Dr. Showalter Did Not Assess Whether His Appendix A Cores Would Lead to Inhibition

Showalter Deposition (Ex. 2018)

Q So, Dr. Showalter, in considering your Appendix A, you have not done an analysis to determine which of the bicyclic five-six systems you cite would be more or less likely to be functional inhibitors of Btk if they were appended as the claims describe with a phenoxyphenyl back pocket binder and the linker warhead structure that's in Claim 1. Right?

A I have not done such an analysis.

Ex. 2018, 163:8-17 (objection omitted)

Showalter Deposition (Ex. 2118)

Q And just so I understand. With respect to the Appendix A Z prime structures, you did not do any modeling of those to determine which would be more or less likely to have -- to form compounds that would meet the functional limitations.

Is that correct?

A That's correct, no modeling was done.

Q And that includes that you did not attempt to account for Dr. Veal's analysis that certain of the E2, E3, or E4 scaffolds would not lead to productive functional binding.

Is that right?

A That's correct.

Ex. 2118, 53:22-54:13

PO Response, at 54-55, 78-82; PO Sur-Reply, at 4; Eck Decl. (Ex. 2010), ¶¶180-181

Dr. Showalter Did Not Assess Whether His Appendix A Cores Had Precedent in the Context of Tyrosine Kinase Inhibitors

Showalter Deposition (Ex. 2018)

Q And so when you were studying the literature to identify these, were any of the references that you used references that described the inhibition properties of compounds including these cores against tyrosine kinase inhibitors?

A So I looked at not necessarily -- I did not look at medicinal chemistry literature to confirm that these cores had been utilized to make tyrosine kinase inhibitors. These are cores that

Ex. 2018, 151:11-20 (objection omitted)

Showalter Deposition (Ex. 2118)

Q So you didn't attempt to do any sort of broad literature search beyond the structures that you were aware of from the EGFR program?

A So, no, I did not do an exhaustive search. That would have taken a lot of time, and I was working on my declaration and other parts of this project. So I did not invest the time to actually determine all of the reversible inhibitors that would have used heterobicyclic structures.

Ex. 2118, 37:4-14 (objection omitted)

PO Response, at 54-55, 78-82; PO Sur-Reply, at 4

Dr. Showalter Did Not Model the Appendix A Cores, but Agrees that a POSA Would Use Modeling to Select Substitutions

Showalter Deposition (Ex. 2118)

Q And just so I understand. With respect to the Appendix A Z prime structures, you did not do any modeling of those to determine which would be more or less likely to have -- to form compounds that would meet the functional limitations.

Is that correct?

A That's correct, no modeling was done.

Ex. 2118, 53:22-54:7

Showalter Deposition (Ex. 2118)

Q You agree, then, though, that that decision of whether to do further substitution would be informed by modeling. Correct?

A Modeling would be one -- certainly one tool that one could utilize to assess which open sites are substitutable.

Ex. 2118, 42:5-11 (objection omitted)

Q You do agree, however, that a modeler might have been able to provide some insight into which molecules are less likely to work?

A That -- that is one useful aspect of modeling, yes.

Ex. 2118, 28:8-12

PO Response, at 54-56, 78-82; PO Sur-Reply, at 3-4, 21; Eck Decl. (Ex. 2010), ¶¶180-182

Structural Modeling Avoids Experimentation

Veal Publication 2009 (Ex. 2120)

referenced examples below. However, the personal view is that docking or scoring energies should be used as a filter to winnow down possible analogs of interest to a number on the order of 20% of the original possibilities and from that point both binding energies and visual inspection, often in conjunction with medicinal chemists, should be used to guide selection of the final set of analogs to pursue synthetically.

Ex. 2120.0030

Showalter Deposition (Ex. 2118)

21 A So I just said earlier that you could use
22 modeling to -- to weed out compounds that you
1 think would not meet the functional limitations.

Ex. 2118, 19:21-20:1

Both Parties' Experts Agree that Modeling Would Rule Out Non-Working iBTKIs

Eck Declaration (Ex. 2010)

209. Employing these virtual docking tools, applying the teachings of the '803 Patent as well as the specific structural information available for BTK (*i.e.*, EX2001.0003-0005 (PDB: 3GEN)), and applying the sophisticated understanding in 2011 of the structure-function relationship for the components of irreversible BTKIs of the claims, a POSA would have routinely identified and excluded structures that were plainly not operable—*i.e.*, structures that would not be accommodated within the known structural conformation of BTK bound to a BTK inhibitor with ibrutinib-like binding. Visualizing the docking of a candidate BTKI could be accomplished in a matter of minutes.

see also supra §§VII.B.2, X.A.2.b. In 2011, a POSA would have used virtual docking to predict which Z'-scaffolds for ibrutinib-like BTKIs would satisfy the need for H-bonds to the hinge ***and*** the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481. These virtual docking and modeling tools would have ruled out inappropriate compounds. *See supra* §§X.A.3.b(3), XI.B. Therefore, by viewing Z' in isolation,

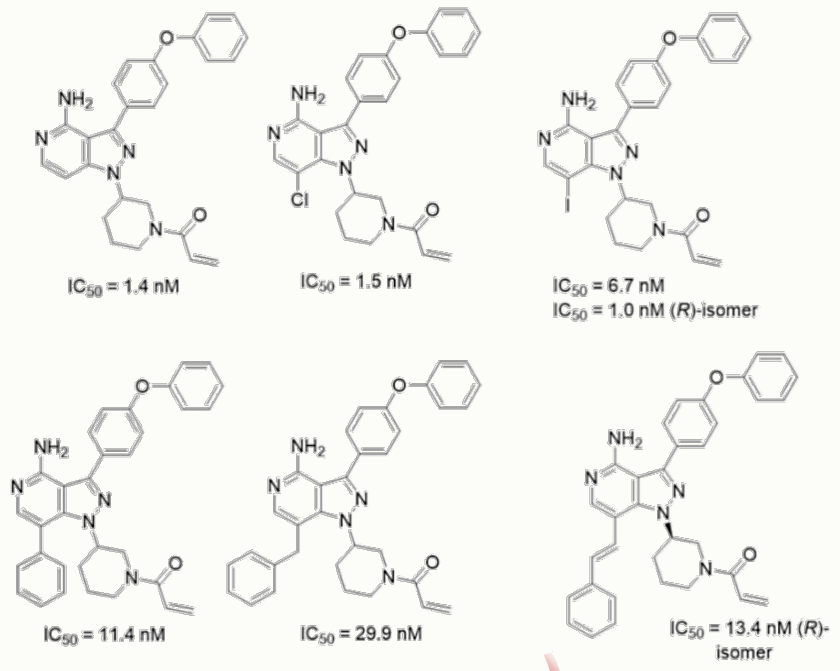
Ex. 2010, ¶¶ 209, 219

PO Response, at 80-81; PO Sur-Reply, at 10-11

Petitioner Cannot Carry Its Burden with Select Examples of Non-Working Embodiments

Petition Tried to Show Varied Activity, but Only Identified Potent Ibrutinib-like iBTKIs

Showalter Declaration (Ex. 1003)



EX1036 (summarized).

Ex. 1003, ¶176

Petition *failed to identify a single compound* that was not a potent ibrutinib-like iBTKI

Showalter Deposition (Ex. 2018)

Q And again, you would agree with me that all of these are showing potency or high potency against Btk. Correct?

A So I would argue, again based on our discussion earlier, that this is -- you have to look at the context of the time period when these -- when a series is discovered.

2010, 2011, these would all be classified as highly potent or let me just say potent. As of 2019 the standard had changed and, therefore, some of these data I would view as not representing necessarily highly potent compounds. They are potent, but not highly potent.

Ex. 2018, 131:17-132:8 (objection omitted)

Eck Declaration (Ex. 2010)

opinions. The '432 Publication shows that structures falling with the genus of the Challenged Claims are BTKIs, with potent IC_{50} ranging from 1-30 nM. *See* EX1036.011-083 (example structures), .084-085 (IC_{50} values). Accordingly, the

Ex. 2010, ¶159

PO Response, at 60; PO Sur-Reply, at 24

Dr. Showalter Belatedly Raised Two New Post-Priority References at Deposition, but a POSA Would Have Recognized the Compounds as Not Potent

Eck Declaration (Ex. 2010)

183. I understand that after Dr. Showalter submitted his declaration in support of Petitioner's Petition, Dr. Showalter belatedly pointed to two post-priority references in his deposition that he claims meet the structural limitations of the Challenged Claims and are "inactive": U.S. Patent No. 10,358,446 ("'446 Patent") and an ACS Medicinal Chemistry Letter ("Zhang 2020"). *See* EX2018, 12:11-15:12; EX2024; EX2063. I have reviewed these references and have

Ex. 2010, ¶183

'446 Patent (Ex. 2024)

Eck Declaration (Ex. 2010)

184. I identified three compounds from the '446 Patent that meet the structural limitations of the Challenged Claims: compound 20, compound 30, and compound 122. EX2024.0027, .0031, .0061. The '446 Patent reports BTK inhibition of these compounds as IC_{50} ranges: compound 20 (10-100 nM), compound 30 (>10000 nM), and compound 122 (1000-10000 nM). *Id.*, .0118-0119. With an IC_{50} value in the 10-100 nM range, compound 20 is a potent inhibitor of BTK, confirming the common structural features of the Challenged Claims result in BTK inhibition. As for compounds 30 and 122, docking into the Marcotte structure reveals these compounds as poor candidates for irreversibly inhibiting BTK as required by the claims. As I have explained, in 2011, a POSA reading the

Ex. 2010, ¶184

Zhang 2020 (Ex.2063)

Eck Declaration (Ex. 2010)

185. Zhang 2020 discloses two compounds that meet the structural limitations of the Challenged Claims and reports BTK inhibition of these compounds with IC_{50} values: compound 7 (>1000 nM) and compound 8 (2.1 nM). EX2063, Fig. 3 (.0002). Docking these compounds into the Marcotte structure using Maestro/Glide indicates that both can be accommodated in the BTK active site, with the phenoxyphenyl positioned in the back pocket of BTK and the linker-warhead approaching Cys481. However, the docking score was markedly better for Compound 8 as compared with Compound 7 (-9.3 for compound 8 as compared with -6.5 for Compound 7). Accordingly, a POSA would have prioritized Compound 8 over Compound 7 for synthesis and further testing. Zhang 2020 describes Compound 7 as having "weaker potency" and its activity would have been readily identified in a straightforward IC_{50} kinase assay. EX2063.0002. As

Ex. 2010, ¶185

PO Response, at 60-61 n.8

Dr. Veal Agrees that Modeling Predicts Binding for Majority of Compounds Modeled

Veal Declaration (Ex. 1106)

[6] I also modeled other compounds with reported IC_{50} values, specifically Compounds 8, 10, and 11 of Zhang, Compound 20 of the 446 Patent, and Compound 2 of WO'185. EX1146. The docking poses and scores for these compounds were consistent with their reported IC_{50} values. Those results, however, do not change my opinion that modeling is not predictive. The fact that modeling is sometimes consistent and sometimes inconsistent with experimental data underscores that modeling cannot accurately predict irreversible inhibition of Btk.

Ex. 1106, ¶118 n.6

Veal Deposition (Ex. 2119)

Q. So compound 7, compound 8, compound 10, and compound 11 from Zhang, you concluded that the modeling was consistent with the activity; is that right?

A. Yes, that's correct.

Q. Okay. And you also conclude that compound 20 from the '446 patent, its modeling was consistent with its activity; right?

A. Yes, the compounds you're referring to are the subset where, you know, the Glide scoring seemed to align with the IC50s. Obviously, as indicated, there were multiple other compounds where that was not the case.

Ex. 2119, 206:10-207:1 (objection omitted)

PO Sur-Reply, at 11, 22-24

Dr. Veal's Modeling of the E4 Example Scaffold Does Not Undermine Predictability

1. Dr. Veal's analysis confirms the power of modeling and a POSA's ability to predict from modeling whether a compound would bind BTK
   - *See* PO Sur-Reply, at 10-12
2. Dr. Veal only modeled one compound with the E4 scaffold; no attempt to identify any substitutions that would bind BTK
   - *See* Veal Decl. (Ex. 1106), ¶¶150-152
3. Dr. Veal's modeling of the '803 Patent's E4 example scaffold was belatedly raised on reply, depriving Patent Owner of the opportunity to provide responsive evidence
   - *See* Veal Decl. (Ex. 1106), ¶¶150-152; PO Sur-Reply, at 1-2
4. No evidence in the record about how other compounds with the E4 scaffold would bind BTK

Petitioner's Select Examples of Non-Working Embodiments Do Not Satisfy Its Burden on Non-Enablement

Two Embodiments Where Modeling May Not Predict Activity ≠ Non-Enablement

Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005)

"It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention."

Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984)

"It is not a function of the claims to specifically exclude . . . possible inoperative substances . . ."

Dr. Veal Applies an Incorrect Standard in Assessing Predictability, Focusing on Identifying Improved iBTKIs

Veal Deposition (Ex. 2119)

13 And to be clear, all of this takes quite a
14 bit of work to do as well as a computational
15 chemist. And, again, the idea is to increase your
16 probability of success, although the probability
17 remains low.

Ex. 2019, 99:13-17 (objection omitted)

4 Q. And you keep saying "low probability of
5 success." Is your definition of low probability of
6 success achieving improved properties over the
7 compound that you're trying to optimize?
9 A. Yes, I think that's correct. I think, you

Ex. 2019, 91:4-9 (objection omitted)

PO Response, at 89-91; PO Sur-Reply, at 11, 22-24

No Undue Experimentation to Identify a Therapeutically Effective Amount

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

'803 Patent, Specification

Example 7 Clinical Trial to Determine Safety and Efficacy of Compounds of Formula (D)

The purpose of this clinical trial is to study the side effects and best dose of a compound of Formula (D) and to determine its efficacy in the treatment of patients diagnosed with recurrent B-cell lymphoma.

Study Design

Cohorts of 6 patients each receive a compound of Formula (D) at 1.25, 2.5, 5.0, 8.3, 12.5, 17.5 mg/kg/d until the MTD is established. In cases where MTD is not reached, dosing levels are increased beyond 17.5 mg/kg/d by 33% increments. Patients receive daily treatment for 28 days followed by a 7 day rest period (one cycle). Tests for Btk occupancy by the drug ("occupancy") are performed on Day 1, 2, 8, 15 and 29 during Cycle 1 and on Day 1 and 15 of Cycles 3, 5, 7, 9, and 11. If ≤1 DLT ("dose-limiting toxicity") is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Patients are enrolled in

Ex. 1001, 136:15-33

C. Measure pharmacodynamic (PD) parameters to include drug occupancy of Btk, the target enzyme, and effect on biological markers of B cell function. Specifically, this study examines the pharmacodynamics (PD) of the drug in peripheral blood mononuclear cells (PBMCs) using two PD assays. The first PD assay measures occupancy of the Btk active site by the drug using a specially designed fluorescent probe. The second PD assay measures inhibition of B cell activation by stimulating the PBMCs ex vivo at the BCR with anti-IgM/IgG, and then assaying cell surface expression of the activation marker CD69 by flow cytometry The PD biomarkers are measured in vitro from a blood sample removed from patients 4-6 hours following an oral dose of the drug. These assays determine what drug levels are required to achieve maximal occupancy of Btk and maximal inhibition of BCR signaling. When possible, similar studies are conducted on circulating tumor cells isolated from blood of patients.

Ex. 1001, 137:9-26

Spurgeon Declaration (Ex. 2014)

128. Once a compound having ibrutinib's structural features as recited in the claims is shown to inhibit BTK, in order to practice the claimed methods, a POSA need only identify a therapeutically effective dose. Here, as discussed above, the specification provides significant guidance on how to identify therapeutically effective doses by using the unique approach of measuring BTK occupancy. Following that guidance, a POSA would have been able to assess doses to identify those that occupy BTK using the straightforward assay described in the specification. *See supra* §IX.A.1.d. These assays are straightforward to conduct

Ex. 2014, ¶128

Specification Teaches a POSA to Use a Novel Method to Identify Therapeutic Doses Using BTK Occupancy

PO Response, at 32-34, 83-84

Dr. Rosen's Proposed Problems Do Not Undermine Enablement

- Enablement does not require regulatory approval
  - *See* Institution Decision, at 29; PO Response, at 88; *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1370 (Fed. Cir. 2023); *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 662 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018); *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995)
- The claims do no require proof of safety
  - *See* Institution Decision, at 9-10; PO Response, at 26-27, 84-85, 88, 94; Ex. 1001, 24:58-64; *see also United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1370 (Fed. Cir. 2023)
- Preclinical testing before clinical trials in patients is standard industry practice
  - *See* PO Response, at 73-74, 83-85; PO Sur-Reply, at 18-19; Rosen Dep. (Ex. 2021), 221:1-223:20; Spurgeon Decl. (Ex. 2014), ¶¶125-133; *see also Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1338-39 (Fed. Cir. 2013); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 923 (Fed. Cir. 2011)

Dr. Rosen Cites No Evidence of an Ibrutinib-like iBTKI that Inhibits BTK but Would Not Work in Claimed Method

Rosen Deposition (Ex. 2021)

Q. And you've not -- sorry. You've not identified any BTK inhibitor that binds to another protein or induces another mechanism that prevents it from treating CLL or SLL?

A. Just as I said before, just the compounds that are available. And I don't know any negative results.

Ex. 2021, 219:12-18

Q. And you have not identified any examples of a compound that inhibits BTK but doesn't kill a CLL/SLL cell?

A. I'm sure they exist. I haven't particularly studied that. That's not my own work.

Q. Right. And you didn't identify any of those examples in preparing your declaration; right?

A. No, but it's unlikely, if they discovered something that bound or inhibited and it didn't work, that it would be published.

Ex. 2021, 94:4-13

PO Response, at 35, 87-88; PO Sur-Reply, at 17-19

Routine Experimentation Is Not Undue

Cephalon, Inc. v. Watson Pharms., Inc., 707 F.3d 1330, 1338-39 (Fed. Cir. 2013)

"[A] considerable amount of experimentation is permissible, if it is merely routine[.]"

"[T]he fact that a clinician's involvement may be necessary to determine effective amounts of the single compound effervescent agent and its corresponding soluble acid source does not itself constitute undue experimentation."

"[E]xtensive experimentation does not necessarily render the experiments unduly extensive where the experiments involve repetition of known or commonly used techniques."

Eli Lilly & Co. v. Actavis Elizabeth LLC, 435 F. App'x 917, 923 (Fed. Cir. 2011)

"Enablement is not negated if a reasonable amount of experimentation is required to establish dosages and formulation of an active ingredient."

PO Response, at 73-74, 83-84

CONCLUSION

Petitioner Failed to Establish Any Ground of Unpatentability

- Record supports that a Final Written Decision should find the following:
  - The Challenged Claims are described
  - The Challenged Claims are enabled
  - The specification of the ’317 Application, filed June 3, 2011, supports the Challenged Claims
  - Petition’s §102 and §103 references post-date the priority date of the Challenged Claims and thus Grounds 3 and 4 fail

PO Response, at 3 & n.1, 29-94

BACKUP

A POSA Would Have Been Highly Skilled

No Dispute that the POSA Would Have Been Highly Skilled

Showalter Declaration (Ex. 1003)

253. In the field of covalent Btk inhibition, the level of skill was relatively high (*see supra* Section VII), but the art and nature of the invention were unpredictable and not much was known in the state of the prior art.

Ex. 1003, ¶253

Rosen Declaration (Ex. 1005)

265. In the field of irreversible BTKIs, the level of skill was relatively high (*supra* Section VII), but the art and nature of the invention were unpredictable and not much was known in the state of the prior art.

Ex. 1005, ¶265

PO Response, at 86

POSA Definition: Experts Agree that a POSA Would Account for Modeling

Showalter Deposition (Ex. 2118)

Q All right. And so is it your understanding then or your view that a POSA would not take into account the modeling of binding interactions?

A So a POSA would take into account the use of modeling. But the issue is at what stage of a project you would engage a modeler.

Ex. 2118, 10:10-16

Eck Declaration (Ex. 2010)

125. For the '803 Patent, a POSA in June 3, 2011 would have been a team, with at least one member having at least a medical degree with training in hematology and oncology, including several years of clinical experience in treating hematologic malignancies, and another member or members having at least a Ph.D. in chemistry, organic chemistry, or related field with training as a medicinal chemist and in the structure of kinases or structure-function relationship of kinase inhibitors. The POSA team would include at least one member having at least a Ph.D. in chemistry, organic chemistry, biochemistry, or related field with training in the structure-function relationship of kinase inhibitors.

Ex. 2010, ¶125

PO Response, at 28; PO Sur-Reply at 3

Predictability of Binding to Kinase Active Site (Hinge)

Experts Agree that ATP's Adenine Hydrogen-Bonds to the Conserved Kinase Active Site (Hinge)

Showalter Deposition (Ex. 2018)

Q Okay. Great. And so you agree that by 2011 it was known that the adenine of the kinase's ligand ATP forms the hydrogen bonds with the kinase hinge region, that was something that was understood by a POSA?

A That was well established.

Ex. 2018, 111:5-10

Showalter Declaration (Ex. 1003)

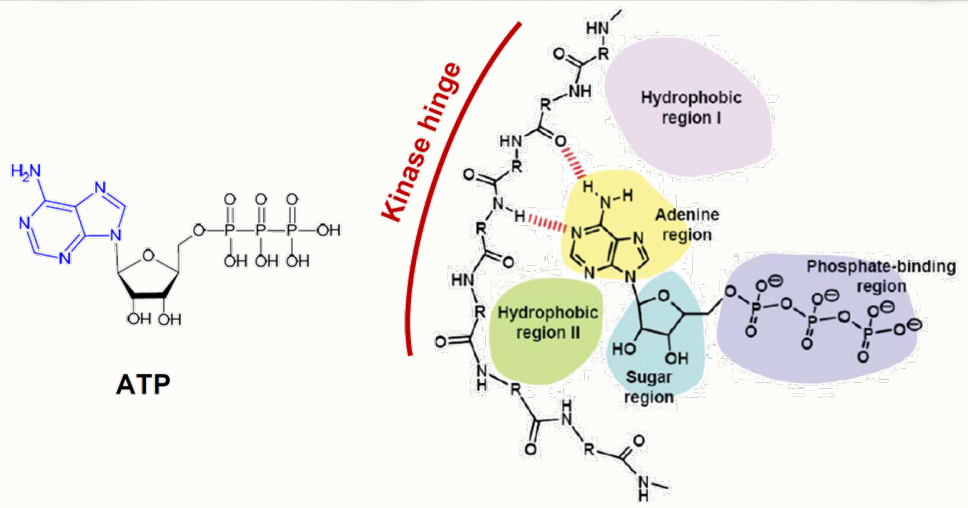
to adenine. As of 2010/2011, it was known that adenine formed hinge region interactions between the amino-substitution and the N5 heteroatom. *See* EX1052.002; EX1073.001-.003. These interactions were recapitulated in

Ex. 1003, ¶54

Eck Declaration (Ex. 2010)

two lobes of the protein. *See* EX1052.002; EX1077.002. In 2011, the adenine of the kinase's native ligand ATP was known to form key H-bonds with the kinase hinge region. *See* EX1052.003, .007 (entry 1 of table 2, showing that as of 2008,

Ex. 2010, ¶61



ATP binding to kinase (EX2048, Fig.1 (.0001) (annotated))

Ex. 2010, ¶45

PO Response, at 14-15; PO Sur-Reply, at 6; Eck Decl. (Ex. 2010), ¶61

Experts Agree that Scaffold Swapping Would Be Used to Identify New Scaffolds for Use in Kinase Inhibitors

Veal Publication 2009 (Ex. 2120)

16.3.3.2. Novel Scaffold Identification. An increasing role for computational chemistry in the realm of kinase drug discovery is to assist in the design of novel scaffolds. The intellectual property environment for kinases is highly competitive, increasingly crowded, and now a central issue in discovery efforts. One method for addressing this challenge is to design and synthesize novel templates, including so-called scaffold morphing or hopping, and as such de novo design has arguably been used more in the kinase target space than in any other protein systems class. As with computational screening methods,

Ex. 2120.0026

Veal Deposition (Ex. 2119)

Q. Okay. And so in that instance where there's a known binding mode for a ligand to a target protein, then the application of modeling in computational chemistry can be very valuable; is that right?

A. The application of computational chemistry can lead to suggestions about, you know, how to improve that, you know, core scaffold that's binding to the target.

I'm not sure what you mean by "very valuable."

Q. Okay. That works.

So it -- they can help you identify how to improve the core scaffold that's binding to the target.

A. It can suggest, you know, derivatives of the core scaffold that you could then try and synthesize and then test in a biological assay.

Ex. 2119, 41:16-42:13 (objections omitted)

Eck Declaration (Ex. 2010)

105. Thus, in 2011, a POSA could generate additional inhibitors from ibrutinib, whose structure the '803 Patent taught resulted in potent inhibition of BTK in patients. *See* EX2028.0004-0005 (describing a "powerful approach" to

106. Moreover, consistent with the '803 Patent's direction to use Z'-scaffolds that bind the BTK active site, the art provided examples of successful swaps. EX2028.0004-0005 (scaffold swapping to replace the amino-indazole core of a known KDR kinase inhibitor with a pyrimido-diazapinone analog); EX2038, Fig. 1 (.0001) (describing similar scaffold swapping).

107. The '803 Patent specification's Formula E invokes this approach of scaffold-swapping in calling for the use of structures that bind to the highly conserved BTK active site. EX1001, 61:65-62:17. A POSA reading this teaching would have recognized the applicability of scaffold-swapping of kinase hinge-binding elements across kinase inhibitor programs to attach substituents shown to result in productive inhibition of the kinase target. EX2028.0005 ("This concept of scaffold swapping is, in principle, applicable to virtually every kinase inhibitor program, provided that structural information can be generated on both the original series and the scaffolds of interest.").

Ex. 2010, ¶¶105, 106, 107

PO Response, at 23; PO Sur-Reply, at 7, 21

Modeling and Scaffold Swapping Were Used to Identify New Scaffolds for Use in Kinase Inhibitors

Akritopoulou-Zanze 2009 (Ex. 2028)

Swapping fragments

The fragments identified, as described above, serve as excellent starting points for the generation of new leads against a variety of protein kinases. A powerful approach for the utilization of these novel kinase scaffolds is in lead modification and optimization. In this strategy, the hinge-binding element of a given kinase lead is replaced, based on structural information, with the novel scaffold. One example of this is given in Figure 5 in the design of novel inhibitors for KDR kinase [17]. Many highly potent KDR inhibitors

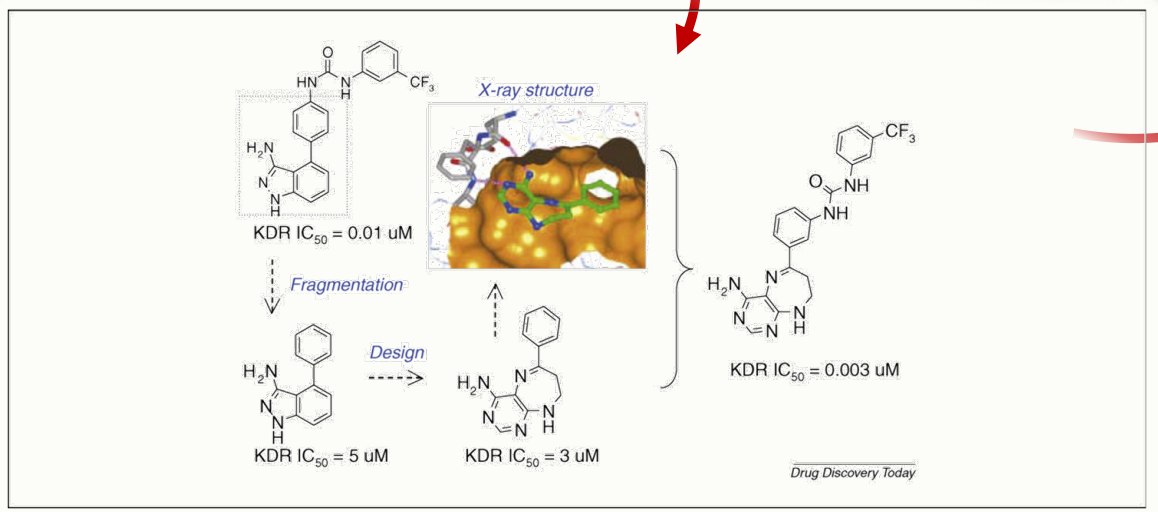


FIGURE 5

Fragment-swapping. Starting with a potent KDR kinase inhibitor (top left), a pyrimido-diazapinone analog (bottom center) of the amino-indazole core of the parent inhibitor (bottom left) exhibited comparable potency and was confirmed to bind to the hinge region by X-ray crystallography (top center shows complex of the pyrimido diazapinone core with the kinase PAK4). Structure-based design was then used to guide the placement of the phenyl–urea moiety onto the diazapinone core to yield highly potent, novel inhibitors.

Ex. 2028.0004, Fig. 5

Akritopoulou-Zanze 2009 (Ex. 2028)

serves as a benchmark for any potential mimetics. We designed and synthesized a novel pyrimido diazepine analog of this hinge element that exhibits comparable potency, with an IC_{50} value of 3 μM. X-ray structural information on this core, and subsequent modeling, led to the incorporation of the phenylurea functionality, resulting in the rapid generation of potent lead compounds (IC_{50} values less than 5 nM) with strong IP positions. This concept of scaffold swapping is, in principle, applicable to virtually every kinase inhibitor program, provided that structural information can be generated on both the original series and the scaffolds of interest. Thus, the novel heterocycles identified and validated through this work serve as a molecular tool-kit that can guide the medicinal chemist in making significant but rational modifications to a lead series with a high probability of maintaining or even increasing potency.

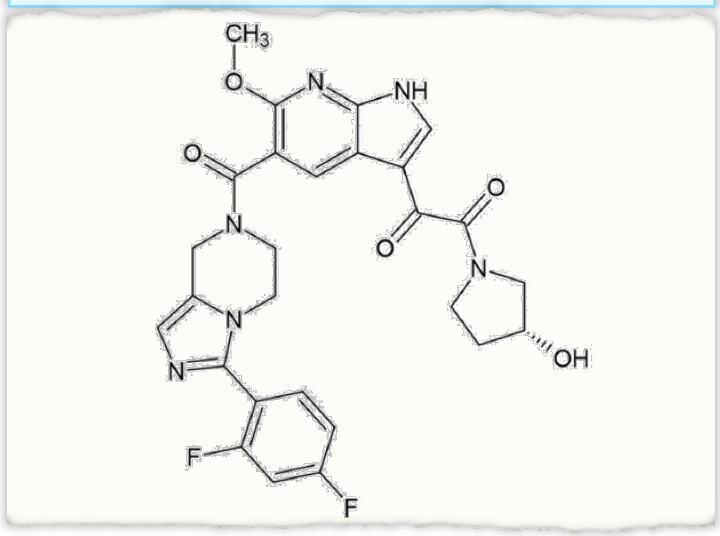
Ex. 2028.0004-0005

PO Response, at 23, 52; Eck Decl. (Ex. 2010), ¶¶103-107

A POSA Knew Many Heterocyclic Cores that Were Not Fully Aryl

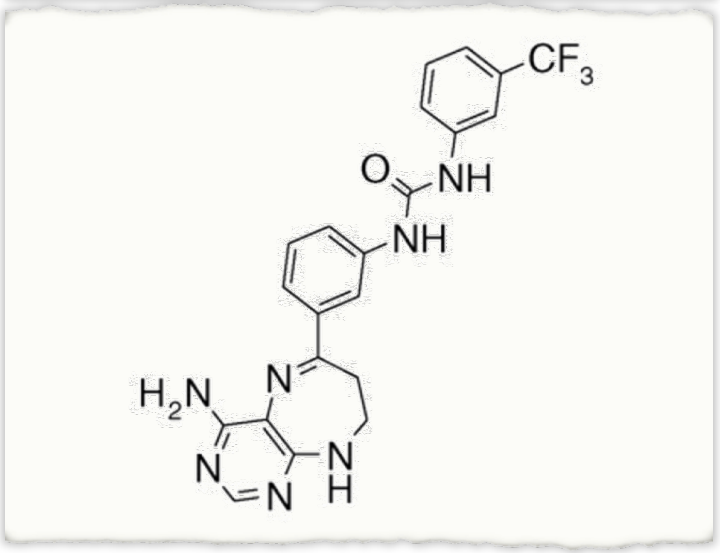
Prior Art Discloses Diverse Heterocyclic Scaffolds, Including Partially-Saturated Scaffolds

Murali Dhar 2007 (Ex. 2055)



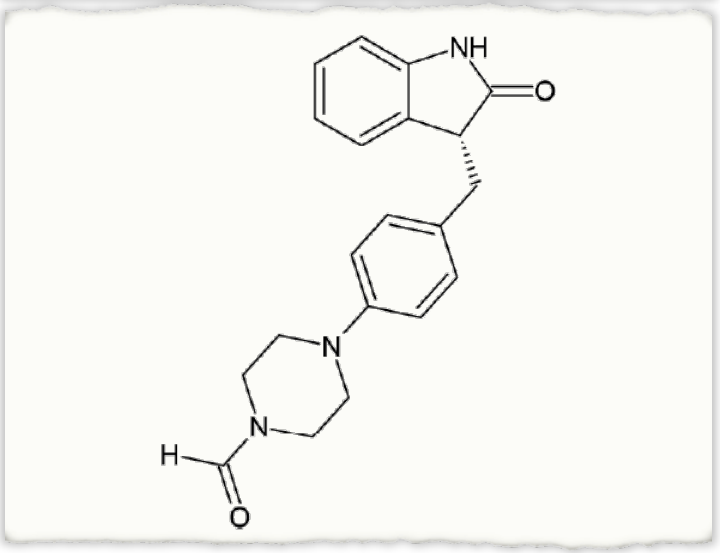
Ex. 2010, ¶171 (citing Ex. 2055 (PDB: 2QD9))

Akritopoulou-Zanze 2009 (Ex. 2028)



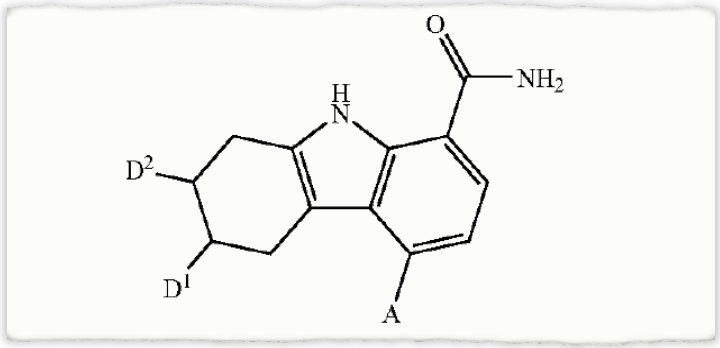
Ex. 2028, Fig. 5 (.0004) (excerpted)

Mohammadi 1997 (Ex. 2053)



Ex. 2010, ¶171 (citing Ex. 2053 (PDB: 1AGW))

U.S. Patent App. Pub. No. 2010/0160303 (Ex. 2026)



Ex. 2026, claim 10 (excerpted)

Gracias 2008 (Ex. 2038)

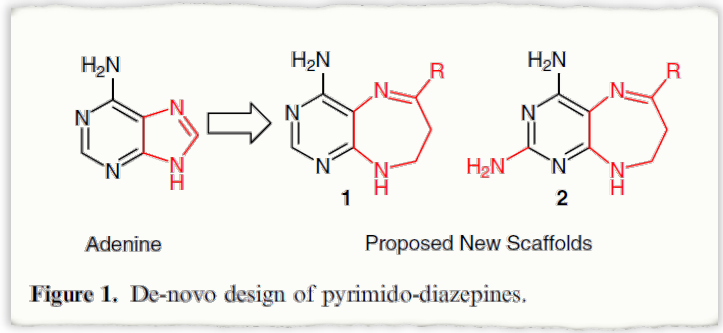
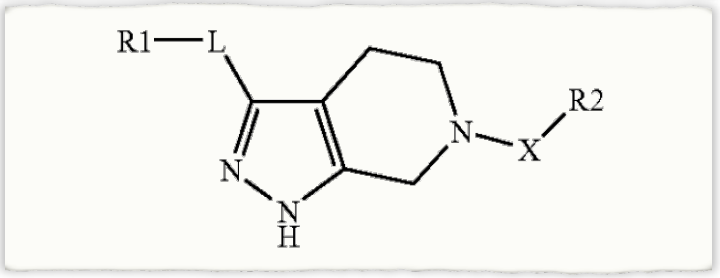


Figure 1. De-novo design of pyrimido-diazepines.

Ex. 2038, Fig. 1 (.0001)

U.S. Patent No. 7,435,820 (issued in 2008) (Ex. 2023)



Ex. 2023, 2:1-6

PO Response, at 52, 64-65; Eck Decl. (Ex. 2010), ¶171

Dr. Showalter's Flawed Analysis

Dr. Showalter's Analysis Is Contradicted by the Evidence

- ✗ Asserted Z' Binding to Kinase Active Site Was Unpredictable
- ✗ Asserted State of the Art Provided Limited Guidance
- ✗ Claimed Different Aromaticity Means Different Binding
- ✗ Claimed Zanubrutinib Is Not an Adenine Mimic

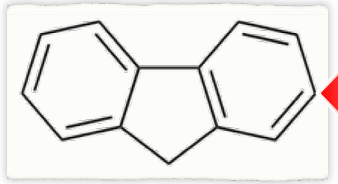
Petition, at 10-20, 29-34, 57-60, 65-67, 83-84, 90-91; Showalter Decl. (Ex. 1003), ¶¶39-76, 109-121, 141-158, 188-193, 240, 242, 254-256, 279

PO Response, at 14-17, 21-24, 43-54, 57-62; Eck Decl. (Ex. 2010), ¶¶45-46, 60-68, 71, 83-89, 92-102, 111-118, 155-179

Dr. Showalter Disregards ’803 Patent’s Permissive “Aryl” Definition

’803 Patent, Specification

Fluorenyl Has Central Non-Aromatic Ring



Ex. 2010, ¶66 & n.6

As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, fluorenyl, and indenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

Ex. 1001, 15:4-12

Showalter Deposition (Exs. 2018, 2118)

17 A Fluorenyl has two benzene rings attached
18 to each other by a single bond. And then off of
19 those benzene rings those -- those two rings get
20 connected by a single carbon which is -- which is
21 not aromatic. That ring is not aromatic.

Ex. 2018, 140:17-21

22 Q Right. And you agree that with respect
1 to fluorenyl, that encompasses a multi-ring system
2 in which some of the rings are aromatic and one of
3 the rings is not aromatic. Right?
5 A So that fluorenyl is a tricyclic ring
6 system. The two -- the distal rings, if you will,
7 the two rings on -- the two rings that are
8 aromatic that are fused to a nonaromatic central
9 ring.

Ex. 2118, 44:22-45:9 (objection omitted)

Dr. Showalter Admits Fluorenyl Has Central Non-Aromatic Ring

Dr. Showalter Disagrees with ’803 Patent’s Permissive “Aryl” Definition

Showalter Deposition (Ex. 2118)

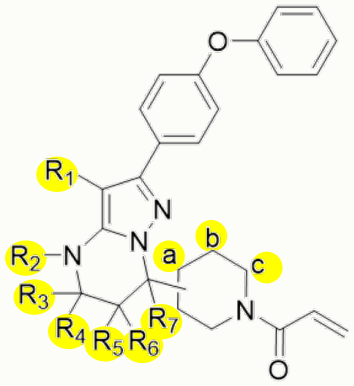
22 Q So your view is that fluorenyl is not an
1 example of an aryl group in the '803 patent?
2 A That's my position. Furthermore, as
3 discussed later, for a ring to be aromatic or a
4 ring system to be aromatic, it must conform to
5 Huckel's rule, which specifies that an aromatic
6 ring or ring system has four N plus 2 electrons, N
7 being an integer.
8 So if you look at fluorenyl, using that
9 definition, you have two aromatic rings that are
10 connected by one bond. Okay? If you count up the
11 electrons here, it's going to be six with each
12 aromatic ring. So it's 12 total electrons. That
13 does not conform to the formula of Huckel for N
14 plus 2.

Ex. 2118, 45:22-46:14

PO Response, at 16-17, 68-70; Eck Decl. (Ex. 2010), ¶¶65-68

To Arrive at Inflated Calculations, Dr. Showalter Alleges that a POSA Would Individually Substitute Each and Every Available Position on Z'

Showalter Declaration (Ex. 1003)



Brukinsa core A modification

R_1 - R_7 can be up to 21 variations each: 21 x 21 x 21 x 21 x 21 x 21 x 21 = 1,801,088,541
Each of R_3/R_4, R_5/R_6, R_7/piperidine on core fused 6 membered ring piperidine acrylamide moiety can have three attachment points (a, b, c) to the core fused 6-membered ring (3 variations each)

compounds = 1,801,088,541 x 3 = 5,403,265,623

Ex. 1003, ¶168

Showalter Deposition (Ex. 2118)

Q So your view is that a POSA would, in fact, consider substituting at each and every available position on Z prime?

A I think a POSA would -- would consider based -- based on a Z prime, substitution at any given open position.

Ex. 2118, 41:20-42:4 (objection omitted)

PO Response, at 56; PO Sur-Reply, at 21

Dr. Showalter's Excessive Substitutions Underlying His Calculations Defy Common Sense and Known Drug Design Principles

Both Parties' Experts – *Including Dr. Showalter* – Agree that a POSA Would Be Guided By Lipinski's Rules

Showalter Deposition (Ex. 2018)

A So that depends. As of 2010, 2011, investigators sort of hung their hat onto Lipinski's rules. But Lipinski later modified his definition. He says molecular weight 500 is not a requirement, it can be higher. And if you look,

Ex. 2018, 146:13-17

A So 2010, 2011, you would -- you would likely have been influenced -- would have likely been influenced by Lipinski rules. So they would have wanted to maintain lower molecular weight compounds.

Ex. 2018, 158:11-15

Q But again, as we've discussed, a person of ordinary skill would be wanting to follow Lipinski and to have an orally bioavailable compound and something that's a realistic compound, so they wouldn't do that. Right?

A So I think a POSA would realize that you wouldn't want to generate every compound in the universe.

Ex. 2018, 161:2-9

Scott Declaration (Ex. 2012)

46. Lastly, although a POSA would have understood that some substitutions could be tolerated, adding multiple (or many multiple) substituents to Z', as Dr. Showalter proposes, would defy rational drug design and common sense. Too many substituents, especially large ones such as aromatic rings, would increase the molecular weight to significantly above 500 Da, where achieving any level of oral exposure would be unlikely. Further, the introduction of multiple substituents would be likely to give the molecule undesirable physicochemical properties and violate additional Lipinski guidelines, e.g., high lipophilicity (cLogP >5), or too many H-bond donors and acceptors. Accordingly, Dr. Showalter's substitution opinion contradicts common sense and known guiding principles of small molecule drug design.

Ex. 2012, ¶46

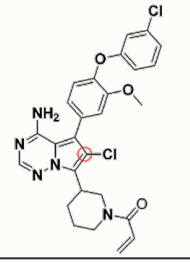
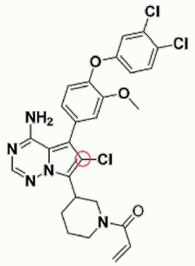
PO Response, at 56

Dr. Showalter's Excessive Substitutions Underlying His Calculations Ignore the Knowledge of a POSA

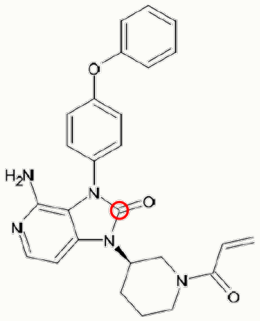
Scott Declaration (Ex. 2012)

43. First, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that there would typically be at most one or two positions on Z' where additional substituents beyond the phenoxyphenyl, linker, and hinge-binding substituents might be tolerated. These would be parts of the BTKI (as shown in the ibrutinib-like binding mode in Marcotte) directed toward solvent or cavities within BTK where substitutions can be accommodated. Examples of locations where additional substitutions could have been accommodated on Z' are shown in the below table of prior art structures, with the substituted locations on Z' circled in red. *See* EX2027 at Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1). As shown in the table (wherein the structures have been generated from their chemical name in ChemDraw), these substitutions to the Z' scaffold resulted in potent BTKIs. These examples show that a POSA reading the '803 Patent would have known where to make the substitutions on Z' and which positions on Z' could accommodate such substitutions in order to still bind to BTK.

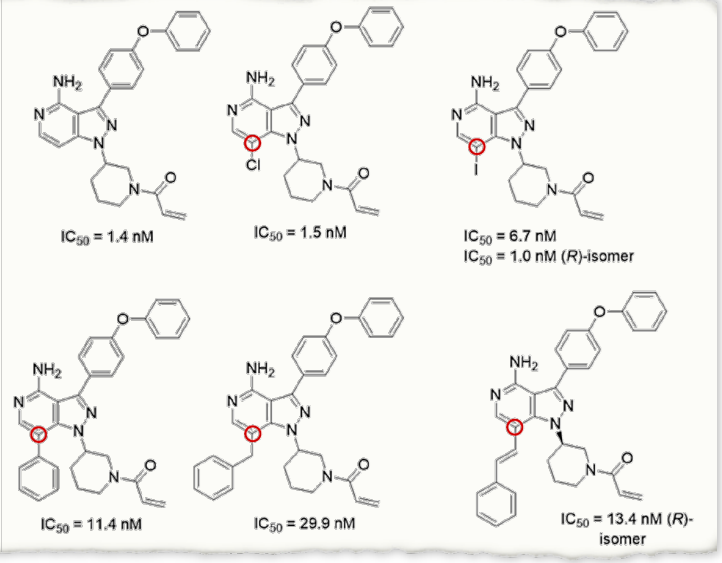
Ex. 2012, ¶43

Example	Name	Structure	IC50 (nM)
32	1-(3-(4-amino-6-chloro-5-(4-(3-chlorophenoxy)-3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)prop-2-en-1-one		2
32(1)	1-(3-(4-amino-6-chloro-5-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-l-yl)prop-2-en-1-one		2

Ex. 2012, ¶43



Tolebrutinib



Ex. 2012, ¶44

PO Response, at 56

No Dispute a POSA in 2011 Would Also Use Pan 2007

Showalter Deposition (Ex. 2018)

Q The question is, again, doesn't that suggest that the way a person of ordinary skill would pursue making any given inhibitor in this system would be to look at a homology model of the known information, ibrutinib, or ibrutinib analog, in the context of Btk, and use that to inform which molecules to synthesize, both in terms of what core to use as well as any substitutions on that core?

A So to the extent there was crystal -- well, to the extent that there was information regarding homology models, and there was in the Pan article, one would use that information to look at other candidate ligands toward making a new inhibitor.

Ex. 2018, 178:15-179:9 (objection omitted)

Eck Declaration (Ex. 2010)

109. Indeed, a POSA in 2011 would have understood that Pan revealed significant structural information about how ibrutinib-like BTKIs interact with BTK. Having the structural information from Marcotte about ibrutinib's binding mode, a POSA would have understood that Pan reports irreversible BTKIs, including ibrutinib, that covalently bind to and irreversibly inhibit BTK's Cys481. EX1060.001-004; *see also* EX2018, 54:4-13, 55:12-60:6. The '803 Patent further confirms that ibrutinib irreversibly inhibits BTK, reporting its occupancy of BTK in patients in clinical trials. *E.g.*, EX1001, 138:33-36.

110. A POSA in 2011 would have readily appreciated the structural features of the irreversible BTKIs reported in Pan, with the phenoxyphenyl interacting with the back pocket and the linker-warheads interacting with and binding Cys481. EX1060.001-003.

Ex. 2010, ¶¶109-110

PO Response, at 20, 25-26, 41, 60, 66, 69; Eck Decl. (Ex. 2010), ¶¶112, 153

Dr. Rosen's Flawed Analysis

Dr. Rosen's Flawed Analysis

- Dr. Rosen highlights irrelevant differences in side effects between zanubrutinib and ibrutinib
- Dr. Rosen makes unsupported assertions of unpredictability
- Dr. Rosen conflates standards for enablement with FDA approval

PO Response, at 33-38, 73-74, 83-85, 87-88, 92-93; PO Sur-Reply, at 18-19; Spurgeon Decl. (Ex. 2014), ¶¶59-60, 72-73, 100, 102, 105-107, 109-111, 113, 126, 130, 140-141; *see also* Institution Decision, at 9-10, 29

Dr. Rosen Points to Irrelevant Differences Between Ibrutinib and Zanubrutinib

Dr. Rosen and His Cited Reference Recognize that the Compounds Have Similar Side Effects

Rosen Deposition (Ex. 2021)

Q. So both ibrutinib and zanubrutinib have reported increased incidences of A-fib over background.

A. Both are above background, Imbruvica dramatically higher.

Q. And you report in paragraph 89, which spans over to two pages, a table comparing adverse events amongst the three approved BTKIs.

Do you see that?

A. I do.

Q. Okay. And so these are adverse events that have been reported and collected for ibrutinib, acalabrutinib, and zanubrutinib; right?

A. Yes.

Q. And you agree, for example, that infection adverse events have been reported in all three -- for all three BTK inhibitors.

A. Yes.

Q. And bleeding adverse events have been reported for all three BTK inhibitors.

A. Yes.

Q. And we just discussed that atrial fibrillation adverse events have been reported for all three BTK inhibitors.

A. To different degrees, yes.

Q. Right. And rash, diarrhea adverse events have been reported at least for ibrutinib and zanubrutinib; right?

A. Yes.

Q. And other -- endothelial cell and lymphoid tissue adverse events have been reported for both ibrutinib and zanubrutinib?

A. Yes.

Ex. 2021, 154:11-155:21

Estupiñán 2021 (Ex. 1048)

Petitioner's Expert's Cited Reference

While the overall incidence of the toxicities is reduced, both acalabrutinib and zanubrutinib are associated with a range of dermatologic AEs not different from those described for ibrutinib. These include bruising and ecchymoses, panniculitis,

Ex. 1048.011, .013 (Fig. 1)

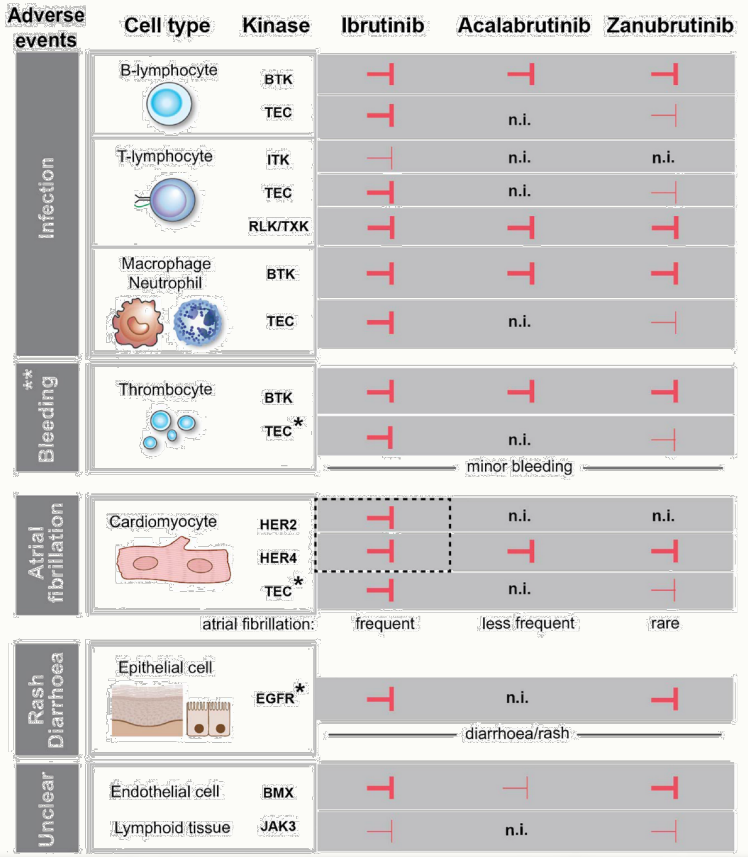


FIGURE 1 | Effects of FDA-approved BTK-inhibitors targeting tyrosine kinases with conserved cysteine. Inhibition of the kinases is depicted with ⊣ and ⊣ corresponding to strong and weak inhibition, respectively. ** Major bleedings are more frequent upon ibrutinib treatment versus more selective BTKi. "The association

PO Response, at 93; Spurgeon Decl. (Ex. 2014), ¶160

Dr. Rosen Points to Irrelevant Differences Between Ibrutinib and Zanubrutinib

Alleged Differences Are Largely Due to Ibrutinib Providing Valuable Insights to Field

Spurgeon Declaration (Ex. 2014)

94. Similarly, subsequent clinical trial protocols for BTK inhibitors incorporated response criteria identifying lymphocytosis compared to pre-treatment baseline as not being a sign of disease progression. The table below presents exemplary reports from subsequent clinical trials of BTK inhibitors, which account for the development of lymphocytosis by incorporating lessons learned from ibrutinib studies and confirm that lymphocytosis is a class effect of inhibiting BTK. This is now the gold standard for all BTK inhibitor trials.

Generic name	Clinical trial number	Relevant report
zanubrutinib	NCT03206918[3]	"ORR is defined as the number of participants who achieve a best response of CR or, CRi, Nodular Partial Response, PR, and PR with *Lymphocytosis as assessed by IRC per the modified IWCLL Guidelines* in participants with *CLL* and the Revised Criteria for Response for Malignant Lymphoma in participants with SLL."
tirabrutinib	NCT01659255[4]	ORR defined to include "partial remission (PR, *nodal PR*)" and "CTC Grade 3 lymphocytosis *considered an expected outcome of therapy*"
zanubrutinib vs. ibrutinib	NCT03734016[5]	"ORR percentage . . . using the 'modified' 2008 [iwCLL] guidelines with modification for *treatment-related lymphocytosis* for participants with CLL and per Lugano Classification for non-Hodgkin lymphoma (NHL) for participants with [SLL]"

Ex. 2014, ¶94

Spurgeon Declaration (Ex. 2014)

106. Later irreversible BTK inhibitors, such as BeiGene's zanubrutinib, have been shown to have certain differences from ibrutinib largely because ibrutinib provided valuable insights to the field. For example, later protocols were able to take into account patient characteristics so as to exclude populations who may be more likely to experience side effects observed in the ibrutinib clinical trials.

Ex. 2014, ¶106

PO Response, at 33-34, 38

Dr. Rosen Cites No Evidence of Lymphocytosis Unpredictability

Rosen Declaration (Ex. 1005)

99. It is my opinion that a BTKI's structure, including the Z'-structure, will impact in unpredictable ways whether and at what dose that BTKI will result in lymphocytosis.

100. Lymphocytosis is "a rise in lymphocyte counts." EX1002.558. The specification does not provide any support to demonstrate that all of the claimed BTKIs would result in lymphocytosis when administered to an individual. As described below, the specification only discloses that patients exhibited lymphocytosis when administered a single BTKI, IMBRUVICA. *See infra* Section V.B. The specification also discloses that at sufficient doses, patients will exhibit lymphocytosis when administered a BTKI. EX1001, 2:1-4. Specifically, it states that, "[i]n some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy." This disclosure indicates that not all treatments will result in lymphocytosis. It does not explain, however, which BTKIs or what amounts would or would not result in lymphocytosis or why that is the case. This demonstrates that even if the structure of a BTKI is known, whether and at what dose that BTKI will result in lymphocytosis is unpredictable such that experimentation is necessary.

Ex. 1005, ¶¶99-100

***No Citation* for Opinion**

PO Response, at 35-36, 87-88; Spurgeon Decl. (Ex. 2014), ¶113

Enablement Does Not Require Meeting FDA Regulatory Standards for Safety and Efficacy

United Therapeutics Corp. v. Liquidia Techs., Inc., 74 F.4th 1360, 1370 (Fed. Cir. 2023)

A failed safety study "may be an issue for the FDA[,]" but it is not an issue for enablement of a "therapeutically effective" dose.

Institution Decision, at 29

Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.,
276 F. Supp. 3d 629, 662 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018)

"FDA approval is not required to enable a patent claim to a medicinal compound or a method of treatment."

In re Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995)

"FDA approval . . . is not a prerequisite for finding a compound useful within the meaning of the patent laws."

PO Response, at 88

Preclinical Testing Before Clinical Trials in Patients Is Standard Industry Practice

Showalter Deposition (Ex. 2118)

Q. And those in vitro assays, pre-clinical studies in cells and animal models, and clinical studies are standard tests that are conducted on drug candidates; right?

A. They're standard but, for each drug, they may be different.

Ex. 2021, 221:8-12

Spurgeon Declaration (Ex. 2014)

125. As discussed above, the specification teaches that occupying and thus irreversibly inhibiting BTK treats CLL/SLL patients and induces lymphocytosis. As also discussed above, the specification further teaches a novel and straightforward method for identifying a therapeutic dose of an irreversible BTK inhibitor within the claims by monitoring BTK occupancy in patient blood samples. §IX.B.1.a, Because of this teaching, practicing the claimed methods would require only reasonable experimentation. Dr. Rosen identifies preclinical in vitro testing and cell and animal models, *e.g.*, measuring IC_{50} values, animal toxicity studies, pharmacokinetic and pharmacodynamic testing, to practice the claimed methods of treating CLL/SLL patients. EX1005, ¶¶241-248. But the testing that he identifies are all standard requirements that have to be conducted for any compound intended to be administered to human patients. EX2021, 221:1-223:20.

Ex. 2010, ¶125

PO Response, at 73-74, 83-85; PO Sur-Reply, at 18-19

Dr. Veal's Flawed Analysis

Dr. Veal's Flawed Analysis

- Dr. Veal's attempts to minimize use of modeling contradicted by prior publications and own analysis
- Dr. Veal's prior publications confirm known, diverse heterocyclic scaffolds for use in kinase inhibitors
- Dr. Veal's focus on two purportedly inactive embodiments does not demonstrate non-enablement

PO Sur-Reply, at 8-11, 22-24

Dr. Veal's Publications Confirm Usefulness of Modeling

Veal Publication 2009 (Ex. 2120)

16.3.3.2. Novel Scaffold Identification. An increasing role for computational chemistry in the realm of kinase drug discovery is to assist in the design of novel scaffolds. The intellectual property environment for kinases is highly

Ex. 2120.0026

referenced examples below. However, the personal view is that docking or scoring energies should be used as a filter to winnow down possible analogs of interest to a number on the order of 20% of the original possibilities and from that point both binding energies and visual inspection, often in conjunction with medicinal chemists, should be used to guide selection of the final set of analogs to pursue synthetically.

Ex. 2120.0030

PO Sur-Reply, at 10-11

Dr. Veal's Publications Confirm Diversity of Known Heterocyclic Scaffolds in Kinase Inhibitors

Veal Publication 2009 (Ex. 2120)

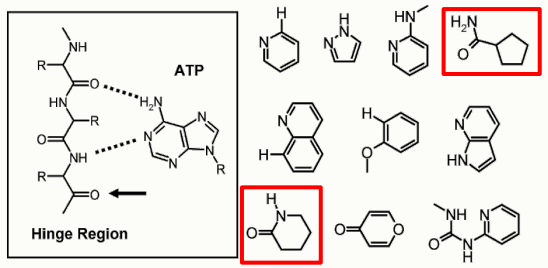
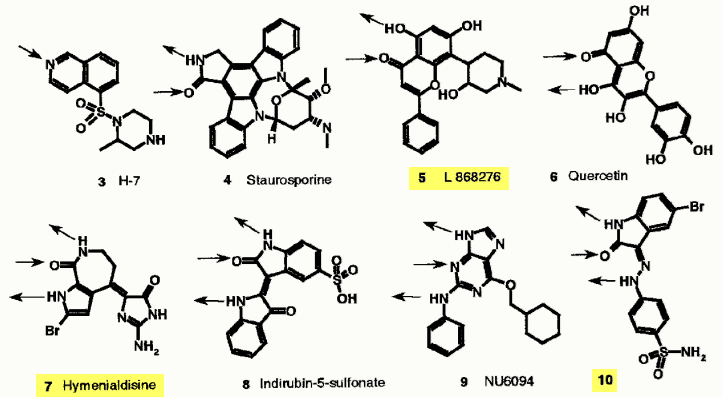


Figure 16.5. Representative substructures that can be used in developing screening libraries. The structures all have precedent as adenine mimetics for protein kinases.

Ex. 2120, Fig. 16.5 (.0023) (annotated)

Veal Publication 2004 (Ex. 2121)



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

Ex. 2121, Scheme 2.2 (.0026) (annotated)

Veal Deposition (Ex. 2119)

Q. Okay. And the substructures that you told the field in 2009 were adenine mimetics included structures that weren't fully aromatic; correct?

A. Yes.

Q. Okay. And so in 2009, you would agree then that adenine mimetics did not have to be fully aromatic; correct?

A. Yes.

Ex. 2119, 62:9-18 (objections omitted)

Veal Deposition (Ex. 2119)

Q. And additionally, by 2004, there were structures, scaffolds known to hydrogen bond to the hinge that were not fully aromatic; correct?

A. Yes.

Ex. 2119, 112:18-21

PO Sur-Reply, at 8-9

Dr. Veal Agrees that Modeling Predicts Binding for Majority of Compounds Modeled

Veal Declaration (Ex. 1106)

[6] I also modeled other compounds with reported IC_{50} values, specifically Compounds 8, 10, and 11 of Zhang, Compound 20 of the 446 Patent, and Compound 2 of WO'185. EX1146. The docking poses and scores for these compounds were consistent with their reported IC_{50} values. Those results, however, do not change my opinion that modeling is not predictive. The fact that modeling is sometimes consistent and sometimes inconsistent with experimental data underscores that modeling cannot accurately predict irreversible inhibition of Btk.

Ex. 1106, ¶118 n.6

Veal Deposition (Ex. 2119)

Q. So compound 7, compound 8, compound 10, and compound 11 from Zhang, you concluded that the modeling was consistent with the activity; is that right?

A. Yes, that's correct.

Q. Okay. And you also conclude that compound 20 from the '446 patent, its modeling was consistent with its activity; right?

A. Yes, the compounds you're referring to are the subset where, you know, the Glide scoring seemed to align with the IC50s. Obviously, as indicated, there were multiple other compounds where that was not the case.

Ex. 2119, 206:10-207:1 (objection omitted)

PO Sur-Reply, at 11, 22-24

Petitioner's Select Examples of Non-Working Embodiments Do Not Satisfy Its Burden on Non-Enablement

Two Embodiments Where Modeling May Not Predict Activity ≠ Non-Enablement

***Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005)**

"It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention."

***Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)**

"It is not a function of the claims to specifically exclude . . . possible inoperative substances . . ."

Dr. Veal Applies an Incorrect Standard in Assessing Predictability, Focusing on Identifying Improved iBTKIs

Veal Deposition (Ex. 2119)

And to be clear, all of this takes quite a bit of work to do as well as a computational chemist. And, again, the idea is to increase your probability of success, although the probability remains low.

Ex. 2019, 99:13-17 (objection omitted)

Q. And you keep saying "low probability of success." Is your definition of low probability of success achieving improved properties over the compound that you're trying to optimize?

A. Yes, I think that's correct. I think, you

Ex. 2019, 91:4-9 (objection omitted)

PO Response, at 89-91; PO Sur-Reply, at 11, 22-24

Specification Guidance and Examples

Specification Describes Clinical Effects of Irreversibly Inhibiting BTK in CLL/SLL Patients

'803 Patent, Specification

Example 6—Clinical Trial to Determine Efficacy of a Btk Irreversible Inhibitor in CLL and SLL Patients

Effect of Treatment on Lymph Node SPD

As shown in FIG. **6**, patients treated with a Btk irreversible inhibitor had an immediate and marked nodal response to treatment. 85% of evaluable patients achieved a partial response and even more had some LN shrinkage. 80% of patients with measurable LN disease achieved a 50% reduction in their SPD within 2 cycles of therapy. FIG. **7** shows the remarkable shrinkage in Lymph node post-treatment for the 57 year-old patient described supra. Change in Lymph Node and absolute lymphocyte count (ALC)

levels. There is a sustained decrease in disease burden shown by the LN sum of perpendicular diameters. Thus, with some variability in timing, many patients show a marked decrease in tumor burden in both peripheral blood and in LN disease with sustained treatment.

Ex. 1001, 134:26-28, 135:45:54, 135:63-67 (Example 6)

Example 11: Clinical Trial with Btk Inhibitor

The interim Phase II data confirm that a Btk inhibitor is highly active in both treatment-naïve and relapsed/refractory CLL/SLL patients

Class-specific rapid lymph node reduction with concurrent lymphocytosis seen in the majority of patients

2008 CLL IWG objective responses (PR+CR) and nodal responses appear to be durable and independent of high risk genomic features

A high proportion (85%) of relapsed or refractory patients are free-of-progression at 6 months (420 mg cohort)

Ex. 1001, 140:28, 143:27-36 (Example 11)

Example 14: Phase II Study of Btk Inhibitor + Ofatumumab in R/R CLL

Results

6 Patients have been evaluated for DLT through end of cycle 2. 0 DLTs occurred in these patients.

4 patients have had end of cycle 3 scans and blood counts. 3 of 4 are responder per IWG criteria. Our response rate is 75% for these pts.

Ex. 1001, 146:6-7, 147:35-40 (Example 14)

PO Response, at 31-32, 74-75; Spurgeon Decl. (Ex. 2014), ¶¶76-89, 118

Claim Construction

Claim Construction: "Therapeutically Effective Amount"

'803 Patent, Specification

The term "therapeutically effective amount," as used herein, refers to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms s B-cell lymphoproliferative disorder (BCLD). The result can be reduction and/or alleviation of the signs, symptoms, or causes of BCLD, or any other desired alteration of a biological system. The term

Ex. 1001, 24:58-64

Institution Decision

methods of using a compound"). Moreover, we find Patent Owner has the better position that the term "therapeutically effective amount" should be construed according to its express definition in the Specification and not according to the separate and distinct definition of "effective amount," as Petitioner suggests. That is, we decline to import a safety limitation to the term "therapeutically effective amount" that only appears in the definition for "effective amount." *Compare* Ex. 1001, 24:58–62 *with id.* at 24:66–25:2 (referencing "undue adverse side effects" in the definition of "effective amount" but not "therapeutically effective amount"). Thus, we construe the term "therapeutically effective amount" to mean "a sufficient amount of an agent of a compound being administered which will relieve to some extent one or more of the symptoms [of] B-cell lymphoproliferative disorder (BCLD)."

Paper 9, at 9-10

PO Response, at 26-27

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 29th day of January, 2025, a true and correct copy of the foregoing **Patent Owner's Demonstratives** was served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

David I. Berl
Kevin Hoagland-Hanson
WILLIAMS & CONNOLLY LLP
680 Maine Ave SW
Washington, DC 20024
(202) 434-5000
dberl@wc.com
khoagland-hanson@wc.com

By: / David P. Frazier /

David P. Frazier (Reg. No. 47,576)
david.frazier@lw.com
Latham & Watkins LLP
555 Eleventh Street, NW, Ste. 1000
Washington, D.C. 20004-1304
Telephone: 202.637.2200
Fax: 202.637.2201

Counsel for Patent Owner
Pharmacyclics LLC