

BeiGene USA, Inc. and BeiGene, LTD., LLC

Petitioner

v.

Pharmacyclics LLC

Patent Owner

Case PGR2024-00009

Patent 11,672,803

Patent Owner's Demonstratives

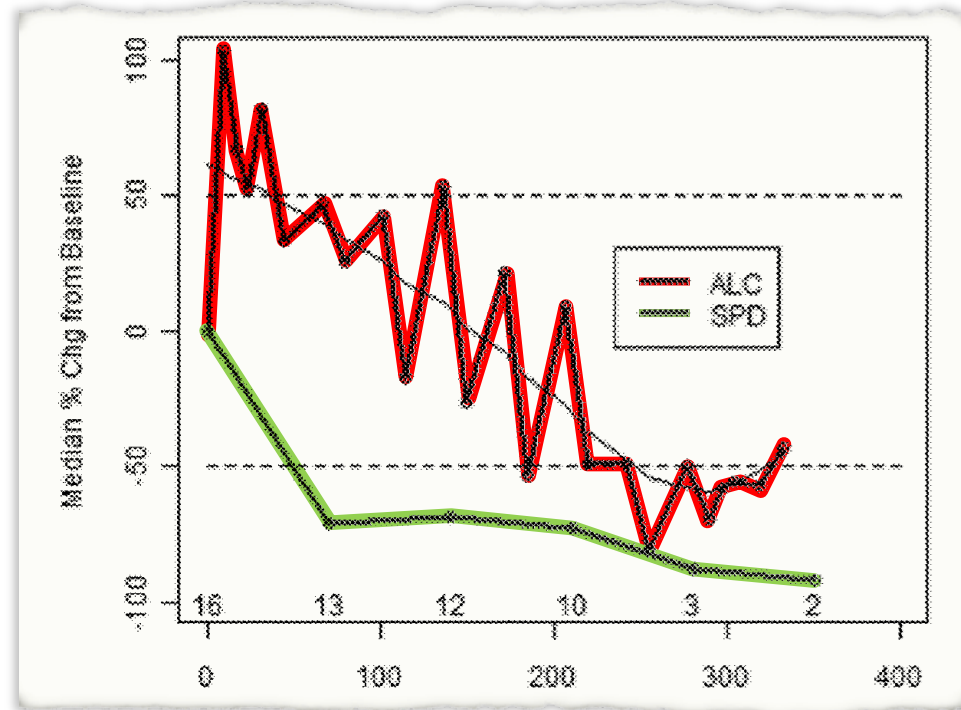
January 30, 2025

INTRODUCTION

Pharmacocyclics' Invention Changed Paradigm of Treating CLL/SLL

- Continuous dosing of ibrutinib showed spike in **lymphocytes**, reduced **lymph node size**, and improved symptoms

'803 Patent, Specification



Ex. 1001, Fig. 5 (annotated)

inhibitor nearly 6 months ago. Typical of the majority of CLL patients treated with a Btk irreversible inhibitor, there was an initial, rapid, and prominent reduction in nodal disease and spleen size, with a corresponding rise in the circulating lymphocyte count, likely a consequence of the inhibitory effects of a Btk irreversible inhibitor on lymphocyte homing to the nodal and splenic compartments. Simultaneous with these changes, patients reported symptomatic improvement consistent with the resolution of bulky disease. Over time, the initial rise in lymphocytes returns to pre-treatment levels in spite of sustained reductions in adenopathy and splenomegaly. Cases such as this seen with a Btk

Ex. 1001, 135:30-41

PO Response, at 7-10, 31

Pharmacyclics' Invention Changed Paradigm of Treating CLL/SLL

2008 Treatment Guidelines (Ex. 2002)

5. Definition of response, relapse, and refractory disease

Table 4. Response definition after treatment for patients with CLL, using the parameters of Tables 1 and 3

Parameter		CR*	PR*	PD*
Group A				
Lymphadenopathy†	None > 1.5 cm		Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None		Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None		Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL		Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline

Ex. 2002.0005-.0006

2018 Treatment Guidelines (Ex. 2003)

5.3.4. An increase in the number of blood lymphocytes by 50% or more with at least $5 \times 10^9/L$ B lymphocytes. Certain therapies (eg, kinase inhibitors) may cause lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count by itself does not uniformly indicate an increased tumor burden, but may reflect redistribution of leukemia cells from lymphoid tissues to the blood. This should be predefined in the protocol of clinical trials for therapies in which redistribution of disease occurs. In such cases, increased lymphocytosis alone is not a sign of treatment failure or PD.¹⁰¹

Ex. 2003.0010

PO Response, at 8, 31, 75; Spurgeon Decl. (Ex. 2014), ¶¶61-62, 64-65

'803 Patent Claims Methods of Treating CLL/SLL with iBTKIs Having Ibrutinib's Structural Features

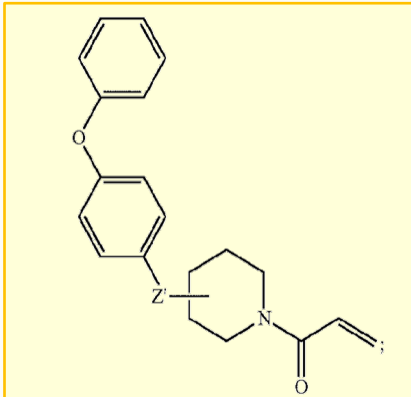
'803 Patent, Claim 1

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

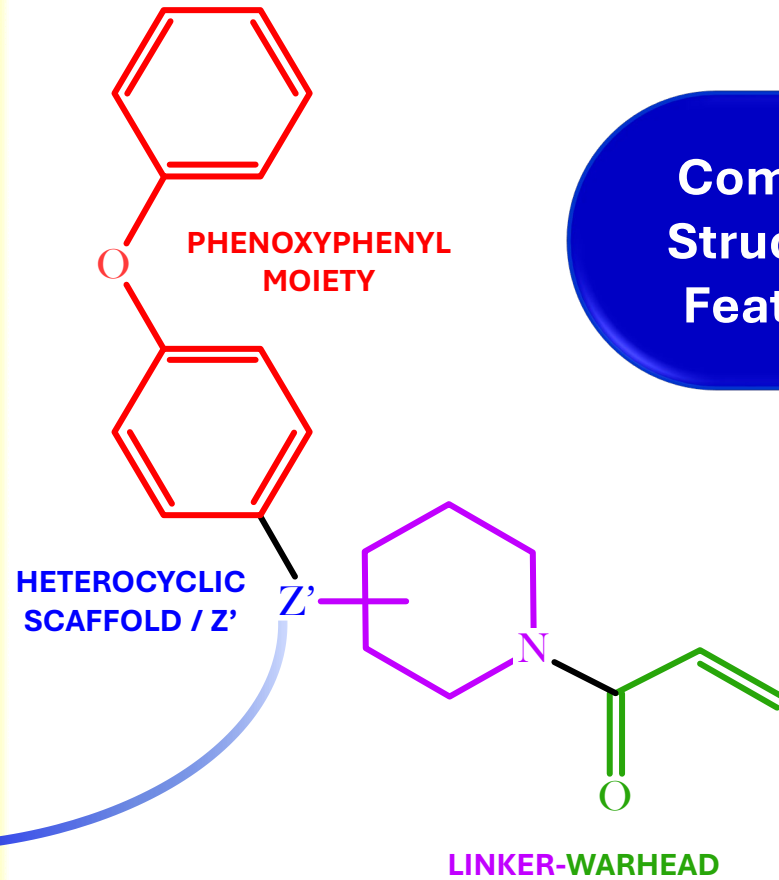
orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity;

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:

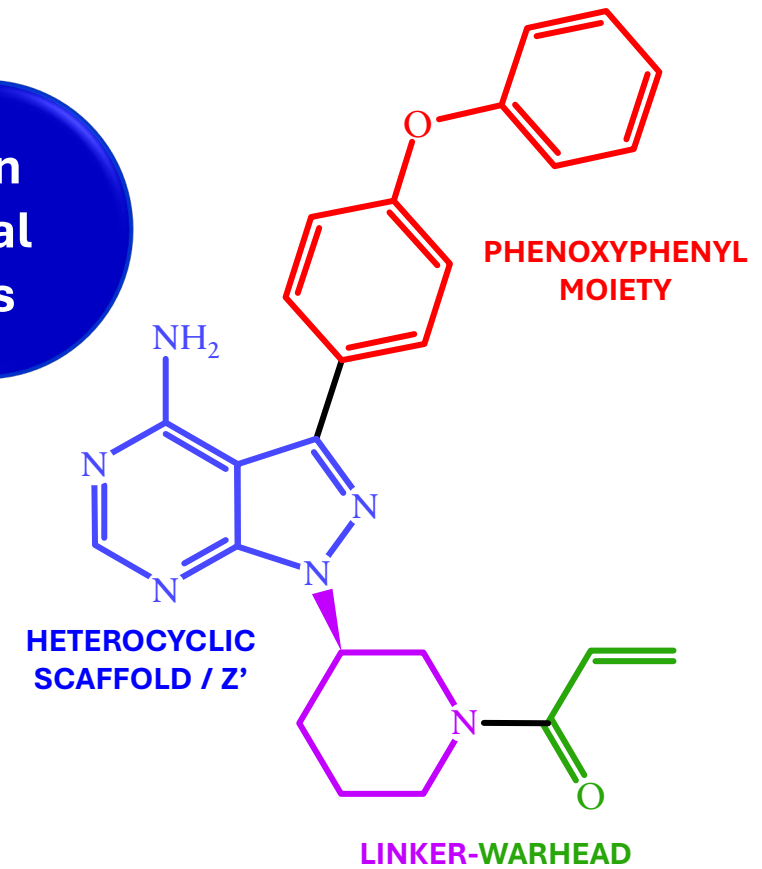


wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and wherein the irreversible inhibitor of Btk forms a covalent bond with Cys⁴⁸¹ of a Bruton's tyrosine kinase.



Ex. 1001, claim 1 (annotated)

Ibrutinib

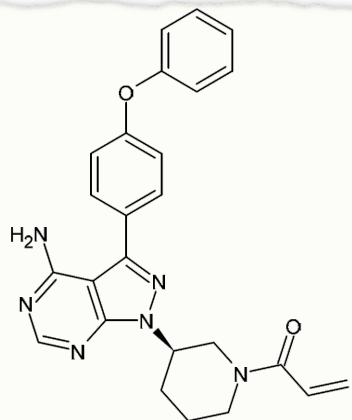


Ex. 1001, 65:9-25 (annotated)

PO Response, at 4-6, 12-13, 39-40, 42

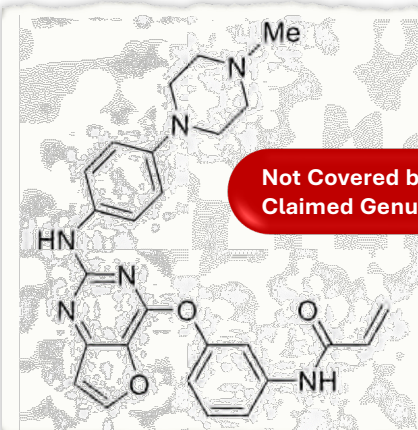
Method of Treatment Employs Defined Genus of iBTKIs

Ibrutinib



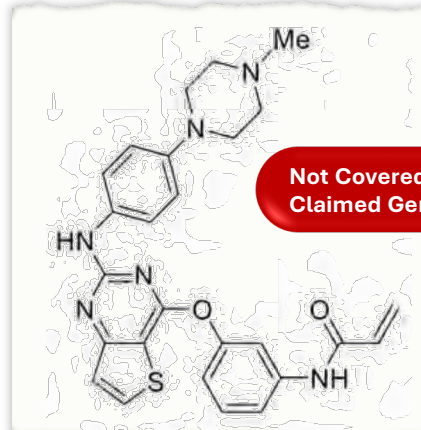
Ex. 1003, ¶1277

Poseltinib



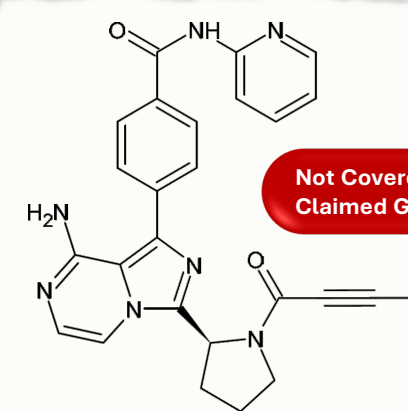
Ex. 1076.009

Olmutinib



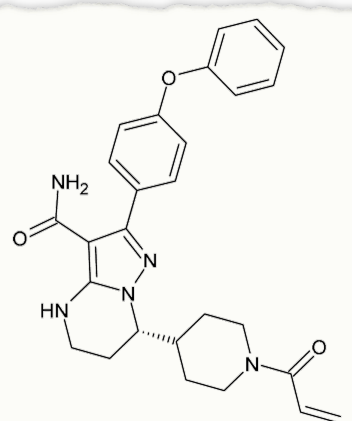
Ex. 1076.009

Acalabrutinib



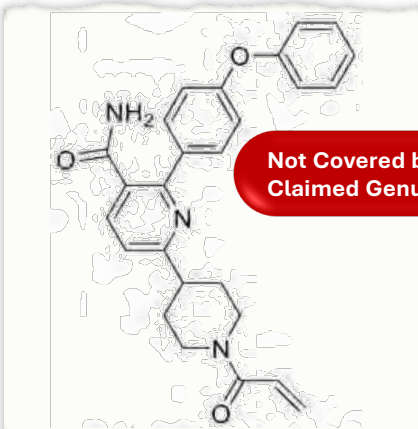
Ex. 1003, ¶1277

Zanubrutinib



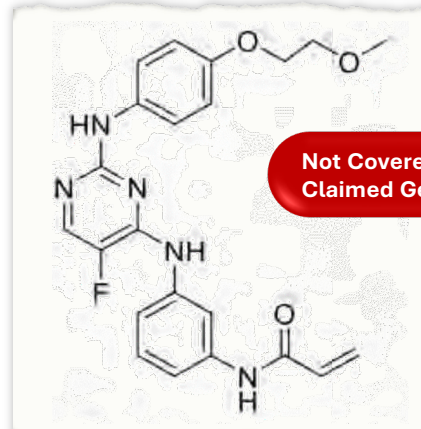
Ex. 1003, ¶1277

Orelabrutinib



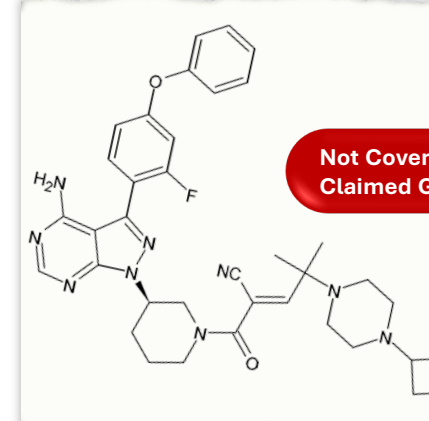
Ex. 1076.010

Spebrutinib



Ex. 1076.010

Rilzabrutinib



Ex. 1003, ¶1277

Petition, at 96-97; PO Response, at 4-6, 24, 51-52, 61; PO Sur-Reply, at 12-13

Written Description

- 1. Claims recite common structural features disclosed in specification that drive irreversible BTK inhibition**
- 2. A POSA can visualize members of the genus that irreversibly inhibit BTK**
 - a. The structural features that specifically bind to BTK are fixed
 - b. The heterocyclic scaffold makes predictable interactions with the conserved BTK active site
 - c. Modeling allows visualization of complete molecules and their binding to BTK
- 3. Specification teaches that irreversible BTK inhibition results in lymphocytosis and treatment of CLL/SLL**

Enablement

- 1. A POSA can visualize members of the genus that irreversibly inhibit BTK**
 - a. The structural features that specifically bind to BTK are fixed
 - b. The heterocyclic scaffold makes predictable interactions with the conserved BTK active site
 - c. Modeling allows visualization of complete molecules and their binding to BTK
- 2. Specification teaches that irreversible BTK inhibition results in lymphocytosis and treatment of CLL/SLL**
- 3. Petitioner improperly focuses on the cumulative effort to make every claimed embodiment**
- 4. No undue experimentation to identify a therapeutically effective amount from guidance in the specification**

WRITTEN DESCRIPTION

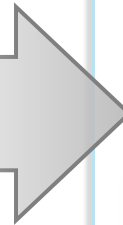
Common Structural Features

Written Description Satisfied By Common Structural Features



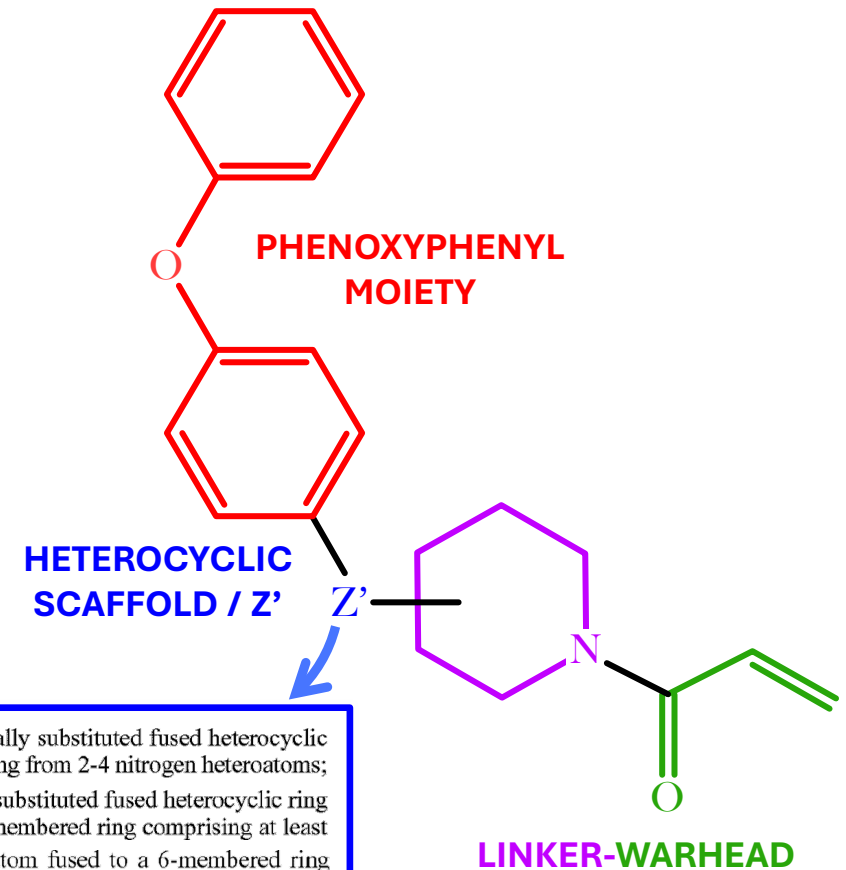
Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336, 1350 (Fed. Cir. 2010)

“[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.”



'803 Patent, Claim 1

Common Structural Features



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

Ex. 1001, claim 1 (excerpted and annotated)

PO Response, at 4-6, 29-30, 39-40, 46

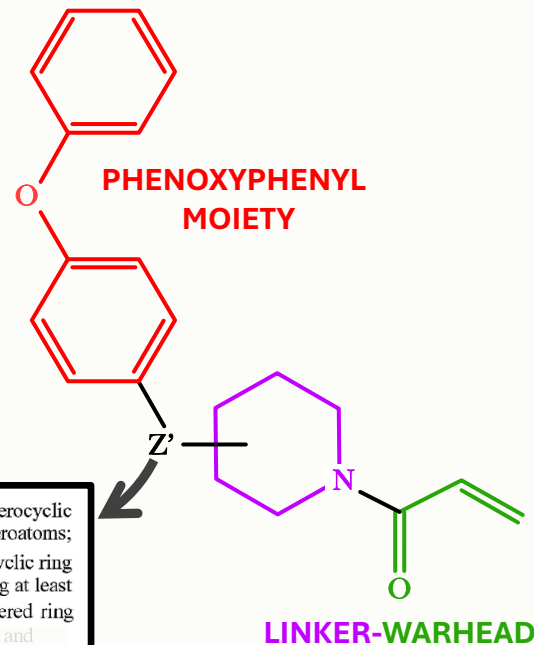
Specification's Preference for Ibrutinib Guides a POSA to the Claimed Combination of Fixed Features

Institution Decision

There is no dispute that the Specification describes the phenoxyphenyl hydrophobic moiety and the linker-warhead of IMBRUVICA. But the

Paper 9, at 25

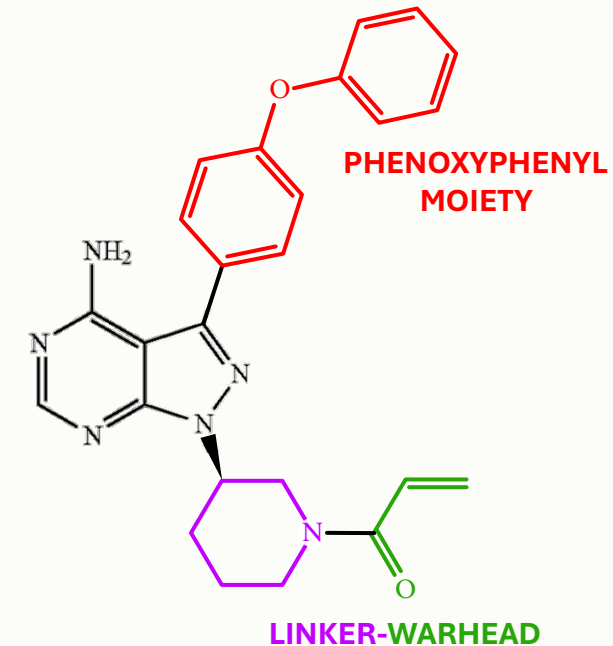
'803 Patent, Claim 1



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

Ex. 1001, claim 1 (excerpted and annotated)

'803 Patent, Specification – Ibrutinib

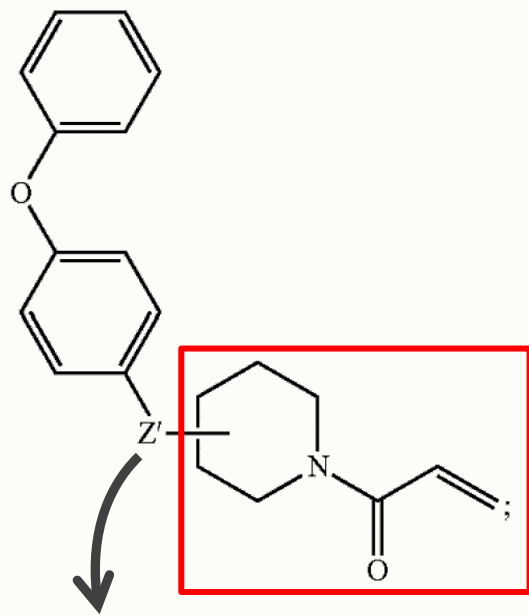


Ex. 1001, 65:9-25 (annotated)

PO Response, at 4-6, 39, 66-67

Specification Guides a POSA to the Claimed Linker-Warhead

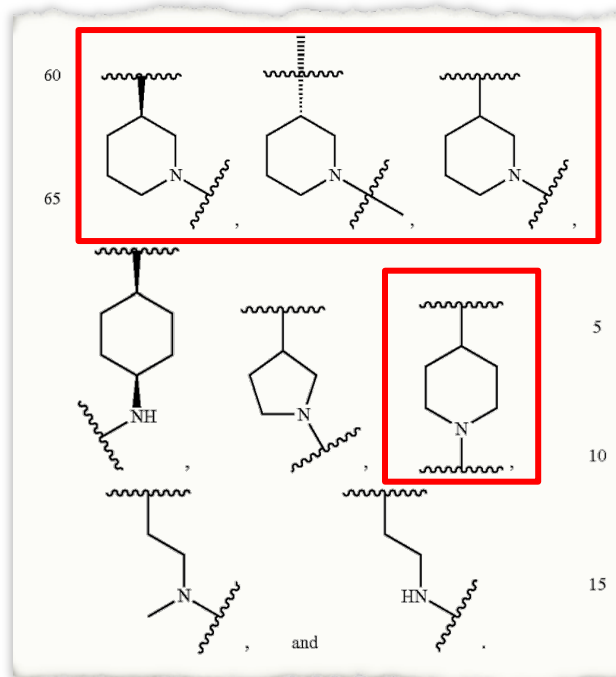
'803 Patent, Claim 1



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

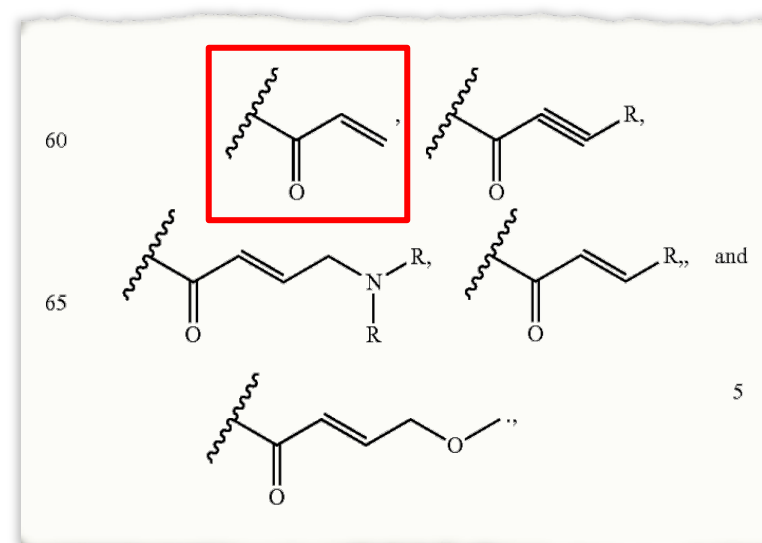
Ex. 1001, claim 1 (excerpted and annotated)

'803 Patent, Specification



Ex. 1001, 52:58-53:19 (annotated)

Claimed linker structure in four out of eight embodiments



Ex. 1001, 54:56-55:10 (annotated)

Claimed warhead structure in one out of five embodiments

Specification Teaches that the Linker-Warhead Forms an Irreversible Covalent Bond to BTK's Cys481

'803 Patent, Specification

refractory multiple myeloma. In some embodiments, the Btk inhibitor forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase, a Bruton's tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog. In

Ex. 1001, 3:18-21

The Btk inhibitor compounds described herein are selective for Btk and kinases having a cysteine residue in an amino acid sequence position of the tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk. Generally, an irreversible inhibitor compound of Btk used in the methods described herein is identified or characterized in an in vitro assay, e.g., an acellular biochemical assay or a cellular functional assay. Such assays are useful to determine an in vitro IC_{50} for an irreversible Btk inhibitor compound.

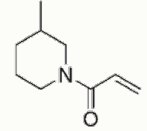
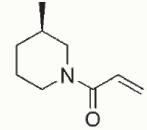
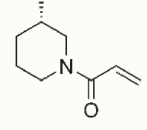
Ex. 1001, 45:56-65

pts from cohorts 1-3 are evaluable. The ORR is 42%; 1 CR (SLL), 7 PR (4 CLL/SLL, 2 MCL and 1FL). In cohort 2, PD demonstrate complete occupancy of Btk by a compound of Formula (D), with >95% enzyme occupancy 4 hours post dose in all pts. Basophil degranulation, a Btk-dependent cellular process, was completely inhibited up to 24 hrs. T-cell responses were not affected, and no significant depletion of peripheral blood B, T or NK cell counts was observed. Positive correlation ($R^2=0.93$) was found between Btk active-site occupancy in PBMCs (mean of Days 1 and 8) and a compound of Formula (D) plasma AUC $_{0-\infty}$ (Day 1) at the 1.25 mg/kg dose.

Ex. 1001, 138:27-43

Pan 2007 (Ex. 1060)

Table 3. Assay data for irreversible inhibitors.

Compd	R	Btk IC_{50} [nM]	Ramos Cell Ca Flux IC_{50} [nM] ^[a]
4		0.72	10
13		< 0.5	10
14		1.4	7

Ex. 1060, Tbl. 3 (.003) (excerpted)

(Table 3). We confirmed the irreversibility of these compounds using two methods: 1) after recombinant Btk was pretreated with compounds, its activity was not recovered by multiple washings with inhibitor-free medium;^[15] and 2) a major peak was observed by mass spectrometry corresponding to the molecular weight of a 1:1 covalent complex between compound 4 and Btk.^[16]

Ex. 1060.002

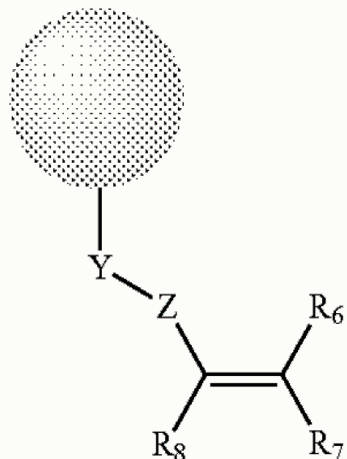
Institution Decision, at 4; PO Response, at 19-20, 32-33, 40-42, 75-76, 82; Eck. Decl. (Ex. 2010), ¶¶75, 79, 198, 212

Specification Guides a POSA to the Heterocyclic Scaffold of the Claimed Ibrutinib-like iBTKIs

'803 Patent, Specification – Formula E

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

Formula (E)



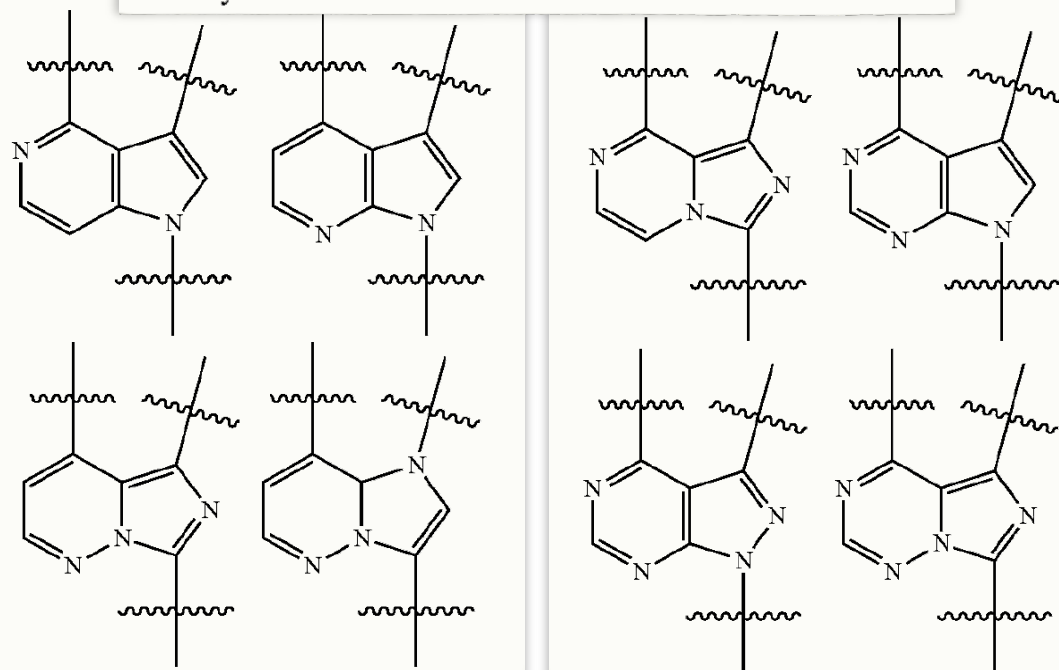
wherein:

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

Ex. 1001, 61:66-62:17

'803 Patent, Specification

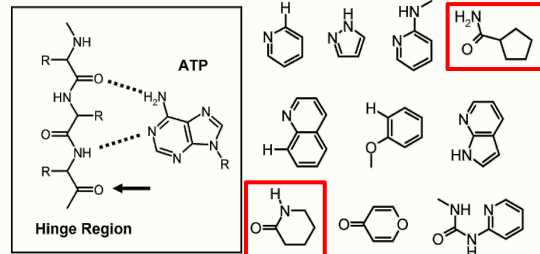
In some embodiments, $\odot$ is a substituted fused biaryl moiety selected from



Ex. 1001, 62:44-63:21

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

Veal Publication 2009 (Ex. 2120)



- Pyridine-like with ortho aromatic H
- Phenol / anisole with ortho H
- Pyrrole-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.

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

Veal Deposition (Ex. 2119)

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

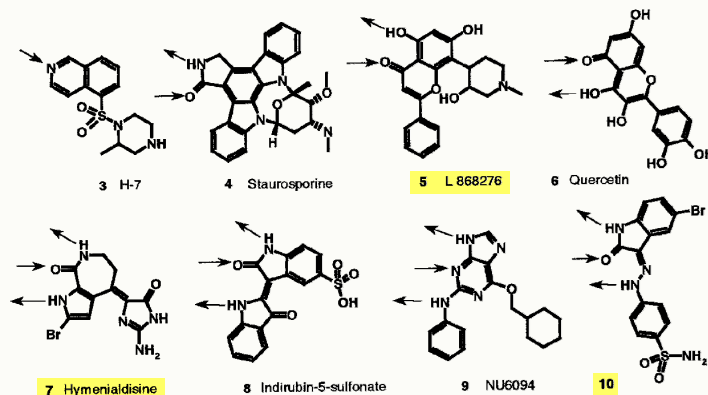
13 A. Yes.

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

18 A. Yes.

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

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)

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

21 A. Yes.

Ex. 2119, 112:18-21

PO Sur-Reply, at 8-9

Written Description

- **Specification describes the common structural features of ibrutinib-like iBTKIs**
 - See PO Response, at 31-66; PO Sur-Reply, at 5-6, 13-18
- **Petitioner's experts failed to carry Petitioner's burden of proving the specification does not describe common structural features**
 - A. Dr. Showalter lacked expertise in kinase inhibitor design and failed to account for structure/function modeling
 - See PO Response, at 3, 28, 46-49, 54-62, 79-80, 86; PO Sur-Reply, at 2-5, 12, 16, 21; Eck Decl. (Ex. 2010), ¶¶71, 111-118, 125-126, 154-164, 180-182, 209
 - B. Dr. Rosen focused on irrelevant differences, such as FDA approval and differences in side effect profile
 - See PO Response, at 37-38, 84, 88, 92-93; Spurgeon Decl. (Ex. 2014), ¶¶59-60, 72-73, 100, 102, 105-107, 109-111, 126, 130, 140-141; see also Institution Decision, at 9-10, 29
 - C. Dr. Veal contradicted his own publications on use of modeling in kinase inhibitor design
 - See PO Sur-Reply, at 8-11

A POSA Could Visualize Ibrutinib-Like iBTKIs for Use in the Method

A POSA Reading the Specification Would Understand Pan and Marcotte's Teachings as a Guide for Visualizing iBTKIs

'803 Patent, Specification

in situ or other in situ carcinomas **Results:**

29 pts (12 follicular, 7 CLL/SLL, 4 DLBCL, 4 mantle, 2 marginal) with a median of 3 prior therapies have been enrolled on cohorts 1-4. Therapy was well tolerated with most adverse events <grade 2. One protocol defined DLT (dose delay >7 d due to neutropenia) was observed. 19/22 pts from cohorts 1-3 are evaluable. The ORR is 42%; 1 CR (SLL), 7 PR (4 CLL/SLL, 2 MCL and 1FL). In cohort 2, PD demonstrate complete occupancy of Btk by a compound of Formula (D), with >95% enzyme occupancy 4 hours post dose in all pts. Basophil degranulation, a Btk-dependent cellular process, was completely inhibited up to 24 hrs. T-cell responses were not affected, and no significant depletion of peripheral blood B, T or NK cell counts was observed. Positive correlation ($R^2=0.93$) was found between Btk active-site occupancy in PBMCs (mean of Days 1 and 8) and a compound of Formula (D) plasma AUC_{0-∞} (Day 1) at the 1.25 mg/kg dose.

Ex. 1001, 138:27-43

Marcotte 2010 (Ex. 2001)

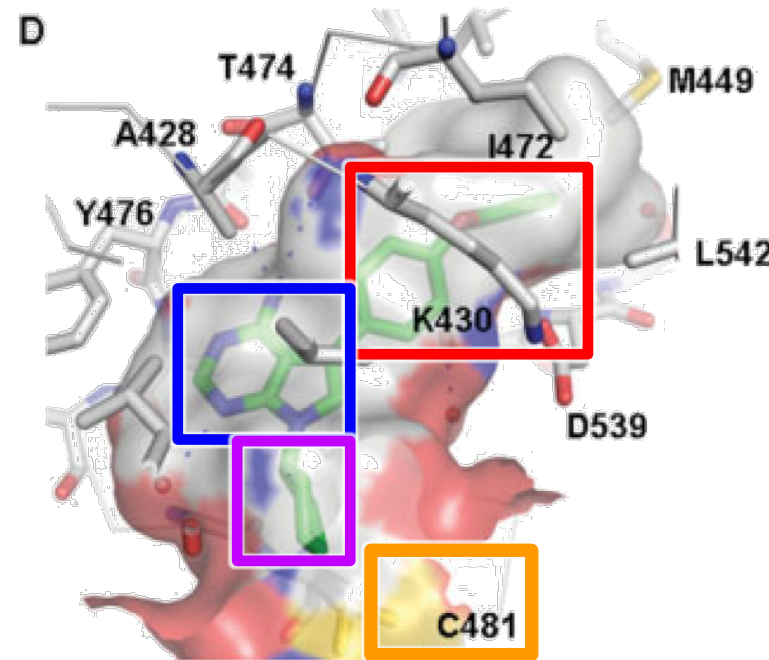


Figure 2. BTK-KD/B43 crystal structure. A: Chemical structure of B43. B: Electron density (2Fo-Fc map at 1 sigma) for B43 within a surface representation of the BTK protein in the human BTK-KD-B43 complex. C: Overall view of the BTK kinase domain bound to B43. Inhibitor (green), amino-terminal lobe (green), carboxy-terminal lobe (gray), C-helix (red), hinge (blue), and activation loop (yellow). D: Close-up of the active site and residues within 5 Å of the bound B43. The surface is colored according to the convention of base (blue) and acid (red). The active site cysteine is shown with a yellow surface.

Ex. 2001, Fig. 2D (.0003) (annotated)

Pan 2007 (Ex. 1060)

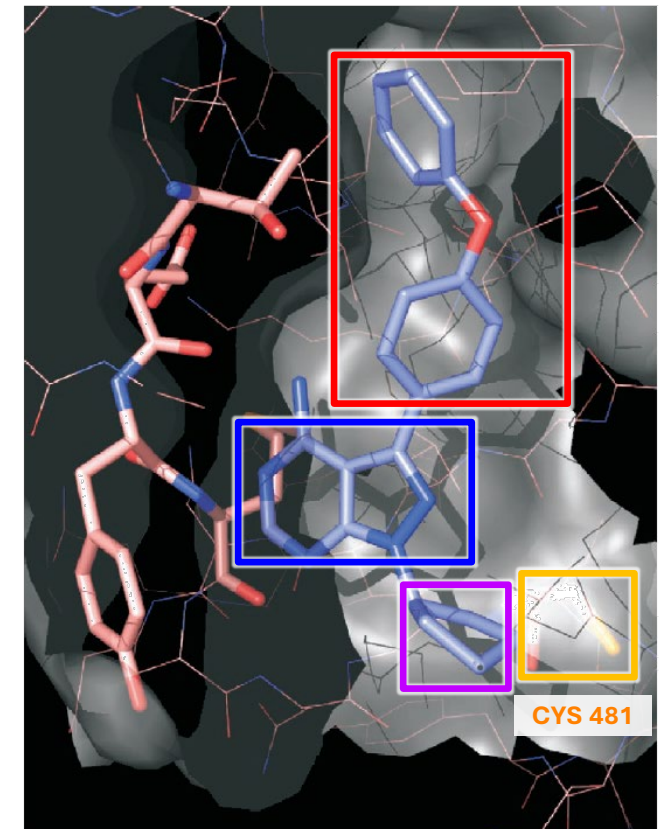


Figure 1. The proposed binding mode of compound 1 in a homology model of Btk; the highlighted residues on the left side are Thr-Glu-Tyr-Met; the residue at the bottom right corner is the irreversibility handle Cys 481.

Ex. 1060.001-002 (annotated)

PO Response, at 17-19, 25-26, 32-33, 41, 46-47, 60; Eck Decl. (Ex. 2010), ¶¶ 71, 75, 108-118, 153

Marcotte Confirms the Orientation and Binding of Key Structural Features of Ibrutinib-like iBTKIs

Veal Deposition (Ex. 2119)

9 Q. Okay. And Marcotte confirms that the
10 phenoxyphenyl group attached to the adenine mimic
11 scaffold binds within the hydrophobic back pocket of
12 Btk; correct?

14 A. Yes.

2 Q. Right. And, in fact, then Marcotte, in its
3 crystal structure of this similar compound, confirms
4 that the adenine mimic scaffold makes hydrogen bonds
5 to the hinge region of Btk; correct?

6 A. Yes.

13 Q. And Marcotte later, in solving the crystal
14 structure of this similar compound, confirmed that
15 the -- that the cyclo group off of the scaffold was
16 oriented towards the cysteine group of Btk; correct?

17 A. Yes, it's binding in the same place as the
18 ribose of ATP.

Ex. 2119, 141:9-14 (objection omitted), 142:2-6, 142:13-18

Eck Declaration (Ex. 2010)

EX2001.0003-0005 (PDB: 3GEN); EX2018, 43:20-46:11. The Marcotte structure provided detailed information about the geometry of this ligand in the BTK active site as well as specific amino acid interactions such as hydrogen-bonds between the inhibitor and the BTK hinge. See EX2001.0003-0005. This information

112. For example, Marcotte shows how the phenoxyphenyl enters the BTK hydrophobic “back pocket” and also participates in a pi-stacking interaction with the phenylalanine in the kinase DFG-motif. See EX2001.0003-0005. Marcotte also details the H-bond interactions of heterobicyclic scaffold of the inhibitor with the BTK hinge region. See *id.* Finally, Marcotte shows how the cyclopentyl ring of the inhibitor occupies the space generally occupied by ATP ribose, in close proximity to Cys481, indicating the general positioning of the linker-warhead of ibrutinib and related compounds. See EX2001.0003-0004. A POSA in 2011 would have had

Ex. 2010, ¶¶71, 112

PO Response, at 17-19, 46-47, 86; PO Sur-Reply, at 6-8

Petitioner's Expert Admits that Marcotte Allows Visualization of Ibrutinib-Like iBTKIs For Use in Claimed Methods

Showalter Deposition (Ex. 2018)

20 Q You agree that this Marcotte 2010
21 document, which is Exhibit 2001, would have been
22 important information for a person of ordinary
1 skill in the art who was developing an inhibitor
2 of Btk?

5 A This document would have been a helpful
6 document. I don't -- I submit that it wouldn't --
7 that a POSA would have been able to -- a POSA
8 would be able to imagine inhibitors of Btk without
9 having seen this document.

Ex. 2018, 43:20-44:9 (objection omitted)

11 A So a POSA, based on the literature as of
12 2010, 2011, would have been aware of aromatic --
13 aromatic-aromatic cores, fused ring systems in
14 which both -- in which both rings are aromatic.
15 And that would be a likely starting point for the
16 POSA. The POSA would have been aware of ring
17 systems that had already been investigated toward
18 generating tyrosine kinase inhibitors that were
19 not irreversible but were reversible.

20 So it would have been certainly kind of
21 an easy transition to go from a reversible to an
22 irreversible inhibitor simply from what was known
1 in the literature regarding various cores which
2 were reversible inhibitors. And most of these
3 would have been -- or many of these -- not most of
4 these, but many of these would have been
5 adenine-type mimetics.

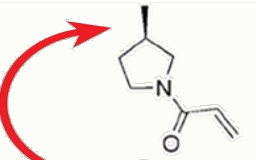
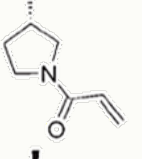
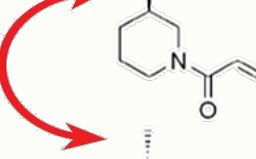
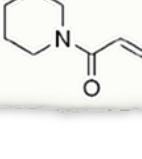
Ex. 2018, 157:11-158:5

PO Response, at 17-18, 43-44, 46-47, 65; Eck Decl. (Ex. 2010), ¶¶ 71, 111-118, 153

Pan 2007 Shows that the Linker-Warhead Can Bind Cys481 from a Variety of Orientations

Pan 2007 (Ex. 1060)

Table 3. Assay data for irreversible inhibitors.

Compd	R	Btk IC ₅₀ [nM]	Ramos Cell Ca Flux IC ₅₀ [nM] ^[a]
11		1.6	24
12		1.9	90
13		<0.5	10
14		1.4	7

Ex. 1060, Tbl. 3 (.003) (excerpted and annotated)

Showalter Deposition (Ex. 2018)

18 A So I would agree in the context of the
19 data presented here that the stereochemical
20 orientation does not have a major impact.

21 But that's -- this data is -- has to be
22 viewed in the context that we're looking at a
1 single core, single Z' relative to the '803 claim
2 section. We're looking at a single core.

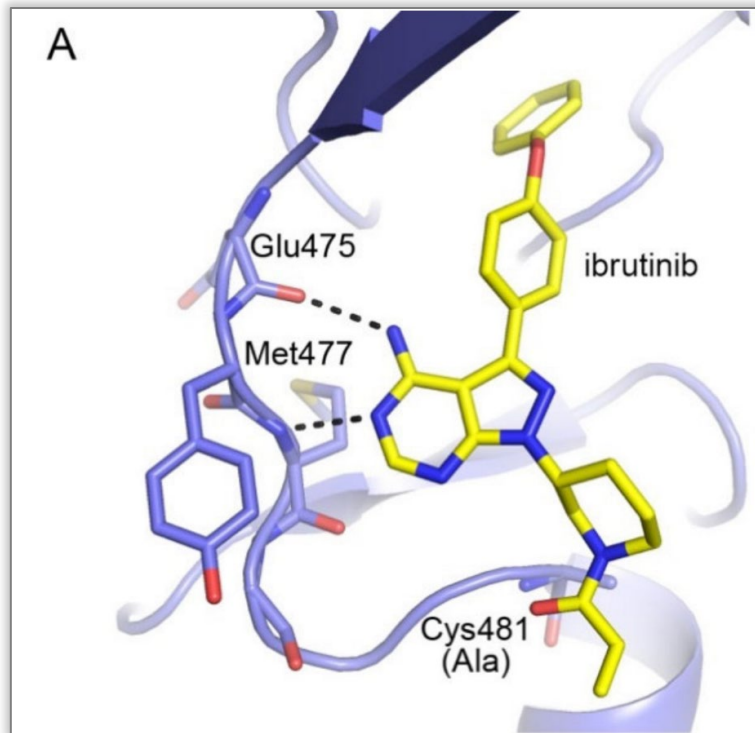
Ex. 2018, 96:18-97:2

A POSA Could Visualize Binding of Ibrutinib-Like iBTKIs

Eck Declaration (Ex. 2010)

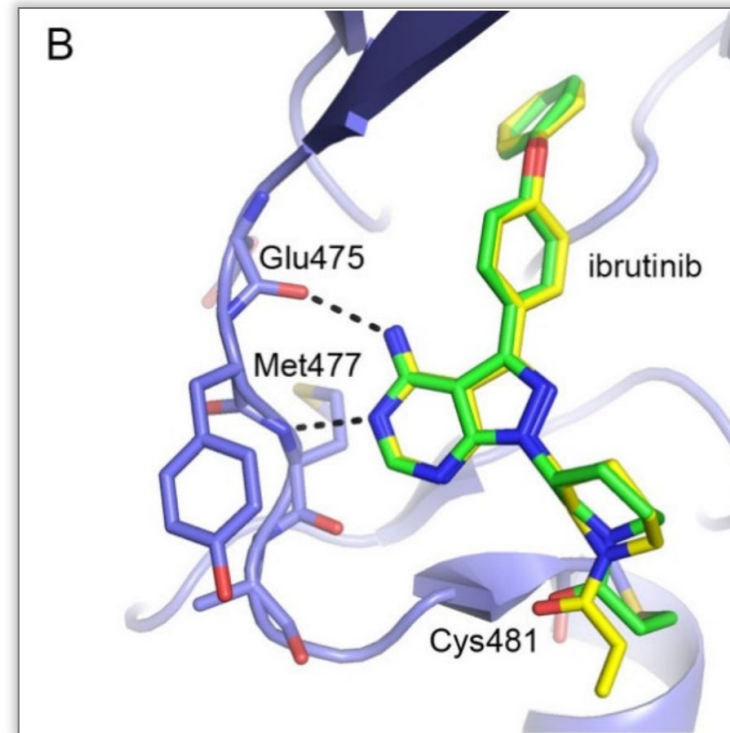
Ibrutinib

Docking of Ibrutinib into Marcotte



Ex. 2010, ¶116

Crystal Structure of Ibrutinib Bound to BTK



Ex. 2010, ¶116

PO Response, at 47-48

Heterocyclic Scaffold's Interactions with BTK Active Site Were Predictable

Claimed Methods Limited to iBTKIs Based on Ibrutinib's Structural Features

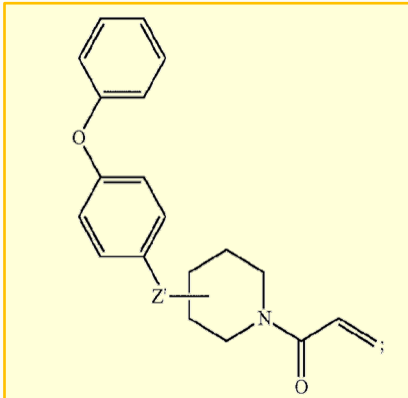
'803 Patent, Claim 1

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;

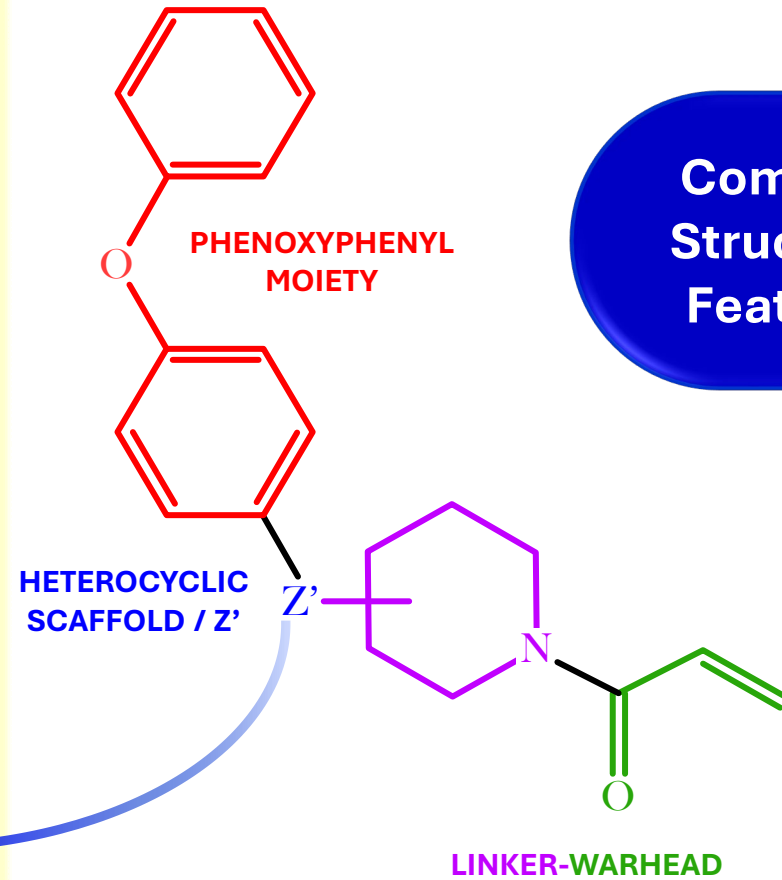
wherein lymphocytosis is not considered progression of the CLL or SLL, and

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



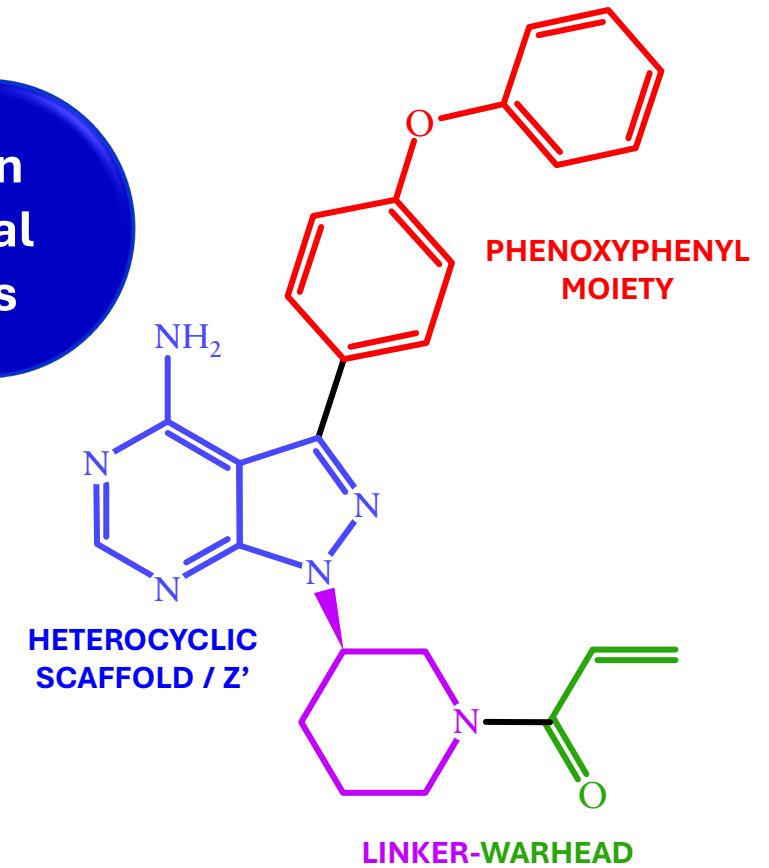
wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one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

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



Ex. 1001, claim 1 (annotated)

Ibrutinib



Ex. 1001, 65:9-25 (annotated)

PO Response, at 4-6, 12-13, 39-40, 42

Conservation of BTK Active Site Yields Predictability in Kinase Inhibitor Design

Veal Publication 2004 (Ex. 2121)

The primary attractiveness of the ATP site is that it affords a deep hydrophobic cleft for the adenine of ATP (or in some cases the guanine of GTP) that is common to all kinases and yet highly varied in shape. The commonality of binding elements provides inhibitor design features that can be applied to all kinases, whereas the exploitation of unique structural features provides the basis for achieving selectivity.

Ex. 2121.0025-0026

Zain and Vihinen 2021 (Ex. 1075)

ATP-Binding Pocket

The overall sequence similarity of PTKs is rather low, still they show conserved protein folds. The ATP binding site is among the most conserved regions. Figures 2A, B show the amino acids

Ex. 1075.003

PO Response, at 14-17, 21-24; PO Sur-Reply, at 12-13, 16-17; Eck Decl. (Ex. 2010), 1145-46, 60-68, 83-84

Dr. Showalter Admits He Is Not an Expert in Protein Kinase Structure

Showalter Deposition (Ex. 2018)

18 Q And Btk, for example, belongs to the
19 large kinases family known to have conserved
20 active sites. Right?

21 A So I'm not an expert on the structural,
22 actual structural aspects of protein kinases.

1 That's more in the realm of a protein chemist, but
2 that is my understanding.

Ex. 2018, 103:18-104:2

PO Response, at 28, 48-49, 55, 57, 79-80; PO Sur-Reply, at 3, 12, 16

Conserved BTK Kinase Active Site Amenable to Modeling

Ghose 2008 (Ex. 1052)

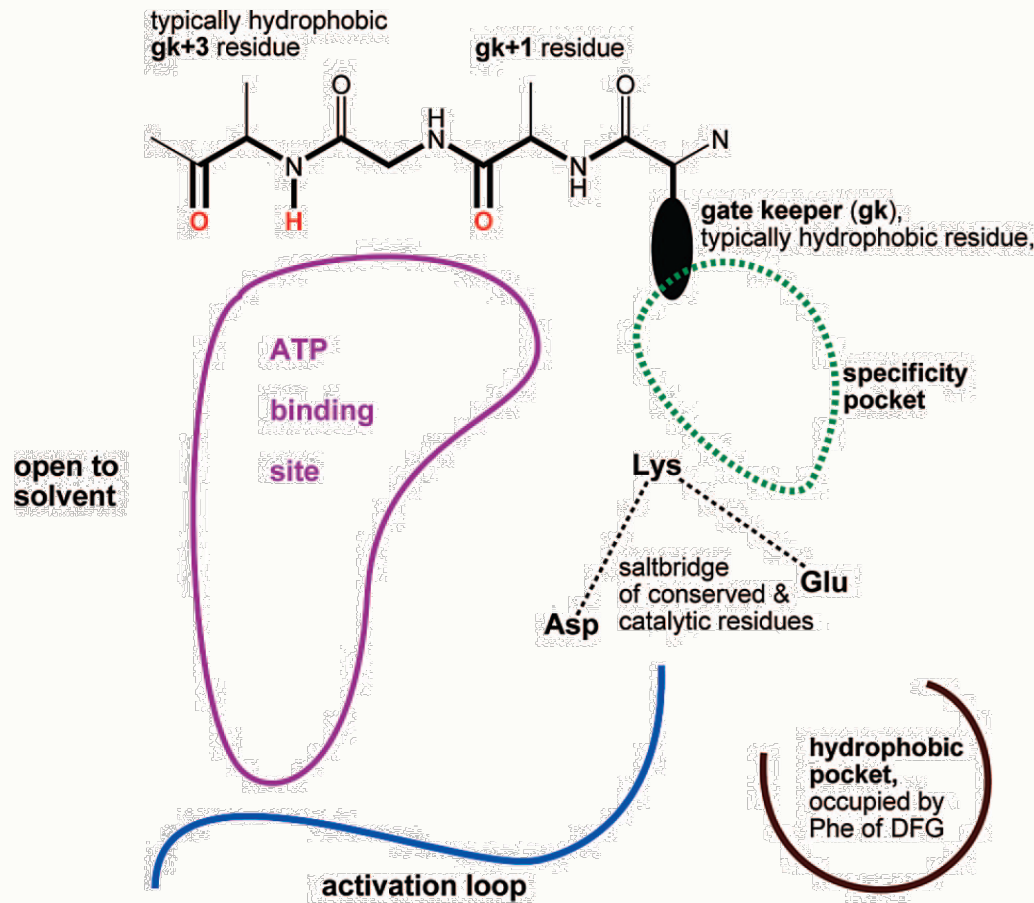


Figure 2. A 2D representation of the kinase binding site. The north

An understanding of the ATP binding site compressed into 2D is very helpful, since medicinal chemists do and will continue to use simple sketched structures, either on paper or a computer, to conceive of and design new inhibitors. It is therefore very practical to introduce a simplified 2D schematic of the active site (see Figure 2) for the purpose of visualizing the binding poses of various kinase inhibitors.

The high degree of structural similarity of the ATP binding site and the presence of key interactions sites for ligand recognition lend itself to an informatics-driven analysis of protein–ligand interactions across the kinome.

Ex. 1052.002, Fig. 2

Petitioner's Cited Prior Art Describes Rules for Predicting Active Site (Hinge) Binding

Ghose 2008 (Ex. 1052)

Empirical Rules To Predict Hinge Binding Orientation

The preceding analyses supports the conclusion that most kinase inhibitors form two, some even three hydrogen bonds with the hinge, involving one hydrogen acceptor flanked by one or two hydrogen donors. This array on the ligand serves to complement the backbone NH and two backbone C=O pointed toward the ATP binding pocket. It appears straightforward to identify the moieties most likely to be involved in hinge binding on the ligand, but it may be less clear which of the two hydrogen acceptors from the kinase hinge region (gk+1 or gk+3) will be engaged by a ligand. Similarly, it may not be apparent why

Ex. 1052.019

An understanding of inhibitor binding modes of many structurally diverse ligands bound to proteins of a discrete target family is undoubtedly very useful for ligand design. In this article we have only surveyed the binding modes of kinase inhibitors; however, the same approach may be similarly useful for other classes of proteins. The conclusion for kinase inhibitor molecules is that their binding modes can be categorized in terms of the ligand core structure and a few simple empirical rules. The extremely rapid growth of available kinase structures may require revision of these rules or addition of qualifiers for them to remain relevant for future ligands. Medicinal chemists may find the prediction rules devised herein helpful to quickly formulate a binding mode hypothesis for a potential ligand.

Ex. 1052.020-.021

If proteins change their structures in an apparently unpredictable way, the utility of structure-aided drug design appears to be limited. However, in reality the situation may not be that grave for kinases, as most parts of the ATP binding site show limited movement (except for the most flexible protein features such as the activation loop and to a lesser extent the P-loop; see Figure 1). As a consequence, through an analysis of the binding modes of different types of kinase ligands, one can anticipate the binding mode of a related ligand with "kinase inhibitor features". Such an analysis is extremely useful in deciding, for instance, where to place a hydrogen acceptor or donor atom, install a solubilizing group, or include a hydrophobic modification.

Ex. 1052.002

PO Response, at 58-59, 86-87; Eck Decl. (Ex. 2010), ¶¶155-157

Modeling Is How a POSA Visualizes a Compound's Binding to BTK

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

Ghose 2008 (Ex. 1052)

All qualifying files from the previous step were read into Maestro (www.schroedinger.com) and examined visually to determine if the coordinate set contains a fully solved kinase domain. Entries were then prepared in the following manner:

Ex. 1052.003

Veal Deposition (Ex. 2119)

19 Q. Right. So the two things together, the
20 visualization of how the compound is binding to the
21 target, as well as the calculation of how well that
22 compound is binding, both of those feed into the
1 computational chemist's ability to prioritize
2 structures on their likelihood of being successful
3 inhibitors; correct?
5 A. Yes.

Ex. 2119, 94:19-95:5 (objection omitted)

PO Response, at 25-26, 46-47; PO Sur-Reply, at 11-12; Eck Decl. (Ex. 2010), ¶¶115-118, 153

Experts Agree that Modeling Would Be Used to Visualize 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

Ex. 2120.0026

Veal Deposition (Ex. 2119)

10 Q. So what I -- so one of the things that you
11 mentioned is that -- the way that computational
12 chemistry is most effective is when there's a known
13 binding mode for a ligand to a target protein; is
14 that fair?

15 A. Yes, that's fair.

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

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

Ex. 2119, 41:10-42:3 (objection omitted)

Eck Declaration (Ex. 2010)

153. As I have explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would have used virtual docking to aid in identifying irreversible ibrutinib-like BTKIs. *See supra* §VII.B; *see also* EX2018, 52:12-53:4, 117:10-21, 171:18-173:16, 177:10-179:9. Therefore, a POSA reading the '803 Patent would have been able to visualize the Z'-scaffolds that 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.

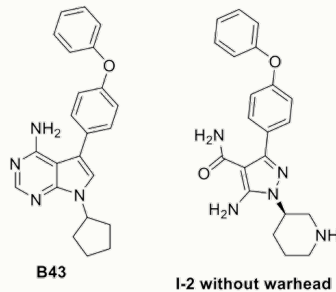
207. As I have explained, in my opinion, consistent with the teachings set forth in the '803 Patent, the structural information of Marcotte (PDB: 3GEN) would have provided a POSA with data for use in virtual docking and modeling of the irreversible BTKIs of the claims. *See supra* §VII.B.2. Marcotte provides

Ex. 2010, ¶¶153, 207

PO Response, at 46-47, 78; PO Sur-Reply, at 3, 7, 10, 21

Petitioner Itself Used Marcotte Structure For Virtual Docking of a Zanubrutinib Analog to Predict BTK Binding

Guo 2019, Supporting Information (Ex. 2039)



Petitioner's Own
Reference

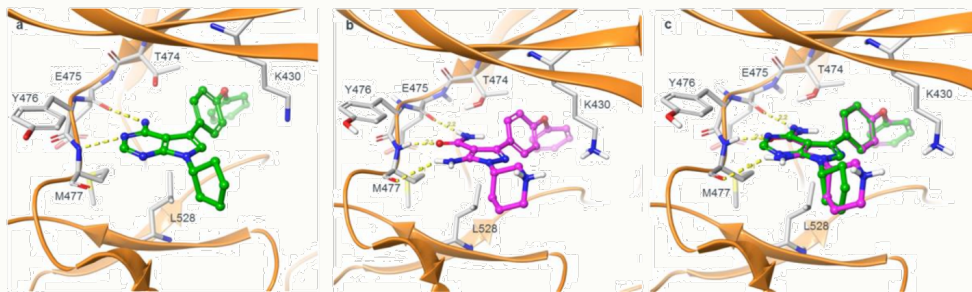


Figure 1: (a) Binding mode of B43 in the ATP pocket of BTK from published crystal structure (PDB ID: 3GEN). (b) Predicted binding pose of I-2 without warhead in the ATP pocket of BTK. (c) Pose alignment between B43 and I-2 without warhead. BTK is shown as ribbon and colored in orange. Compound B43, I-2 without warhead and the amino-acid residues of BTK interacting with compounds are shown as stick and are colored in green, magenta and grey, respectively. The figure is generated using Schrödinger software (Maestro11.2 in Schrödinger Suite 2017-2).

Ex. 2039, Fig. 1 (.0003-0004)

Eck Declaration (Ex. 2010)

2011. *See supra* §VII.B.2. Similar to what a POSA would have done in 2011, Petitioner itself used the Marcotte 3GEN crystal structure to predict how a zanubrutinib analog would bind to BTK. *See* EX2039, Fig. 1 (.0003-0004); EX2018, 128:16-130:6. As shown below, Petitioner's modeling shows precise alignment between these structural features of Marcotte and zanubrutinib, EX2039, Fig. 1 (.0003-0004), which were later confirmed in the crystal structure of zanubrutinib bound to BTK. *Compare* EX1044, Fig. 2B (.004).

Ex. 2010, ¶164

PO Response, at 25-26; PO Sur-Reply, at 8

Aromatic Nature of Heterocyclic Rings Not Important for Predictability

Petitioner's Attempt to Divide Z' Structures Based on Aromaticity Is Illusory

First, the claim language and the construction of “optionally substituted fused heterocyclic ring system,” *i.e.*, Z'-structure, prescribe four subgenera. EX1003, ¶¶143-147. While the Structural Limitations narrow the Z'-structure to a 5-membered ring fused to a 6-membered ring, the specification provides that each ring 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

PETITION FOR POST GRANT REVIEW OF

U.S. PATENT NO. 11,672,803

Showalter conservatively calculates that the Challenged Claims are directed to the use of potentially billions of structurally diverse species derived from the following three categories of variations. EX1003, ¶¶175-178; Appendix A.

First, the claim language and the construction of “optionally substituted fused heterocyclic ring system,” *i.e.*, Z'-structure, prescribe four subgenera. EX1003, ¶¶143-147. While the Structural Limitations narrow the Z'-structure to a 5-membered ring fused to a 6-membered ring, the specification provides that each ring 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.*

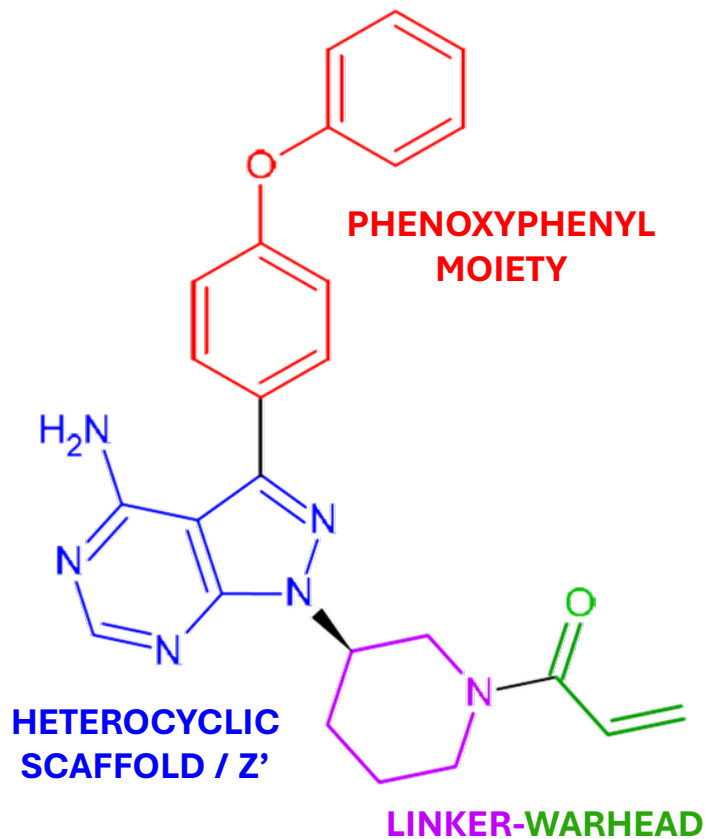
58

Petition, at 58

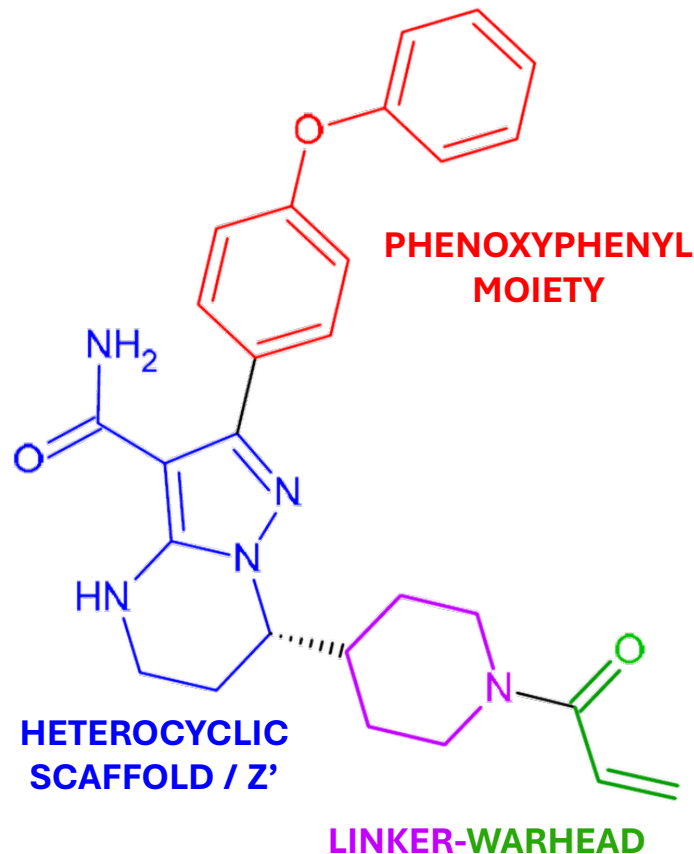
Petition, at 58; PO Response, at 50-54

Zanubrutinib Confirms the Common Structural Features of the Claims

Ibrutinib (IMBRUVICA)



Zanubrutinib (BRUKINSA)

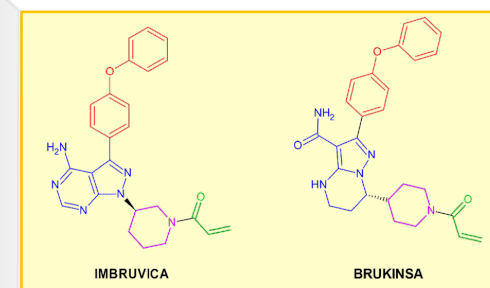


Petition, at 10 (annotated) (citing Ex. 1003, ¶139)

PETITION FOR POST GRANT REVIEW

OF

U.S. PATENT NO. 11,672,803



EX1003, ¶139.

There are a number of key differences between IMBRUVICA and BRUKINSA: (1) the aromaticity of the fused heterocyclic ring system ("ring system"); (2) the heteroatom pattern of the ring system; (3) the substitution pattern on the ring system; and (4) the linker. EX1003, ¶¶39-48. All of these differences pertain to what the Challenged Claims recite as Z', the optionally substituted fused heterocyclic ring systems (hereinafter "Z'-structure"). *Id.* Each of these differences affects how IMBRUVICA and BRUKINSA function. *Id.*; *infra* III.D.

First, as illustrated below, IMBRUVICA and BRUKINSA have distinct ring systems. EX1003, ¶¶40-41. Specifically, IMBRUVICA's ring system is biaryl—the 5-membered and 6-membered rings are both aromatic. *Id.* In contrast, BRUKINSA's ring system is non-biaryl—the 5-membered ring is aromatic but the

10

Petition, at 10
PO Response, at 24

Zanubrutinib and Ibrutinib Show Nearly Identical Binding of Common Structural Features

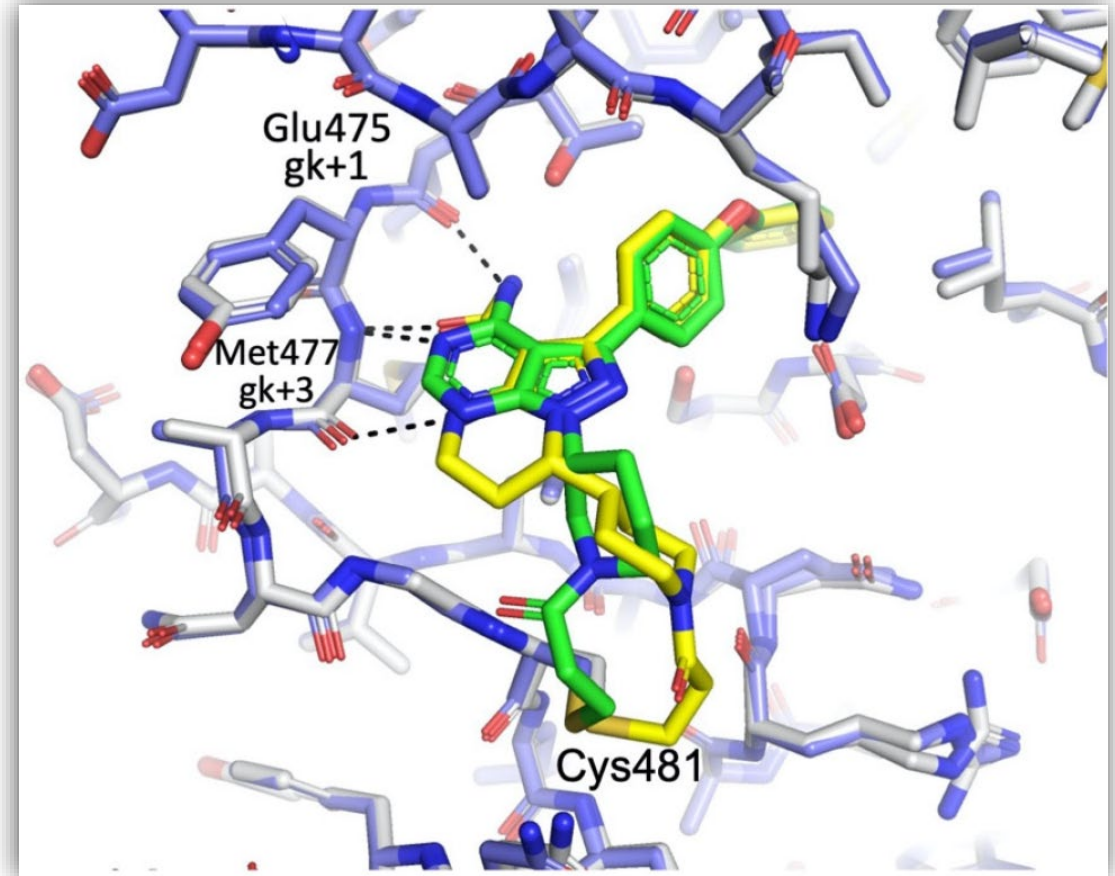
Eck Declaration (Ex. 2010)

94. Additionally, as shown in the below overlay of BTK-ibrutinib (PDB: 5P9J) and BTK-zanubrutinib (PDB: 6J6M), ibrutinib and zanubrutinib have largely overlapping placement in three-dimensional space, further confirming that the two inhibitors bind to BTK in the same way from a structural perspective. Ibrutinib is shown with carbon atoms colored green, and zanubrutinib is shown with carbon atoms colored yellow.

Ex. 2010, ¶194

95. The precise maintenance of hydrogen bond interactions in zanubrutinib as compared with ibrutinib also allows zanubrutinib to position the phenoxyphenyl substituent exactly as in ibrutinib, preserving the overall structure-function relationship in binding to BTK. The precise correspondence of these

Ex. 2010, ¶195



Ex. 2010, ¶194

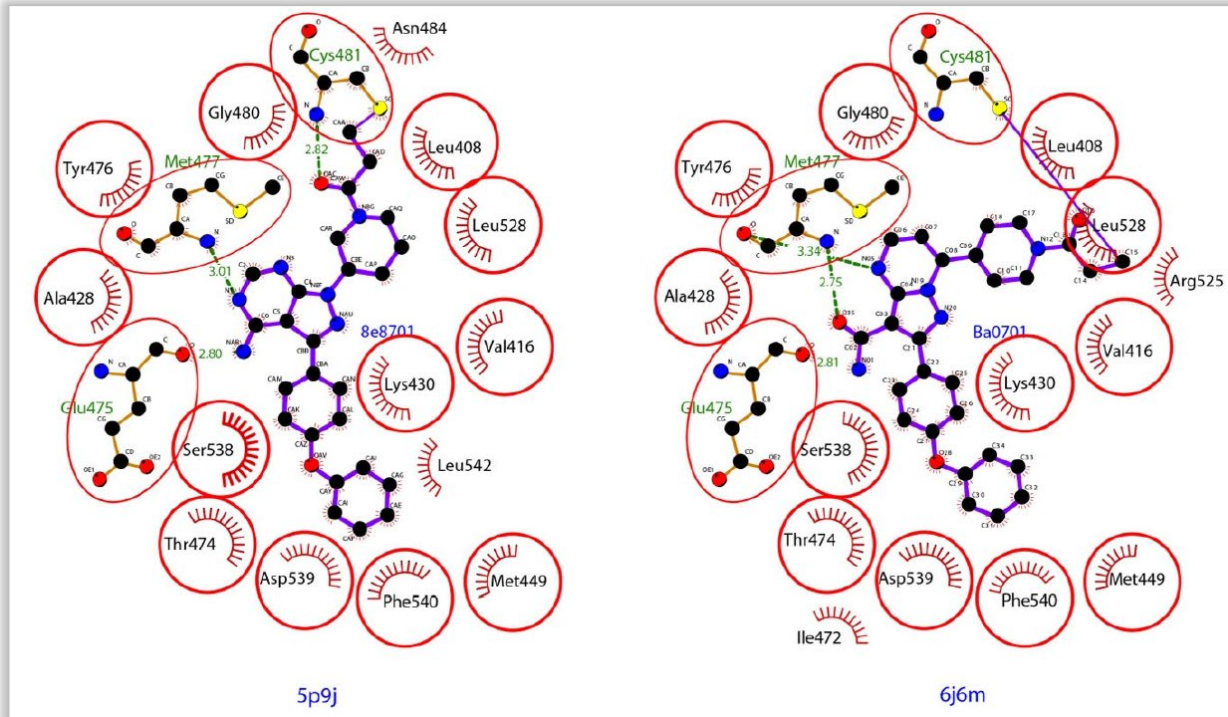
PO Response, at 50-51

Zanubrutinib and Ibrutinib Show Nearly Identical Binding of Common Structural Features

Eck Declaration (Ex. 2010)

Unchallenged

Veal Deposition (Ex. 2119)



Ex. 2010, ¶196

97. As the figure shows, almost **all** of the interactions with BTK are the **same** for ibrutinib (left, PDB: 5P9J) and zanubrutinib (right, PDB: 6J6M) (with areas of conserved interactions highlighted with red circles). Moreover, ibrutinib

Ex. 2010, ¶197

11 Q. My question was in paragraph 80, you did not
12 identify **any different interactions between**
13 **zanubrutinib six-membered ring and Btk** that are not
14 present in ibrutinib; correct?
16 A. There are **no specific interactions**
17 **identified.** However --

Ex. 2119, 197:11-17 (objection omitted)

PO Response, at 50-51, 61; PO Sur-Reply, at 15 & n.4

Ibrutinib and Zanubrutinib Mimic Adenine by H-Bonding to BTK's Active Site

Both Parties' Experts Agree on Adenine Mimic Definition

Veal Publication 2004 (Ex. 2121)

tors. The key features of a purine mimetic are hydrogen bonding functionality, which at a minimum mimics the hydrogen bond formed by N1 of adenine and a planar aromatic or heteroaromatic ring system (Fig. 2.2 B). Many inhibitors also

Ex. 2121.0026

Veal Publication 2009 (Ex. 2120)

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

Ex. 2120, Fig. 16.5 (.0023)

Eck Declaration (Ex. 2010)

167. In my opinion, a POSA would use "adenine mimic" to refer to hinge-binding scaffolds that mimic the interactions of the adenine portion of ATP, not limited to structures that are isosteric (or approximately isosteric) with adenine, as Dr. Showalter narrowly applies. Nevertheless, Dr. Showalter's focus on "adenine

Ex. 2010, ¶167

Under Agreed-Upon Definition, Ibrutinib and Zanubrutinib Mimic Adenine

Eck Declaration (Ex. 2010)

92. Second, ibrutinib and zanubrutinib bind to BTK in the same way from a structural perspective: the heterocyclic scaffolds of ibrutinib and zanubrutinib make the key H-bond interactions with BTK residues that adenine makes. As shown below, zanubrutinib forms the same H-bonds with the hinge of BTK as ibrutinib and adenine.

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)

Ex. 2010, ¶92

PO Response, at 50-52; PO Sur-Reply, at 9

Petitioner's Publication and Cited Art Show Zanubrutinib Mimics Adenine

Petition

In essence, IMBRUVICA has a Z'-structure that is designed to mimic adenine, which is the ring system of ATP (below in blue). EX1003, ¶¶49-51. In

BRUKINSA's Z'-structure, in contrast, does not attempt to mimic adenine.

Paper 2, at 13-14

Contradicted by

Contradicted by

Guo 2023 (Ex. 2020)

Petitioner's Own Reference

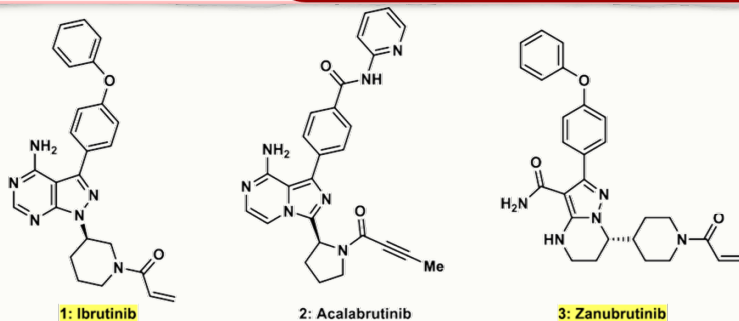


Figure 1. Approved irreversible BTK inhibitors.

inactive BTK conformation. Moreover, five approved BTK inhibitors all have similar hinge binding to ATP. Therefore, we

Ex. 2020.0002

Zhang 2021 (Ex. 1076)

Dr. Showalter's Cited Reference

Table 1. The approved BTK inhibitors and their indications.

1 (Ibrutinib)

5 (Zanubrutinib) [4]

the hinge region. To mimic the intermolecular interactions between ATP adenine and the hinge region, all BTK inhibitors possess a heterocycle core to maintain similar interactions with hinge residues.

Ex. 1076, Tbl. 1 (.011), .005

Brullo 2021 (Ex. 1044)

Dr. Showalter's Cited Reference

amino group on the heteroaromatic core nucleus. On the basis of the crystallographic data available, ibrutinib and zanubrutinib share similar bioactive conformations within the wild-type Btk binding site (Figure 2B) [30,31]. Therefore, beside the covalent bond with Cys481, the two complexes are mainly stabilized by similar interactions which include the cation- π contact between the phenoxyphenyl ring and Lys430 side chain and the hydrogen bonds with Met477 and Glu475 backbones (Figure 2C,D). It is clearly demonstrated that

Ex. 1044.003

Showalter Deposition (Ex. 2018)

13 Q You agree that zanubrutinib is mimicking
14 the interaction of ATP or adenine?
17 A So as I recall from the crystal structure
18 which was determined I believe around 2015 of
19 Brukinsa with Btk, it showed similar but not the
20 same hydrogen bond donor interactions with the
21 hinge region as ATP.

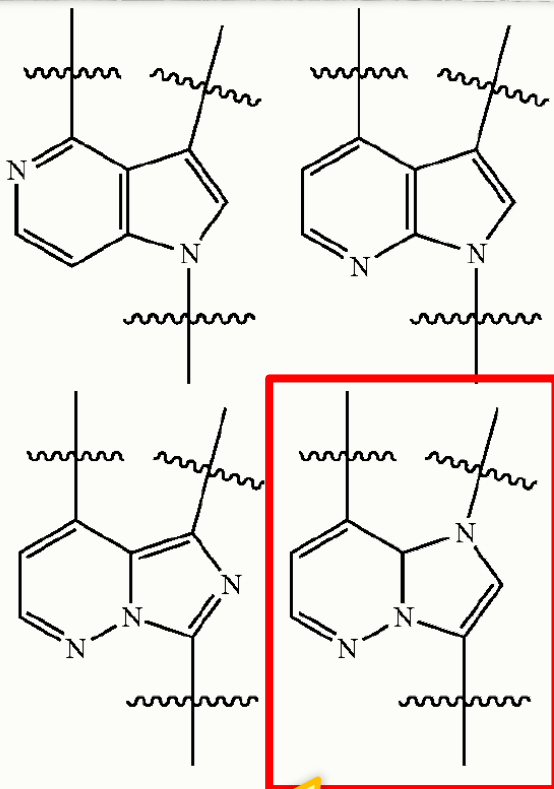
Ex. 2018, 85:13-21 (objection omitted)

PO Response, at 50-52, 61; Eck Decl. (Ex. 2010), ¶¶93, 162, 167

The Specification Defines Aryl Broadly

'803 Patent, Specification

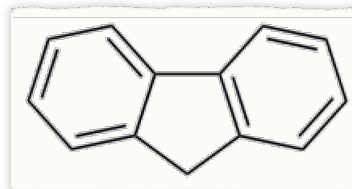
In some embodiments,  is a substituted fused biaryl moiety selected from



Ex. 1001, 62:44-67
(annotated)

Scaffold Is Not Aromatic

Fluorenyl Has Central Non-Aromatic Ring



Ex. 2010, ¶166 & n.6

Permissive "Aryl" Definition

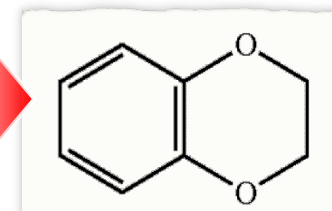
As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited 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

Permissive "Non-Aromatic Heterocycle" Definition

As used herein, the term "non-aromatic heterocycle", "heterocycloalkyl" or "heteroalicyclic" refers to a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. A "non-aromatic heterocycle" or "hetero-

Definition Includes Structure with Aromatic Portion



Ex. 1001, 18:21-25

Ex. 1001, 17:30-18:33

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

Irreversible BTK Inhibition Results in Lymphocytosis and Treatment of CLL/SLL

Lymphocytosis Is a Class Effect of Irreversible Inhibition

'803 Patent, Specification

inhibitor nearly 6 months ago. Typical of the majority of CLL patients treated with a Btk irreversible inhibitor, there was an initial, rapid, and prominent reduction in nodal disease and spleen size, with a corresponding rise in the circulating lymphocyte count, likely a consequence of the inhibitory effects of a Btk irreversible inhibitor on lymphocyte homing to the nodal and splenic compartments. Simul-

Ex. 1001, 135:30-36

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

Ex. 1001, 143:27-31

Petitioner and Dr. Rosen Acknowledged Class Effect in Pre-Litigation Publications

BRUKINSA FDA Label
Apr. 2023 (Ex. 1012)

Petitioner's FDA Label

Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Ex. 1012.008

Ma & Rosen 2011 (Ex. 2022)

Dr. Rosen's Own Reference

weeks of the treatment. The lymphocytosis will gradually decrease over the ensuing months, with improved quality of response with time. This phenomenon is likely due to the unique impact of Btk inhibition on promoting lymphocyte trafficking out of the protective lymph nodes and bone marrow microenvironment. Therefore,

Ex. 2022.0003

PO Response, at 10-11, 33-36, 75; Spurgeon Decl. (Ex. 2014), ¶¶90-94, 113

Irreversible Inhibition Results in the Claimed Clinical Effect

Specification Shows Occupancy Leads to Efficacy

'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

in situ or other in situ carcinomas Results:

29 pts (12 follicular, 7 CLL/SLL, 4 DLBCL, 4 mantle, 2 marginal) with a median of 3 prior therapies have been enrolled on cohorts 1-4. Therapy was well tolerated with most adverse events $<$ grade 2. One protocol defined DLT (dose delay $>$ 7 d due to neutropenia) was observed. 19/22 pts from cohorts 1-3 are evaluable. The ORR is 42%; 1 CR (SLL), 7 PR (4 CLL/SLL, 2 MCL and 1 FL). In cohort 2, PD demonstrate complete occupancy of Btk by a compound of Formula (D), with $>$ 95% enzyme occupancy 4 hours post dose in all pts. Basophil degranulation, a Btk-dependent cellular process, was completely inhibited up to 24 hrs. T-cell responses were not affected, and no significant depletion of peripheral blood B, T or NK cell counts was observed. Positive correlation ($R^2=0.93$) was found between Btk active-site occupancy in PBMCs (mean of Days 1 and 8) and a compound of Formula (D) plasma AUC $_{0-\infty}$ (Day 1) at the 1.25 mg/kg dose.

Ex. 1001, 138:27-43

PO Response, at 32-34, 77-78, 88; Spurgeon Decl. (Ex. 2014), ¶¶95-99

No Dispute that if Compound Irreversibly Inhibits BTK, It Is Effective in the Claimed Method

Rosen Deposition (Ex. 2021)

5 A. I would say that when you have a molecule if
6 you're saying that has been shown to inhibit BTK and
7 it is occupying BTK, then presumably, it would lead
8 to killing.

Ex. 2021, 39:5-8

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

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

Ex. 2021, 219:12-18

Spurgeon Declaration (Ex. 2014)

BTK based on the significant information regarding BTK structure in 2011. Thus, in the context of the claims to methods of treating CLL/SLL with a specific class of irreversible BTK inhibitors having common structural features to ibrutinib, a POSA would have understood based on ibrutinib's demonstrated activity that irreversible BTK inhibitors with ibrutinib's features could similarly occupy and inhibit BTK and treat CLL/SLL in patients.

Ex. 2014, ¶137

§IX.A.1.c. Further, Dr. Rosen cites no evidence or example that an irreversible BTK inhibitor having the claimed structural features would not induce lymphocytosis, and I am not aware of any such example. See §IX.A.3. I therefore disagree with Dr. Rosen's unsupported, conclusory assertion that lymphocytosis was unpredictable.

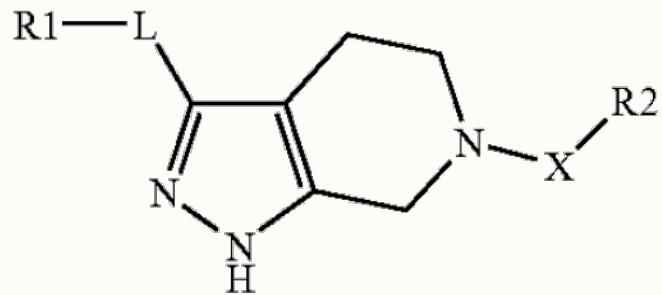
Ex. 2014, ¶143

PO Response, at 31-38, 87-88

The Specification Need Not Describe Every Species

U.S. Patent No. 7,435,820

(issued in 2008) (Ex. 2023)



Ex. 2023, 2:1-6

Veal Declaration (Ex. 1106)

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

Ex. 1106, ¶154



Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003)

“[A]n applicant is **not required** to describe in the specification every conceivable and possible future embodiment of his invention[]” nor must it describe “**all species that [the] claim encompasses.**”

PO Response, at 30, 39, 45, 52; Petitioner Reply, at 9; PO Sur-Reply, at 14-16, 19-20

ENABLEMENT

'803 Patent Claims Methods of Treating CLL/SLL with iBTKIs Having Ibrutinib's Structural Features

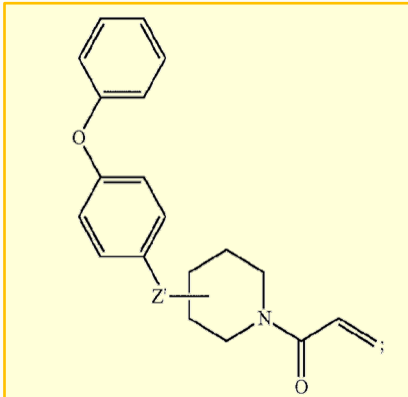
'803 Patent, Claim 1

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

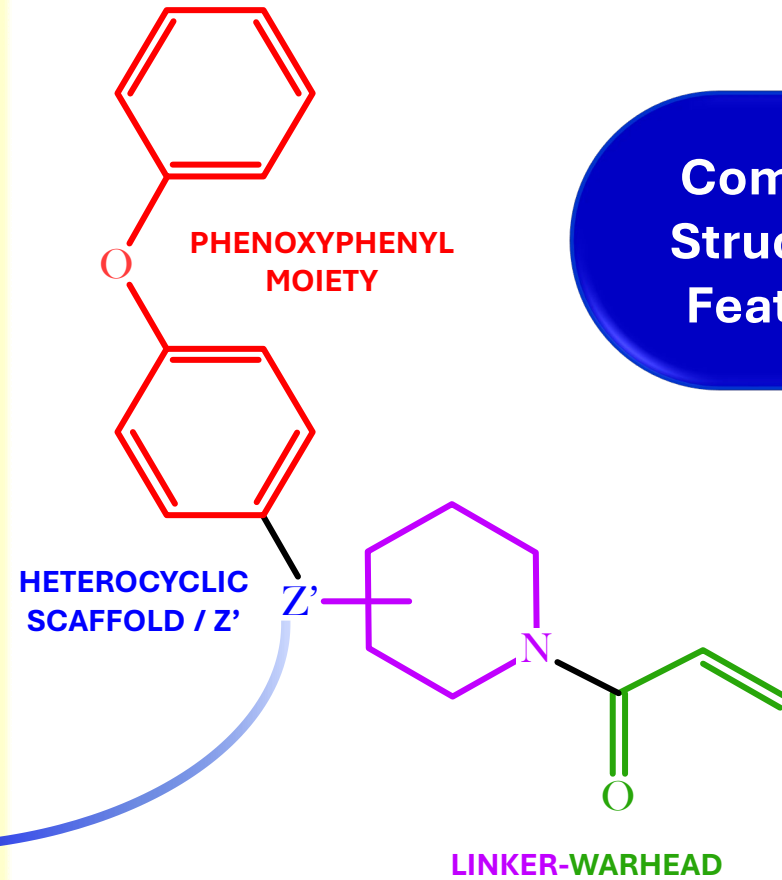
orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity;

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:

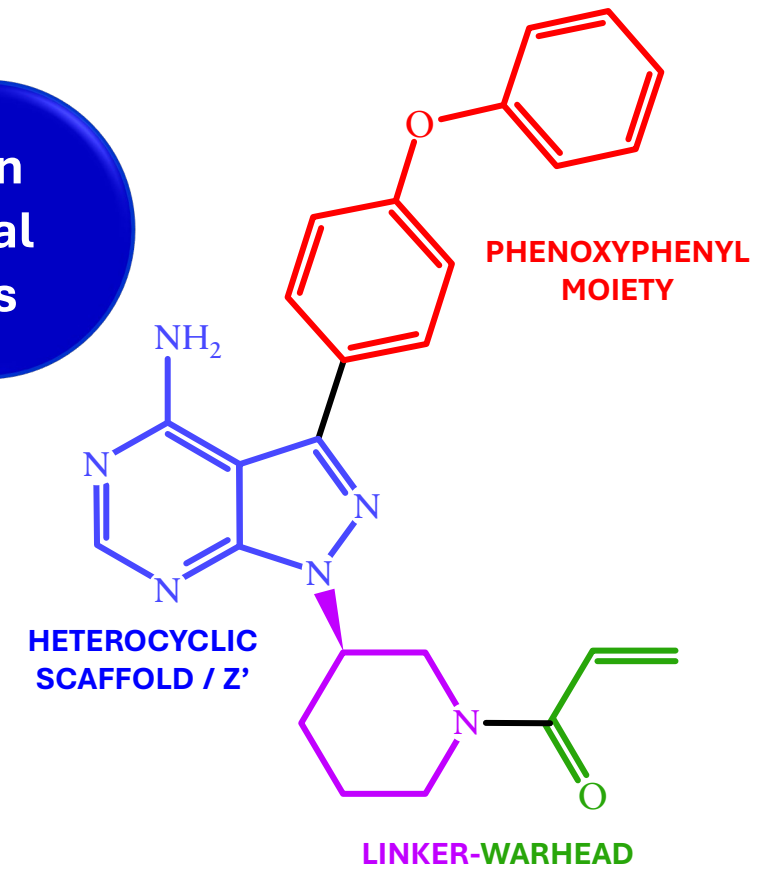


wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms; wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom; and wherein the irreversible inhibitor of Btk forms a covalent bond with Cys⁴⁸¹ of a Bruton's tyrosine kinase.



Ex. 1001, claim 1 (annotated)

Ibrutinib



Ex. 1001, 65:9-25 (annotated)

PO Response, at 4-6, 12-13, 39-40, 42, 74-77

A POSA Would Have Been Highly Skilled and State of the Art on Kinase Active Site Binding Was Predictable

- No dispute that a POSA would have been highly skilled
 - See Ex. 1003 (Showalter Decl.), ¶253; Ex. 1005 (Rosen Decl.), ¶265; PO Response, at 86
- No dispute that a POSA would account for modeling
 - See Ex. 2118 (Showalter Dep.), 10:10-16; Ex. 2010 (Eck Decl.), ¶125; PO Response, at 28, 78-81, 86-87; PO Sur-Reply at 3
- The conservation of the BTK kinase active site yields predictability in selecting Z'
 - See Ex. 2121.0025-0026; Ex. 1075.003; PO Response, at 14-17, 21-24, 86-87; PO Sur-Reply, at 12-13, 16-17; Eck Decl. (Ex. 2010), ¶¶45-46, 60-68, 83-84
- Petitioner's cited prior art describes rules for predicting kinase active site (hinge) binding
 - See Ex. 1052.002, .019-021; PO Response, at 58-59, 86-87; Eck Decl. (Ex. 2010), ¶¶155-157
- Because of the sophisticated structure-function relationship, modeling was predictive of the expected function
 - See Ex. 1001, 138:27-43; Ex. 2001, Fig. 2D (.0003); Ex. 1060.001-002; PO Response, at 17-19, 25-26, 32-33, 41, 46-48, 60, 75-82, 86-87; Eck Decl. (Ex. 2010), ¶¶71, 108-118, 153

Dr. Eck Confirms a POSA Could Visualize the Full Scope of Claim 1

Eck Deposition (Ex. 1110)

21 Q. I think what are you saying is that there
22 is a distinction between making and using a compound
23 that falls within the scope of the invention versus
24 drawing out and envisioning all of the possible
25 compounds that fall within the discovery mentioned; is
1 that correct?

4 A. It's my opinion that a POSA can envision
5 all possible molecules that fall within the scope of
6 the claims. I think that that can be -- the '803
7 specification, what's known in the art, makes it
8 possible to -- there is no structure that is not
9 possible to envision or to recognize, but that's a
10 very different thing than setting out an exercise of
11 specifically visualizing and recognizing every
12 possible structure figuratively.

Ex. 1110, 164:21-165:12 (objection omitted)

13 Q. When you say, "a POSA could visualize every
14 molecule that falls within the scope of the claim,"
15 how many molecules are we talking about here?

16 A. Again, as we have discussed at some length,
17 I haven't tried to calculate that.

18 Q. Then how do you know a POSA can envision
19 all of them if you can't -- I just don't follow that
20 logic.

21 A. So, again, I am trying to speak very
22 clearly here.

23 Q. Okay.

24 A. There is no molecule in the claim that
25 can't be visualized or recognized in my opinion.

Ex. 1110, 165:13-25

19 Q. How would a POSA use virtual docking to
20 identify all of the possible Z'-scaffolds that meet
21 the structural limitations of the claim and also
22 satisfy the need for H-bonds to the hinge, the ability
23 for the phenoxyphenyl to occupy the back pocket, and
24 for the linker-warhead to covalently bind?

25 A. I don't think I have said that a POSA would
1 be -- would use that to identify all. I can't imagine
2 that a POSA would want to set about figuring out all
3 of the possible ways to inhibit BTK with the molecule
4 of these claims. But I think for any particular
5 potential BTK inhibitor I think a POSA could very
6 readily do that analysis.

Ex. 1110, 53:19-54:6

No Evidence that a POSA Would Be Unable to Identify Compounds
Across the Full Scope of Claimed Ibrutinib-like iBTKIs

Petitioner and Its Experts Used Wrong Standard for Undue Experimentation

Petitioner and Its Experts Erroneously Focus on the Cumulative Effort to Test Every Ibrutinib-Like iBTKI

Petition

b) Quantity of Experimentation

In 2010/2011, a POSA would need to synthesize and screen the billions of candidates that satisfy the Structural Limitations to determine whether they would covalently bind. EX1003, ¶236. This would have taken undue time and effort. *Id.*

Petition, at 83

Showalter Deposition (Ex. 2118)

22 Q All right. And that, again, goes to the
1 idea that, am I correct that your enablement
2 opinion is grounded in the amount of
3 experimentation that would be required to test all
4 of the 4 million or more species that you count as
5 within the structural limitations?
6 A Yes.

Ex. 2118, 56:22-57:6

Veal Deposition (Ex. 2119)

1 Q. Okay. And so when you say there's a lot of
2 work to construct the compounds to generate the
3 Z-prime scaffolds, so are you envisioning that a
4 POSA would need to generate every single possible
5 Z-prime scaffold to evaluate in the experimentation
6 that you're describing in this paragraph?
8 A. Yes. That's where you would start is with
9 that assumption.
10 Q. Okay. Okay. And that was how you
11 approached understanding how to assess the quantity
12 of experimentation.
14 A. Yes. I think that is correct. It's the
15 idea that when you have a lot of scaffolds -- and
16 I'd have to look back at what the Haas
17 declaration -- Dr. Showalter -- sorry -- declaration
18 to, you know, get that specific number of scaffolds.
19 But then where it blows up is all the different --
20 you know, the common or toil explosion, if you
21 will -- you know, all the different positions you
22 could, you know, put -- put substitutions on. And
1 so he did those calculations, which I concur with,
2 and I am saying that from a modeling perspective, to
3 look at all the different scaffolds and then to look
4 at all the possible substitution would be an
5 enormous effort.

Ex. 2119, 236:1-237:5 (objections omitted)

PO Response, at 82; PO Sur-Reply, at 19



Amgen Inc. v. Sanofi, 598 U.S. 594, 615 (2023)

“[E]nablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim[.]”