

Filed on behalf of: Pharmacyclics LLC

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

BeiGene USA, Inc. and BeiGene, LTD.,  
Petitioner,

v.

Pharmacyclics LLC,  
Patent Owner.

---

PGR2024-00009  
Patent 11,672,803

---

**DECLARATION OF DAVID A. SCOTT, PH.D.  
IN SUPPORT OF PATENT OWNER'S RESPONSE**

**Table of Contents**

|       |                                                                                                                                                                  |    |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| I.    | Introduction .....                                                                                                                                               | 1  |
| II.   | Background and Qualifications.....                                                                                                                               | 1  |
| III.  | Materials Reviewed and Considered .....                                                                                                                          | 4  |
| IV.   | Relevant Timeframe and Level of Ordinary Skill in the Art.....                                                                                                   | 7  |
| V.    | The '803 Patent Claims.....                                                                                                                                      | 9  |
| VI.   | The Z' Scaffold of the Irreversible BTKIs in the '803 Patent Claims<br>Would Be Expected to Make H-Bonds to the Hinge Region of BTK<br>.....                     | 12 |
| VII.  | A POSA Reading the '803 Patent Would Have Understood<br>Ibrutinib-Like Irreversible BTKIs Could Have Sufficient Properties<br>to Inhibit BTK in Patients .....   | 17 |
| VIII. | Dr. Showalter's Opinion on Substituting Z' for Use in the<br>Compounds of the '803 Patent Claims Is Contrary to Principles Of<br>Small Molecule Drug Design..... | 25 |
| IX.   | Conclusion.....                                                                                                                                                  | 32 |

**I. INTRODUCTION**

1. I have been retained by Pharmacyclics LLC (“Patent Owner” or “Pharmacyclics”) to provide my opinions concerning the technology relevant to U.S. Patent No. 11,672,803 (EX1001) (“’803 Patent”). I am being compensated for my work in this matter at my customary hourly rate of \$400 and being reimbursed for reasonable expenses. My compensation is not contingent upon the substance of my opinions or the outcome of this matter.

**II. BACKGROUND AND QUALIFICATIONS**

2. In 1996, I received my Masters in Chemistry (First Class) from the University of St. Andrews, having completed the integrated four-year course. In my final year at St. Andrews, I was awarded the Irvine Jubilee Medal for most distinguished student. I received my Ph.D. in organic chemistry from the University of Oxford in 2000. I continued my training at the University of Texas, Austin, where I was a postdoctoral researcher in the laboratory of Professor Philip Magnus from 2000 to 2002.

3. Since completing my degrees and training, I have worked as a medicinal chemist for over twenty years, focusing on drug discovery and early pharmaceutical development, particularly for kinase inhibitors.

4. From 2002 to 2013, I worked at AstraZeneca in the Oncology Research and Development group, initially as a Scientist, then as a Senior Scientist,

and with promotion to Principal Scientist in 2007. I led or participated on teams that developed inhibitors for several different tyrosine kinases including colony-stimulating factor-1 receptor (“CSF-1R”), Janus kinase 2 (“JAK2”), and tropomyosin receptor kinase (“Trk”). Specifically, I was the chemistry team leader in charge of the CSF-1R kinase project, which delivered two development candidates, AZD6495 and AZD7507. For this and other kinase projects, my teams were responsible for the design and synthesis of kinase inhibitors to optimize biological activity, selectivity, physical properties, and the pharmacokinetic profiles. As part of these teams, I also contributed to the discovery of two other kinase inhibitors, AZD6918 (Trk) and AZD1480 (JAK2), both of which progressed to human clinical trials. As a chemistry team leader, I collaborated with colleagues in other disciplines to guide the overall project strategies. In addition to my work developing kinase inhibitors, I worked on other target classes at AstraZeneca, leading a chemistry team that developed small molecule inhibitors of PARP6.

5. Since 2014, after leaving AstraZeneca, I have worked in the Medicinal Chemistry Core at the Dana-Farber Cancer Institute, leveraging my medicinal chemistry experience and expertise. From 2014 to 2018, I served as a Lead Scientist, and since 2018, I have been a Principal Scientist and Director of the Medicinal Chemistry Core. I have been the project leader responsible for four

industry-sponsored drug discovery collaborations. In this capacity, I have directed chemists at Dana-Farber and at Contract Research Organizations (“CROs”) to optimize small molecule therapeutics for diverse targets, including two kinases. I am the project leader on our epidermal growth factor receptor (“EGFR”) project, which has delivered an allosteric EGFR inhibitor (EAI-432) into development.

6. I have thirty-seven peer reviewed publications, many of which relate to kinase inhibitors. During my time at AstraZeneca, I was first-author of five publications from 2008 to 2013 related to CSF-1R kinase inhibitors. At Dana-Farber, my work led to two publications on TNK inhibitors, including the use of “scaffold morphing,” which refers to a medicinal chemistry approach to identify novel chemical series with the potential for improved potency and properties over existing series. We used scaffold morphing to modify our previous TNK2 inhibitor (XMD8-87) with the aim of improving its pharmacokinetic properties while retaining the key hydrogen bond interactions to the hinge region. I have also co-authored publications on other kinases, including allosteric inhibitors of EGFR, Focal Adhesion Kinase (“FAK”), B-Raf kinase, and JAK2 kinase. Further, I have co-authored publications on covalent inhibitors, and on the optimization of bioavailability through the control of physicochemical properties and modulation of H-bond acceptor strength. The full list of my peer-reviewed publications is included in my *curriculum vitae* (“CV”).

7. Moreover, I am a named inventor on twenty-three World Intellectual Property Organization (“WIPO”) publications, which have led to at least six issued U.S. patents. For example, I am a named inventor of International Publication No. WO 2005/049033 A1, titled “Preparation of Pyrazole Derivatives as Inhibitors of Receptor Tyrosine Kinases.” As another example, I am a named inventor of International Publication No. WO 2020/231726 A1, titled “Small-Molecule Focal Adhesion Kinase (FAK) Inhibitors.” The full list of my WIPO publications and U.S. patents is included in my CV.

8. The above summary is not intended to be exhaustive. A copy of my CV is EX2013, is being served simultaneously with this Declaration, and is incorporated here by reference.

### **III. MATERIALS REVIEWED AND CONSIDERED**

9. All of the opinions contained in this Declaration are based on the documents I considered and my education, years of professional experience, and knowledge. In forming the opinions expressed in this Declaration, while drawing on my experience in the field of kinase inhibitors and medicinal chemistry, I considered the following documents. To the extent a document is not listed in the below table or not cited in my Declaration, the document did not affect my opinion or was cumulative to other documents included in the below table.

| Ex.  | Description                                                                                                                                                                                                                     |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1001 | United States Patent No. 11,672,803                                                                                                                                                                                             |
| 1003 | Declaration of Hollis D. Showalter, Ph.D.                                                                                                                                                                                       |
| 1014 | IMBRUVICA Prescribing Information (Revised May 2023)                                                                                                                                                                            |
| 1036 | U.S. Patent Publication No. 2020/0140432                                                                                                                                                                                        |
| 1049 | L. Garuti, et. al. "Irreversible Protein Kinase Inhibitors", Current Medicinal Chem., 2011; 18:2981-2994                                                                                                                        |
| 1052 | Arup K. Ghose, et. al. "Knowledge Based Prediction of Ligand Binding Modes & Rational Inhibitor Design for Kinase Drug Discovery", J. Medicinal Chem. 2008; 51(17); 5149-5171                                                   |
| 1053 | Yunhang Guo, et. al. "Discovery of Zanubrutinib (BGB-3111), a Novel, Potent, and Selective Covalent Inhibitor of Bruton's Tyrosine Kinase", J. Medicinal Chem. 2019; 62:7923-7940                                               |
| 1073 | Fatih M. Uckun and Sanjive Qazi, "Bruton's tyrosine kinase as a molecular target in treatment of leukemias and lymphomas as well as inflammatory disorders and autoimmunity", Expert Opinion 2010; 20(11):1457-1470             |
| 1077 | Jianming Zhang, et. al. "Targeting cancer with small molecule kinase inhibitors", Nature reviews Jan. 2009; 9:28-39                                                                                                             |
| 1099 | Rajan Swami and Aliasgar Shahiwala, "Impact of physiochemical properties on pharmacokinetics of protein therapeutics", Euro. J. Drug Metab Pharmacokinet 2013; 38:231-239                                                       |
| 2001 | Douglas J. Marcotte et al., <i>Structures of Human Bruton's Tyrosine Kinase in Active and Inactive Conformations Suggest a Mechanism of Activation for TEC Family Kinases</i> , 19 Protein Science 429 (2010) ("Marcotte 2010") |
| 2013 | <i>Curriculum Vitae</i> of David A. Scott, Ph.D.                                                                                                                                                                                |
| 2018 | Deposition transcript of Hollis Showalter, Ph.D., <i>BeiGene USA, Inc. v. Pharmacyclics LLC</i> , No. PGR2024-00009 (P.T.A.B. July 18, 2024) ("Showalter Dep.")                                                                 |

| Ex.  | Description                                                                                                                                                                                                                                                                           |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2027 | International Patent Application Publication No. WO 2010/126960 A1                                                                                                                                                                                                                    |
| 2028 | Irini Akritopoulou-Zanze & Philip J. Hajduk, <i>Kinase-Targeted Libraries: The Design and Synthesis of Novel, Potent, and Selective Kinase Inhibitors</i> , 14 Drug Discovery Today 291 (2009)                                                                                        |
| 2031 | Caterina Bissantz et al., <i>A Medicinal Chemist's Guide to Molecular Interactions</i> , 53 J. Med. Chemistry Persp. 5061 (2010)                                                                                                                                                      |
| 2034 | Stephane De Cesco et al., <i>Covalent Inhibitors Design and Discovery</i> , 138 Eur. J. Med. Chemistry 96 (2017)                                                                                                                                                                      |
| 2040 | Doris Hafenbradl et al., <i>In Vitro Characterization of Small-Molecule Kinase Inhibitors</i> , ch. 1 (pp. 3–43) in PROTEIN KINASES AS DRUG TARGETS (Bert Klebl, Gerhard Müller & Michael Hamacher eds., 2011)                                                                        |
| 2042 | Lee A. Honigberg et al., <i>Supporting Information</i> (pp. 1-2) to <i>The Bruton Tyrosine Kinase Inhibitor PCI-32765 Blocks B-Cell Activation and Is Efficacious in Models of Autoimmune Disease and B-Cell Malignancy</i> , 107 Proc. Nat'l Acad. Scis. 13075 (2010) (Exhibit 1055) |
| 2048 | Laurent Le Corre et al., <i>Synthesis and Biological Evaluation of a Triazole-Based Library of Pyrido[2,3-d]pyrimidines as FGFR3 Tyrosine Kinase Inhibitors</i> , 8 Organic Biomolecular Chemistry 2164 (2010)                                                                        |
| 2052 | Frank Lovering et al., <i>Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success</i> , 52 J. Med. Chemistry 6752 (2009)                                                                                                                             |
| 2059 | Juswinder Singh et al., <i>The Resurgence of Covalent Drugs</i> , 10 Nature Revs. Drug Discovery 307 (2011)                                                                                                                                                                           |
| 2060 | Michael J. Waring, <i>Lipophilicity in Drug Discovery</i> , 5 Expert Op. Drug Discovery 235 (2010)                                                                                                                                                                                    |

#### **IV. RELEVANT TIMEFRAME AND LEVEL OF ORDINARY SKILL IN THE ART**

10. I have been informed that the priority date for the '803 Patent for this proceeding is at least June 3, 2011. Therefore, I have conducted my analysis of the relevant technology based on what was known in the field in June 2011. To the extent I reference knowledge in the field "in 2011," that knowledge would have been available as of June 3, 2011. My conclusions about the teaching of the patent and knowledge of a POSA would also apply to the filing dates of the non-provisional patent applications to which the '803 Patent claims priority, which I understand to be April 24, 2013, November 26, 2013, September 26, 2017, April 27, 2018, and August 8, 2019. To the extent I address information available after June 2011 it is either indicative of the state of the art in June 2011 or confirms my conclusions that later developments in the field would not change my analysis.

11. I have been informed that to assess the level of ordinary skill in the art, one considers the types of problems encountered in the field, the prior solutions to those problems, the sophistication of the technology, and the educational level of active workers in the field.

12. For the '803 Patent, a person of ordinary skill in the art ("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-activity relationships 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-activity relationships of kinase inhibitors.

13. I understand that Dr. Showalter has proposed that a POSA “would have been part of a team that included at least (1) a member that had at least a Ph.D. in chemistry, organic chemistry, or related field with training as a medicinal chemist (‘chemist member’), and (2) a member that had at least a medical degree with training in hematology and oncology, including several years of clinical experience in treating hematologic malignancies (‘clinical member’).” EX1003, ¶136. Dr. Showalter’s definition does not expressly account for the relevance of the wealth of structural information available about the kinase active site and the developed understanding of the structure-activity relationships of kinase inhibitors in June 2011. A proper definition would explicitly account for this relevant knowledge, i.e., “at least one member having at least a Ph.D. in chemistry, organic chemistry, biochemistry, or related field with training in the structure-activity relationships of kinase inhibitors.” My opinions set forth in this Declaration would not change under Dr. Showalter’s definition.

14. I would have qualified as a member of the POSA team as of the claimed June 3, 2011 priority date of the '803 Patent, and I believe that I have a sufficient level of knowledge, experience, and education to provide expert opinions in the field of the '803 Patent.

## **V. THE '803 PATENT CLAIMS**

15. The '803 Patent is directed to methods of treating chronic lymphocytic leukemia ("CLL") or small lymphocytic lymphoma ("SLL") by continuously dosing a therapeutically effective amount of a defined class of irreversible BTK inhibitors ("BTKIs") wherein lymphocytosis is not considered progression of the CLL or SLL. *See* EX1001.

16. I understand that this proceeding relates to claims 1-8, 12, and 20 ("Challenged Claims"). I understand that claims 1 and 8 are independent claims of the '803 Patent and that claims 2-7 and 12 (which depend on claim 1), and 20 (which depends on claim 8) are dependent claims of the '803 Patent. I also understand that these dependent claims include all the limitations of the claims from which they depend.

17. Independent claim 1 is reproduced below, and recites:

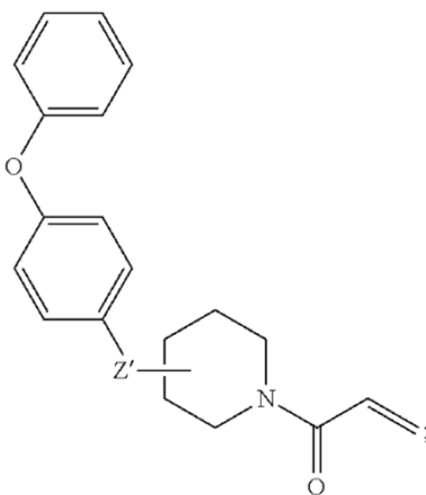
1. A method for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual comprising:

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 [of] 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 Cys<sup>481</sup> of a Bruton's tyrosine kinase.

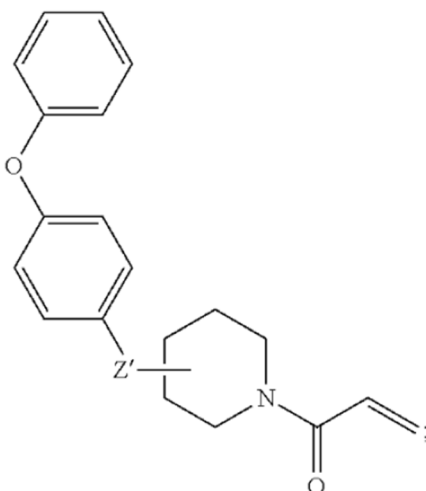
EX1001, 151:33-152:4.

18. Independent claim 8 is similar to independent claim 1, but has the additional requirement that "said administration of the therapeutically effective amount is an amount that results in >90% of the Btk active sites in the peripheral

blood mononuclear cells of the individual being occupied by the irreversible inhibitor of Btk twenty-four hours following said administration.” EX1001, 152:46-153:23.

19. I understand that the dependent claims include additional limitations but share essentially the same structural components for the irreversible BTK inhibitors (“BTKIs”) to be used in the claimed method.

20. These claims recite irreversible BTKIs with the following structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms (dependent claims 12 and 20 specify 3 nitrogen heteroatoms) and wherein the optionally substituted fused heterocyclic ring system consists of a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom. A POSA reading the '803 Patent would have understood that the Z' scaffold would form one to three hydrogen bonds (“H-bonds”) with BTK’s hinge region, as explained

below. Additionally, the compounds recited in the Challenged Claims have two fixed components: the phenoxyphenyl moiety and the linker-warhead. The class of irreversible BTK inhibitors recited in the claims are “ibrutinib-like” as they include the structural features of ibrutinib that correlate with the ability to irreversibly inhibit BTK. As I understand Dr. Eck discusses in further detail, a POSA reading the '803 Patent would understand that the phenoxyphenyl moiety binds within BTK's back-pocket and that the linker-warhead forms a covalent bond with Cys481 of BTK.

**VI. THE Z' SCAFFOLD OF THE IRREVERSIBLE BTKIS IN THE '803 PATENT CLAIMS WOULD BE EXPECTED TO MAKE H-BONDS TO THE HINGE REGION OF BTK**

21. A POSA reading the '803 Patent would understand that BTK is a protein kinase. Protein kinases catalyze the phosphorylation of target substrates in the body upon binding of an ATP molecule. ATP binds within BTK, like all protein kinases, at the “active site,” which is located between two lobes of the kinase that are linked by a flexible hinge region. *See* EX1052.002. The transfer of a phosphate group from ATP to a target substrate is essential for catalysis and modulates the activity of the target. *See* EX1077.002.

22. In the context of the Z' structure in the '803 Patent, a POSA would have understood that Z' is mimicking the role of the adenine of ATP (blue structure in the figure below). *See* EX1077.003 (“Most kinase inhibitors discovered to date

are ATP competitive and present one to three hydrogen bonds to the amino acids located in the hinge region of the target kinase, thereby mimicking the hydrogen bonds that are normally formed by the adenine ring of ATP.”); EX2028.0002 (“[T]he vast majority of kinase inhibitors make at least one hydrogen bonding interaction with the hinge region . . . .”); EX1052.020 (describing the “availability of three hydrogen bond forming moieties in the hinge region of kinases” and the observation that “one, two, or all three are engaged by various ligands,” i.e., inhibitors); *see also* EX2018, 114:4-10.

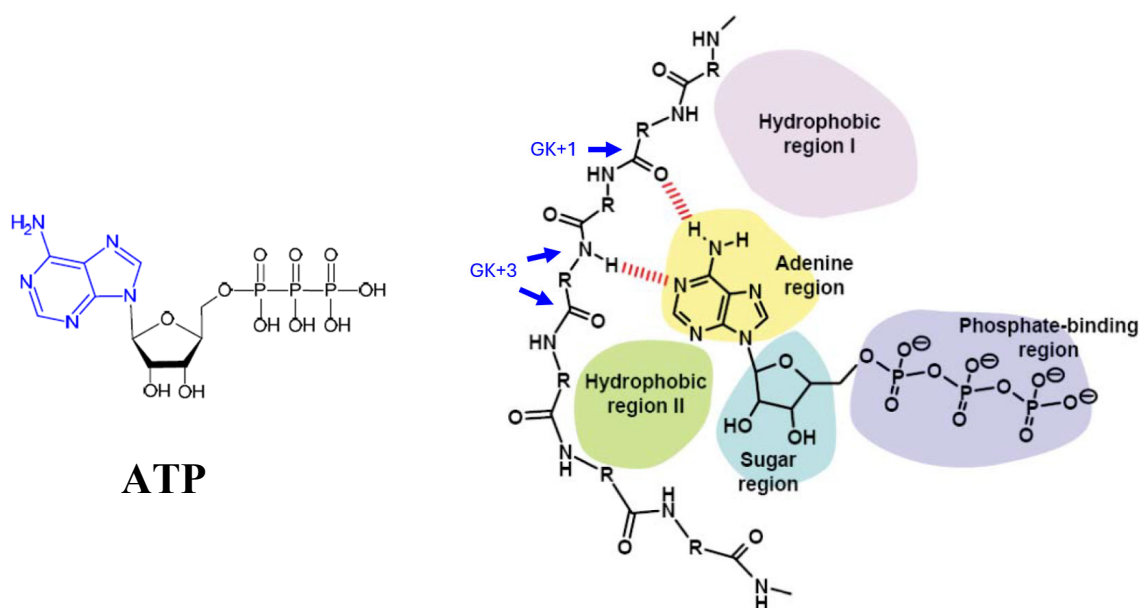


Fig. 1 Pharmacophore model of ATP binding site.

EX2048, annotated Fig. 1 (.0001). As I understand Dr. Eck discusses further, a POSA would also be aware based on the '803 Patent and other available information, ibrutinib itself makes these interactions with BTK's hinge. For example, in June 2011, a crystal structure of a compound with ibrutinib-like

binding to BTK was available from Marcotte et al., showing these interactions between the scaffold and the BTK hinge. *See* EX2001.0003-0005, Fig. 2D (.0003) (BTK-KD/B43, PDB: 3GEN); *see also* EX2018, 43:20-46:11.

23. A POSA reading the '803 Patent would have understood that adenine hydrogen bonds to specific amino acid residues of the kinase hinge, commonly referred to as the "GK +1" and "GK+3" residues because of their distance from the "gatekeeper" residue of the kinase active site (one or three amino acid positions from the gatekeeper, respectively). *See* EX1052.002; EX2048, Fig. 1 (.0001); EX2018, 111:5-10 (Dr. Showalter explaining that it "was well established" in 2011 that the adenine of the ATP forms the H-bonds with the kinase hinge). The H-bonds formed between ATP's adenine and the kinase hinge are shown as red dashed lines in the figure above. The hinge is labeled to identify the "GK +1" and "GK+3" residues.

24. H-bonds are among the most important non-covalent interactions that dictate binding of a small-molecule natural substrate (e.g., ATP) or drug (e.g., kinase inhibitor) to its protein target (e.g., kinase). *See* EX2031.0005. In an H-bond, a hydrogen atom is partially shared between two electronegative atoms, frequently oxygen and nitrogen. The hydrogen is covalently bonded to an electronegative *donor* atom and shared with a different electronegative *acceptor* atom. The electronegative donor atom pulls electron density away from the

hydrogen atom so that it develops a partial positive charge. Because of that partial positive charge, the hydrogen atom of the donor atom can have an electrostatic attraction to the partial negative charge of the electronegative acceptor atom.

25. A POSA in 2011 would have known that the adenine serves as an H-bond donor to GK+1 and H-bond acceptor to GK+3. *See* EX1052.002, .003, .007 (entry 1 of table 2, showing that 40 unique kinases have this same binding mode to an adenine scaffold).

26. In 2011, the potential of individual chemical groups to make H-bond interactions was well-known and well-understood. *See* EX2031.0005-0009. In fact, the details of H-bond strengths, distances, and angular preferences for different donor/acceptor pairs had been empirically determined. *See id.* H-bond strengths and the propensity of specific groups to form H-bonds had also been determined by quantum chemical calculations. *See* EX2031.0006-0007. Thus, a medicinal chemist in 2011 could consider a Z' scaffold for use in the claimed ibrutinib-like irreversible BTKIs and identify the atoms capable of serving as H-bond donors and acceptors. *See* EX1052.019.

27. A POSA considering potential Z' structures for use in ibrutinib-like irreversible BTKIs for the claimed method also understood basic empirical guidelines about these H-bond hinge interactions. *See, e.g.,* EX1052.019; EX2031.0006. For example, not satisfying a H-bond donor has more drastic

energetic consequences than not satisfying an acceptor, so most kinase inhibitors include a scaffold that acts at least as an H-bond acceptor to the GK+3 H-bond donor, but may leave one (or both) of the H-bond acceptors of the hinge residues unsatisfied. EX2031.0006; *see also* EX1052.019 (“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.”).

28. A POSA reading the '803 Patent to identify additional ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the Z' scaffold should form H-bonds with the GK+1 and GK+3 residues of the hinge region and would require an H-bond acceptor and donors at suitable locations in the molecule to do so. *See* EX1073.002, Fig. 1 (.003) (identifying structure of BTK hinge region with H-bond donor and acceptor locations where kinase inhibitors “would be expected” to form “1-3 hydrogen bonds with the protein backbone”); EX1052.002; EX2028.0002-0003. In other words, a POSA's knowledge of the need for H-bonds with the kinase hinge would have guided the choice of the Z' heterocyclic scaffold of an ibrutinib-like irreversible BTKI for use in the claimed method of the '803 Patent. As I understand Dr. Eck discusses in detail, a POSA would understand the appropriate orientation for these H-bond donor and acceptor

elements in the context of the structure of the BTK hinge as shown in Marcotte. EX2001.

**VII. A POSA READING THE '803 PATENT WOULD HAVE UNDERSTOOD IBRUTINIB-LIKE IRREVERSIBLE BTKIS COULD HAVE SUFFICIENT PROPERTIES TO INHIBIT BTK IN PATIENTS**

29. The '803 Patent describes that ibrutinib was able to inhibit BTK in patients, even at the lowest dose tested (1.25 mg/kg/day). EX1001, 138:40-43. Ibrutinib exhibits suboptimal pharmacological properties—it is “practically insoluble” with low bioavailability (2.9%)—and yet the '803 Patent describes that it was able to be administered to and treat patients, ultimately achieving FDA approval for its effects in inhibiting BTK. *See* EX1014.033, .035; *see also* EX1014.003; EX2018, 89:13-90:3. Because the '803 Patent describes that ibrutinib effectively inhibited BTK in patients, a POSA would have understood that the ibrutinib-like irreversible BTKIs of the claims could also be effective at inhibiting BTK in a patient despite a non-optimal pharmacokinetic (“PK”) profile.

30. A POSA considering ibrutinib-like irreversible BTKIs for use in the '803 Patent's claimed methods would have understood that the overall PK profile of a drug is the result of processes such as absorption, distribution, metabolism, and excretion/clearance (“ADME”). *See* EX2040.0038. The PK profile of a small molecule is largely determined by its physicochemical properties: a “successful drug candidate . . . requires a balanced physicochemical profile that determines the

pharmacokinetic (PK) behavior of a small-molecule inhibitor in animals.”  
EX2040.0015.

31. A POSA considering ibrutinib-like irreversible BTKIs for use in the '803 Patent's claimed method would have understood that for a drug to be suitable for oral administration, it must achieve some degree of bioavailability (the proportion of drug that reaches systemic circulation after absorption across the gastrointestinal (“GI”) tract). Oral administration requires sufficient drug solubility in the aqueous environment of the GI tract to allow for absorption. *See* EX2040.0040. Solubility largely depends on the drug's physicochemical properties (e.g., lipophilicity, hydrogen bonding, molecular size, ionization ( $pK_a$ )). *See* EX2040.0040; *see also* EX2060.0006. After dissolution, absorption for oral drugs that enter the circulation (blood) from the GI tract through passive transport through cells and membranes is impacted by factors including polar surface area (PSA), the number of H-bond donors and acceptors, lipophilicity, and molecular weight. *See* EX2040.0040.

32. In June 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that certain physicochemical properties could be calculated and/or predicted from the ibrutinib-like irreversible BTKI's structure. *See* EX2040.0040. Indeed, “[a]ll these parameters [molecular weight, octanol/water partition coefficient, number of H-

bond donors/acceptors, and PSA] can be calculated *in silico* by commercial programs [available in 2011] that might be helpful in characterizing the physiochemical properties of a compound before it is even synthesized.” *Id.* As of 2011, based on my own experience, R&D departments had commercial software (such as the industry-standard drawing package, ChemDraw) and proprietary models that calculated these properties and would use them to predict other compound properties such as solubility. In 2011, it was routine to consider the physicochemical properties of compounds to be synthesized to help prioritize those with the potential for good PK properties.

33. Critically, a POSA reading the '803 Patent and identifying additional ibrutinib-like BTKIs for use in the claimed method would have understood the potential impact of physicochemical properties on absorption and taken that impact into account by applying widely-accepted compound design guidelines. *See* EX2040.0040. In particular, as Petitioner's expert Dr. Showalter agrees, a POSA would have been aware of the “Lipinski rule of five,” which “defined a widely accepted concept of drug-likeness on the basis of cutoff values for key physicochemical properties.” *Id.*; *see* EX2018, 50:10-51:12. Lipinski highlighted the upper limits for properties likely to impact the chances of good oral bioavailability for small molecules. These guidelines identified that “compounds are likely to show poor absorption when their molecular weight is >500 Da, their

calculated octanol/water partition coefficient  $\log P$  is  $>5$ , the number of their H-bond donor functions is  $>5$ , and the number of their H-bond acceptor functions is  $>10$ .” EX2040.0040. In addition, for passive transport across cell membranes, a POSA would have sought to limit polar surface area to less than about 120 Å. *Id.*

34. Petitioner’s own cited post-2011 reference acknowledges what a POSA would have been aware of in 2011, stating that “[p]hysiochemical properties, such as molecular weight, size, partition coefficient, acid dissociation constant and solubility have a great impact on pharmacokinetics of traditional small molecule drugs and [are] substantially used in development of small drugs.” EX1099.001. Additionally, Petitioner’s cited reference further explains that for traditional small molecule drugs (in contrast to protein drugs), it is possible to “predict and control” certain physiochemical properties with “Lipinski’s rule of five and subsequent work by other authors.” *Id.*

35. In fact, in 2011, a POSA reading the ’803 Patent to consider Z’ scaffolds for the ibrutinib-like irreversible BTKIs for use in the claimed method would have known that specific functional groups and structural features could be incorporated to improve its solubility and, therefore, absorption. *See* EX2040.0040. For example, a POSA would have understood that certain ionizable groups and increased saturation (i.e., less rigid, more flexible structural features) had been used to address solubility concerns. EX2040.0040-0041; EX2052.0001-

0004. Petitioner's own post-2011 publication acknowledges these structural impacts on solubility and PK. EX1053.002 ("Possibly due to the rigidity of the tricyclic core, the pharmacokinetics (PK) properties of [certain compounds] in rat were consistently poor . . . As we reasoned the rigid conformation of the tricycle core led to the poor pharmacokinetics (PK) property . . ."); *id.* at .004 (acknowledging "[r]educing a molecule's overall lipophilicity is a useful approach for improving oral absorption").

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

37. A POSA considering candidate ibrutinib-like irreversible BTKIs would have understood that for a covalent inhibitor to be effective, it needs to achieve sufficient exposure levels to covalently bind BTK, with exposure levels being driven by absorption (largely determined by solubility and permeability) and metabolic stability. However, a POSA would have understood that for the irreversible BTKIs of the claims, the rate of metabolic clearance is less critical because as the specification teaches, these irreversible inhibitors act by covalently binding and occupying BTK. EX1001, 137:9-26, 138:33-43. Once covalently bound to BTK, “[t]he prolonged duration of drug action on the target effectively uncouples the pharmacodynamics of the drug from the pharmacokinetics of exposure, as target inhibition persists after the drug has been cleared.” EX2059.0006; EX1049.001 (describing irreversible inhibitors have “longer duration of action” compared to non-covalent inhibitors because they “do not readily dissociate and the inhibition continues even after the inhibitor leaves the circulation”); EX1049.001 (explaining that irreversible inhibitors “need not exhibit prolonged circulating blood levels to achieve a desired effect”). The below figure explains what a POSA in 2011 would have understood from the specification about why *in vivo* metabolic clearance is less important for an ibrutinib-like irreversible BTKI than a non-covalent inhibitor. See EX2034, Fig. 14 (.0008). As the figure shows, target inhibition persists for longer for the irreversible inhibitor as

compared to the non-covalent inhibitor because the covalently-bound compound continues to inhibit the target and is not impacted by metabolism in the same manner as the unbound reversible inhibitor. *See id.*

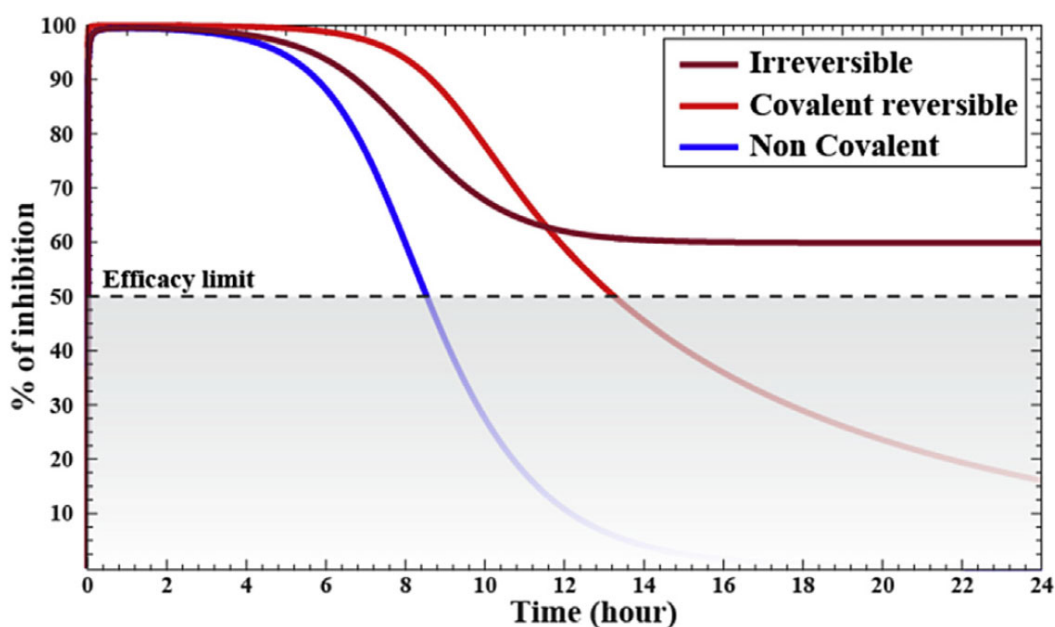


**Fig. 14.** Simulation (using Matlab) of the effect of pharmacokinetics (PK) on the fractional occupancy of a given target by different types of inhibitors. The parameters are such that  $k_{in}$  and  $k_{out}$  are  $1 \text{ h}^{-1}$ . Non-covalent inhibitor:  $K_i = 1 \text{ nM}$ ,  $k_f = 1.107 \text{ s}^{-1} \text{ M}^{-1}$ . Reversible covalent inhibitor:  $k_f = 1.107 \text{ s}^{-1} \text{ M}^{-1}$ ,  $k_1 = 0.01 \text{ s}^{-1}$ ,  $k_2 = 0.1 \text{ s}^{-1}$ ,  $k_2 = 0.01 \text{ s}^{-1}$ . Irreversible inhibitor:  $k_f = 1.107 \text{ s}^{-1} \text{ M}^{-1}$ ,  $k_1 = 0.01 \text{ s}^{-1}$ ,  $k_2 = k_{inact} = 0.1 \text{ s}^{-1}$ ,  $k_2 = 0 \text{ s}^{-1}$ .

*See id.*

38. Here, the fact that the ibrutinib-like irreversible BTKIs of the claims covalently bind BTK means that inhibition persists even after the remaining unbound drug has been cleared. *See* EX2059.0006. Indeed, preclinical PK data showed that ibrutinib does not have high exposures levels for a sustained period of time. *See* EX2042. And yet, the '803 Patent describes ibrutinib to be

therapeutically effective to treat CLL/SLL in patients. *See, e.g.*, EX1001, 135:63-67, 139:48-140:25, 142:55-143:10, 143:27-36, 147:35-40. Ibrutinib's successful use as an FDA-approved drug confirms that an optimized PK profile is not necessary for an ibrutinib-like irreversible BTKI to have a therapeutic effect.

39. Indeed, Petitioner admitted that suboptimal PK for a covalent inhibitor would not prevent *in vivo* efficacy in its post-2011 publication, explaining that a covalent inhibitor may have lower bioavailability and higher clearance than a traditional inhibitor and still have prolonged activity in an *in vivo* pharmacodynamic (PD) model. *See* EX1053.002. In its publication, Petitioner explained that “[f]or traditional reversible inhibitors, a drug candidate target profile in terms of pharmacokinetics would have high oral bioavailability, low clearance, and reasonable half-life, ***while a covalent inhibitor can persist in vivo PD even after it has disappeared.***” *Id.* (emphasis added).

40. Moreover, as Dr. Showalter acknowledged, in June 2011, a POSA would have understood certain techniques and strategies could enhance low bioavailability. *See* EX2018, 89:13-90:3. Again, the '803 Patent's teaching that the practically insoluble ibrutinib was able to effectively inhibit BTK in patients provided significant validation that compounds with similar structural features to ibrutinib (i.e., phenoxyphenyl, linker-warhead, H-bond donors/acceptors sufficient for hinge interactions as required by the '803 Patent claims) would similarly have

sufficient PK properties to inhibit BTK in patients. I have not seen evidence that a BTKI structurally similar to ibrutinib would not be able to be administered to a patient to inhibit BTK.

**VIII. DR. SHOWALTER'S OPINION ON SUBSTITUTING Z' FOR USE IN THE COMPOUNDS OF THE '803 PATENT CLAIMS IS CONTRARY TO PRINCIPLES OF SMALL MOLECULE DRUG DESIGN**

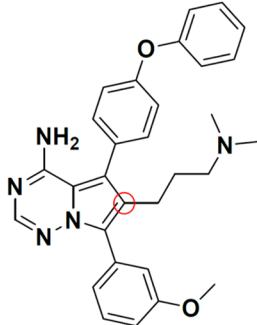
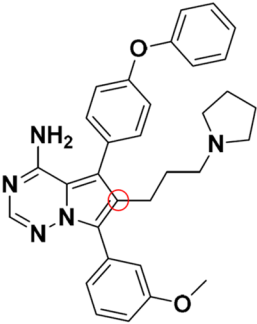
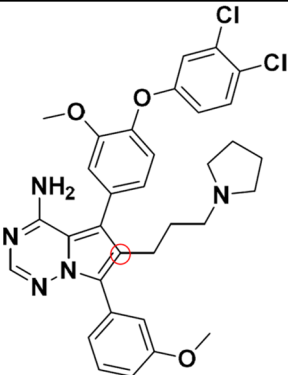
41. Dr. Showalter opines on the number of potential Z' scaffolds covered by the Challenged Claims of the '803 Patent. In particular, Dr. Showalter opines that each "fused heterocyclic ring system[]" "allow[s] for a vast number of structural species due to the diversity of the optional substitutions present on the ring system." EX1003, ¶159. To arrive at his large number of potential Z' scaffolds, Dr. Showalter opines that multiple substituents can be added to the ring system and that "the number of substitutions permitted by 'optionally substituted' *can be potentially infinite*." EX1003, ¶162 (emphasis added); *see also* EX1003, ¶¶168-174. Because the claims require the compounds to function as orally administered drugs that inhibit BTK, I disagree.

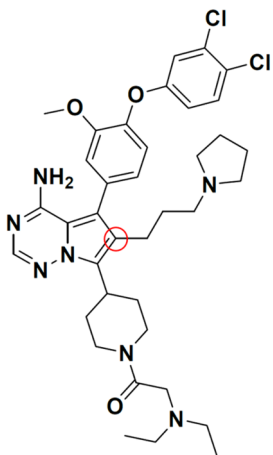
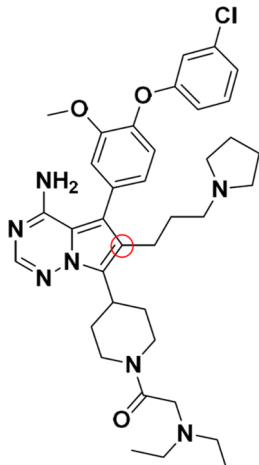
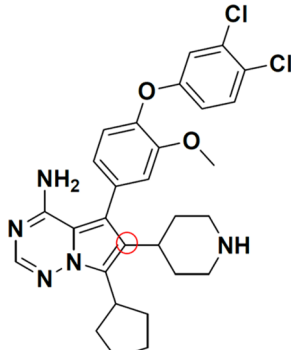
42. As I have explained, in June 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have accounted for widely-accepted small molecule design guidelines (e.g., Lipinski's rule of five) and the known structure-function relationship for ibrutinib-like BTKI binding to BTK. EX2001. As discussed above and as I understand Dr. Eck

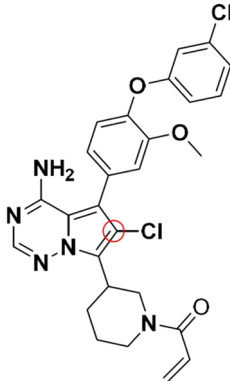
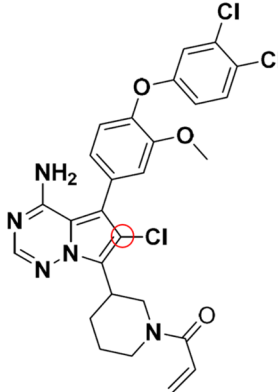
discusses in more detail, the Marcotte crystal structure of a compound having ibrutinib-like binding to BTK would have provided significant guidance in how a compound with ibrutinib's structural features would bind to BTK. *See* EX2001.0003-0005, Fig. 2D (.0003) (BTK-KD/B43, PDB: 3GEN); *see also* EX2018, 43:20-46:11. This structural information, including the understanding that the Z' scaffold would be involved in H-bonding to the BTK hinge residues, and the general guiding principles of small molecule drug design would have directed a POSA reading the '803 Patent in the selection of substitutions for the Z' scaffold to use in the claimed method.

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.

| Example | Name                                                                                                                              | Structure                                                                            | IC50 (nM) |
|---------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------|
| 16(1)   | 6-(3-(dimethylamino)propyl)-7-(3-methoxyphenyl)-5-(4-phenoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine                           |    | 5.8       |
| 16(2)   | 7-(3-methoxyphenyl)-5-(4-phenoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine                         |   | 6.5       |
| 16(3)   | 5-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-7-(3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine |  | 12        |

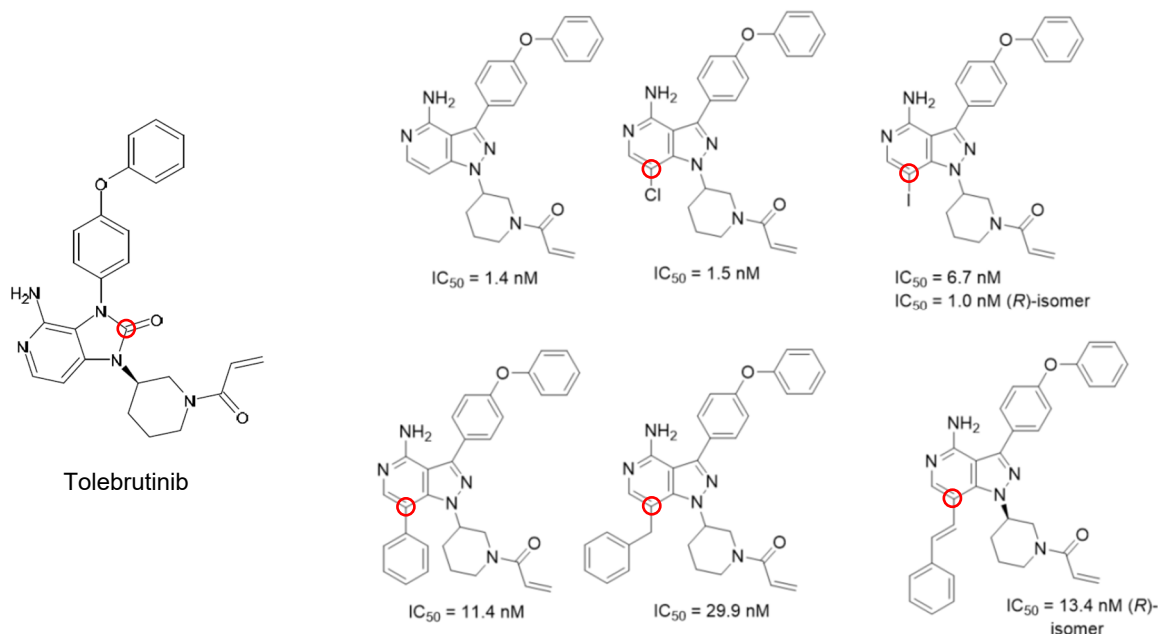
| Example | Name                                                                                                                                                               | Structure                                                                            | IC50 (nM) |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------|
| 21      | 1-(4-(4-amino-5-(4-(3, 4-dichlorophenoxy)-3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)-2-(diethylamino)ethanone |    | 16        |
| 21(1)   | 1-( 4-(4-amino-5-(4-(3-chlorophenoxy)-3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f] [1,2, 4]triazin-7-yl)piperidin-1-yl)-2-(diethylamino)ethanone   |   | 22        |
| 25(1)   | 7-cyclopentyl-5-(4-(3, 4-dichlorophenoxy)-3-methoxyphenyl)-6-(piperidin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine                                                  |  | 62        |

| Example | Name                                                                                                                               | Structure                                                                           | IC <sub>50</sub> (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-1-yl)prop-2-en-1-one |  | 2                     |

EX2027.0063-0064 (Examples 16(1), 16(2), 16(3)), .0066 (Examples 21, 21(1)), .0068-0069 (Example 25(1)), .0073-0075 (Examples 32, 32(1)), .0091 (disclosing IC<sub>50</sub> values).

44. Second, post-priority structures further show where a POSA in 2011 would have understood limited substitutions may be tolerated on Z'. As shown in the figure below, examples of these locations (circled in red) can be seen in tolebrutinib with its carbonyl (=O) substituent off the 5-membered ring of Z' and the series of BTKIs identified by Dr. Showalter from EX1036, where the 6-membered rings are substituted at a location that projects toward a solvent-exposed

area off the ATP-binding site as a POSA would have understood from Marcotte (see EX1052.002 (Fig. 2); EX2001).



EX1003, ¶49 (annotated), ¶76 (annotated) (citing EX1036). Again, as can be seen from the above examples, these substitutions to the Z' scaffold resulted in potent BTKIs.

45. Third, in 2011, a POSA reading the '803 Patent would have understood that making substitutions at other positions would likely result in a steric clash and prevent binding to the BTK hinge region. The potential for such a clash and interference with hinge-binding could readily be visualized by docking potential compounds in the Marcotte structure, as I understand Dr. Eck discusses in more detail. See EX2001. Dr. Showalter's calculations are flawed because he incorrectly proposes substitutions at locations on Z' that a POSA would have

recognized as interfering with the ability to make the appropriate H-bonds to the hinge and bind to BTK. *See, e.g.*, EX1003, ¶168. And, as he admits, in considering the compounds with the Challenged Claims he did not analyze whether any of the proposed Z' scaffolds would be more or less likely to be functional inhibitors of BTK if they were used as a scaffold in the compounds of the claims. EX2018, 163:8-17. As I understand Dr. Eck discusses in detail, the structural information available to a POSA from Marcotte would have allowed a POSA to recognize the compounds expected to bind to BTK.

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.

**IX. CONCLUSION**

47. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. Further, I am aware that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001. I declare under penalty of perjury that the foregoing is true and correct.

Executed on 6 AUG 2024 (date), in BOSTON, MA (city, state).

  
\_\_\_\_\_  
David A. Scott, Ph.D.