLC v. Gilead Scis. Inc.

941 F.3d 1149, 1162 (Fed. Cir. 2019)

“First, Idenix argues that ‘[w]hen required to take all of the claim limitations into account, Gilead’s witnesses described the claims as embracing only a ‘small’ number of compounds.’ . . . This analysis is backwards. Gilead’s expert testified that, in order for the ’597 patent to teach which 2'-methyl-up nucleosides effectively treat HCV, the patent would need to detail ‘how to get from a large number [of candidate compounds] to a relatively speaking small number [of effective compounds].’ . . . In other words, the ’597 patent leaves a POSA searching for a needle in a haystack to determine which of the ‘large number’ of 2'-methyl-up nucleosides falls into the ‘small’ group of candidates that effectively treats HCV. The size disparity between those two groups requires significant experimentation, which weighs against enablement, not for it.”

See also Amgen v. Sanofi, 987 F.3d 1080, 1087 (Fed. Cir. 2021).

See, e.g., Petition at 57-60, 82-88, Reply at 4-5, 23-24, 26 (collecting cites).

Patent Owner's Expert Conceded the Z' Structure Defines a Genus of Billions of Compounds

Dr. Hollis Showalter
Petitioner's Expert

142. The number of structural species encompassed by these Structural Limitations is at least in the billions (as explained below, due to the recursive nature of the permitted substitutions, it can actually be infinite). My conservative calculation is based on the following parameters defined by the claim language of these Structural Limitations and the construction of “optionally substituted fused heterocyclic ring system.” Specifically, the structural limitations prescribe four subgenera that allow for a large number of structurally distinct species. Further, the vast number of structural species arises from the diversity of the fused heterocyclic ring systems coupled with the diversity of substitution patterns for each ring system, which are affected by a variety of factors, including the aromaticity of the ring systems (*i.e.*, biaryl *v.* non-biaryl), substitution patterns (*i.e.*, type, number, and position of substitutions present on the ring system), and heteroatom patterns (*i.e.*, type, number, and position of heteroatoms in the ring system).

Showalter Decl. (EX1003) ¶¶ 141-178; see also Petition at 57-60, Reply at 4-5 (collecting cites); Showalter Reply Decl. (EX1105) ¶¶ 16-35; Veal Reply Decl. (EX1106) ¶¶ 227-30.

Dr. Michael J. Eck
Patent Owner's Expert

- Q.** I understand. That was my question about just the Z'-structure itself. So to be fair and to be clear, just looking at the Z'-structure itself, as described in that claim, you would agree that that alone, by itself, encompasses billions of possible structures?
- A.** Again, considering it aside from the claim, I would agree that that could potentially encompass billions of structures according to Dr. Showalter's calculations.

Eck Dep. Tr. (EX1110) at 42:18-43:18; see also Reply at 4-5 (collecting cites); Showalter Reply Decl. (EX1105) ¶ 19; Veal Reply Decl. (EX1106) ¶¶ 185, 248, 254.

Patent Owner's Expert Also Conceded That Only a Subset of Z' Structures Will Form Compounds That Meet Additional Functional Requirements

Eck Declaration

151. First, as I have explained, in 2011, a POSA reading the '803 . . .

X.A.1.b. The need for the linker-warhead to be oriented generally towards Cys481 would limit the scope of acceptable Z'-scaffolds.

* * *

152. Second, as I have also explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the phenoxyphenyl group would need to be oriented to allow for binding within BTK's hydrophobic back pocket, which would limit the scope of acceptable Z'-scaffolds. *See supra* §§VI.D.2, VII.A.3, X.A.1.c. The

* * *

218. As I have explained, proper consideration of a POSA's knowledge about the kinase hinge region in June 2011 from the '803 Patent and art would limit the scope of acceptable compounds to those that have a Z'-scaffold that functions as a hinge-binding element and makes the necessary one to three H-bonds with the BTK hinge region. *See supra* §§VI.D.3, VII.A.4, X.A.2. Moreover, as discussed

Eck Declaration (EX2010) ¶¶ 151, 152, 218.

Dr. Michael J. Eck

Patent Owner's Expert

Q. Okay. What is the size of the genus of what you refer to as, "acceptable Z'-scaffolds"?

A. I have no idea. I haven't tried to do that calculation.

* * *

A. The answer is I wouldn't put a number on it. You know, I would say comfortably more than hundreds but beyond that, you know, without – yeah, just not – haven't done that analysis, haven't thought about how I would do that analysis precisely, and so I don't want to try to put a number on it.

Eck Dep. Tr. (EX1110) at 44:17-45:10.

Patent Owner Attempts to Narrow the Genus Based on a Wide Range of Properties From the Prior Art

Patent Owner Response

The claims' requirement that the ibrutinib-like iBTKI be orally administered would additionally limit the candidate structures. In considering ibrutinib-like iBTKIs for use in the claimed method, a POSA would be guided by well-known principles to optimize a structure's oral bioavailability, including constraints on molecular weight, lipophilicity, and H-bond donors and acceptors. EX2012 ¶¶31-36, 46. Petitioner's suggestion that a POSA would have "infinitely" substituted Z' defies common sense. Petitioner identifies no example of any BTK inhibitor, kinase

Patent Owner Response at 81.

David Scott

Patent Owner's Expert

36. Additionally, in considering Z' scaffolds for use in the compounds of the '803 Patent claims, a POSA would have been aware of available tools to assess "ADME-related characteristics of ATP-competitive protein kinase inhibitors" to evaluate candidate ibrutinib-like irreversible BTKIs. EX2040.0039. A POSA considering candidate ibrutinib-like irreversible BTKIs would have had available "a toolbox of diverse in vitro ADME technologies" that had been "developed and proven to be useful for the prediction of the PK parameters of an inhibitor." EX2040.0015, .0038. In particular, "[t]o address drug absorption in vitro, scientists . . . [were] advised to embrace a whole set of models and methods that determine solubility, lipophilicity, ionization, permeability, and the interaction with transporters." EX2040.0041; see also EX2040.0038-0039, 0043-0046; EX2040, Tbl. 1.2 (.0039).

Scott Decl. (EX2012) ¶ 36.

- Q. The fact that it's greater than 500 wouldn't on its own disqualify it from being pursued as a potential therapeutic to a POSA, right?
- A. A chemist would look at all the properties of a compound and all the data to decide which ones to pursue.

Scott Dep. Tr. (EX1117) at 68:15-20.

Patent Owner's Expert Conceded That All of the Substituents Recited in the '803 Patent Could Potentially Work

David Scott

Patent Owner's Expert

Q. Would a POSA potentially use every one of these LSRS exemplary substitutions listed?

A. I don't know.

Q. Why don't you know?

A. A POSA would choose specific substituents for a specific reason and that would depend on the context of the molecule in question.

* * *

Q. Is it your view that any of these LSRS optional substitutions listed would not work?

A. I've not seen any evidence that they wouldn't.

Q. And you agree that the specification provides these as exemplary optional substitutions for the claimed molecules, right?

A. Yes.

Scott Dep. Tr. (EX1117) at 91:6-14, 92:7-16; see also Reply 3-4, EX1105 ¶ 25.

The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, acyl, nitro, haloalkyl, fluoroalkyl, amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. By way of example an optional substituents may be L_sR_s , wherein each L_s is independently selected from a bond, $-O-$, $-C(=O)-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-NH-$, $-NHC(O)-$, $-C(O)NH-$, $S(=O)_2NH-$, $-NHS(=O)_2$, $-OC(O)NH-$, $-NHC(O)O-$, $-(\text{substituted or unsubstituted } C_1-C_6 \text{ alkyl})$, or $-(\text{substituted or unsubstituted } C_2-C_6 \text{ alkenyl})$; and each R_s is independently selected from H, (substituted or unsubstituted C_1-C_4 alkyl), (substituted or unsubstituted C_3-C_6 cycloalkyl), heteroaryl, or heteroalkyl. The protecting

'803 Patent at 19:57-20:7.

Even Adopting Patent Owner's Assumptions, Conservatively There Would Still Be Over 4 Million Potential Ring Systems to Test

Showalter Reply Declaration

32. Consistent with Dr. Scott's testimony, my updated calculations assume that each of the 1,726 Appendix A ring systems has only 3 positions available for substitution after the hydrophobic moiety and linker-warhead have been added—two of which can be any of the 12 optional substitutions listed in Table 1 and one of which can only be one of the 6 optional substitutions capable of forming an H-bond. This latter limitation is based on Dr. Scott's statement that a POSA would know that Z'-scaffold must form 1-3 H-bonds with Btk.³ EX2012, ¶20. With these parameters, there would be a total of 864 (6×12^2) species for each ring system.

33. Further, the Structural Limitations do not prescribe the attachment points in the linker. Hence, the linker can be connected to the Z'-scaffold at three different points—leading to $3 \times 864 = 2,592$ species per ring system.

34. Finally, Appendix A contains 1,726 ring systems, meaning the total number of possible ring systems for independent claims 1 and 8⁴ is **4,473,792** ($1,726 \times 2,592$).

Showalter Reply Decl. (EX1105) ¶¶ 31-35, 37.

Patent Owner did not dispute in sur-reply the factual underpinnings of this calculation.

Sur-Reply at 4-5.

Patent Owner's Expert Proposed to Model Each Compound Individually

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q. Okay. So reading the patent, which of those eight would they – would be in the category of at least some that would be able to be used to make an ibrutinib-like BTK?
- A. So as I said, as we sit here, I haven't done that analysis. As we sit here today, I can't answer that question, but I can tell you that as a POSA or as a member of a POSA team, how I would approach that, right. So, you know, taking, for example, the structure in the lower left in Column 63, that looks to me as a POSA, like a promising structure for making a BTK-like inhibitor. I would propose an amine substitution in the first position that's indicated for, you know, for substitution. I would propose the phenoxyphenyl in the second and the linker-warhead of the claims in the third.

I would consult with my medicinal chemist colleague for an opinion as to whether he agreed that that would be good. I would carry out a docking exercise to assess how well it fit within the active site of BTK. And, yeah, and will thereby have visualized a new BTK inhibitor, ibrutinib-like. "New" in the sense of one that, you know, has been invented and described here, but probably not been synthesized and tested previously.

E.g., Eck Dep. Tr. (EX1110) at 72:6-73:5; see also, e.g., Reply 10-13 (collecting cites); Veal Reply Decl. (EX1106) ¶¶ 98, 107, 188-91, 244-252.

Patent Owner's Expert Admitted It Would Take Him About an Hour to Model Each "Fully-Formed" Inhibitor

Dr. Michael J.
Eck
*Patent Owner's
Expert*

Q. According to you, visualizing the docking of a candidate BTKI could be accomplished in a matter of minutes, right?

A. That's correct.

Q. So you could take that scaffold structure and in a matter of minutes visualize whether it would be a candidate BTKI, right?

A. We're talking about two different things. So as I've – the section of my declaration that you're quoting from, I'm talking about taking a fully-formed inhibitor and docking it. Here, we are talking about taking a scaffold and elaborating it into a fully-formed inhibitor.

Q. How long would that take?

A. I mean, if I were in my office, at my work station, you know, I could in a matter of, you know, I think less than an hour, have a clear sense of where I would want to attach the phenoxyphenyl and the linker-warhead and the other substitutions that I might be interested in adding in order to achieve hydrogen bonds with the hinge. Others who are – you know – what am I trying to say? Yeah, I'm not particularly fast. I'm slow and deliberate. Others could probably do it even faster.

Eck Dep. Tr. (EX1110) at 94:1-95:1; see also, e.g., Veal Reply Decl. ¶ 247.

Experimentation Required to Model at Rate of One Potential Inhibitor *Per Minute* Is Far Greater Than Federal Circuit Precedent Permits

Veal Reply Declaration

247. Even if modeling could have been used, modeling the full scope of the structurally diverse claimed compounds satisfying the Structural Limitations alone would have required extensive efforts. *See supra* Section VIII.A.1.a)(5). As explained above, the Structural Limitations encompass both *known and unknown* Z'-scaffolds and evaluating the full scope of the compounds satisfying the Structural Limitations would require evaluating *known and unknown* structures, which Dr. Eck acknowledged would take a "significant amount of time," which he has not tried to estimate or determine how to execute. EX1110, 128:3-129:6, 129:13-16, 129:23-130:3. Dr. Eck contends that modeling a compound would have only taken "a matter of minutes." EX2010, ¶209. Even so modeling the full scope of structurally diverse compounds satisfying the Structural Limitations still would have required extensive efforts. Specifically, modeling 4 million potential candidates would have taken over 7 years assuming each one could be modeled and evaluated in a single minute, and modeling billions would have taken far longer.

Veal Reply Decl. (EX1106) ¶ 247; *see also*, e.g., Reply at 23-24 (collecting cites).

Cephalon, Inc. v. Watson Pharms., Inc.

707 F.3d 1330, 1339 (Fed. Cir. 2013)

“Permissible experimentation is, nevertheless, not without bounds. This court has held that experimentation was unreasonable, for example, where it was found that eighteen months to two years’ work was required to practice the patented invention.”

Modeling Not Sufficient: Petitioner's Expert Showed That Modeling Is Not Predictive of Binding BTK

Reference	Compound	Glide Docking Score	Reported IC ₅₀ Value	Reported IC ₅₀ Value Source
	Ibrutinib*	-10.5	2.0 nM	EX2063.0002 (Fig. 3)
	Zanubrutinib*	-9.3	0.3 nM (S isomer); 11 nM (R isomer)	EX1053.005 (Table 6)
WO'289 (EX1108)	Compound 81	-9.7	5,900 nM	EX1108, [0642], Table II
WO'185 (EX1109)	Compound 9	-10.3	> 1000 nM < 100,000 nM	EX1109, [00348]

Veal Reply Decl. (EX1106) ¶¶ 99-104, 114-138 (annotated).

- More negative docking scores suggest tighter binding
- Compounds with an IC₅₀ value of >1000 nM are inactive
- None of Patent Owner's experts disagreed with these thresholds

See Veal Reply Decl. (EX1106) ¶¶ 97, 119; Showalter Reply Decl. (EX1105) ¶ 39.

Both Parties' Experts Agreed That Modeling Must Be Validated by Synthesis and Experimental Testing

Veal Reply Declaration

101. As described below, modeling in 2010/2011 (and even today) would not have accurately predicted whether a compound will irreversibly inhibit Btk. Therefore, experimental testing would have been required in order to determine whether any given structure will irreversibly inhibit Btk. The binding of a ligand or inhibitor to a protein target is a complex physicochemical process involving both enthalpic and entropic interactions, and covalent modification adds additional complexity. Even today, modeling necessarily uses multiple approximations to represent what can only accurately be measured by applying quantum mechanics to a large dynamic system consisting of the ligand, protein, solvent, counterion, and other potential cofactors. This is beyond the scope of computer capabilities even today. Thus, modeling and structure aided drug design is used to improve probabilities of success but has significant limitations and cannot replace experimental testing.

Veal Reply Decl. (EX1106) ¶ 101;
see also, e.g., Petition at 83-88, Reply at 11-12, 23-24 (collecting cites).

David Scott

Patent Owner's Expert

- Q. If a modeler were to tell you that a candidate kinase inhibitor would inhibit the target based on their modeling, would you take them at their word?
- A. I would want to understand the work they had done and the information the model was based upon.
- Q. Would you do any additional testing to confirm that they were correct?
- A. I'm not sure I understand what you mean by testing.
- Q. Would you run an assay to confirm that the inhibitor actually inhibits the target?
- A. Oh, I see. Yes, it's valuable to validate predictions of modeling with data, and that's something that we would have done.

Scott Dep. Tr. (EX1117) at 40:18-41:13.

Patent Owner Admitted That Some Human Testing Would Be Required

Patent Owner Response

b. **No Undue Experimentation Would Be Needed to Identify a Therapeutically Effective Amount**

The specification teaches a POSA to use a novel method to identify therapeutic doses using BTK occupancy to confirm BTK binding and irreversible inhibition. §V.B.1; EX2014 ¶¶128-129. Such assays can be conducted on readily accessible patient blood samples, allowing prompt feedback that a particular dose inhibits BTK in a patient and confirm its therapeutic effect as required by the claims. EX2014 ¶128. The specification's teaching of ibrutinib's properties would guide a

Response at 83.

Patent Owner's Expert Admitted Obtaining Patient Blood Samples Requires Prior Preclinical Testing

Dr. Stephen E. Spurgeon
Patent Owner's Expert

- Q. At what dose would you administer the BTKI to the patient?
- A. Well, based on what the specification teaches, I would administer the dose that caused BTK inhibition based on the assay and based on the specification, so that had greater than 90 percent BTK occupancy in PBMCs. That's the dose I would use
- Q. And in order to measure the occupancy, you would need to first administer that BTKI to the patient, right, and then draw their blood and run the assay, correct?
- A. That is correct.
- Q. So at what dose would you administer the BTKI to the patient before you draw their blood and run the assay?
- A. I don't know the specific dose.
- Q. Why not?
- A. Because I don't have access to the – ready access or complete access to the preclinical data.

Spurgeon Dep. Tr. (EX1119) at 135:16-136:13; see also Petition at 83-88, Reply at 25-26 (collecting cites).

Other *Wands* Factors: Guidance and Examples, Predictability of Art etc.

The POSA's "Informed Choices" Would Not Limit the Necessary Amount of Experimentation

Patent Owner Sur-Reply

Petitioner cannot show undue experimentation without analyzing the extent to which a POSA could select compounds expected to work in the claimed methods and the extent to which those selection choices would be successful. *Id.* 78-85. Instead, Petitioner resorts to improper reliance on the alleged cumulative effort required to screen every member of the genus, without regard to a POSA's informed choices.

Sur-Reply at 5.

See, e.g., Petition at 88-92, Reply at 23, 25-26 (collecting cites).

Enablement Inquiry Is Not Limited to the Most Desirable Parts of the Genus

Idenix Pharms. LLC v. Gilead Scis. Inc.

941 F.3d 1149, 1162 (Fed. Cir. 2019)

“Second, Idenix argues that the claim is not broad because ‘evidence showed that the POSA, with common sense, the claims, and the specification as guidance, would focus on a narrow set of candidates.’ . . . This factor, however, considers the scope of the claim as written, not just the subset of the claim that a POSA might practice. Idenix does not, and cannot, argue that the scope of the claim is actually limited to this narrow set of candidates. ‘[A]s a matter of law, NS5B activity is *not* a claim limitation.’ . . . We therefore conclude that the breadth of the claims weighs in favor of non-enablement.”

Patent Owner Sur-Reply

Formula E, as understood by a POSA, teaches that various components can be used to bind within the active site of BTK because of the well-established structure-function relationship. POR 23-24, 43-46. It is precisely because of the well-understood binding within the kinase active site that, as Dr. Veal admits, scaffold swapping and morphing was known in the field. Indeed, Dr. Veal's pre-litigation publications identify exactly this practice. EX2120.0026; EX2119, 119:7-16 (admitting modeling would be used to identify new scaffolds for use in kinase inhibitors). As guided by Formula E, a POSA looking to succeed would understand how to select appropriate scaffolds with the fixed components to achieve the specification's teaching of inhibiting BTK to treat CLL/SLL patients. POR 43-50;

Sur-Reply at 21.

Patent Owner's Expert Conceded That He Had Not Performed the Analysis Necessary to Determine Whether the E1 to E8 Cores Would Bind to BTK

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q. So a POSA would read this patent, and you said would understand – that at least some of them would be able to be used to make an ibrutinib-like BTK inhibitor; which ones? You read the patent.
- A. I read the patent. I can take a minute to remind myself, for example, which one is, you know, is precisely ibrutinib.
- Q. You don't need to do that because we know that ibrutinib is ibrutinib.
- A. I think we can agree that a POSA would well understand that.
- Q. What about the other ones that are not ibrutinib?
- A. As I said, I haven't – I haven't gone through them one by one and done that analysis.

In Fact, If Modeling Is Predictive, Petitioners’ Expert’s Unrebutted Modeling Showed That at Least Three of E1 to E8 Are Not Expected to Bind to BTK

141. Below is a table summarizing the most negative docking scores I obtained for various structures with non-biaryl cores (including Structure E4) and two biaryl cores disclosed in the specification (Structures E2 and E3). Notably, while the inventors of the 803 Patent suggested using BTKIs comprising the E2-E4 cores, modeling suggests that compounds comprising these Z'-scaffolds do not irreversibly inhibit Btk.

Reference	Compound	Fused Heterocyclic Ring System Subgenus	Glide Docking Score
803 Patent (EX1001)	Structure E2	Biaryl	-8.5
803 Patent (EX1001)	Structure E3	Biaryl	-8.6
803 Patent (EX1001)	Structure E4	5-non-aro, 6-non-aro	-7.4
820 Patent (EX2023)	Formula I scaffold	5-aro, 6-non-aro	-7.4
EX2055	PDB: 2QD9	5-aro, 6-non-aro	-7.5
EX2046	PDB: 5TR6/5TT7	5-non-aro, 6-aro	-6.9

Veal Reply Decl. (EX1106) ¶¶ 139-152.

Nor Would A “Well-Established Structure-Function Relationship” Short Circuit Experimentation

Patent Owner Sur-Reply

Formula E, as understood by a POSA, teaches that various components can be used to bind within the active site of BTK because of the well-established structure-function relationship. POR 23-24, 43-46. It is precisely because of the well-understood binding within the kinase active site that, as Dr. Veal admits, scaffold swapping and morphing was known in the field. Indeed, Dr. Veal’s pre-litigation publications identify exactly this practice. EX2120.0026; EX2119, 119:7-16 (admitting modeling would be used to identify new scaffolds for use in kinase inhibitors). As guided by Formula E, a POSA looking to succeed would understand how to select appropriate scaffolds with the fixed components to achieve the specification’s teaching of inhibiting BTK to treat CLL/SLL patients. POR 43-50;

Sur-Reply at 21.

Patent Owner Asserts That the POSA Would Be Guided Toward Structures With Certain Functional Requirements—Guidance Not in the Specification

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q.** Can you identify structures that would be common to all of the species of Z'-scaffolds that would satisfy those requirements
- A.** So the claim species have many structural features in common. So as I've laid out in the declaration, it's very clear that there is a phenoxyphenyl that's required. It's very clear that there is a specific linker-warhead, the pepperidine (phonetic) with the attached acrylamide that's required.

With respect to the Z'-structure, it will be required that it be able to appropriately position the phenoxyphenyl to bind in the back pocket and simultaneously appropriately position the linker-warhead to react with Cys481. So Z's that are within the claim will have that structural feature. Additionally, they will have to sterically fit within the ADP binding site and form from one to three hydrogen bonds with the hinge.

Idenix Pharms. LLC v. Gilead Scis. Inc.

941 F.3d 1149, 1161-62 (Fed. Cir. 2019)

“Idenix argues that the ’597 patent provides this guidance because a POSA would understand NS5B to be the ‘target’ enzyme or would understand that the modified nucleoside must have ‘either the natural -OH (hydroxyl) or a mimicking substitute at 2’-down.’ . . . But reliance on a POSA is insufficient to meet the enablement requirement. A patent owner is ‘required to provide an enabling disclosure in the specification; it cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification.’”

Moreover, the Prior Art Demonstrates That Varied Z' Structures, Resembling the Scope of the Genus, Were Not Known to Bind BTK

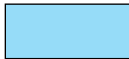
Patent Owner Response

EX2010 ¶¶168-171. A POSA would have been aware of numerous hinge-binding elements, including those with non-aromatic (i.e., partially saturated and non-planar) portions. *Id.* ¶¶168-175; EX1052.003, .012-.013 (partially saturated scaffolds 30, 31, 33, 37, 39); EX2028.0004, Fig. 5 (disclosing a “highly potent, novel inhibitor[]” with partially saturated scaffold); EX2023, 2:1-6 (kinase inhibitors with 5:6 heterocyclic scaffold having saturated 6-membered ring); EX2026, cls. 1, 10 (BTKIs with partially saturated hinge-binding scaffold); EX2055; EX2038.0001, Fig. 1; EX2053.

Response at 52.

Supp. 3d at 639, 645-46. Similarly, here there were numerous known heterocyclic scaffolds that bound to the “highly conserved” kinase hinge. EX2010 ¶¶83-89, 147-148; §II.C.3; EX1077.003-.004; EX2028.0002-.0004; EX1052.003-.018; EX2023, 2:1-6; EX1073.009, Tbl. 2 (BTKIs); EX2026, cls. 1 & 10, [0023], [0076] (BTKIs); EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1) (BTKIs). As taught in the specification’s Formula E, a POSA would understand heterocyclic scaffolds make predictable interactions with the kinase hinge. EX2010 ¶¶83-89, 147-148; EX1052.002; EX2028.0001-.0005. Further, a POSA would have access to

Response at 64-65.

-  scaffold not a Z' structure
-  biaryl
-  modeling shows not expected to bind

See, e.g., Reply at 8-9 & n.4; Veal Reply Decl. (EX1106) ¶¶ 63-68, 139-143, 153-161, 171, 195, 211, 214-220.

Moreover, the Prior Art Demonstrates That Varied Z' Structures, Resembling the Scope of the Genus, Were Not Known to Bind BTK

Patent Owner Response

EX2010 ¶¶168-171. A POSA would have been aware of numerous hinge-binding elements, including those with non-aromatic (i.e., partially saturated and non-planar) portions. *Id.* ¶¶168-175; EX1052.003-.012-.013 (partially saturated scaffolds 30, 31, 33, 37, 39); EX2028.0004, Fig. 5 (disclosing a “highly potent, novel inhibitor[]” with partially saturated scaffold); EX2023, 2.1-6 (kinase inhibitors with 5.6 heterocyclic scaffold having saturated 6-membered ring); EX2026, cls. 1, 10 (BTKIs with partially saturated hinge-binding scaffold); EX2055; EX2038.0001, Fig. 1; EX2053.

Response at 52.

Supp. 3d at 639, 645-46. Similarly, here there were numerous known heterocyclic scaffolds that bound to the “highly conserved” kinase hinge. EX2010 ¶¶83-89, 147-148; §II.C.3; EX1077.003-.004, EX2028.0002-.0004, EX1052.003-.018, EX2023, 2:1-6; EX1073.009, Tbl. 2 (BTKIs); EX2026, cls. 1 & 10, [0023], [0076] (BTKIs); EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1) (BTKIs). As taught in the specification’s Formula E, a POSA would understand heterocyclic scaffolds make predictable interactions with the kinase hinge. EX2010 ¶¶83-89, 147-148; EX1052.002; EX2028.0001-.0005. Further, a POSA would have access to

Response at 64-65.

-  scaffold not a Z' structure
-  biaryl
-  modeling shows not expected to bind
-  not BTK inhibitor

See, e.g., Reply at 8-9 & n.4; Veal Reply Decl. (EX1106) ¶¶ 63-68, 139-143, 153-161, 171, 195, 211, 214-220.

Wyeth & Cordis Corp. v. Abbott Lab'ys

720 F.3d 1380, 1386 (Fed. Cir. 2013)

“Here, the specification similarly discloses only a starting point for further iterative research in an unpredictable and poorly understood field.

Synthesizing candidate compounds derived from sirolimus could, itself, require a complicated and lengthy series of experiments in synthetic organic chemistry. Even putting the challenges of synthesis aside, one of ordinary skill would need to assay each of at least tens of thousands of candidates. . . . The specification offers no guidance or predictions about particular substitutions that might preserve the immunosuppressive and antirestenotic effects observed in sirolimus. The resulting need to engage in a systematic screening process for each of the many rapamycin candidate compounds is excessive experimentation.”

Amgen Inc. v. Sanofi

598 U.S. 594, 613-14 (2023)

“Amgen seeks to monopolize an entire class of things defined by their function—every antibody that both binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors. The record reflects that this class of antibodies does not include just the 26 that Amgen has described by their amino acid sequences, but a ‘vast’ number of additional antibodies that it has not.”

“[Amgen] says[] its broad claims are enabled because scientists can make and use every undisclosed but functional antibody if they simply follow the company’s ‘roadmap’ or its proposal for ‘conservative substitution.’ We cannot agree. These two approaches amount to little more than two research assignments.”

Grounds 3 and 4: Anticipation and/or Obviousness

Patent Owner Concedes the Challenged Claims Are Anticipated and/or Obvious If the Claims Are Not Entitled to Patent Owner's Asserted Priority Date

Patent Owner Response

VI. Grounds 3 and 4: Petitioner's Asserted References Are Not Prior Art

The specification filed in June 2011 fully describes and enables the challenged claims for all the reasons described above. Thus, the claims are entitled to at least the June 2011 priority date. Because Byrd published in 2013 and the IMBRUVICA label published in 2016, after the June 2011 priority date, Petitioner's references are not prior art and cannot anticipate or render obvious the challenged claims.

Response at 94.

Rebuttal Slides

After Filing '280 Application, Patent Owner Entered Amendments in March 2022

23. **(Currently Amended)** A method for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual comprising:

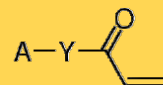
orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity; and

wherein lymphocytosis is not considered progression of the CLL or SLL, and

wherein the individual achieves a complete response.

32. **(New)** The method of claim 23, wherein the irreversible inhibitor of Btk forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase.

34. **(New)** The method of claim 32, wherein the inhibitor of Btk has the structure:



wherein:

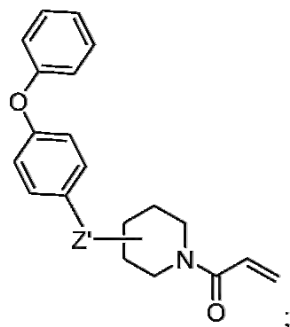
A is a moiety that binds to the active site of Btk; and

Y is a substituted heterocycloalkylene.

EX1002.426-27.

Due to a Series of Section 112 Rejections, Applicant Continually Narrowed Scope of Genus, Relying on Specification's Formula E for Support

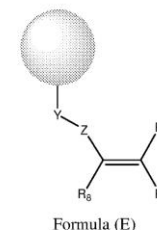
Applicant hereby incorporates by reference in their entirety the arguments presented in the Response to Non-Final Office Action, dated August 23, 2022. However, solely for the purpose of expediting prosecution and without conceding to any of the rejections, claims 23 and 42 have been amended herein to specify a particular genus of small molecule, irreversible Btk inhibitors having **the particular chemical structure:**



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2–4 nitrogen heteroatoms. Support for these amendments can be found, at least, for example, at para. [0222] (small organic molecule), para. [0070] (heterocyclic ring, optionally substituted), para. [0073] (fused), para. [0071] (ring system), paras. [0082]–[0084], para. [00261] and throughout the specification and claims as originally filed.

EX1002.578-579.

[00260] In one embodiment the irreversible inhibitor of a kinase has the structure of Formula (E):



wherein:

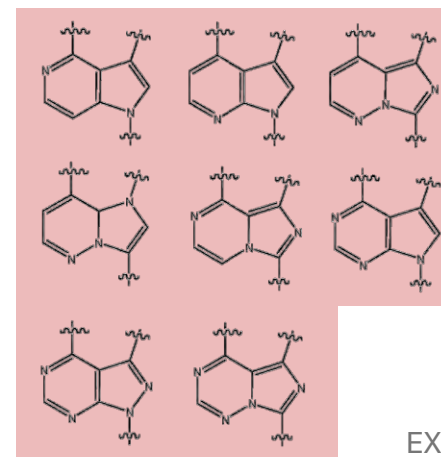


wherein is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

EX1002.124-125.

[00261]

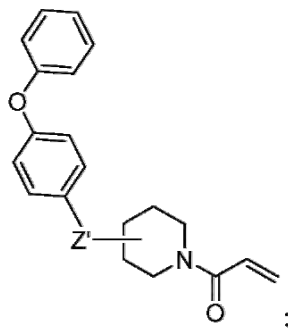
In some embodiments, is a substituted fused biaryl moiety selected from



EX1002.125-126.

Due to a Series of Section 112 Rejections, Applicant Continually Narrowed Scope of Genus, Relying on Specification's Formula E for Support

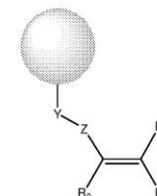
Applicant respectfully traverses both rejections together. However, solely for the purpose of expediting prosecution, claims 23 and 42 have been amended to specify a particular genus of small molecule, irreversible Btk inhibitors having the particular chemical structure, **which specifies the size of the rings and amount of nitrogen heteroatoms in each ring**:



wherein Z' is an optionally substituted fused heterocyclic ring system and wherein the optionally substituted fused heterocyclic ring system comprises **a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom**. Accordingly, the claimed fused heterocyclic ring system cannot include, three or more rings, and the size of the rings is limited as in p 79 of the specification.

EX1002.638.

[00260] In one embodiment the irreversible inhibitor of a kinase has the structure of Formula (E):



Formula (E)

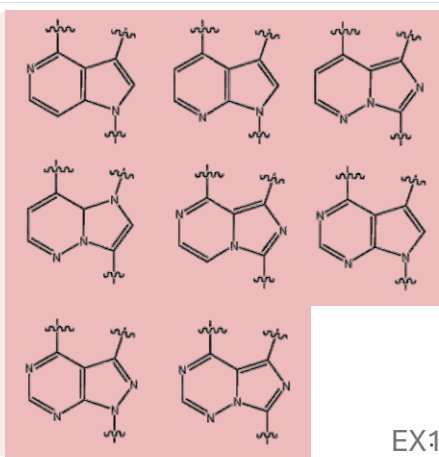
wherein:



wherein is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

EX1002.124-125.

[00261] In some embodiments, is a substituted fused biaryl moiety selected from



EX1002.125-126.

Modeling Only Serves As a Tool to Approximate If an Individual Potential Inhibitor, Already Drawn, Might Bind BTK

Dr. Michael J.
Eck
*Patent Owner's
Expert*

- Q. When you say, “a POSA could visualize every molecule that falls within the scope of the claim,” how many molecules are we talking about here?
- A. Again, as we have discussed at some length, I haven’t tried to calculate that.
- Q. Then how do you know a POSA can envision all of them if you can’t – I just don’t follow that logic.
- A. So, again, I am trying to speak very clearly here.
- Q. Okay.
- A. There is no molecule in the claim that can’t be visualized or recognized in my opinion.
- Q. Got you.
- A. Setting about visualizing or recognizing every one of the many is a very different thing.

Dr. Veal Has Greater Experience in Molecular Modeling Than Dr. Eck

Dr. Michael J. Eck
Patent Owner's Expert

Q. Okay. And in your lab when you've been talking about the use of this software for virtual ligand screening, is it typically someone else in your lab that's using the software, or is it typically you that's using the software?

A. As I said, it's typically my trainees or staff scientists.

* * *

Q. So you did speak to your computational chemistry post-doc with respect to the work you've done in this case?

A. I asked questions of it. I didn't enlist him to do the work for me, but if I had a question, I would ask him.

E.g., Eck Dep. Tr. (EX1110) at 18:20-19:1, 19:11-16.

Dr. James M. Veal
Petitioner's Expert

Q. And in your role as vice president of research, did you perform modeling for any projects?

A. I did. Actually, you know, so after I left Glaxo, so that was, I guess, in the 2003 time frame, I went to a company Serenex, which was the one maybe listed previous to this. So I went into biotech. And at biotech, you wear many hats. And even as I have moved up in terms of position, I have still continued to have an active role in the computational chemistry effort. And that's just the nature of biotech where, you know, you may have, you know, senior roles, if you will, presentations to investors and the like, but you also have day-to-day discipline roles. And even to this day, in my current company, 858 Therapeutics, I still perform computational chemistry. Our biology founders still does, you know, assays in the lab. Our organic chemist founder still actively is involved in preparing synthetic schemes. So that's the nature of biotech. You wear hats where you have senior cross-functional roles but you still also have active roles with regards to your specific discipline.

Q. And in addition to doing modeling – some of the modeling yourself, you also rely on junior team members to perform modeling that you review; is that right?

A. Not at Pamlico. And thinking out through my career history, I think at Quantical Pharmaceuticals, we had others that were doing modeling – or one other that was – you know, not even a dedicated modeler. That person was still a medicinal chemist as well. So I've been the one that does the dedicated computational chemistry.

E.g., Veal Dep. Tr. (EX2119) at 48:8-49:19.

Petitioner's Expert Testified That Modeling Cannot Predict Whether Compounds Will Be Active

**Dr. James M.
Veal**

*Petitioner's
Expert*

- Q.** Okay. Would modeling allow you to predict whether any of these substructures would actually bind the target or not?
- A.** No, it would not. It would be used for the purpose of identifying compounds, again, from internal corporate collection, you know, reducing, you know, hundreds of thousands or millions of compounds in a corporate collection down to 10 to 20,000 or to identify compounds from external vendors to acquire and bring in for testing. And only then after you tested the compounds would you hope that some percentage – likely, you know, a small percentage would show activity against a kinase of interest.

CERTIFICATE OF SERVICE

I hereby certify that on January 29, 2025, I caused a true and correct copy of the foregoing Petitioners' Demonstrative Exhibits to be served by electronic means, as agreed by the parties, upon the following:

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