

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

Pharmacyclics LLC
Patent Owner.

PGR2024-00009
U.S. PATENT NO. 11,672,803

REPLY DECLARATION OF JAMES M. VEAL, PH.D.

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. QUALIFICATIONS	3
III. RELEVANT LEGAL STANDARDS.....	9
A. Written Description	9
B. Enablement	10
C. Claim Construction.....	11
IV. RESPONSE TO DR. ECK’S AND DR. SCOTT’S DEFINITION OF PERSON OF ORDINARY SKILL IN THE ART	12
V. THE 803 PATENT.....	17
A. Challenged Claims.....	17
B. Overview of the Specification	21
1. The Specification Does Not Disclose that the Linker-Warhead Will Necessarily Result In Covalently Binding Cys481.....	22
2. The Specification Does Not Disclose that the Phenoxyphenyl Will Necessarily Result In Selectively Binding to Btk’s “Back Pocket”	23
3. The Specification Does Not Disclose that Z’-scaffolds Will Necessarily Result In 1-3 Hydrogen Bonds with Btk’s Active Site.....	24
VI. GENERAL KNOWLEDGE IN THE FIELD.....	27
A. The State of the Art in 2011 Provided Little More Information than the 803 Patent	27
1. Marcotte’s Teachings Were Limited.....	27
2. Ghose’s Teachings Were Limited.....	31
3. Pan’s Teachings Were Limited	32
4. Akritopoulou-Zanze’s Teachings Were Limited	33
5. The Available Z’-Scaffolds Were Limited or Irrelevant	35
a) 820 Patent.....	37
b) 303 Publication and EX2050	37
c) 960 Publication	38
d) 10 PDB Structures.....	38

e) Waterson	39
6. Zanutrutinib Was Not Available in 2011 And Confirms the Structural Diversity of the Claimed Genus.....	39
B. Scaffold Swapping.....	46
1. Zhang’s Teachings Were Limited.....	47
2. Ghose’s Teachings Were Limited and Show That Testing is Required to Determine Binding of a Target Kinase	49
3. Akritopoulou-Zanze’s Teachings Show That Testing is Required to Determine Binding of a Target Kinase	50
4. Gracias’s Teachings Show That There Was a Focus on Developing Adenine Mimetic Kinase Inhibitors and Testing is Required to Determine Binding of a Target Kinase	51
5. Pan’s Teachings Show That Testing is Required to Determine Binding of a Target Kinase	53
C. Modeling/Docking	53
1. Modeling/Docking Software Available in 2010/2011	53
a) Modeling Results Were Highly Variable and Depended on User Set Parameters.....	57
b) Modeling Would Not Have Accurately Predicted Irreversible Inhibition of Btk	59
2. Modeling/Docking of Specific Structures.....	63
a) Structures Modeled by Dr. Eck.....	63
b) Structures Modeled with Reported IC ₅₀ Values.....	70
c) Z’-Scaffolds Modeled	90
VII. CLAIM CONSTRUCTION	106
VIII. RESPONSE TO DR. ECK’S ASSERTIONS REGARDING WRITTEN DESCRIPTION.....	107
A. The Specification Does Not Provide Written Description Support for the Claimed Irreversible BTKIs	107
1. Independent Claims 1 and 8.....	107
a) No Common Structural Features for the Claimed Irreversible BTKIs	108

b) No Blaze Marks for Irreversible BTKIs	138
2. Dependent Claims	141
IX. RESPONSE TO DR. ECK'S ASSERTIONS REGARDING ENABLEMENT	141
A. The Specification Does Not Provide Enabling Support for the Challenged Claims	141
1. Independent Claims 1 and 8	142
a) Amount of Direction or Guidance Presented, Working Examples, Nature of the Invention	142
b) Quantity of Experimentation	144
c) Breadth of the Claims	147
d) Unpredictability of the Art, State of the Prior Art, Relative Skill of Those in the Art	149
2. Dependent Claims	150
X. DECLARATION	151

I. INTRODUCTION

1. My name is Jim Veal. I have been retained by Petitioners BeiGene USA, Inc. and BeiGene, LTD. (“Petitioner” or “BeiGene”) as an independent expert witness in the above-captioned post grant review (“PGR”), in which Petitioner requests that the U.S. Patent and Trademark Office cancel as unpatentable independent claims 1 and 8, and dependent claims 2-7, 12 and 20 (“Challenged Claims”) of U.S. Patent No. 11,672,803 (“the 803 Patent”).

2. I provide this declaration to respond to certain issues raised in the declarations of Dr. Michael J. Eck (EX2010) and Dr. David A. Scott (EX2012). Based on my experience, I disagree with Dr. Eck that the Challenged Claims are entitled to a priority date of June 3, 2011 and are patentable under the written description and enablement requirements of 35 U.S.C. § 112(a).

3. I understand from Dr. Showalter’s Declaration that the Structural Limitations of the Challenged Claims cover potentially billions of structurally diverse Bruton’s tyrosine kinase inhibitors (“BTKIs”). EX1003, ¶¶96, 141-142. I also understand that Dr. Eck agrees that the Z’-scaffold¹ of the Challenged Claims

¹ Z’-scaffold is the same as Z’-structure in the Petition: “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.” Petition at 27-28.

itself encompasses billions of structures. *See* EX1110, 42:21-43:18, 46:11-47:6. I understand that Patent Owner (“PO”) has criticized Dr. Showalter’s calculations, and that Dr. Showalter has concluded that the Structural Limitations are still broadly directed to at least 4 million species even when accounting for PO’s criticisms. EX1105, ¶¶31-35. In any event, my opinions are the same whether the Structural Limitations encompass either potentially billions or 4 million structurally diverse species. *Id.*² In my opinion, the specification would not allow a person of ordinary skill in the art (“POSA”) to visualize or recognize the claimed genus encompassing structurally diverse members that irreversibly inhibit Bruton’s tyrosine kinase (“Btk”) by covalently binding Cys481 or another residue of Btk. Further, in my opinion, a POSA would be required to engage in undue experimentation to make and use the full scope of the Challenged Claims.

4. I further disagree with Dr. Eck that modeling capabilities available in 2011 along with what was known in the art and disclosed in the 803 Patent could have in any way allowed for accurate prediction of covalent binding of Btk for the

² I understand that Dr. Showalter has also concluded that, even accounting for PO’s criticisms, the Structural Limitations of claims 12 and 20 are still broadly directed to over 1.7 million species. EX1105, ¶34 n.4. Regardless, my opinion that the 803 Patent lacks sufficient written description and enablement support remains the same.

full scope of compounds that satisfy the Structural Limitations of the Challenged Claims in 2011 (or even today). The 803 Patent does not mention the use of molecular modeling or computational chemistry techniques. Additionally, even if modeling may have been used to provide some insight regarding which structures are less likely to irreversibly inhibit Btk, modeling the full scope of BTKIs that satisfy the Structural Limitations of the Challenged Claims would have required extensive trial and error testing and could not have accurately predicted whether such BTKIs would irreversibly inhibit Btk. Rather, significant, experimental testing would have been required to determine which compounds satisfying the Structural Limitations of the Challenged Claims would in fact irreversibly inhibit Btk. That I do not specifically address other opinions of Dr. Scott or Dr. Eck is not intended to imply that I agree with such opinions.

5. I have reviewed the documents referenced in this declaration, including Dr. Showalter's Opening and Reply Declarations (EX1003, EX1105). I understand they have been submitted as exhibits in conjunction with BeiGene's Petition, Pharmacyclics' POR, or BeiGene's Reply.

II. QUALIFICATIONS

6. I have expertise in small molecule drug discovery, including kinase inhibitors, for the treatment of diseases such as cancer and inflammatory disorders.

I have contributed to and led drug discovery efforts at both large pharma and biotech. I have experience in the oversight and management of small molecule drug discovery programs from the target evaluation stage through lead optimization, Investigational New Drug (“IND”) application filing, and entry into clinical trials. I have been a part of interdisciplinary project teams where my role was as the project team computational chemist, and where I worked closely on a day-to-day basis with other team members, including medicinal chemists, biochemists, cell biologists, and pharmacokinetic specialists. These drug discovery projects have included multiple kinase family targets, including for example, CDK2, P38, CDK4, VEGFR2, HER2, and PLK1. Thus, I believe I have good knowledge of how the pharma industry conducted drug discovery efforts targeting protein kinases such as Btk and more specifically how molecular modeling was utilized as part of those drug discovery efforts.

7. Currently I am the Chief Scientific Officer of 858 Therapeutics, a venture capital backed biotechnology company, which I co-founded in 2019. My role at 858 Therapeutics has included managing cross-functional drug discovery efforts leading to the discovery of ETX-19477 (PARG inhibitor) and ETX-20052 (QPCT/L inhibitor).

8. In 1983, I received a B.A. in Chemistry with Specialization in Biological Sciences from Duke University. In 1989, I received a Ph.D. in Molecular Biophysics from The Florida State University – The Institute of Molecular Biophysics. I received formal training as a physical chemist, computational chemist, and NMR spectroscopist and wrote my dissertation on the interaction of DNA with the complex bis-(1,10-phenanthroline) copper(I).

9. In 1992, I completed my postdoctoral fellowship in computational chemistry at GlaxoSmithKline, and my formal training in computational chemistry is reflected by multiple publications. See J.M. Veal, and F.K. Brown, “Investigation of Thioformacetal Modified Nucleic Acids by Quantum Mechanics, Molecular Mechanics, and Molecular Dynamics,” *J. Amer. Chem. Soc.* 1995; 117(7), 1873-1880; J.M. Veal, X. Gao, and F.K. Brown, “A Comparison of DNA Oligomer Duplexes Containing Formacetal and Phosphodiester Linkers using Molecular Dynamics and Quantum Mechanics,” *J. Amer. Chem. Soc.* 1993; 115(16), 7139-7145; Radhakrishnan, I., Patel, D., Veal, JM, and Gao, X., “Solution Conformation of a G.TA Triple in an Intramolecular Pyrimidine.Purine.Pyrimidine DNA Triplex,” *J. Amer. Chem. Soc.* 1992; 114(17), 6913-6915.

10. From 1992-2003, I worked as a research investigator at GlaxoSmithKline. I contributed to drug discovery and lead optimization efforts

across multiple research programs and served as chemistry chair of the committee that was responsible for the evaluation of new kinase drug targets. I was a member and co-inventor on the discovery teams that identified development candidates directed at the inhibition of the kinases CDK2 and P38. Additionally, I was an integral member of discovery teams for three compounds that advanced to clinical trials, including pazopanib (Votrient), a VEGFR2/PDGFR inhibitor for which I am a co-inventor and that is FDA approved for the treatment of renal cell carcinoma; lapatinib (Tykerb) a HER2/EGFR inhibitor that is FDA approved for the treatment of breast cancer; and GSK461364, a PLK1 inhibitor for which I am a co-inventor. I led modeling efforts for protein kinases, G protein-coupled receptors, and other macromolecules, and supervised multiple senior computational chemists. I was responsible for using computational chemistry techniques to design a kinase focused screening library (~20,000 compounds) that was derived from the larger GSK compound collection and compounds available for purchase from commercial vendors; this focused kinase library was used as an initial chemical screen to identify starting point inhibitors for new kinase targets of interest at GSK. I developed expertise and obtained significant experience in using structure aided drug discovery techniques and developing software applications (C, C++, Java, Perl, PHP, Python, HTML, SQL).

11. From 2003-2008, I worked at Serenex, Inc. as a Director of Structural Chemistry and Informatics (2003-2005) and Senior Director of Structural Chemistry and Informatics (2005-2008). I contributed to drug discovery and lead optimization efforts across multiple research programs including HSP90, DHFR, and Aurora kinase, had a primary leadership role in Serenex's Hsp90 discovery effort, and co-invented SNX-5422, which advanced to phase 2 clinical trials in cancer. I was responsible for the analytical chemistry, computational chemistry, and informatics groups, including guiding the analytical chemistry group's role in pharmacokinetic analysis and leading the mass spectrometry component of Serenex's proteomics effort. I developed advanced chemoinformatic techniques to create a repository of existing compounds for a proteomics-based screening platform and designed and led the implementation of an advanced chemical registry and biology records database that was specialized for proteomics data searching and interfacing with LIMS systems workflow.

12. From 2009-2011, I served as Vice President of Research at Pamlico Pharmaceutical Inc. I led cross-functional research efforts for drug discovery including Hedgehog, Nedd8, TGR5, and GPR120 programs. I co-invented the Hedgehog inhibitor SHR-1539 (PI-722), which advanced to clinical trials in China.

13. From 2012-2015, I worked at Quantice! Pharmaceuticals Inc. as a Distinguished Research Fellow (2012-2015) and Executive Director of Celgene Quantice! Research (subsidiary of Celgene) (2015). I had a senior leadership role in drug discovery research efforts, supervised biochemistry and cell pharmacology groups, and co-invented trotabresib (CC-90010, BRD4 inhibitor) and pulrodemstat (CC-90011, LSD1 inhibitor).

14. In 2015, I co-founded Jecure Therapeutics. From 2015-2019, I served as Chief Scientific Officer. I managed cross-functional drug discovery efforts leading to the discovery of JT-194 and JT-522 as development candidates for the inhibition of NLRP3 and treatment of inflammatory disorders.

15. I am a co-inventor on 55 patent applications, which include claimed inventions directed to kinase inhibitors and tyrosine kinase inhibitors.

16. I have authored or coauthored 47 publications. These include, for example, “Practical Use of Computational Chemistry in Kinase Drug Discovery,” in *Kinase Inhibitor Drugs*, “Binding mode of the 4-anilinoquinazoline class of protein kinase inhibitor: X-ray crystallographic studies of 4-anilinoquinazolines bound to cyclin-dependent kinase 2 and p38 kinase,” and “Kinases” in *Methods and Principles in Medicinal Chemistry: Protein Crystallography in Drug Discovery*. I have served as a reviewer for Journal of the American Chemical Society,

Proceedings of the National Academy of Sciences, Journal of Physical Organic Chemistry, Biochemistry, and Biorganic and Medicinal Chemistry Letters.

17. My curriculum vitae (EX1107) provides further information regarding my professional experience, expertise, and presentations.

18. I am being compensated at my standard rate of \$500/hour. My compensation is in no way contingent upon my opinions or the outcome of the proceeding.

III. RELEVANT LEGAL STANDARDS

19. I am not an attorney, and therefore my understanding of patent law and the legal standards set forth in this declaration is based on explanations provided to me by counsel.

A. Written Description

20. To satisfy the written description requirement of 35 U.S.C. § 112, I understand that the specification must reasonably convey to those skilled in the art that the inventor had possession of the claimed subject matter. To demonstrate possession, I understand that the specification must provide sufficient description of the claimed subject matter across the full scope of the claim.

21. I further understand that an “*ipsis verbis*” or verbatim disclosure is not required to satisfy the written description requirement. Where, however, there is no

verbatim disclosure, I understand that functionally defined genus claims require a written description in the specification such that a POSA would have been able to visualize or recognize the claimed genus by searching for blaze marks in the specification that guide a skilled artisan to the claimed genus.

22. Alternatively or in addition, I further understand that functionally defined genus claims require a written description in the specification that will show either a representative number of species to demonstrate possession of the full 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 full scope of the genus (as distinguished from structures that will not possess the claimed property).

B. Enablement

23. To satisfy the enablement requirement under 35 U.S.C. § 112, I understand that the specification of a patent must teach a POSA how to make and use the full scope of the claimed invention without undue experimentation. I understand that this enabling disclosure must be sufficient to meet this requirement across the full scope of the claims.

24. I further understand that determining whether the requisite amount of experimentation is undue may include consideration of: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3)

the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

C. Claim Construction

25. I understand that the numbered paragraphs at the end of the disclosure of a U.S. Patent are the patent “claims” that define the metes and bounds of the claimed invention. I understand that certain claims of the 803 Patent are being challenged in the present PGR proceeding.

26. I have been informed that, in this proceeding, the Board must determine the scope of the claims by giving the claims their ordinary and customary meaning in light of the specification, as the claims would be interpreted by a POSA.

27. I understand that patent claims generally include a “transitional” term or phrase, such as “consisting” or “comprising,” which may connect the preamble of the claim to the body of the claim. I have been informed that if a claim uses the term “consisting” as a transition term, that means that the claim is a “closed” claim, which means that the claim is limited to the claim features that follow the transition term and nothing else. On the other hand, I understand that the transition term “comprising” denotes an “open” claim, which means that the claim is not limited to

only the features recited in the claim, but could encompass the listed elements as well as other unrecited elements.

IV. RESPONSE TO DR. ECK'S AND DR. SCOTT'S DEFINITION OF PERSON OF ORDINARY SKILL IN THE ART

28. In responding to Dr. Eck and Dr. Scott, I have been asked to review the 803 Patent from the perspective of a member of the POSA team as of June 2011.

29. 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.

30. I understand that PO and its experts, Dr. Scott and Dr. Eck, agree with Petitioner’s definition of clinical member. EX2012, ¶12; EX2010, ¶125. I also understand that they disagree with the definition of a chemist member. *Id.* Instead, they propose that the POSA team ***must*** 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 relationship (“SAR”)] of kinase inhibitors,***” and ***could optionally*** include an additional member “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.” EX2012, ¶¶12-13; EX2010, ¶¶125-126 (emphasis added). I understand that Dr. Scott testified that either (1) working as a medicinal chemist on a single kinase project or (2) having experience in modeling can be sufficient training to qualify as a POSA under his definition. EX1117, 55:7-56:5. Therefore, under PO’s definition, I can accurately represent the views of such a member of the POSA team based on my education, training, and experience with respect to modeling. Specifically, I am formally trained as a computational chemist, have used computational tools for 33 years, and have myself performed modeling on small molecules in over 10 kinase drug discovery projects. Even though I have had a senior leadership role in my more recent companies, I have continued to actively perform molecular modeling at those companies.

31. I understand that PO submitted an expert declaration from Dr. Eck, who also contends to qualify as a POSA because he has “developed and expanded on [SAR] for kinase inhibitors.” EX2010 ¶127. I understand Dr. Eck also has some experience in modeling and contends that “virtual docking and modeling tools would have ruled out inappropriate compounds.” EX1110, 17:15-19:1; EX2010 ¶219. Notably, I understand that Dr. Eck has not taken any formal courses or received any formal training with respect to ligand screening or docking software. *See* EX1110, 13:25-14:3, 14:20-15:3, 15:10-13, 15:20-24. I also understand that while Dr. Eck’s

lab uses computational chemistry tools, Dr. Eck does not himself use these tools and typically relies on scientists in his lab who have formal training in computational modeling. *Id.*, 17:22-18:3, 18:20-19:1. In fact, when Dr. Eck performed modeling for this case, he consulted with a computational chemistry post-doc in his lab who he acknowledged has more expertise in computational chemistry than he does. *See id.*, 19:5-21:15.

32. To the extent that PO's definition of a POSA *requires* expertise in modeling, I disagree. Indeed, the 803 Patent never mentions the use of molecular modeling or computational chemistry and modeling has limited predictive value in this context. *See infra* Sections VI.C.1, VIII.A.1.a)(5).

33. For kinase drug discovery projects at pharmaceutical companies, the goal is to identify one or more optimized lead compounds to advance first to preclinical (GLP) toxicology studies and then to clinical testing. *See* EX1117, 101:11-20; EX1105, ¶10. Typically, the first step of such a project involves screening one or more libraries of thousands to hundreds of thousands of compounds that the company has already synthesized or purchased. *Id.* This would involve running enzyme assays to test all compounds in the library for inhibition against the kinase of interest. *Id.* This is consistent with Dr. Scott's experience when working at AstraZeneca. EX1117, 33:12-33:19 ("In the case of a kinase inhibitor project, a

company might have a collection of compounds that have shown activity against other kinases and that would often be a very good starting point for a new project.”), 33:20-34:13 (“I believe the entire AstraZeneca collection might have been hundreds of thousands of compounds. I think we did a more focused screen on compounds that were likely to have confirmed the compounds we thought could have a chance of activity against JAK2 and that would have been a subset of the larger collection”); *see also id.*, 32:14-33:44, 37:5-38:4. In my experience in drug discovery, modeling may be used to reduce or filter the total number of compounds to be screened to identify hits, but modeling used in this context should be considered as improving the efficiency of the screening process and in no way be considered predictive of affinity without subsequent biological testing.

34. I understand that after active compounds (“hits”) have been identified in assays, medicinal chemists will make additional compounds by optimizing those hits in order to improve their binding affinities and other pharmacological activities for the purpose of identifying the “lead” compound(s) for pre-clinical and clinical testing. EX1105, ¶11. In my experience, modeling may be used during such optimization efforts to better understand the chemical interactions between the kinase inhibitor candidates and the target kinase complex in order to design analogs with improved potency. This is also consistent with Dr. Scott’s experience.

EX1117, 34:14-35:5 (Dr. Scott testifying that he has never worked with a modeler “as part of the initial screening effort” because “[i]t wouldn’t have made sense to do that” when “[t]he value of modeling is, once you have identified -- one of the values of modeling is when you have identified a specific compound of interest.”), 36:21-38:15 (Dr. Scott testifying that working with a modeler “can be very valuable as soon as you’ve identified an active compound” and “[o]n the kinase projects I worked on at AstraZeneca, we would typically engage a modeler once we had identified an active inhibitor”). Even in this step of the process, if a compound is suggested by modeling and synthesized, an enzyme or related assay would always be run to measure inhibition against the kinase of interest.

35. Unlike in a drug discovery project, I understand that the question presented here is not to identify the best compounds within the claimed genus. Indeed, the Challenged Claims do not require any particular potency or efficacy. Rather, I understand that the relevant questions are: (1) whether a POSA could envision *the full scope* of the claimed genus—*i.e.*, whether a POSA could envision which compounds among those that satisfy the Structural Limitations would irreversibly bind Cys481; and (2) whether a POSA could make and use the *full scope* of the claimed genus without undue experimentation—*i.e.* whether a POSA could identify which BTKIs among those that satisfy the Structural Limitations would

irreversibly bind Cys481 without trial-and-error or undue experimentation. *See supra* Section III.A-B.

36. In my opinion, while modeling may provide some insight into which molecules are less likely to inhibit a target kinase, modeling does not always accurately predict inhibition of a target kinase and may contradict experimental results. *Infra* Section VI.C.2.b). In my experience, a POSA would never rely on modeling alone to assess whether a potential inhibitor would covalently bind Cys481 or another residue of Btk. Rather, running assays to measure the inhibition of the target kinase or IC₅₀ value is a necessary step. This is consistent with Dr. Scott's experience. EX1117, 40:18-41:13 (Dr. Scott testifying that he "[w]ould . . . run an assay to confirm that the inhibitor actually inhibits the target" because "it's valuable to validate predictions of modeling with data.").

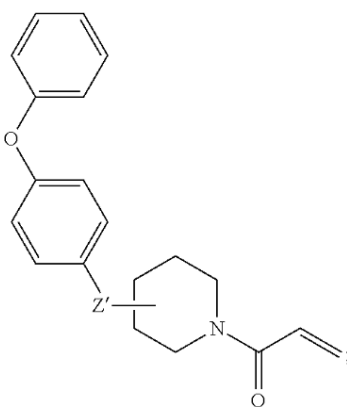
37. In my opinion, the Challenged Claims are unpatentable under any definition of a POSA.

V. THE 803 PATENT

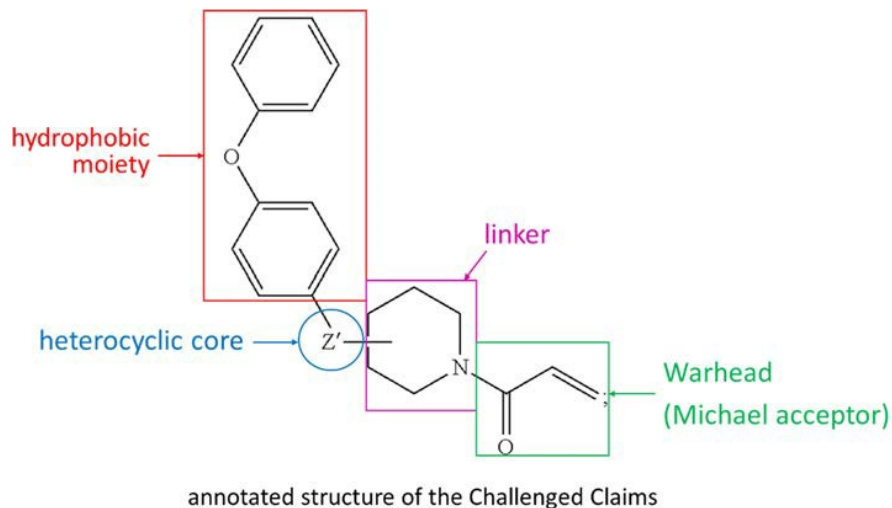
A. Challenged Claims

38. I understand that the Petition challenges independent claims 1 and 8, and dependent claims 2-7, 12 and 20 of the 803 Patent. EX1098 is a claim listing that enumerates each limitation of the Challenged Claims.

39. I understand that the Challenged Claims include “Structural Limitations,” which require that the irreversible BTKI is a “small organic molecule” that has the skeletal structure depicted below, “wherein Z’ is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms” and “wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom.” Petition at 28-29 (defining the Structural Limitations and Functional Limitations of the Challenged Claims).



40. The claimed structure of the Challenged Claims includes four principal components (1) a hydrophobic moiety (*i.e.*, phenoxyphenyl), (2) a heterocyclic core (*i.e.*, Z’, optionally substituted fused heterocyclic ring system), (3) a linker, and (4) a terminal warhead containing the acrylamide Michael acceptor.



41. Dr. Eck used “ibrutinib-like” to mean “irreversible BTKIs having the structural features (based on ibrutinib) recited in the claims: fixed phenoxyphenyl and linker-warhead substituents attached to a central 5:6 heterocyclic scaffold having 2-4 nitrogen heteroatoms, with at least one nitrogen in each ring.” EX2010, ¶39 n.1. In other words, Dr. Eck uses “ibrutinib-like” to refer to any compound that satisfies the Structural Limitations. This definition is misleading. I understand that PO contends that the specification provides written description and enablement support as of June 2011 based on non-provisional patent application, U.S. Patent Application No. 13/153,317 (“317 Application”), the specification of which is identical to the 803 Patent. The specification, however, does not have any verbatim disclosure of the generic Markush formula of the Challenged Claims, nor does it include any definition of “ibrutinib-like.” Therefore, the Markush formula of the

Challenged Claims was not disclosed as of June 2011. Rather, the Markush formula of the Challenged Claims first appeared in 2023 in a claim amendment that PO submitted during the prosecution of the 803 Patent. Petition at 41 (citing EX1002.629). I understand that twelve other patents in the same family issued before the 803 Patent, all of which only claim ibrutinib. EX1003, ¶180 n.4.

42. I disagree that a POSA in 2011 (or even today) would have considered all compounds satisfying the Structural Limitations as ibrutinib-like and in fact a majority of them are not ibrutinib-like. In my opinion, a POSA reading the specification would consider “ibrutinib-like” as “irreversible BTKIs having fixed phenoxyphenyl and linker-warhead substituents and an amino group, which are attached respectively to the C1/N1 and C3/N3 positions of the 5-membered ring and the C4 position of the 6-membered ring of a fused 5:6 biaryl³ Z'-scaffold having 2-4 nitrogen heteroatoms, with at least one nitrogen in each ring. See EX1001, 47:24-48:53, 51:25-40, 56:5-25, 58:50-65, 62:44-63:40.

43. I understand that the Challenged Claims also include “Functional Limitations,” which require that the BTKIs perform the functions of, *inter alia*, (1) being “irreversible,” and/or more specifically, “form[ing] a covalent bond with

³ A POSA would have understood that this disclosure of biaryl in the specification refers to a ring system containing two heteroaromatic rings, and this is how I used the term “biaryl” here.

Cys481 of a Bruton's tyrosine kinase;" (2) "treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)" by administering a "therapeutically effective amount;" and (3) resulting in "lymphocytosis."

B. Overview of the Specification

44. I disagree with Dr. Eck regarding many aspects of what the specification of the 803 Patent discloses. Specifically, I disagree with Dr. Eck that the specification emphasizes or otherwise discloses the claimed linker-warhead, the claimed phenoxyphenyl, or hinge-binding substituents⁴ as common structural features that necessarily *will* result in irreversible inhibition of Btk. As Dr. Eck admitted, a POSA would know that even compounds that have each of these features may not irreversibly inhibit Btk because other characteristics of the compound, such as electrostatics, complementarity, and Van der Waals interactions, would impact the ability to covalently bind to Btk. EX1110, 156:15-157:14, 158:18-159:3, 160:2-21. That is, not all compounds that form hydrogen bonds and properly orient the fixed substituents will necessarily irreversibly inhibit Btk. Further, the specification does

⁴ Hinge-binding substituents are atoms or chemical groups capable of forming H-bonds to the kinase active site (hinge region). Formation of at least one such H-bond is generally recognized by a POSA as being required for kinase active site binding and inhibition.

not reveal any SAR⁵ information because it only discloses that ibrutinib irreversibly inhibits Btk.

1. The Specification Does Not Disclose that the Linker-Warhead Will Necessarily Result In Covalently Binding Cys481

45. Dr. Eck contends that the specification emphasizes the claimed linker-warhead and teaches that irreversibly binding Cys481 of Btk is important for selectivity. EX2010, ¶47. The specification, however, merely teaches that ibrutinib binds to Btk. The specification does not disclose that the presence of the claimed linker-warhead will necessarily result in all compounds satisfying the Structural Limitations covalently binding Cys481. The fact that ibrutinib has the claimed linker-warhead does not teach a POSA that all compounds satisfying the Structural Limitations will covalently bind Cys481.

46. Dr. Eck also contends that the specification discloses that the linker-warhead can approach Cys481 from different directions. EX2010, ¶54. Not so. The specification does not describe how ibrutinib allows for the linker-warhead to be in the precise and proper orientation required to covalently bind Cys481 via a chemical reaction. More importantly, the specification does not disclose that compounds satisfying the Structural Limitations may orient the linker-warhead in a way to

⁵ SAR is the same as structure-function relationship, as used by PO and Dr. Eck.

approach from different directions compared to ibrutinib to covalently bind Cys481 and irreversibly inhibit Btk. Nor does the specification teach which portion(s) of the compounds control or affect the linker-warhead's orientation. Indeed, proper orientation of the linker-warhead is controlled by the Z'-scaffold. EX1003, ¶58. Dr. Eck effectively admitted during his deposition that the Z'-scaffold is the nucleus of the compound that controls in which direction each substituent orients. EX1110, 93:2-18 ("one could start with the scaffold and use the structural information to determine where to place those substituents," *i.e.*, the phenoxyphenyl and linker-warhead).

47. And, while the specification discloses positional and chiral isomers of ibrutinib, it does not disclose from which direction the linker-warhead of those isomers approaches Cys481. Rather, the specification merely states that, "[i]n one aspect, provided herein is a compound selected from" and then lists a number of compounds among which four (compounds 4, 9, 13, 14) represent ibrutinib's positional and chiral isomers. EX1001, 80:37-62.

2. The Specification Does Not Disclose that the Phenoxyphenyl Will Necessarily Result In Selectively Binding to Btk's "Back Pocket"

48. Dr. Eck contends that the specification emphasizes the phenoxyphenyl and teaches its importance for selective binding, and that all of the depicted

irreversible BTKIs in the specification include a phenoxyphenyl, which selectively binds within Btk's hydrophobic back pocket. EX2010, ¶55 (citing EX1001, 65:10-80:35). But those depicted BTKIs that satisfy the Structural Limitations are merely ibrutinib or its positional/chiral isomers. Nowhere does the specification mention Btk's back pocket or disclose that the phenoxyphenyl will necessarily result in all compounds satisfying the Structural Limitations binding the back pocket. The fact that ibrutinib has the phenoxyphenyl does not teach a POSA that all compounds satisfying the Structural Limitations will bind Btk's back pocket.

49. Importantly, the specification does not describe how ibrutinib—let alone any other BTKIs—allows for the phenoxyphenyl to be in the proper orientation to bind Btk's back pocket. As discussed above and acknowledged by Dr. Eck, proper orientation of the phenoxyphenyl is controlled by the Z'-scaffold. EX1003, ¶58; EX1110, 93:2-18. Further, even if the Z'-scaffold were to orient the phenoxyphenyl into the back pocket, it will not necessarily result in the linker-warhead oriented in a way that it could irreversibly bind Cys481.

3. The Specification Does Not Disclose that Z'-scaffolds Will Necessarily Result In 1-3 Hydrogen Bonds with Btk's Active Site

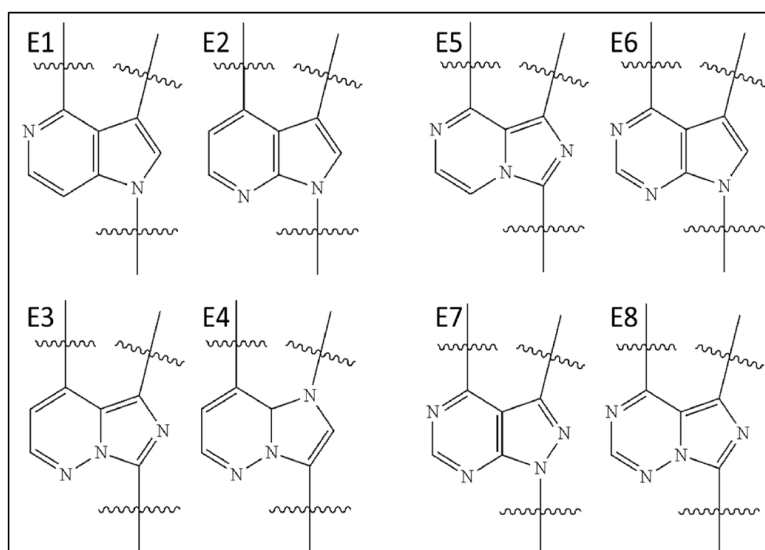
50. Dr. Eck contends that a POSA would have understood from the specification that the Z'-scaffold would form 1-3 hydrogen bonds with the kinase hinge region of Btk. EX2010, ¶39. Not so. The specification mentions nothing

about hydrogen binding with the hinge region of Btk and only discloses that ibrutinib can irreversibly inhibit Btk. In fact, the exemplified compounds that satisfy the Structural Limitations, ibrutinib and its positional or chiral isomers, only form two hydrogen bonds (not one or three) with the hinge region and such information is not disclosed in the specification.

51. Dr. Eck contends that Formula E in the specification provides examples of hinge-binding heterocyclic Z'-scaffolds, which are "fungible and predictable" and not limited to substituted fused biaryl Z'-scaffolds. EX2010, ¶¶65-68, 84. I disagree. Formula E includes an orb that "is a moiety that binds to the active site of a kinase, including a tyrosine kinase." EX1001, 61:65-62:17. Dr. Eck conceded that Formula E is described in the specification with respect to functional, rather than structural, limitations. EX1110, 58:22-59:9, 60:19-62:20, 63:21-65:4. Such functional definition of the orb does not provide any guidance to a POSA regarding the metes and bounds of the scope of Z'-scaffolds that would form H-bonds with the Btk hinge region. Dr. Eck does not believe that the inventors confidently and accurately predicted that the eight cores E1-E8 with the claimed phenoxyphenyl and linker-warhead attached would irreversibly inhibit Btk. *See id.*, 78:16-23. Dr. Eck conceded that a POSA would have understood that the cores (E1-E8) "wouldn't necessarily, you know, with the atoms depicted in these illustrations, make hydrogen

bonds to the hinge.” *Id.*, 69:7-18. Dr. Eck also testified that E1-E8 are unelaborated and not substituted, and he could not say whether a POSA would understand whether these structures would form appropriate hydrogen bonds from reading the specification. *Id.*, 70:16-23. The specification does not disclose that any compounds containing these Z'-scaffolds, other than ibrutinib, will bind the hinge region of Btk.

52. The specification discloses that in some embodiments, the orb of Formula E “is a substituted fused biaryl moiety selected from” the eight structures shown below.



EX1001, 62:44-63:22 (annotated)

53. As shown above, E1-E3 and E5-E8 are biaryl cores, while E4 is a non-biaryl core. I agree with Dr. Showalter’s opinion that a POSA reading the specification would have concluded that the specification’s depiction of E4 was a

mistake. EX1105, ¶¶41-42. A POSA would have reasonably understood that the substituted fused biaryl moiety for the orb of Formula E from the disclosed structures would be limited to the seven biaryl cores (E1-E3 and E5-E8).

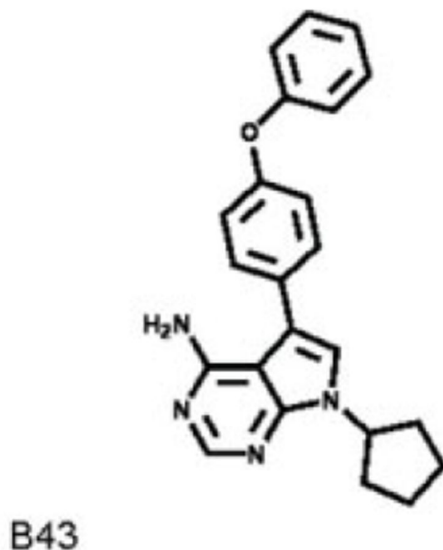
VI. GENERAL KNOWLEDGE IN THE FIELD

A. The State of the Art in 2011 Provided Little More Information than the 803 Patent

54. In my opinion, the state of the art in 2011 provided little information beyond what was disclosed in the specification of the 803 Patent.

1. Marcotte's Teachings Were Limited

55. Dr. Eck contends that Marcotte (EX2001) provides information regarding the geometry of compound B43 in Btk's active site and amino acid interactions between B43 and Btk's hinge region that would have allowed a POSA to understand the effective conformation of ibrutinib for inhibiting Btk and how related molecules could be recognized as irreversible BTKIs for use in the claimed methods. EX2010, ¶71 (citing EX2001.0003-0005); *see also id.*, ¶¶73, 76, 81, 112-114, 116-118. I disagree. Marcotte does not disclose any compound that satisfies the Structural Limitations, irreversibly inhibits Btk, or teach the SAR. Instead, Marcotte discloses Compound B43, a reversible BTKI that has a claimed biaryl Z'-scaffold, the claimed phenoxyphenyl, but a cyclopentyl group instead of the claimed linker-warhead:

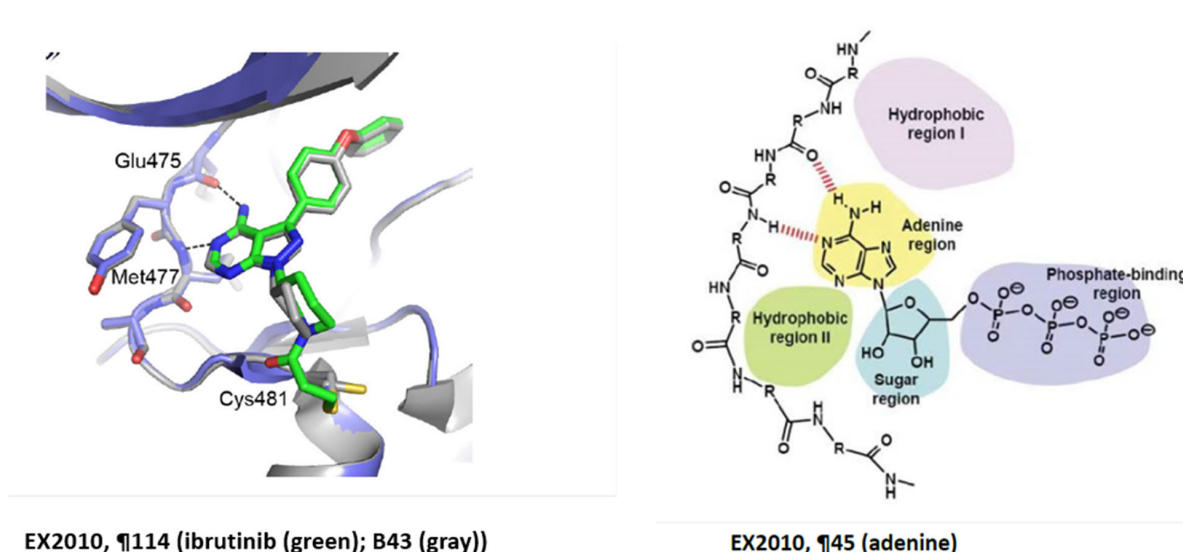


EX2001.0003 (Fig. 2A)

56. Marcotte discloses that B43 with this particular Z'-scaffold happens to form H-bonds to the hinge-region such that the phenoxyphenyl orients into and binds the back pocket and the cyclopentyl group orients near Cys481. EX2001.0003 (Fig. 2(D) depicting “[c]lose-up of the active site and residues within 5 Å of the bound B43”), .0004 (“B43 compound makes several hydrogen bonds to the hinge and occupies a hydrophobic pocket behind the Thr474 gatekeeper residue [Fig. 2(D)].”). Specifically, “the exocyclic amine directly interacts with the gatekeeper Thr474 hydroxyl and the backbone carbonyl of 475, the N-3 of the pyrimidine accepts a hydrogen bond from the backbone amine of Met477, and the N-1 of the pyrimidine forms a water-mediated hydrogen bond network to the hydroxyl of Tyr476 and the backbone carbonyl of Ala478.” EX2001.0005. Marcotte provides no teaching

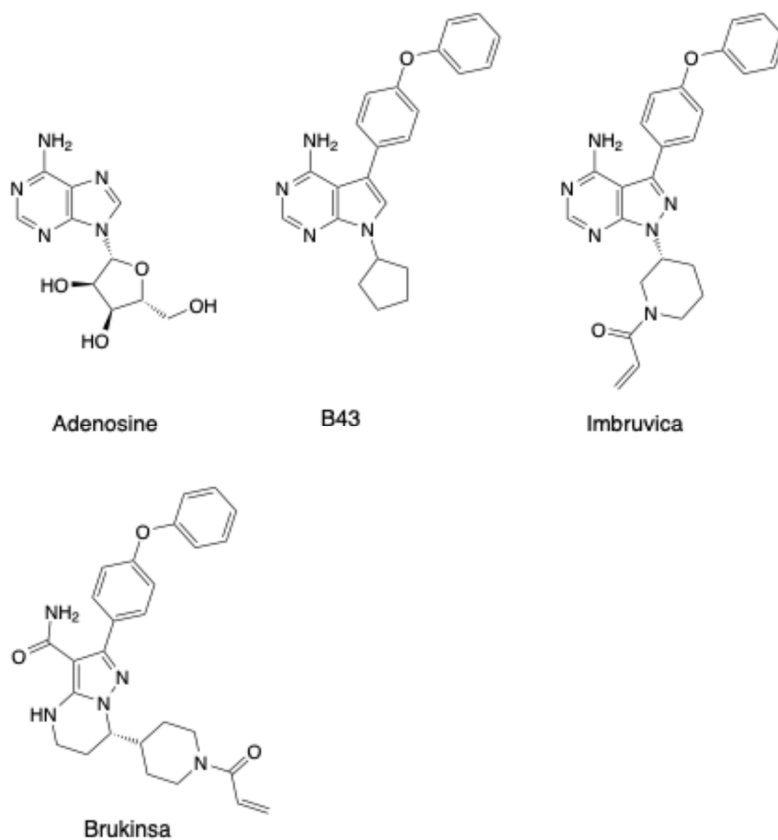
regarding whether replacing the cyclopentyl with the claimed linker-warhead would result in covalent binding. Indeed, proximity to Cys481 alone does not ensure that the two will form a covalent bond because a very specific geometry is required for the linker-warhead to approach and covalently bind Cys48. EX1157; EX1158. It also provides no teaching regarding whether and how compounds with other biaryl Z'-scaffolds or compounds with non-biaryl Z'-scaffolds would form H-bonds such that the phenoxyphenyl orients into and binds the back pocket and the linker-warhead covalently binds Btk.

57. The crystal structure of ibrutinib bound to Btk (which was not available to a POSA in 2011) now reveals that Compound B43 and ibrutinib bind the kinase hinge region similarly to adenine. Dr. Eck's modeling of Compound B43 and ibrutinib, as well as the binding of adenine to the kinase hinge region are reproduced below:



58. Specifically, “[t]he 4-amino pyrrolopyrimidine of B43 occupies the positions of the adenine ring of ATP and the cyclopentyl ring occupies the space generally occupied by the ATP ribose in typical protein kinase structures.” EX2001.0004. Similarly to adenine, B43 has a ring N that accepts a hydrogen bond from the backbone amine of Met477 and an exocyclic amine that interacts with the backbone carbonyl of Glu475. EX2001.0004-.0005. Marcotte, however, does not allow prediction regarding whether and how BTKIs like zanubrutinib, which are not close adenine mimetics and occupy different regions of Btk than ibrutinib and adenine, will irreversibly bind Btk. *See infra* Section VI.A.6. One can see from the figure below the correspondence between adenosine, B43, and ibrutinib, which all contain a biaryl ring system comprising an *amine* substitution attached to the 6-membered ring. This can be contrasted to the distinct structure of zanubrutinib,

which lacks the biaryl ring system and has an *amide* substitution attached to the 5-membered ring.



2. Ghose's Teachings Were Limited

59. Dr. Eck contends that Ghose (EX1052) describes that the specificity pocket adjacent to the hinge region furthers inhibitor selectivity (*see* EX2010, ¶81) and that kinase inhibitors may form 1-3 H-bonds with specific residues of the kinase hinge region (*see* EX2010, ¶92 n. 9, ¶98 n. 10). Figure 2 of Ghose does not disclose the claimed hydrophobic moiety (or that it binds to Btk's back pocket). Regardless, in my opinion, whether a compound will bind and irreversibly inhibit Btk depends

on the holistic structure of the compound and whether different subgroups of the compound can simultaneously satisfy the requirements for H-bonding and forming additional interactions such as binding to the back pocket. Moreover, forming 1-3 H-bonds to Btk's hinge region or binding to Btk's back pocket alone is not sufficient to determine whether a compound will irreversibly inhibit Btk. Dr. Eck agrees that interactions other than forming H-bonds to Btk's hinge region and properly orienting the linker-warhead and hydrophobic moiety impact whether and how a compound will irreversibly inhibit Btk, including electrostatics, Van der Waals interactions, and an overall binding site shape complementarity between the compound and kinase across the entire Btk active site. *See* EX1110, 156:15-157:14, 158:18-159:3, 160:2-21. Ghose describes general features of the protein kinase binding site and reviews examples of existing compounds that bind to various kinases. However, it does not provide prospective insight on whether an untested, new compound will have the holistic structure and combination of features needed to inhibit, let alone covalently modify Btk with its unique set of binding requirements.

3. Pan's Teachings Were Limited

60. Dr. Eck contends that Pan (EX1060) discloses that the linker-warhead covalently binds to Cys481 (EX2010, ¶72) and irreversible inhibitors with a hydrophobic moiety inhibit Btk (EX2010, ¶82). The linker-warhead and

hydrophobic moiety alone, however, are not sufficient to determine whether a compound will covalently bind or irreversibly inhibit Btk. Rather, whether and how a compound will irreversibly inhibit Btk depends on the overall structure and bioactive orientation of the compound within the Btk's kinase domain, including the various structural components and their arrangement and interrelationship. Dr. Eck agrees, however, that the only Z'-scaffold that Pan discloses is the Z'-scaffold of ibrutinib and also that binding interactions other than forming H-bonds to Btk's hinge region and properly orienting the linker-warhead and hydrophobic moiety impact whether and how a compound will irreversibly inhibit Btk. EX1110, 86:18-23, 156:15-157:14, 158:18-159:3, 160:2-21.

4. Akritopoulou-Zanze's Teachings Were Limited

61. Dr. Eck contends that Akritopoulou-Zanze (EX2028) demonstrates that Z'-scaffolds make 1-3 H bonds with the hinge region (EX2010, ¶¶83, 84, ¶92 n. 9, ¶98 n. 10) and that diverse Z'-scaffolds are capable of making hinge interactions (EX2010, ¶84). In my opinion, based on the teachings of Akritopoulou-Zanze and as discussed above with Ghose (EX1052), a POSA would have understood that whether a compound can bind and irreversibly inhibit Btk depends on the holistic structure of the compound – it requires more than just predicting whether and how many H-bonds a Z'-scaffold can form with the hinge region of Btk. Specifically,

Figure 4 shows that the same Z'-scaffold can form multiple binding modes based on the tautomerization of the pyrazole ring, as shown below:

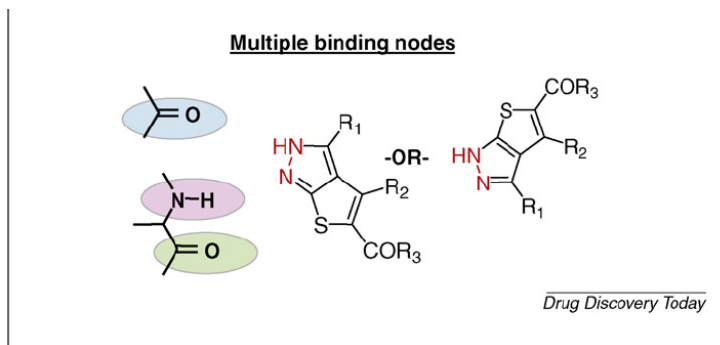


FIGURE 4

De novo design. An example of the *de novo* design of a kinase core by starting with indazole (which is represented in more than 200 kinase patents) and synthetically pursuing the thienopyrazole analog, which was not known as a kinase hinge element at the time of its inception but is now represented in 15 kinase patents. A representative molecule synthesized to evaluate the utility of this core is shown in the right, from which multiple compound libraries were derived. Multiple binding modes were experimentally observed for this chemotype (schematically illustrated at the bottom) based on tautomerization of the pyrazole ring.

EX2028.0004, Fig. 4

62. The authors determined that “[s]urprisingly, in several cases, the same fragment was able to adopt different binding modes with different kinases. In addition, elaboration of a particular core in different ways could induce a change in the binding mode even for the same kinase. This is shown schematically in Figure 4, where tautomerization of the pyrazole ring allowed two distinct hinge-binding modes for this thienopyrazole core based on the substitution pattern. ***These results illustrate the complexity and subtlety of kinase-inhibitor interactions.***”

EX2028.0004 (emphasis added). Therefore a POSA reading Akritopoulou-Zanze

would have understood that whether a compound can bind and irreversibly inhibit Btk requires more than predicting whether the Z'-scaffold can form H-bonds with Btk's hinge region. The variability of whether a specific Z'-scaffold will inhibit a specific kinase such as Btk is further emphasized in Figure 7, which shows how both fragments and more elaborated molecules, having different hinge binding motifs, have distinct affinities for a panel of tested kinases.

REVIEWS

Drug Discovery Today • Volume 14, Numbers 5/6 • March 2009

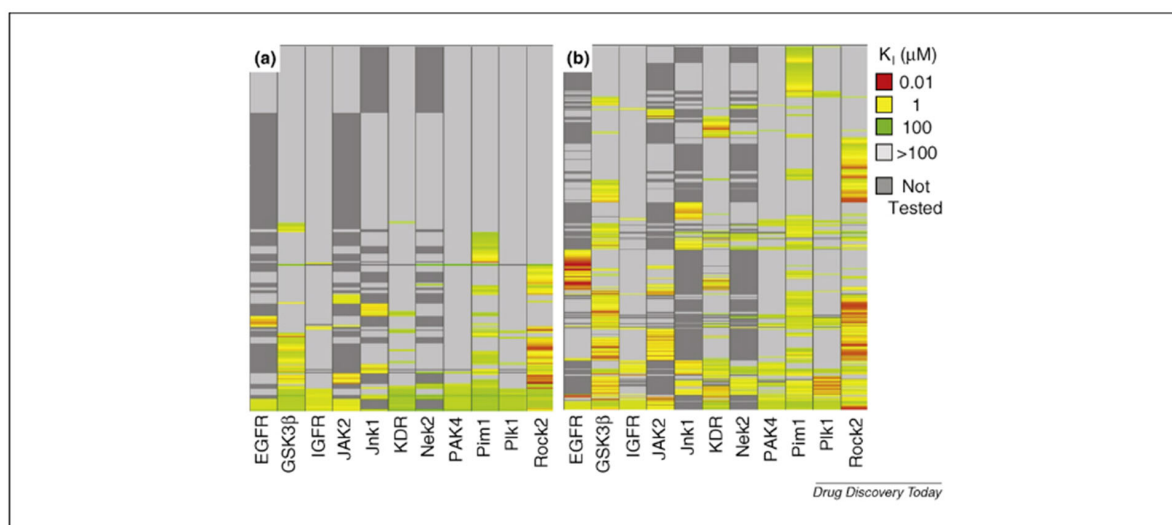


FIGURE 7

Kinase selectivity. Activity heat maps for (a) more than 250 fragments ($(MW) = 250$) and (b) more than 1000 elaborated molecules ($(MW) = 420$) derived from our internal Kinase Initiative against a panel of 11 protein kinases, with inhibitory activities ranging from 1 nM (red) to 100 μ M (bright green).

EX2028.0006, Fig. 7

5. The Available Z'-Scaffolds Were Limited or Irrelevant

63. Dr. Eck contends that a POSA would have understood that diverse heterocyclic Z'-scaffolds are capable of making interactions with the hinge region

of Btk. EX2010, ¶¶84-89; *see also id.*, ¶¶70, 192. The references that Dr. Eck relies on and the Z'-scaffolds disclosed therein provide limited, if any, information to a POSA regarding whether and how the structurally diverse compounds satisfying the Structural Limitations would interact with the hinge region and irreversibly inhibit Btk. Specifically, these references relate to reversible inhibitors, do not disclose whether or how the Z'-scaffold binds the hinge region, do not disclose the use of modeling to develop kinase inhibitors, and/or do not provide guidance on where either the phenoxyphenyl or linker-warhead groups would be attached or if either group would be tolerated. Further, many of the disclosed cores do not satisfy the claimed Z'-scaffold, and the only non-biaryl Z'-scaffold disclosed in these references (Formula I, 820 Patent) did not dock well. *See infra* Section VII.C.2.c)(4). As discussed above and acknowledged by Dr. Eck, proper orientation of the linker-warhead and phenoxyphenyl is controlled by the Z'-scaffold, and a POSA would not have been able to reliably and accurately predict how to attach these substituents to the Z'-scaffolds disclosed in the references that Dr. Eck relies on. EX1003, ¶58; EX1110, 93:2-18. Indeed, I understand that Dr. Eck never attempted to model any compounds satisfying the Structural Limitations comprising any of the available Z'-scaffolds (except ibrutinib) to determine if they would irreversibly inhibit Btk.

a) 820 Patent

64. Dr. Eck relies on a Z'-scaffold disclosed in the 820 Patent (EX2023) that is non-biaryl. EX2010, ¶85. The 820 Patent, however, relates to reversible inhibitors, does not disclose whether or how the Z'-scaffold binds the hinge region, and does not disclose the use of modeling to develop kinase inhibitors. The 820 patent also does not disclose where on the Z'-scaffold a POSA could attach the claimed fixed substituents to allow for covalently binding Btk. Indeed, as I explain further below, a POSA would be led away from using this Z'-scaffold because modeling suggests that compounds with this Z'-scaffold and the claimed fixed substituents would not covalently bind Btk. *Infra* Section VI.C.2.c)(4).

b) 303 Publication and EX2050

65. Dr. Eck relies on cores disclosed in the 303 Publication (EX2026) and EX2050. EX2010, ¶86. The 303 Publication relates to reversible inhibitors, does not disclose whether or how the scaffolds bind the hinge region, and does not disclose the use of modeling to develop kinase inhibitors. Each of the fully aromatic cores, is tricyclic and lacks a nitrogen in the 6-membered ring, different from the claimed Z'-scaffold. The optimized structures also lack a phenoxyphenyl group (or any group that targets the back pocket region of BTK) and were reversible inhibitors, lacking any sort of linker-warhead motif. Additionally, no guidance is provided on

where either the phenoxyphenyl or linker-warhead groups would be attached and if either group would be tolerated. The 303 Publication therefore would have very limited value in informing a POSA regarding the Challenged Claims. EX2050 was not published until 2015, and therefore was not available to a POSA in 2011.

c) 960 Publication

66. Dr. Eck relies on Z'-scaffolds disclosed in the 960 Publication (EX2027). EX2010, ¶87. The Z'-scaffold disclosed in the 960 Publication, however, is biaryl like the Z'-scaffold of ibrutinib and the seven Formula E ring systems. Thus, the Z'-scaffold disclosed in the 960 Publication provides little information beyond what was disclosed in the specification of the 803 Patent. Further, the 960 Publication does not disclose how the Z'-scaffolds bind the hinge region or the use of modeling to develop kinase inhibitors.

d) 10 PDB Structures

67. Dr. Eck relies on ten PDBs with eight distinct hinge-binding cores. EX2010, ¶88. However, only two of the eight cores satisfy the claimed Z'-scaffold (3GEN and 3PJ3). 3GEN is the structure disclosed in Marcotte, while 3PJ3 is a reversible kinase inhibitor with a biaryl Z'-scaffold like ibrutinib and the seven Formula E cores). Note also that the back pocket binding moiety of 3PJ3 is not achieved via connecting a ring directly to the Z'-scaffold, as is required for the

phenoxyphenyl group of the Challenged Claims, but rather requires an intervening amide spacer. Thus, the structure of 3PJ3 provides little information beyond what was disclosed in the specification of the 803 Patent.

e) Waterson

68. Dr. Eck relies on compound 14f (PDB: 5T18) disclosed in Waterson (EX2061). EX2010, ¶89. Waterson, however, was not published until 2016, and therefore would not have been available to a POSA in 2011. In any event, the core of compound 14f does not satisfy the claimed Z'-scaffold. Rather, the core of compound 14f is tricyclic and lacks a nitrogen in the 6-membered ring, different from the claimed Z'-scaffold. Compound 14f also lacks a phenoxyphenyl group (or any group that targets the back pocket region of BTK) and is a reversible inhibitor, lacking any sort of linker-warhead motif. Additionally, no guidance is provided on where either the phenoxyphenyl or linker-warhead groups would be attached and if either group would be tolerated.

6. Zanubrutinib Was Not Available in 2011 And Confirms the Structural Diversity of the Claimed Genus

69. While Dr. Eck relies on zanubrutinib to support his opinions (*see* EX2010, Section VII.A.5), the structure of zanubrutinib was not publicly disclosed until 2015 and a POSA would not have known of its structure in 2011. EX1034; EX1110, 54:14-22, 56:25-57:12, 110:17-22. Dr. Eck's reliance on it is pure

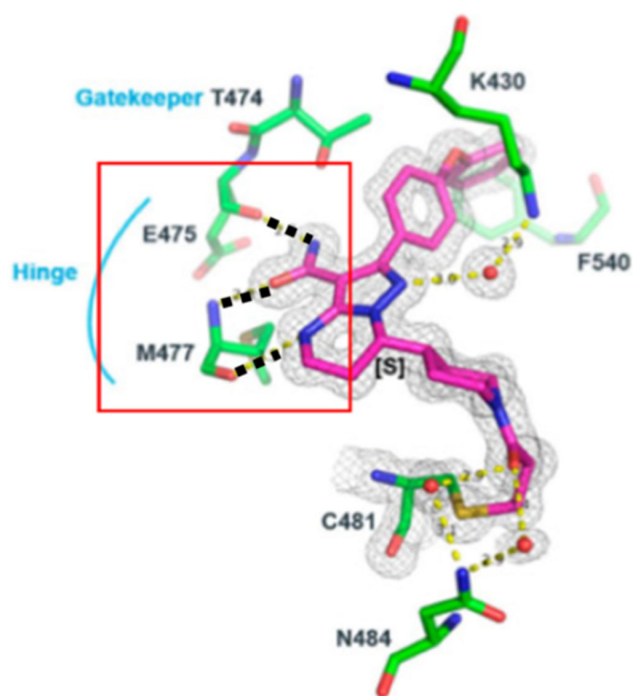
hindsight, especially because he admitted that the inventors of the 803 Patent did not possess zanubrutinib. EX1110, 58:7-10.

70. Compared to ibrutinib, zanubrutinib has a distinct structure with a distinct H-bond binding pattern with Btk's hinge region, has a linker-warhead that approaches Cys481 from a different direction, and occupies a different space. The H-bonds of adenine, ibrutinib, and zanubrutinib with Btk's hinge region are shown in Dr. Eck's own table, which I have reproduced below:

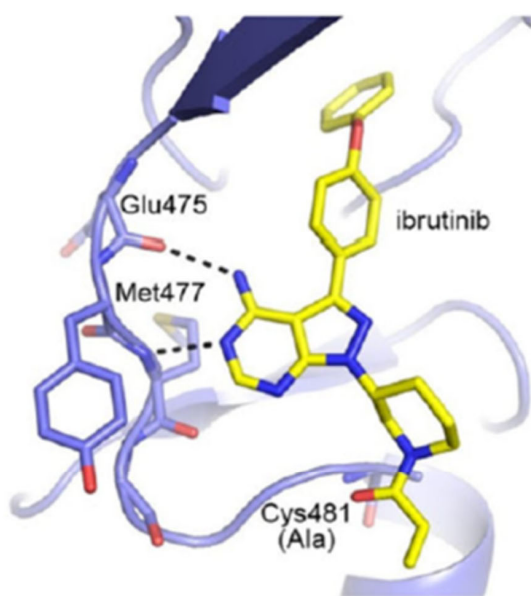
Ligand	BTK Residue	
	GK+3 Met477 (NH, H-bond donor)	GK+1 Glu475 (C=O, H-bond acceptor)
Adenine	Ring N (H-bond acceptor)	-NH ₂ amine substituent (H-bond donor)
Ibrutinib	Ring N (H-bond acceptor)	-NH ₂ amine substituent (H-bond donor)
Zanubrutinib ⁹	-C=O of amide substituent (H-bond acceptor)	-NH ₂ of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

EX2010, ¶92

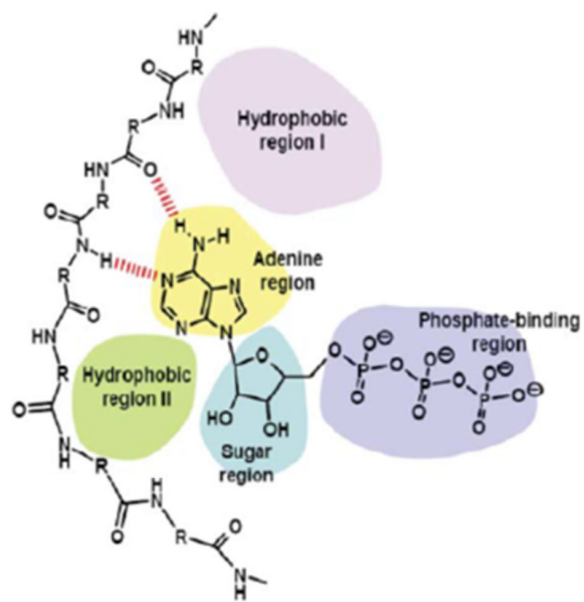
71. As can be seen in Dr. Eck's table and the figures below, zanubrutinib and ibrutinib form distinct H-bonds to Btk's hinge region. Specifically, zanubrutinib has a H-bond acceptor that is a -C=O of its amide substituent, while ibrutinib has a H-bond acceptor that is a ring N (like adenine). Further, zanubrutinib has a H-bond donor that is the NH₂ of its *amide* substituent, while ibrutinib has a H-bond donor that is the NH₂ *amine* substituent (like adenine).



Zanubrutinib



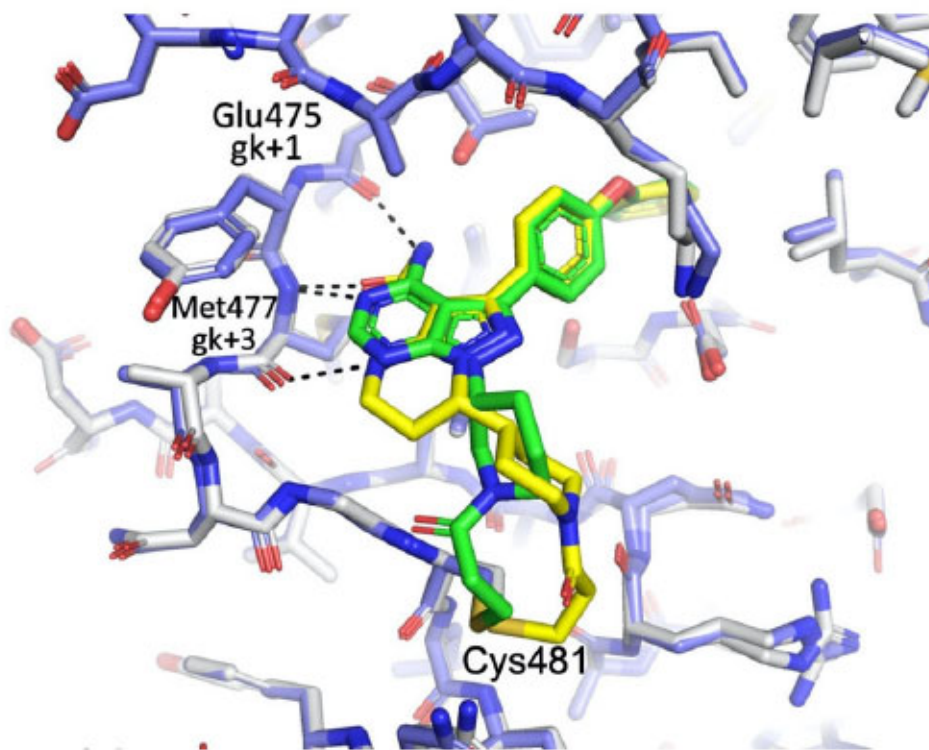
Ibrutinib



Adenine

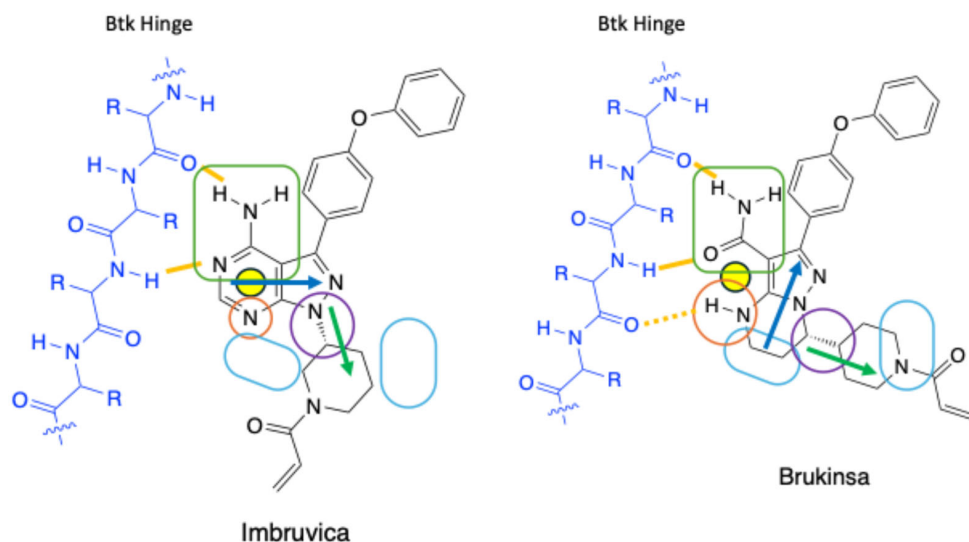
72. Dr. Eck's table includes a footnote, wherein Dr. Eck contends that "[z]anubrutinib also makes a third H-bond to the third available H-bond interaction in the BTK hinge: H-bond acceptor of GK+3 residue Met477." EX2010, ¶92 n. 9 (citing EX1053.005).

73. Likewise, while zanubrutinib (depicted with yellow carbon atoms) and ibrutinib (depicted with green carbon atoms) both bind Cys481, zanubrutinib's and ibrutinib's crystal structures show that, far from overlapping, the two zig and zag in different directions:



EX2010, ¶94

74. The differences in the binding mode and interactions of ibrutinib and zanubrutinib can be seen in the figure below:



75. First, ibrutinib, places a heteroaromatic pyrimidine ring (solid yellow circle) deep in the kinase binding site directly overlapping the location of the identical pyrimidine ring of adenine and Marcotte B43 (as shown above). Zanubrutinib lacks any such analogous ring.

76. Second, ibrutinib forms H-bonds (orange lines) to Btk's hinge region via an amino pyrimidine motif, like adenine and B43, whereas zanubrutinib forms H-bonds via an exocyclic primary amide. Note that for ibrutinib, as well as E1 and E5-E8, any H-bonds to the NH of Met477 would necessarily be part of the Z'-scaffold whereas they are not for zanubrutinib (E2-E4 in my opinion would not be able to form any H-bond to the NH of Met477).

77. Third, zanubrutinib may form a third H-bond via the zanubrutinib ring NH (orange circle) to the C=O of Met477. As described below in the modeling section and shown by X-ray, this H-bond is non-ideal due to a distance of 2.5Å or greater between the donor hydrogen and acceptor oxygen. A POSA would be concerned that it could be unfavorable to form such a weak H-bond versus the H-bonding achievable with water outside the binding site and that such a weak H-bond could hurt potency. Also shown in the figure above, in zanubrutinib this NH H-bond donor is positionally identical to an H-bond acceptor (pyrimidine nitrogen) in ibrutinib, and a POSA would question the tolerability of such a change.

78. Fourth, the orientations of the bicyclic systems (blue arrows) for ibrutinib and zanubrutinib within the Btk binding site are entirely different and nearly perpendicular to each other. The bicyclic system of zanubrutinib is also displaced from Btk's hinge region as compared to ibrutinib. As a result, the substitution pattern on zanubrutinib to enable H-bonding to the hinge region, placement of the phenoxyphenyl into the back pocket, and positioning of the linker-warhead proximal to Cys481 is distinct from that of ibrutinib, as well as the substitution positions of E1-E8. The E1-E8 cores have substitution positions that do not match the zanubrutinib substitution pattern.

79. Fifth, the attachment (purple circle) of the linker-warhead for zanubrutinib is via a sp^3 hybridized carbon with tetrahedral geometry versus an aromatic nitrogen or carbon (planar geometry) for ibrutinib, as well as E1-E8. The vector orientation (green arrow) of the linker-warhead for zanubrutinib versus ibrutinib, as well as E1-E8, relative to Btk's active site is different.

80. Sixth, zanubrutinib occupies regions of the kinase (light blue ovals) that are not at all occupied by ibrutinib. The 6-membered fused ring of zanubrutinib projects into a region of Btk that may be used to generate selectivity for one kinase versus another and can significantly affect binding properties. Although this pocket is not emphasized in Ghose (EX1052), a POSA would have been aware of this part of the kinase binding site, and Dr. Eck in fact references this second hydrophobic pocket in his declaration. EX2010, ¶92 (citing EX2048, Fig.1; EX1077.003, Fig. 1). The non-aromatic nature of the 6-membered fused ring of zanubrutinib and its binding into the second hydrophobic pocket would further distinguish it from other known kinase structures at the time of the priority date. Additionally, the linker-warhead of zanubrutinib also occupies a region of Btk that is not bound by the linker-warhead of ibrutinib as shown in Dr. Eck's figure above.

81. It is my opinion that there is nothing in the 803 Patent that guides one to visualize the zanubrutinib structure. Additionally, the number and magnitude of

changes in the structure of zanubrutinib vs ibrutinib (and E1-E8) support my opinion that a POSA would not have been able to predict whether zanubrutinib could covalently bind Btk.

B. Scaffold Swapping

82. Dr. Eck contends that the 803 Patent teaches scaffold swapping for BTKIs for use in the claimed method and that a POSA reading the 803 Patent would have known how to use ibrutinib and available modeling/docking software to create additional BTKIs with different Z'-scaffolds. EX2010, Section VII.B. The specification, however, does not disclose the use of scaffold swapping or modeling to predict whether a compound will irreversibly inhibit Btk. Instead, the specification expressly instructs a POSA to conduct assays to determine irreversible inhibition. EX1001, 45:60-65 (“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 IC₅₀ for an irreversible Btk inhibitor compound.”) (emphasis added). Moreover, Dr. Eck did not even try to model any of the Formula E structures disclosed in the specification (except ibrutinib) or any of other known scaffolds that he relied on for his scaffold swapping opinions. *See infra* Sections VI.C.2.a), VI.C.2.c).

83. In my opinion, trial and error testing would be required to determine whether any given Z'-scaffold, known or unknown, would bind and irreversibly inhibit Btk.

1. Zhang's Teachings Were Limited

84. Dr. Eck contends that a POSA would have identified Z'-scaffolds by leveraging structural information regarding the binding of ibrutinib and other known hinge-binding elements of kinase inhibitors. EX2010, ¶103 (citing EX1077.007, .009). In my opinion, Zhang (EX1077) provides a POSA with limited information regarding how to identify claimed Z'-scaffolds. While Dr. Eck relies on a disclosure from Zhang regarding "structure-informed design," Zhang emphasizes that "the enrichment factors that are derived from these efforts are *not sufficient to make this approach generally applicable*." EX1077.007 (emphasis added). Similarly, with respect to "[f]ragment-based inhibitor discovery," Zhang states that "only a *limited number* of kinase inhibitors have been developed using this approach." *Id.* (emphasis added). Zhang also discloses that "[k]inase inhibitor design has benefited immensely from crystallography in the elucidation of binding modes and unexpected inhibitor-induced conformational rearrangements." *Id.* at .009. Zhang notes, however, that despite the advances made to discover and validate kinase targets that are the most appropriate to target with inhibitors, "a

number of *significant challenges remain*,” including “a need for more predictive tumour models and better ways to monitor target inhibition in humans in a minimally invasive fashion.” EX1077.010 (emphasis added).

85. Dr. Eck further contends that “binding models based on crystal structures, like Marcotte, would be used to assess analogs that ‘modulate potency, selectivity and pharmacological properties. Isosteric replacements are used to improve these properties while preserving the stereo electronic contacts responsible for binding to the kinase.’” EX2010, ¶115 (quoting EX1077.006-.007). I disagree. This disclosure from Zhang relates to analogue synthesis, which is used to identify new inhibitors based on inhibitors that were previously developed and archived. *See* EX1077.006 (“the analogue synthesis and isosteric replacement approaches are commonly initiated with a lead scaffold that was originally identified as an inhibitor of one kinase and later serendipitously found to be cross-reactive with a new kinase of interest”). The analogue synthesis approach disclosed in Zhang requires the use of *known* core structures, while the Structural Limitations of the Challenged Claims encompass both *known and unknown Z’-scaffolds* and evaluating all of the claimed *Z’-scaffolds* would involve evaluating *known and unknown* structures. Therefore, this analogue synthesis approach would not allow a POSA to identify or investigate the full scope of claimed *Z’-scaffolds*.

2. Ghose's Teachings Were Limited and Show That Testing is Required to Determine Binding of a Target Kinase

86. Dr. Eck contends that a POSA would have been aware of kinase-ligand structures that allow for scaffold swapping, including the 53 distinct scaffolds disclosed in Ghose. EX2010, ¶104. In my opinion, Ghose's teachings provide a POSA with limited information regarding how to identify the claimed Z'-scaffolds. Thirty-seven of the 53 do not satisfy the claimed Z'-scaffold and would therefore provide little to no value to a POSA in visualizing the full scope of the claimed Z'-scaffolds. The 16 Z'-scaffolds that do satisfy the claimed Z'-scaffolds (1, 1a, 1b, 2, 2a, 3, 4, 5, 5a, 11, 15, 16, 22, 32a, 34, and 35) are all biaryl. The specification already discloses the seven Formula E biaryl cores (E1-E3 and E5-E8). Therefore, the biaryl Z'-scaffolds disclosed in Ghose provide a POSA with little more information than the 803 Patent. Further, Dr. Eck did not try to model the binding to Btk of any of the scaffolds disclosed in Ghose.

87. Dr. Eck contends that Ghose describes "the process for lead/scaffold swapping activities of aligning a scaffold of interest to a known active compound and 'follow[ing] the topology of the active compound to add/modify structural moieties in the chosen scaffold' including automated 3D versions of this approach." EX2010, ¶103 (citing EX1052.019-.020); *see also id.* ¶105. Ghose, however, discloses that "all of the aforementioned uses of a kinase knowledge base should be

considered *suitable only for idea generation rather than the routine prediction* of high affinity ligands.” EX1052.021 (emphasis added). Ghose further describes that “the advantages of knowledge based drug discovery depend critically on an increase in information that can only come from *speculative* approaches and *serendipitous* results.” *Id.* (emphasis added). Ghose therefore demonstrates that empirical studies, including the synthesis and testing of potential kinase inhibitors, would be required to determine the binding activity of any given compound. *See* EX2018, 122:15-125:8.

3. Akritopoulou-Zanze’s Teachings Show That Testing is Required to Determine Binding of a Target Kinase

88. Dr. Eck contends that Akritopoulou-Zanze (EX2028) describes a “powerful approach” of generating kinase inhibitors via “scaffold swapping” wherein “the hinge-binding element of a given kinase lead is replaced, based on structural information, with the novel scaffold.” EX2010, ¶105 (citing EX2028.0004-.0005); *see also* EX2010, ¶106 (same). In my opinion, Akritopoulou-Zanze shows that testing is required to determine whether a compound will irreversibly inhibit a kinase of interest.

89. Figure 5 of Akritopoulou-Zanze depicts designing a new kinase inhibitor by replacing a known scaffold with a modified scaffold. This novel scaffold was synthesized and tested and x-ray crystallography was used to confirm

whether the novel scaffold binds the hinge region. *See* EX2028.0003; EX1110, 109:4-7. Further, Akritopoulou-Zanze states that “[t]he synthesis of molecules unknown in the literature carries many difficulties, such as large upfront synthetic methodology development, unexpected and sometimes undesirable physicochemical properties and possible instability issues. In addition, it is imperative for the new scaffolds to contain key functional group in the right parts of the molecule for further functionalization in order to improve on potency and selectivity.” EX2028.0003. While modeling might be used to generate ideas for new scaffolds, a POSA would have understood from Akritopoulou-Zanze that a large amount of experimentation is required to validate the new scaffolds. *See id.* at .0003-.0004 (“[c]ritical for the subsequent utilization of any of these kinase fragments is their validation as bona fide hinge-binders that can be effectively utilized in lead generation and optimization. To this end, *extensive validation of the candidate scaffolds is performed through activity measurements, X-ray structural analysis, and synthetic modification.*”) (emphasis added).

4. Gracias’s Teachings Show That There Was a Focus on Developing Adenine Mimetic Kinase Inhibitors and Testing is Required to Determine Binding of a Target Kinase

90. Dr. Eck contends that EX2038 provides an example of successful scaffold swapping. EX2010, ¶106. Gracias, however, describes that the process for

developing new scaffolds involves testing to determine whether such scaffolds will bind to a kinase of interest. First, the proposed new scaffolds were synthesized and tested against a preliminary panel of five kinases of interest to detect inhibitory activity. EX2038.0002-.0003. Of note, only some of the designed and modeled compounds were active whereas others were inactive, and in fact, only one of the initially modeled and synthesized compounds had an IC_{50} of $< 1 \mu M$, and this was against only one of the five kinases tested (KDR). Thus, in 40 tests (8 compounds vs. 5 kinases), only one example of the modeled compounds had an IC_{50} of better than $1 \mu M$. Moreover, modeling suggested the addition of another NH_2 group to the pyrimidine core to achieve a third H-bond with the hinge region, but all compounds synthesized with this NH_2 group in fact proved to be inactive (best $IC_{50} = 9 \mu M$). The authors then employed additional molecular modeling of such scaffolds and eventually achieved more potent inhibitors but only through significant additional biological testing. *Id.* at .0003. After modeling these new scaffolds, analogs were then prepared in order to validate the modeling hypothesis. *Id.* The kinase inhibitors in Gracias also all possessed the NH_2 -pyrimidine core, that is common to adenine, B43, and ibrutinib. As explained above, however, while ibrutinib forms the same H-bonds to Btk and occupies a similar space as adenine,

zanubrutinib has a distinct structure and forms distinct H-bonds to Btk and occupies a different space. *See supra* Section VI.A.6.

5. Pan's Teachings Show That Testing is Required to Determine Binding of a Target Kinase

91. Dr. Eck contends that a POSA would have understood that Pan (EX1060) reports irreversible BTKIs wherein the phenoxyphenyl interacts with the back pocket and the linker-warhead binds Btk's Cys481. EX2010, ¶¶109-110. Dr. Eck, however, agrees that the scaffold structure in Pan comes from a known, existing scaffold structure, for a reversible compound. EX1110, 86:24-87:6. Further, Pan relied on empirical synthesis and testing to confirm the irreversible inhibition of Btk. EX1060.002; *see also* EX1110, 87:25-88:14. Dr. Eck agrees that Pan did not use modeling to select the new scaffold for development of the new kinase drug. EX1110, 88:15-21 (Dr. Eck testifying that "they had identified it in a screen and then subsequently did the modeling."). Further, Pan does not disclose how modifications to the Z'-scaffold impact covalent binding.

C. Modeling/Docking

1. Modeling/Docking Software Available in 2010/2011

92. Dr. Eck contends that the structural information of Marcotte would have provided a POSA in 2011 with data to use in virtual docking and modeling of BTKIs that satisfy the Structural Limitations of the Challenged Claims. EX2010,

¶111. Dr. Eck, however, provided little information regarding the modeling or docking software that was available in 2010/2011. In response to Dr. Eck's opinions regarding modeling, I have provided a description of the modeling/docking software that was available in 2010/2011 below.

93. By 2010/2011, various docking software had been developed for academic and commercial use. EX1130.002. For example, Glide was available for molecular modeling of small molecules such as kinase inhibitors. *See* EX2035.0005-0006. Modeling using Glide involves four main steps. EX2037.

94. *First*, the user must prepare the protein and ligand structures for modeling. Typically, protein structures will be imported from sources such as the Protein Data Bank (PDB). However, because PDB structure files often lack necessary information including bond orders, topologies, and/or formal atomic charges, the user must "prepare" the protein and ligand structures by assigning the correct chemical properties. EX2037.0010, .0022-.0025, .0027-.0031.

95. *Second*, the user needs to prepare the space (a receptor grid) for docking. Similarly to the protein/ligand preparation stage, this step also provides the user with the ability to manipulate settings relating to chemical interactions. For example, by generating the receptor grid the user is able to set the suitable force field

used to search for favorable conformations between the protein and ligand molecules. EX2037.0033.

96. *Third*, once the structures of interest and docking space have been prepared, the user proceeds to the docking step. EX2037.0053. Docking is the process of determining the possible poses a ligand can adopt in the binding site of the target kinase. A “pose” refers to the orientation of a ligand conformation relative to the kinase target. To identify these poses, the docking program makes mathematical calculations based on the shape complementarity, ligand conformational preferences, and intermolecular forces which have been guided by the user to some extent. *See* EX2037.0013; EX1130.003; EX1122.002.

97. *Fourth*, after docking the ligand, the docking software will generate a table and docking poses in the workspace in order for the user to visualize the modeling results. EX2037.0085. The software typically generates multiple docking poses for each structure and each docking pose is associated with a specific docking score. A GlideScore (“GScore”) generated from the Glide software is determined through an empirical scoring function that estimates the ligand binding free energy and ranks the poses of different ligands in the database. The docking score attempts to predict binding free energy and is often expressed in kcal/mol units. Therefore, a more negative docking score suggests that the structure will more productively

inhibit the kinase target. *See* EX1134 (“more negative values represent tighter binders”); EX1138.003 (“[t]he more negative the values, the better the binding free energy between the enzyme [] and the ligands.”). A 1.3 kcal/mol difference in docking scores suggests an order of magnitude or 10-fold difference in binding affinity based on the Gibb’s free energy of binding equation. EX1127.002 (“It is not uncommon for the experimental binding affinity to vary up to a factor of 10 (1.3 kcal·mol⁻¹) . . . ”). However, factors such as the system entropy difference following binding may not be considered, and thus equating docking energy differences directly to binding affinity needs to be viewed cautiously.

98. Large scale structure-based virtual screening (“SBVS”) was not developed in 2010/2011. SBVS is a computational method that rapidly identifies potential inhibitors or initial binding hits in a large catalogue of chemical structures by docking molecules into a target protein’s binding site, whereas post-screening molecular docking or modeling is used to model the preferred orientation of a narrowed number of ligands to a target protein in order to understand their chemical interactions and predict drug properties and chemical strategies for optimizing inhibitor potency. EX1139.005 (“[s]tructure-based vHTS . . . consists of using a molecular docking program to determine the binding mode on the protein target for an entire database of existing or virtual compounds.”). Notably, Dr. Scott co-

authored an article published in 2020 that discloses that the “ability to carry out large-scale SBVSs on computer clusters in an accessible, efficient, and flexible manner has remained elusive” which led to the development of a new platform called VirtualFlow. EX1118.002. VirtualFlow aims to prepare and efficiently screen ultra-large ligand libraries of compounds, and as of 2020, was considered an advancement in the field. *Id.* Dr. Scott admitted that this article outlines a process to virtually prepare and screen very large numbers of compounds *in a way that had not been routine previously*. EX1117, 47:6-11, 48:12-18.

**a) Modeling Results Were Highly Variable and
Depended on User Set Parameters**

99. The docking results are highly variable and depend on how the input structure is prepared during the modeling process in 2011 (and even today). EX1124.013 (“docking results can be affected by how one prepares the input structure – which could lead to confusion for any unsuspecting user who repeats a docking experiment with *almost exactly the same procedure, but obtains wildly different results.*”) (emphasis added).

100. Modeling users have control, and in some instances, are required to specify or manipulate a number of settings relating to chemical interactions, all of which impact the docking score. Specifically, during ligand and protein preparation, users must exercise their best judgment when performing actions such as assigning

tautomer states, applying partial or formal charges, adjusting certain amino side chain rotamers (*i.e.*, asparagine and glutamine), and adjusting hydrogen atoms (especially for groups such as hydroxyls). During generation of the receptor grid, users must also exercise their best judgment when scaling appropriate chemical charges and determining which, if any, constraints to select for the docking process. During ligand docking, users must decide whether to apply any applicable constraints during the docking process or after the docking process is completed. A POSA would have understood that “seemingly negligible variations in ligand input coordinates, and even changing the atom order in a ligand input file, can produce unexpectedly large variations in the docking output.” EX1124.001. Further, “[i]nput prepared by different individuals, or even by the same person at different times, can show variations due to the source of the molecule (SMILES string, SD file, etc.), the order in which the ligand atoms are drawn, the input conformation generation method (e.g., Corina, ligprep, conformational search) and the geometry optimization method used to refine the structure (force fields applied, solvation, cut-offs, etc.).” *Id.* at .013. These variations in input data can further “be magnified by long iterative calculations such as molecular mechanics minimizations, molecular dynamics, and protein-ligand docking.” *Id.* at .001. As Dr. Eck acknowledged, “in a particular docking run, there could be differences in score that depend on the

specifics of how the experiment was – how the docking exercise was done and in two separate docking runs, would not necessarily expect to come up with the same value.” EX1110, 137:12-138:3.

**b) Modeling Would Not Have Accurately Predicted
Irreversible Inhibition of Btk**

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

102. A POSA would have appreciated that in 2010/2011 (and even today) scoring functions commonly used in molecular docking programs were “still too

inaccurate for a reliable prediction.” EX1126.002; *see also* EX1135.002 (“while docking is a powerful technology for early enrichment, ligand docking scores are not expected to and generally do not correlate with measured potency.”). For example, docking involves various challenges including: “(i) the prediction of ligands proper orientation; (ii) the prediction of the binding energies; and (iii) the prediction of novel, effective drugs by using the structural knowledge obtained from the methods.” EX1132.002 . Further, “docking methods are not reliable for predicting binding energies due to the simple scoring functions they use” and “the biggest challenge of the docking method (and also its principal problem) is the accurate prediction of binding energies, which has major implications for the prediction of novel effective drugs.” *Id.* at .001, .002. Thus, docking methods have specific limitations and are not a substitute for experimental testing. *See* EX1137.009 (“[docking methods] do not substitute experiments and all docking methods have their specific limitations which should be realized by users to better appreciate the strengths and weaknesses of each approach.”).

103. Even if modeling is used, empirical testing is required because modeling results often contradict experimental results. A White Paper published by Schrodinger in 2023 discloses that “ligand docking scores are not expected to and generally do not correlate with measured potency. As a result of these limitations,

most resources spent on virtual screens using traditional methods are often wasted...” EX1135.002. Moreover, in a study comparing docking results in modeling software, including Glide, and reported biological activities for 141 enantiomer pairs, the “test failed for all modes and targets” and it was noted that “common docking scoring functions do not discriminate correctly between true potent and weak active compounds.” EX1132.001, .008. Further, “several benchmarking studies indicate that docking scoring functions poorly predict the affinities of ligands for their targets.” *Id.* at .008.

104. Dr. Eck’s own experience demonstrates that modeling results may contradict experimental results and therefore modeling does not always accurately predict whether a structure will irreversibly inhibit a target kinase. Specifically, Dr. Eck is a co-author of an article that was published in 2016 relating to the discovery of a dual inhibitor that inhibits both Btk and MNK. EX1111; EX1110, 24:17-25:9. In order to identify a scaffold, Dr. Eck and his co-authors searched a kinase inhibitor database that contained known structures. EX1111.007; EX1110, 25:19-26:10. When assessing inhibitory activity, Dr. Eck and his co-authors performed both modeling and empirical testing. EX1111.007-009, .016 (Fig. 2(E)-(G)); EX1110, 27:14-32:21; *see also* EX1110, 29:2-3 (Dr. Eck testifying that he did not do the modeling). While the empirical testing, including IP kinase assays measuring IC₅₀

values, suggested that the inhibitor was a non-covalent inhibitor of MNK1 and MNK2, the modeling results suggested that the inhibitor was a covalent inhibitor of MNK2. EX1111.007-009, .016 (Fig. 2(F)-(G)); EX1110, 27:14-29:1. Dr. Eck testified that such modeling was a “relatively speculative docking exercise.” EX1110, 29:14-31:1. Dr. Eck also testified that “[t]ypically, in the course of an inhibitor discovery project, you want to know whether the inhibitor does in fact inhibit. So *it would be routine to proceed as well with biochemical assays to measure inhibition of the kinase of interest* by the molecule of interest.” EX1110, 36:25-37:11 (emphasis added). Dr. Eck’s testimony and the contradictory results that Dr. Eck and his co-authors obtained when performing modeling and empirical testing support my opinion that modeling is not reliably and accurately predictive and experimental testing is required to determine whether a compound will bind and irreversibly inhibit a kinase of interest. This is also consistent with Dr. Scott’s experience. EX1117, 40:18-41:13 (Dr. Scott testifying that he would run an assay to confirm the inhibitor actually inhibits the target because “it’s valuable to validate predictions of modeling with data.”).

2. Modeling/Docking of Specific Structures

a) Structures Modeled by Dr. Eck

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

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

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

107. When Dr. Eck modeled each structure, he obtained the top five docking poses because “[a]n important part of the docking exercise is understanding where a potential variability can come in.” EX1110, 152:6-153:2. Dr. Eck testified that analyzing whether modeling results suggest that a structure will productively irreversibly inhibit Btk requires assessing both the docking scores and docking poses. *See* EX1110, 155:4-10, 161:6-11, 162:11-163:4. I disagree with Dr. Eck, however, that a computer program could assess such modeling results in 2010/2011 or even now. *See* EX1110, 163:5-164:20. In my opinion, analyzing docking scores and docking poses in 2010/2011 or even now would require a human being to assess whether a structure would be active or productively irreversibly inhibit Btk.

(1) Dr. Eck's Native Files

108. For ibrutinib, Dr. Eck created two separate files, each of which contains multiple docking poses. One of Dr. Eck's native files discloses four docking poses for ibrutinib, wherein the most negative Glide docking score is -11.049. EX1113; EX2113. This particular docking pose of ibrutinib is the docking pose depicted in paragraph 116 of Dr. Eck's Declaration. EX1110, 147:15-148:20, 149:2-9. Another one of Dr. Eck's native files discloses five docking poses for ibrutinib, wherein the most negative Glide docking score is -8.781. EX1114; EX2114. This is the structure that Dr. Eck relied on "[a]s a point of reference" for analyzing his modeling results. *See* EX2010, ¶184 n.14; EX1110, 149:10-150:2. As Dr. Eck admitted, however, this structure is not the correct structure of ibrutinib – the vinyl group of the Michael acceptor has been modified to an ethyl group. *See* EX1110, 150:3-15. Further, the docking pose that Dr. Eck provided does not bring the modified Michael acceptor proximal to Cys481 (which has been truncated to Ala481 for docking purposes). Dr. Eck indicated that this mistake (*i.e.*, modeling the incorrect structure of ibrutinib) was due in part to the fact that he is an x-ray crystallographer—rather than a computational chemist—and therefore "usually like[s] to ignore hydrogens and turn them off as distracting." EX1110, 168:10-18. Further, Dr. Eck acknowledged that "in a particular docking run, there could be differences in score that depend on the

specifics of how the experiment was – how the docking exercise was done and in two separate docking runs, would not necessarily expect to come up with the same value” and “it’s important to compare apples to apples, oranges to oranges, and so that’s what I’ve tried to do here by docking ibrutinib in the same run with these other compounds.” EX1110, 137:12-138:3. However, Dr. Eck docked the incorrect structure for ibrutinib “in the same run with these other compounds.” Moreover, he reported the Glide score of -8.8 for ibrutinib in his declaration, based on this inaccurate structure, and did not report the Glide score of -11.0 he achieved when using the correct structure for ibrutinib. EX2010, ¶184 n.14. Thus, Dr. Eck significantly underrepresented the potency, based on modeling, of ibrutinib versus other analogs, including zanubrutinib.

109. For zanubrutinib, Dr. Eck created one file that includes five docking poses. The most negative Glide docking score for zanubrutinib that Dr. Eck obtained was -9.575. EX1115; EX2113; EX1110, 151:1-13. While this is the lowest energy conformer of zanubrutinib, the Michael acceptor is not positioned near Cys481 (which has been truncated to Ala481 for docking purposes). In my opinion, the zanubrutinib structure that is relevant to forming the covalent interaction with Btk is one that has a different docking pose and less negative Glide docking score (-9.062), wherein the Michael acceptor is positioned near Cys481. EX1115; EX2113;

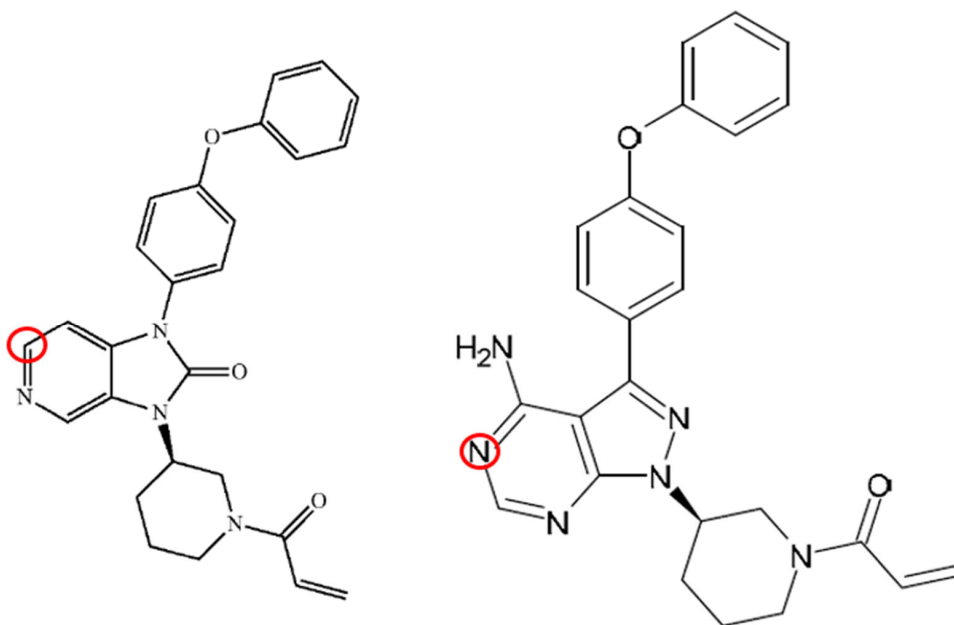
EX1110, 151:14-19. Notably, Dr. Eck also used the zanubrutinib structure with the -9.062 docking score in his Declaration. EX1110, 151:14-152:1.

110. Dr. Eck modeled Compounds 7 and 8 of Zhang 2020. EX2010, ¶185. Notably, Zhang 2020 was not published until 2020 and therefore would not have been available to a POSA in 2011. While the authors had access to and used Glide software, they nevertheless chose to synthesize compounds and measure inhibitory activity in IC₅₀ assays. EX1105, ¶¶47-51. In my opinion, to the extent that modeling or docking is predictive as Dr. Eck suggests, the authors would not have chosen to synthesize and test such compounds.

111. For Compound 7 of Zhang, Dr. Eck created one file that includes five docking poses. EX1116; EX2114. The most negative Glide docking score that Dr. Eck obtained for Compound 7 was -6.483, which corresponds to the docking score (-6.5) disclosed in paragraph 185 of Dr. Eck's Declaration. EX1110, 153:7-19. Dr. Eck's modeling results show that Compound 7 formed two H-bonds to E475 C=O and M477 NH and properly oriented the phenoxyphenyl to bind within Btk's back pocket. EX1110, 156:15-157:14. While Dr. Eck contends that Compound 7 meets the requirements of the orb in Formula E in the 803 Patent. EX1110, 158:2-7. Yet, despite forming two H-bonds and properly orienting the linker-warhead and

phenoxyphenyl, experimental results show that Compound 7 is inactive with an IC_{50} value $> 1,000$ nM. EX2063.0002 (Fig. 3).

112. Dr. Eck modeled compounds 20, 30 and 122 of the 446 Patent, which claims priority to a PCT application filed in October 2016 and issued in July 2019. EX2010, ¶185. Dr. Eck contends that docking Compound 122 of the 446 Patent revealed that this compound was a poor candidate for irreversibly inhibiting Btk where “one pose was obtained in which the phenoxyphenyl group was properly positioned and the linker-warhead was oriented toward Cys481, but the heterocyclic Z'-scaffold was not positioned to make even one H-bond to the hinge.” EX2010, ¶184. Dr. Eck's discussion indicates that a POSA might have been able to predict that Compound 122 would not irreversibly inhibit Btk because Compound 122 lacks a nitrogen at the C5 position of the 6-membered ring (C5 position circled in red) that is present in ibrutinib and that is necessary to form a H-bond to Btk's hinge region (N5 position circled in red). *Id.*



Compound 122 (shown on left); ibrutinib (shown on right)

113. However, Dr. Eck's opinion that a POSA would have recognized that Compound 122 was unlikely to productively bind and irreversibly inhibit Btk is inconsistent with his position that specification discloses E2-E4 as cores that would bind Btk's hinge region. EX2010, ¶¶184, 147 ("A POSA would have understood the specification's Formula E as referring to the understanding that diverse structures would bind within the active site."). That is because E2-E4 also lack nitrogen at the ibrutinib N5 position of the 6-membered ring. This undercuts Dr. Eck's position that a POSA could predict that Compound 122 would not productively bind Btk. Indeed, why would the inventors disclose such Z'-scaffolds lacking a nitrogen at N5

if they would have known in 2011 that such Z'-scaffolds would not productively bind.

b) Structures Modeled with Reported IC₅₀ Values

114. I have performed my own modeling of various structures with reported IC₅₀ values using Glide. Consistent with Dr. Eck's testimony, I specified that the Glide docking process return five docking poses and scores for each structure.

115. In order to assess whether modeling suggests that each structure would be active or productively irreversibly inhibit Btk based on its Glide docking score, I modeled and used the most negative docking scores of four specific structures as references. As references of docking scores that suggest activity or productive binding of Btk, I used two BTKIs that Dr. Eck agrees irreversibly inhibit Btk, ibrutinib (-10.5) and zanubrutinib (-9.3). The differences in my scores versus Dr. Eck's scores for ibrutinib and zanubrutinib may result from the use of a different underlying forcefield in the docking process; I used the widely regarded OPLS5 forcefield, but Dr. Eck did not specify the forcefield he used. As references of docking scores that suggest inactivity or a lack of productive binding of Btk, I used two BTKIs that Dr. Eck agrees do not irreversibly inhibit Btk, Compounds 30 (-8.5) and 122 (-8.3) of the 446 Patent. I have also considered the docking poses for each

structure in order to assess whether modeling suggests that the structure would be active or productively irreversibly inhibit Btk.

116. Below is a table summarizing the most negative docking scores I obtained for various structures when performing modeling using Glide, including the four structures that I used as reference points, which are followed by an asterisk (*).

Reference	Compound	Glide Docking Score	Reported IC ₅₀ Value	Reported IC ₅₀ Value Source
	Ibrutinib*	-10.5	2.0 nM	EX2063.0002 (Fig. 3)
	Zanubrutinib*	-9.3	0.3 nM (S isomer); 11 nM (R isomer)	EX1053.005 (Table 6)
WO'289 (EX1108)	Compound 81	-9.7	5,900 nM	EX1108, [0642], Table II
WO'185 (EX1109)	Compound 9	-10.3	> 1000 nM < 100,000 nM	EX1109, [00348]
446 Patent (EX2024)	Compound 30*	-8.5	≥10000 nM	EX2024.0118-0119
446 Patent (EX2024)	Compound 122*	-8.3	1000-10000 nM	EX2024.0118-0119

117. In my opinion, my modeling results show that modeling does not accurately predict whether a structure will productively bind and irreversibly inhibit Btk. These results support my conclusion that experimental testing is necessary to determine whether any given BTKI structure will irreversibly inhibit Btk.

118. *First*, the Glide modeling results for Compound 81 of WO'289 and Compound 9 of WO185 do not align with the reported IC₅₀ values, as shown below.⁶

Reference	Compound	Docking Score	Reported IC50 Value
WO'289 (EX1108)	Compound 81	-9.7	5,900 nM
WO'185 (EX1109)	Compound 9	-10.3	1000 to <100,000 nM

119. In my opinion, a compound with an IC₅₀ value of greater than 1,000 nM would be inactive or not productively inhibit Btk and such a compound would not satisfy the Functional Limitations of the Challenged Claims. Indeed, Dr. Eck testified that a compound with an IC₅₀ value of 1,000 nM would not fall within the scope of the Challenged Claims because a POSA would not want to administer such a compound to human as the Challenged Claims require. EX1110, 159:17-160:1 (“I think it’s unlikely that one would want to advance micro molar irreversible BTK inhibitor. I can’t imagine that—that anyone would want to do that.”); *see also*

⁶ I also modeled other compounds with reported IC₅₀ values, specifically Compounds 8, 10, and 11 of Zhang, Compound 20 of the 446 Patent, and Compound 2 of WO'185. EX1146. The docking poses and scores for these compounds were consistent with their reported IC₅₀ values. Those results, however, do not change my opinion that modeling is not predictive. The fact that modeling is sometimes consistent and sometimes inconsistent with experimental data underscores that modeling cannot accurately predict irreversible inhibition of Btk.

EX1110, 140:7-11 (Dr. Eck testifying that a compound with an IC₅₀ value greater than 1,000 nM is not a very potent inhibitor).

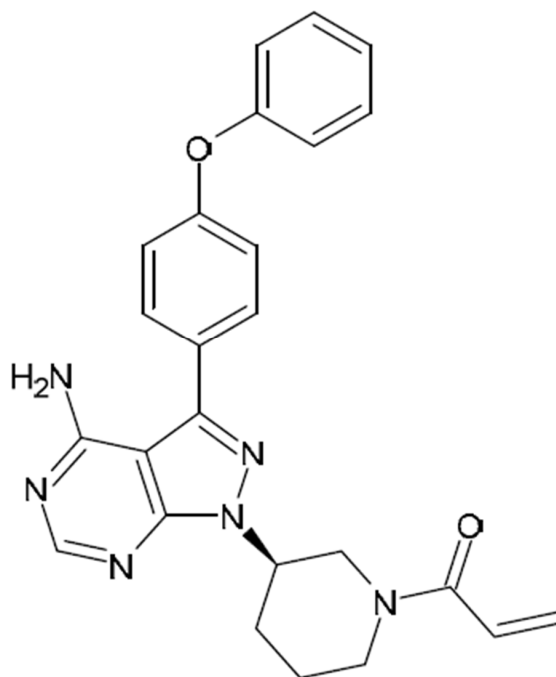
120. *Second*, the modeling results show that modeling does not predict how effectively a compound will irreversibly inhibit Btk. For example, it has been demonstrated that zanubrutinib irreversibly inhibits Btk better than ibrutinib. EX1069.004. When modeling these BTKIs in Glide, however, ibrutinib has a more negative docking score than zanubrutinib, which if predictive, would suggest that ibrutinib will irreversibly inhibit Btk better than zanubrutinib. Specifically, zanubrutinib had a less negative docking score (-9.3) compared to ibrutinib (-10.5). If one were to make the assumption that the difference in the Glide score correlates to a 1.2 kcal/mol difference in binding free energy, the result suggests that zanubrutinib would be nearly 10 times less active than ibrutinib, which does not align with the empirical results. *See* EX1127.002.

121. Below is a further description of my modeling and results for each structure. For each structure, I considered whether the Z'-scaffold would form H-bonds with Btk's hinge region and properly orient the linker-warhead to allow formation of a covalent bond with Cys481 and phenoxyphenyl to bind within Btk's back pocket. Further, it is difficult to determine whether the linker-warhead is

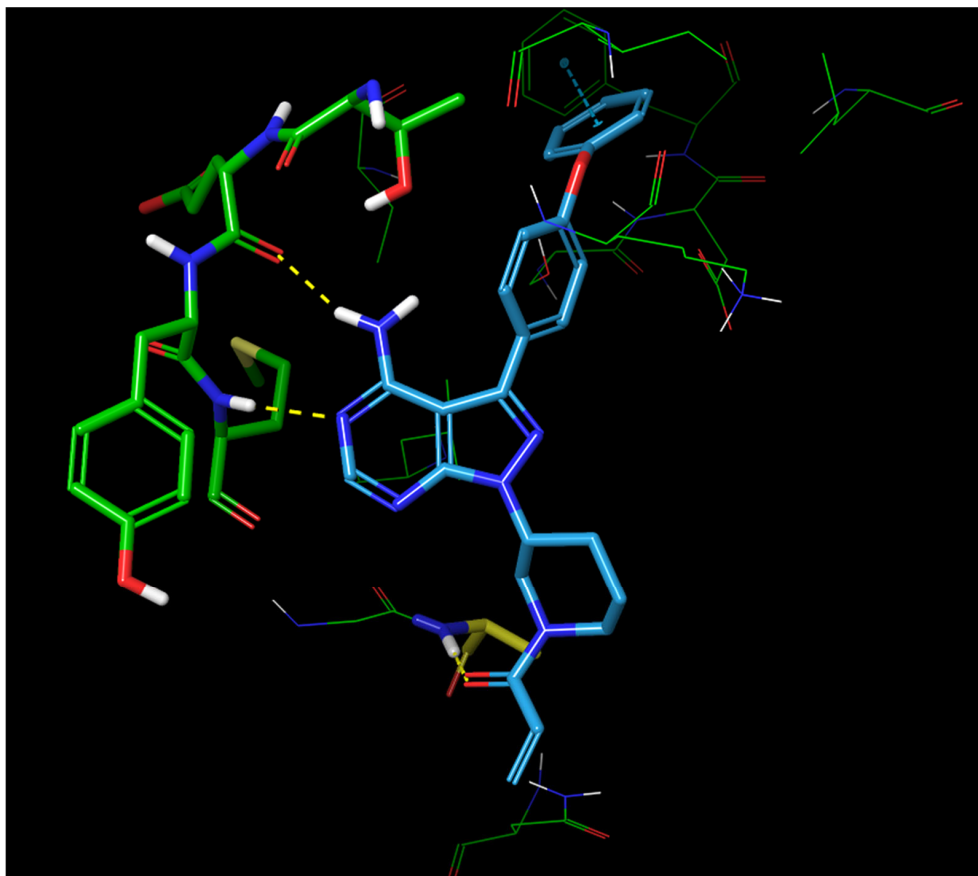
properly oriented to covalently bind Cys481 because it depends on both the conformation of the ligand and the ability of Cys481 to rotate.

(1) Ibrutinib

122. Ibrutinib comprises a biaryl Z'-scaffold, as shown below:



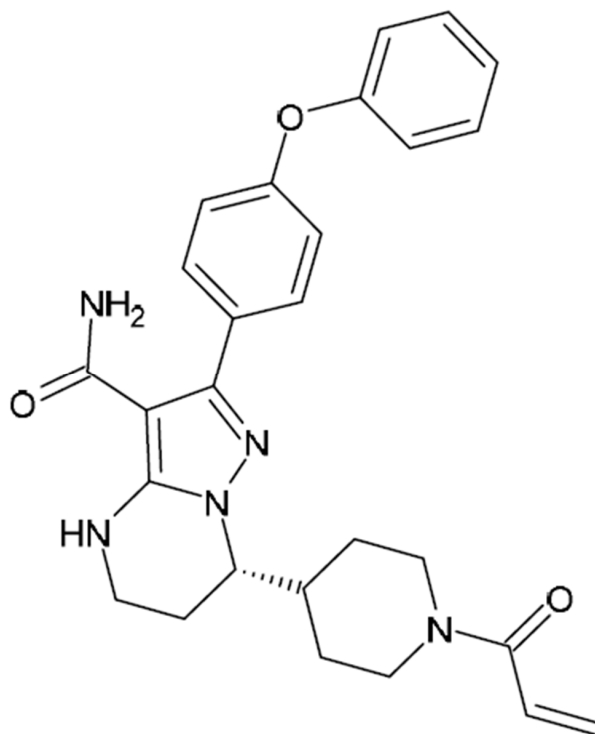
123. The top five docking poses and docking scores of ibrutinib suggest that ibrutinib forms two H-bonds to E475 C=O and M477 NH and properly orients the linker-warhead to covalently bind Cys481 and the phenoxyphenyl to bind Btk's back pocket. Below is the docking pose of ibrutinib with the most negative Glide docking score (-10.5).



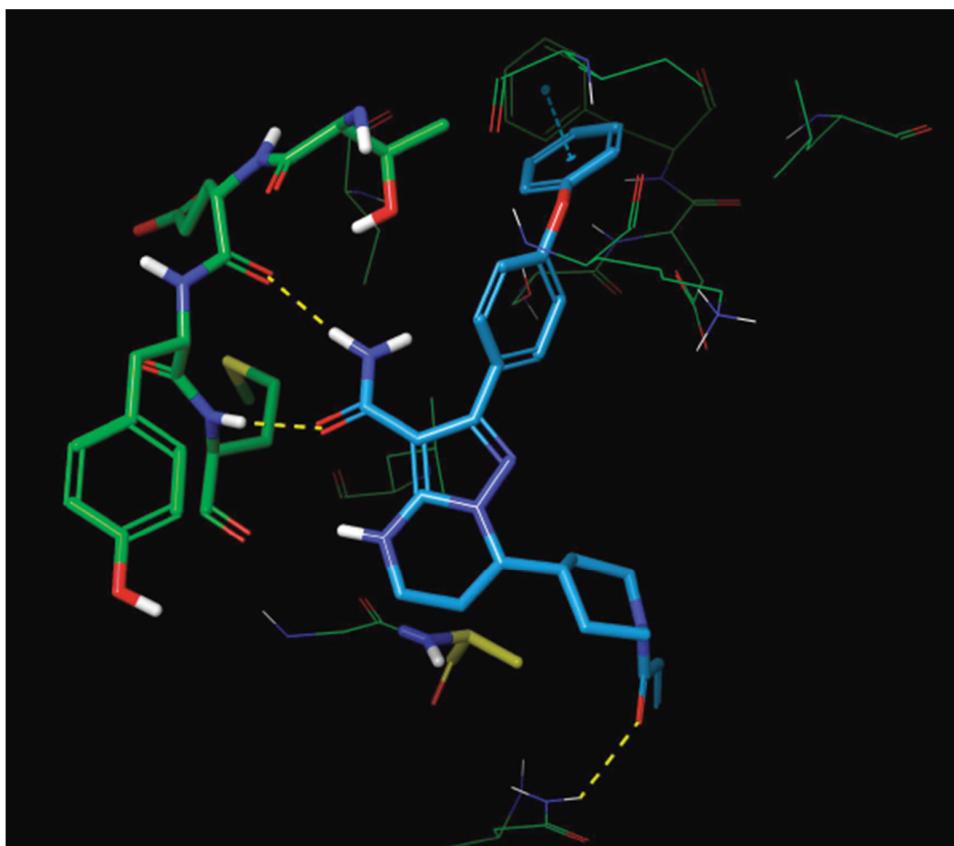
EX1140.001

(2) Zanutrutinib

124. Zanutrutinib, the structure of which was not publicly disclosed until 2015 (*see* EX1034), comprises a non-biaryl Z'-scaffold, as shown below:



125. The top five docking poses and docking scores of zanubrutinib suggest that zanubrutinib forms two H-bonds to E475 C=O and M477 NH, as well as a weaker H-bond/electrostatic interaction with M477 C=O, and properly orients the linker-warhead to covalently bind Cys481 and the phenoxyphenyl to bind Btk's back pocket. Below is the docking pose of zanubrutinib with the second most negative Glide docking score (-9.2). The docking pose with the most negative score (-9.3) did not have the linker-warhead properly positioned to covalently bind Cys481.



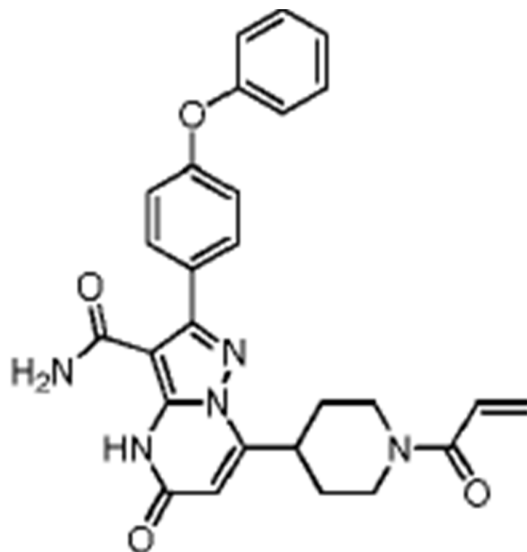
EX1141.002

(3) WO2014173289 (EX1108)

126. While modeling Compound 81 using Glide suggests that this compound will irreversibly inhibit Btk (-9.7), a POSA would have understood that the empirical results show that Compound 81 is inactive, with a high IC₅₀ value of 5,900 nM. EX1108, [0642], Table II. This supports my opinion that modeling does not accurately predict irreversible inhibition of Btk and may result in false positives.

(a) Compound 81

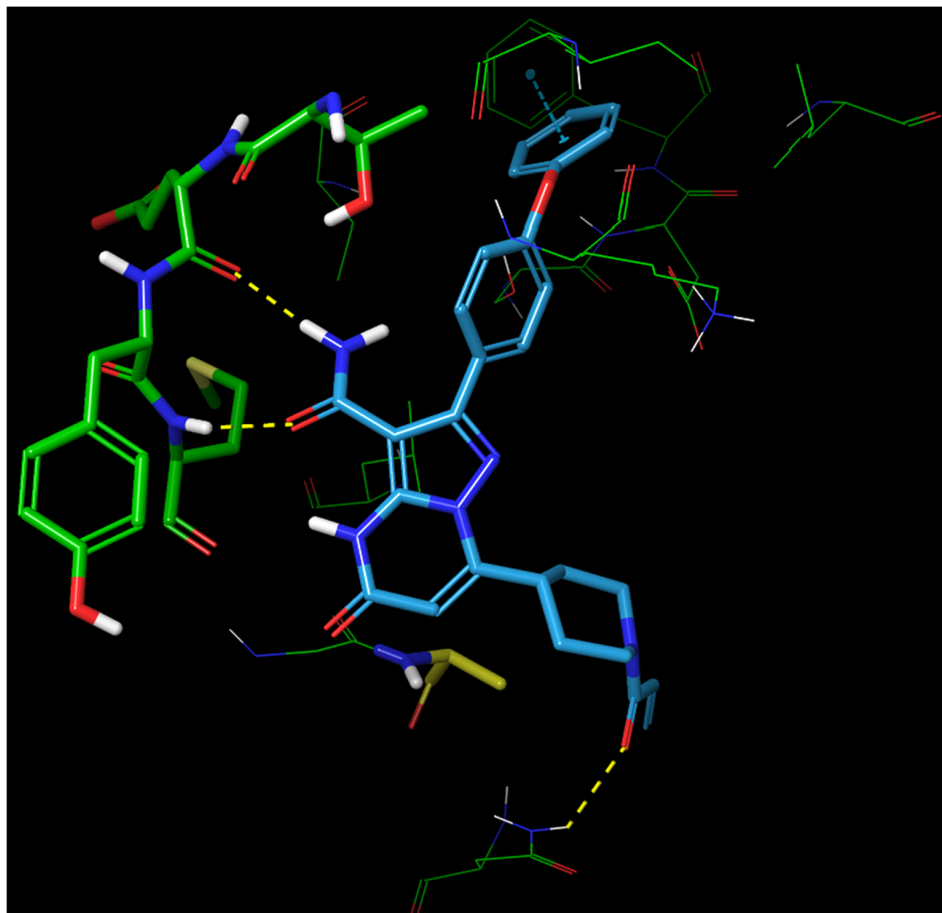
127. Compound 81 comprising a non-biaryl Z'-scaffold is shown below:



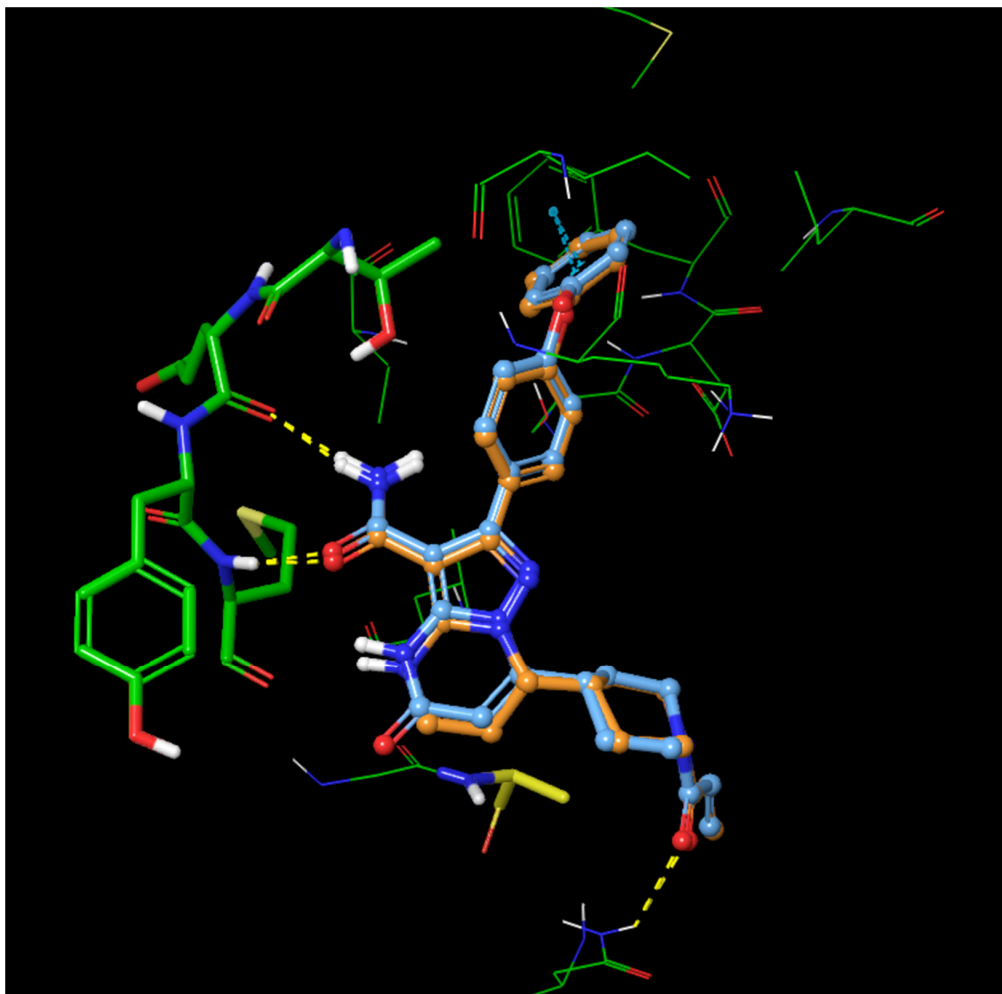
EX1108, [0538]

128. Compound 81 yielded a nice docking pose, which scored better than zanubrutinib. Specifically, there were two H-bonds to E475 C=O and M477 NH, as well as a weaker H-bond/electrostatic interaction with M477 C=O, and the linker-warhead and phenoxyphenyl were properly oriented to form a covalent bond with Cys481 and bind with Btk's back pocket, respectively. There were no bad steric interactions. The overlap of Compound 81 and zanubrutinib binding poses is high as can be seen in the figure below. In my opinion, the reason that the IC₅₀ value of Compound 81 shows inactivity remains unclear but may be because of the lack of the optimal third H-bond or the carbonyl group of the 6-membered ring of Z'-scaffold making unfavorable interactions with Btk residues in its vicinity. Below is

the docking pose of Compound 81 with the most negative Glide docking score (-9.7), as well as the overlap to the preferred docking pose of zanubrutinib.



EX1142.001



EX1156.001

129. Notably, the inventors of WO'289 chose to synthesize and test Compound 81 to obtain its IC₅₀ value despite having access to modeling software in 2014. EX1105, ¶¶54-55. The fact that the inventors were investigating and developing Compound 81 supports my opinion that there was a lack of predictability in 2010/2011 (and even today). In my opinion, if modeling could have accurately

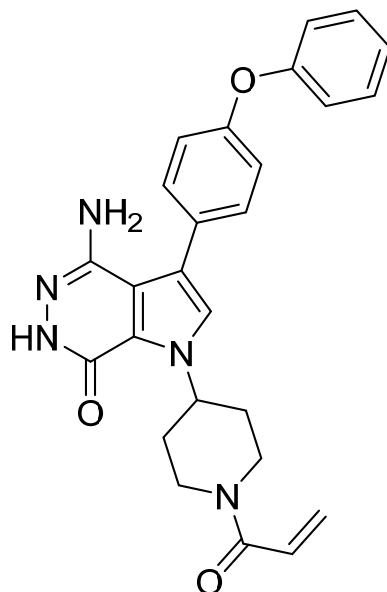
predicted Btk binding, the inventors of WO'289 would not have chosen to synthesize and test this inactive compound.

(4) WO2016007185 (EX1109)

130. While modeling using Glide suggests that Compound 9 will irreversibly inhibit Btk (-10.3), a POSA would have understood the empirical results to show that Compound 9 is inactive, with a high IC_{50} value of greater than 1000 nM but less than 100,000 nM. EX1109, [00348], Table 4. This supports my opinion that modeling does not accurately predict irreversible inhibition of Btk and may result in false positives.

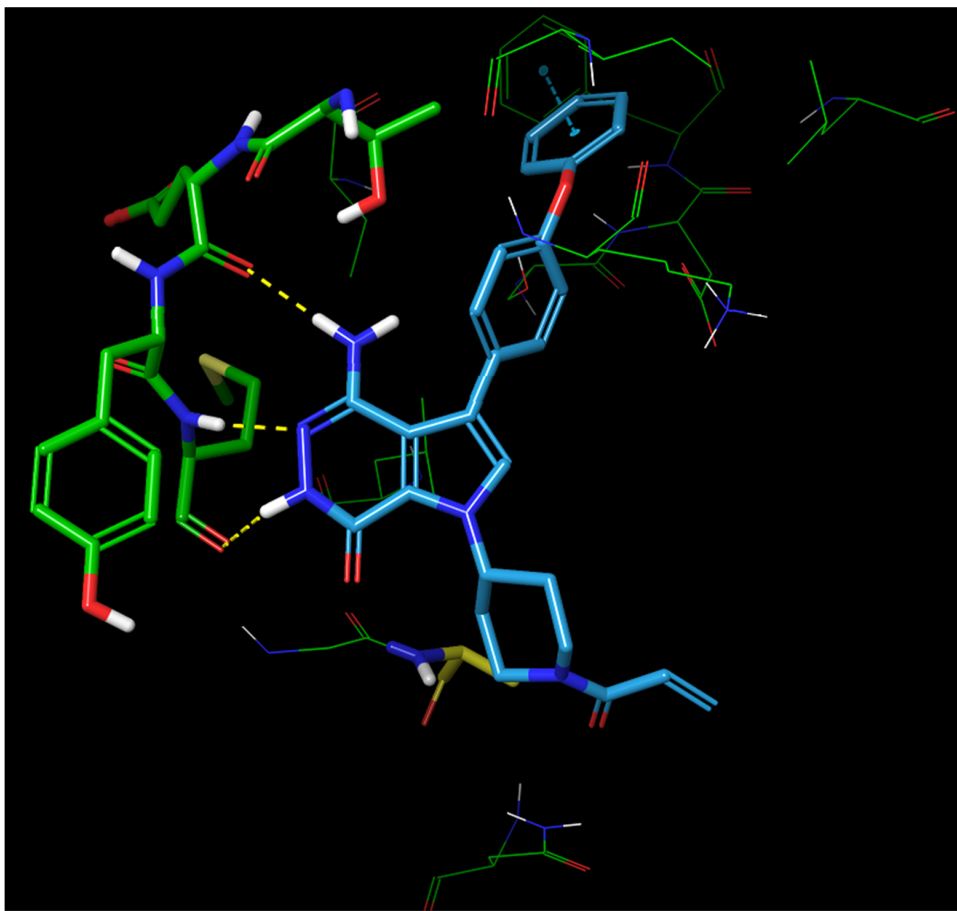
(a) Compound 9

131. Compound 9 is shown below:



EX1109, [00118], Table 1

132. Compound 9 docked well (better than zanubrutinib), forming three H-bonds to E475 C=O, M477 NH, and M477 C=O. Compound 9 also properly oriented the linker-warhead to covalently bind Cys481 and the phenoxyphenyl to bind Btk's back pocket. There was no sign of steric clash. In my opinion, the IC₅₀ value shows Compound 9 is inactive because the carbonyl group on the Z'-scaffold either makes unfavorable interactions with Btk residues in its vicinity or causes a twist of the ligand piperidine ring that moves it into a less favorable conformation. Below is the docking pose of Compound 9 with the most negative Glide docking score (-10.3).



EX1143.001

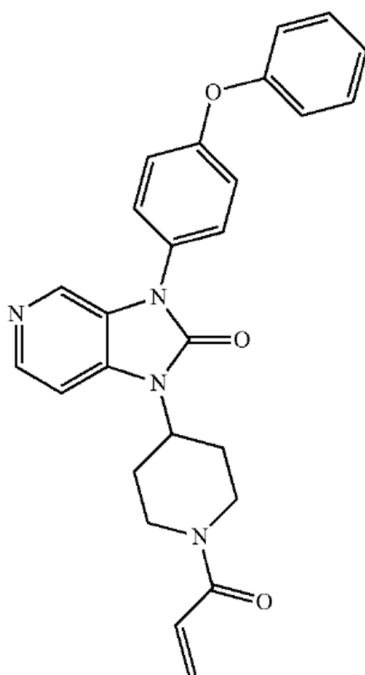
133. Notably, the inventors of WO'185 chose to synthesize and test Compound 9 to obtain its IC₅₀ value despite having access to modeling software in 2014. EX1105, ¶¶56-57. The fact that the inventors were investigating and developing Compound 9 supports my opinion that there was a lack of predictability in 2010/2011 (and even today). In my opinion, if modeling could have accurately predicted Btk binding, the inventors of WO'185 would not have chosen to synthesize and test this inactive compound.

(5) 446 Patent (EX2024)

134. I also modeled Compounds 20, 30, and 122 of the 446 Patent. Compound 20 was found to be active as a BTKI ($IC_{50} > 10\text{-}100\text{ nM}$) whereas Compounds 30 and 122 were inactive ($IC_{50} > 10\text{ }\mu\text{M}$). EX2024.0118-.0119. It is undisputed that the inventors of the 446 Patent had access to modeling software, but nevertheless chose to synthesize and test each of these compounds to obtain their IC_{50} values. EX1105, ¶¶52-53. In my opinion, to the extent that modeling or docking is predictive as Dr. Eck suggests, the authors would not have chosen to synthesize and test compounds.

(a) Compound 30

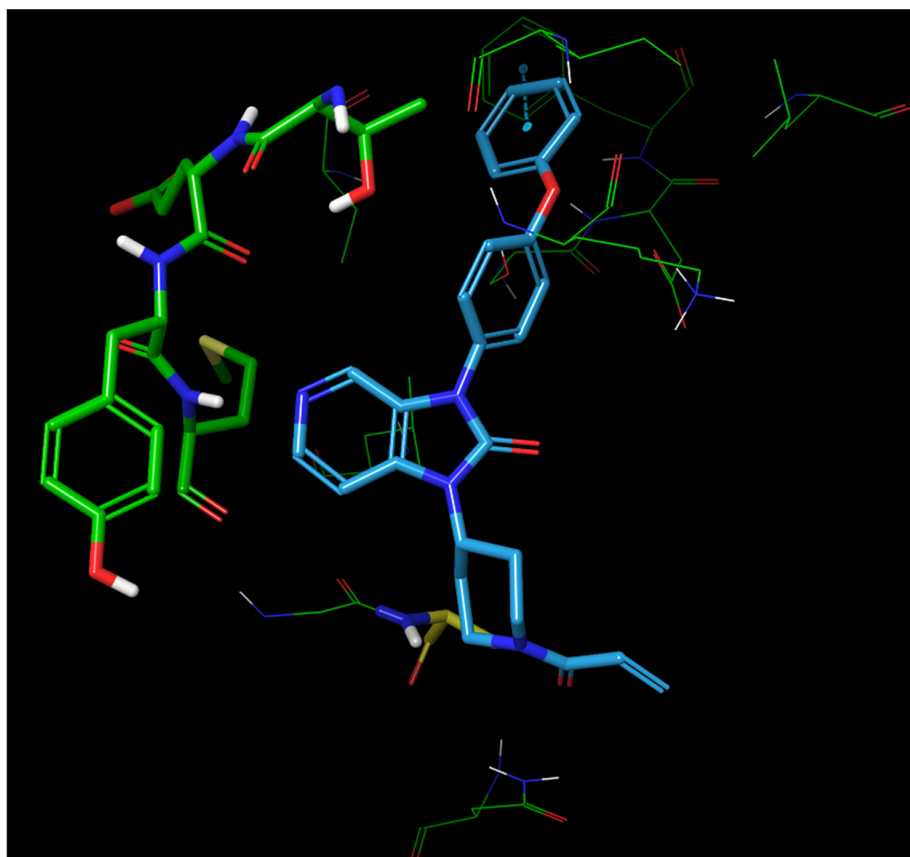
135. Compound 30 is shown below:



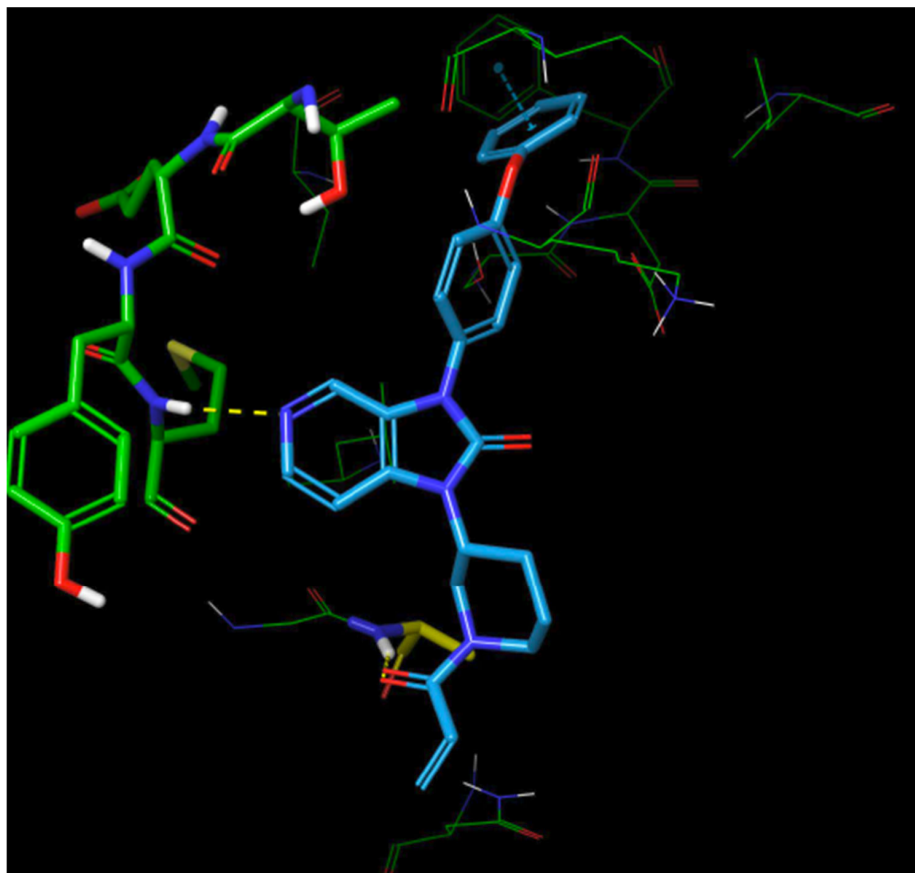
EX2024, 59:1-60:67 (Entry 30)

136. Compound 30 formed one H-bond to M477 NH and the phenoxyphenyl was properly oriented to bind Btk's back pocket. Note that Dr. Eck did not observe a docking pose that properly positioned the phenoxyphenyl group (EX2010 ¶184), but this was not the case in my docking where multiple poses had the phenoxyphenyl properly positioned. However, the Michael acceptor was slightly more removed from Cys481 compared to ibrutinib and Compound 20 docked structures. There may also be unfavorable solvation or electrostatics that reduced the binding interaction energy. In my opinion, the inactivity of Compound 30 ($IC_{50} > 10000$ nM) is most likely due to the sterics of the carbonyl group on the Z'-scaffold causing

a subtle conformational change in the adjacent piperidine ring that then puts this ring and the linker-warhead either in an unfavorable binding interaction with Btk or in a conformation not suitable for covalent modification of Cys481. Below is the docking pose of Compound 30 with the most negative Glide docking score (-8.5). Although Compound 30 had a lower Glide score (-8.5) as compared to Compound 20 (-9.5), the best docking poses observed for Compounds 20 and 30 were similar, as shown below. The Compound 30 score may also be compared to that observed for zanubrutinib (-9.2), and thus a -8.5 score corresponds to an inactive compound and a -9.2 score corresponds to a highly potent low nM to pM inhibitor. In my opinion, these results again highlight the inability of modeling to reliably predict accurate binding affinities for inhibitors.



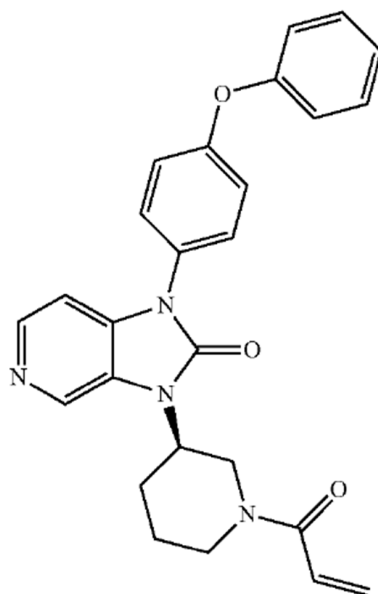
EX1144.001



EX1146.005

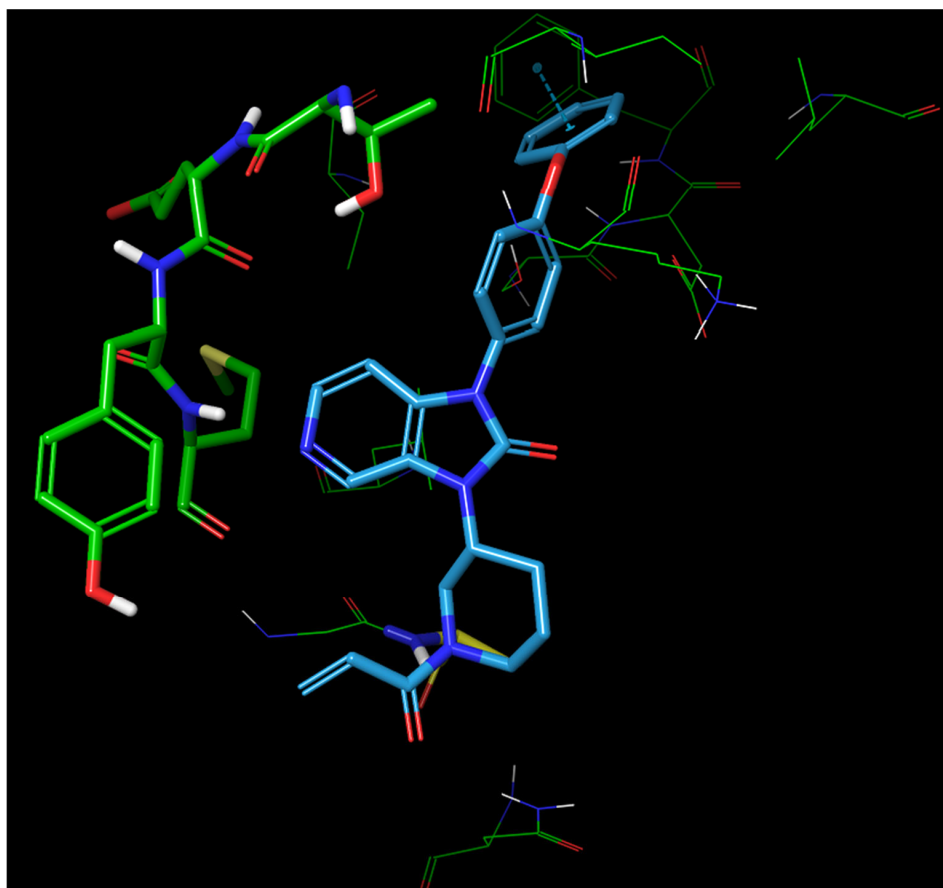
(b) Compound 122

137. Compound 122 is shown below:



EX2024, 119:1-120:67 (Entry 122)

138. Compound 122 properly oriented the linker-warhead and phenoxyphenyl to covalently bind Cys481 and bind to Btk's back pocket, respectively. However, visual inspection of the docking pose also showed that all H-bonding to Btk's hinge region, specifically the NH of Met477, would be poor due to the location of the nitrogen in the pyridine ring as compared to Compounds 20 and 30. The pyridine N would also potentially now be repulsive with the C=O of Met477. Thus, modeling suggests that Compound 122 is inactive and does not productively irreversibly inhibit Btk. Below is the docking pose of Compound 122 with the most negative Glide docking score (-8.7).



EX1145.001

c) Z'-Scaffolds Modeled

139. I performed modeling of various known biaryl and non-biaryl Z'-scaffolds that Dr. Eck alleges that a POSA could easily use to perform "scaffold swapping." EX2010, ¶¶104, 171, 172, 174. Dr. Eck acknowledged that he did not model any of them but to do so a POSA would need to take each of these known scaffolds, use modeling to superimpose them onto ibrutinib's structure, determine where to attach the fixed claimed linker-warhead and phenoxyphenyl, and analyze

whether that particular structure would irreversibly inhibit Btk. EX1110, 75:25-76:15, 91:2-93:18, 95:16-22, 96:2-98:10. Consistent with Dr. Eck's testimony, I modeled each of these Z'-scaffolds, attaching the claimed linker-warhead and phenoxyphenyl to each Z'-scaffold. In my opinion, however, determining where to attach these fixed substituents is a complex task, which is neither routine nor predictable. For each structure, I performed modeling using Glide and obtained Glide docking scores for five different poses for each structure. I then assessed whether modeling suggests that the structure will irreversibly inhibit Btk, using the docking scores of the same four specific structures described above as references and taking the docking poses for each structure into consideration. *See supra* Section VI.C.2.b). Notably, the 803 Patent and art do not disclose that any of these Z'-scaffolds with the claimed linker-warhead and phenoxyphenyl substituents will irreversibly inhibit Btk or satisfy the Functional Limitations.

140. The Z'-scaffolds that I modeled fall within the four subgenera of the Challenged Claims, namely: (1) biaryl – aromatic 5-membered ring fused to an aromatic 6-membered ring; (2) 5-aro, 6-non-aro – aromatic 5-membered ring fused to a non-aromatic 6-membered ring; (3) 5-non-aro, 6-aro – non-aromatic 5-membered ring fused to an aromatic 6-membered ring; and (4) 5-non-aro, 6-non-aro – non-aromatic 5-membered ring fused to a non-aromatic 6-membered ring.

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

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

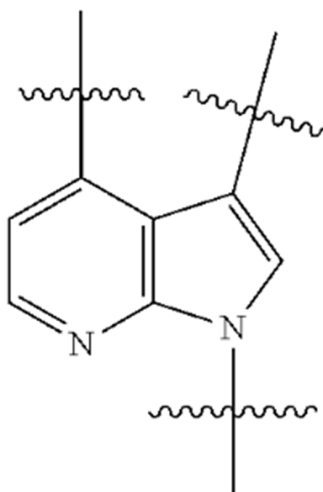
142. If a POSA would rely on modeling to predict whether a compound will irreversibly inhibit Btk (which a POSA would not), a POSA would have concluded that the inventors did not possess any non-biaryl Z'-scaffolds that irreversibly inhibit Btk; modeling suggests that compounds comprising the only non-biaryl scaffolds that Dr. Eck asserts were known in the art, as listed in the above table, do not irreversibly inhibit Btk. Therefore, a POSA would have been led away from using

non-biaryl Z'-scaffolds. Further, modeling suggests that some of the biaryl scaffolds would not irreversibly inhibit Btk, including Structures E2 and E3 disclosed in the specification. This further bolsters my conclusion that at most the inventors did not possess the full scope of Z'-scaffolds and that the only biaryl Z'-scaffolds they possessed were close mimetics of ibrutinib.

143. Below is a further description of my modeling and results for each structure. For each structure, I considered whether the Z'-scaffold would form H-bonds with Btk's hinge region and properly orient the linker-warhead to allow formation of a covalent bond with Cys481 and phenoxyphenyl to bind within Btk's back pocket.

(1) 803 Patent (EX1001), Structure E2

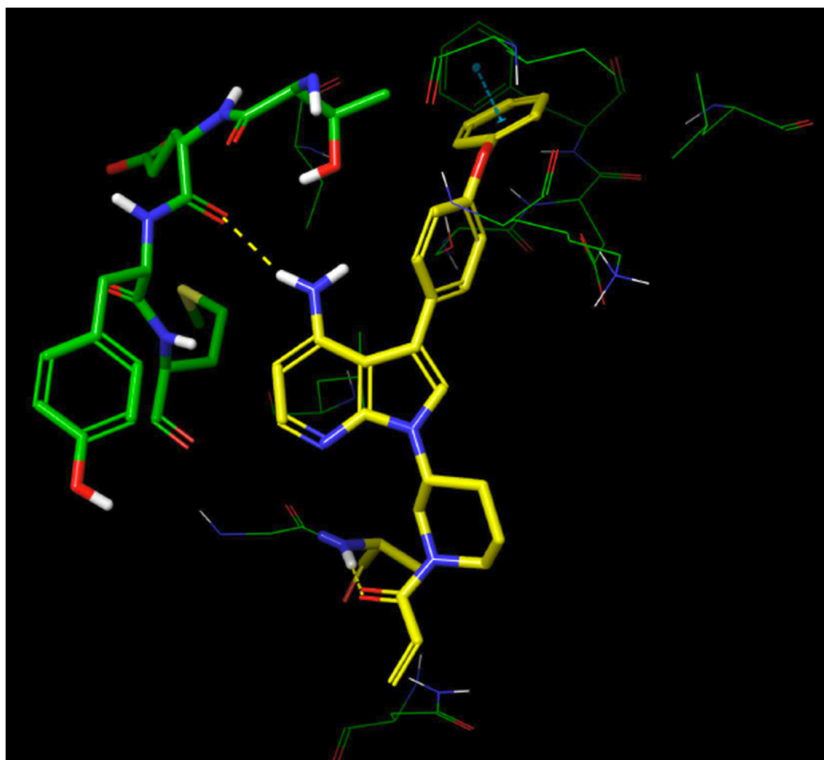
144. Structure E2 comprises a biaryl core, as shown below:



EX1001, 62:44-63:21

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

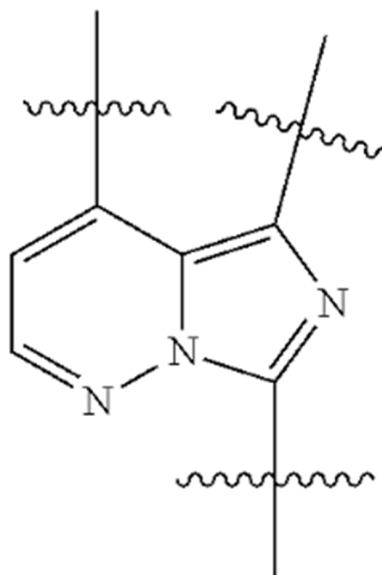
146. Structure E2 properly oriented the linker-warhead and phenoxyphenyl to bind Cys481 and Btk's back pocket, respectively. Modeling suggests that Structure E2 is inactive, however, because it does not form any H-bonds to Btk's hinge region. Below is the docking pose of Structure E2 with attached substituents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



EX1147.001

(2) 803 Patent (EX1001), Structure E3

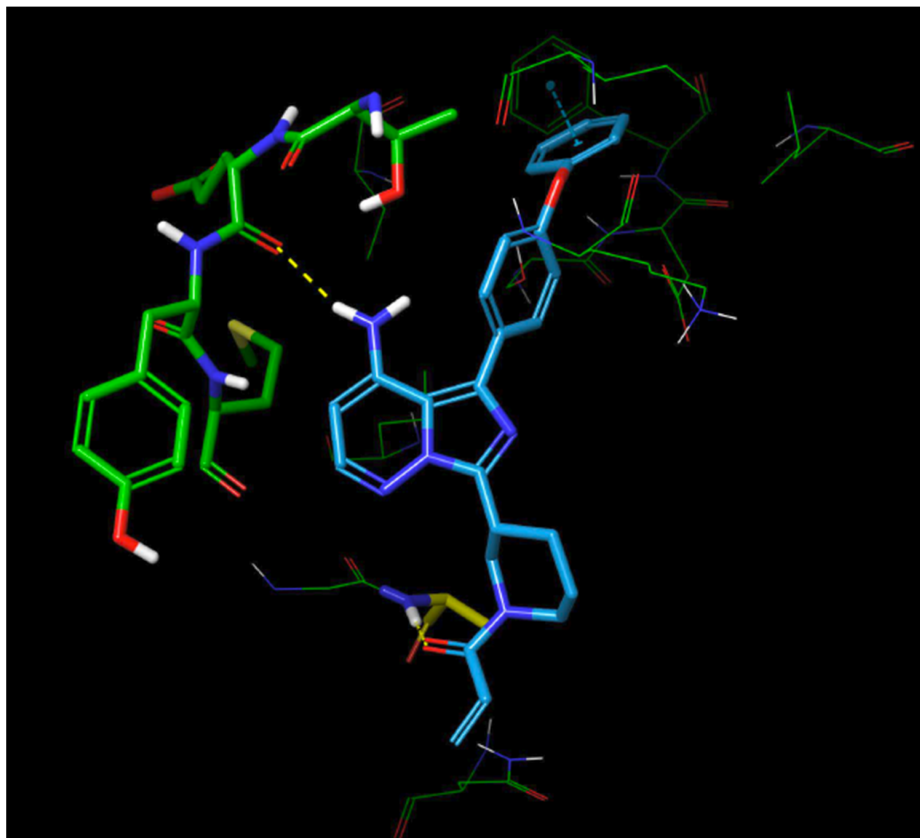
147. Structure E3 comprises a biaryl core, as shown below:



EX1001, 62:44-63:21

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

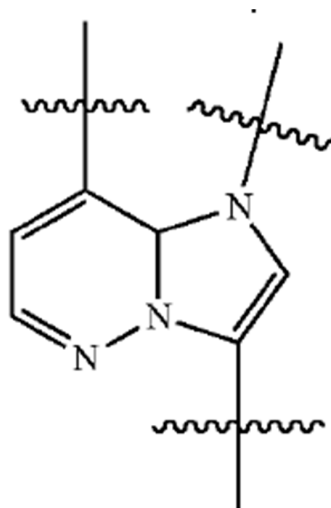
149. Structure E3 properly oriented the linker-warhead and phenoxyphenyl to bind Cys481 and Btk's back pocket, respectively. Modeling suggests that Structure E3 is inactive, however, because it does not form any H-bonds to Btk's hinge region. Below is the docking pose of Structure E3 with attached substituents with the most negative Glide docking score (-8.6).



EX1148.001

(3) 803 Patent (EX1001), Structure E4

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

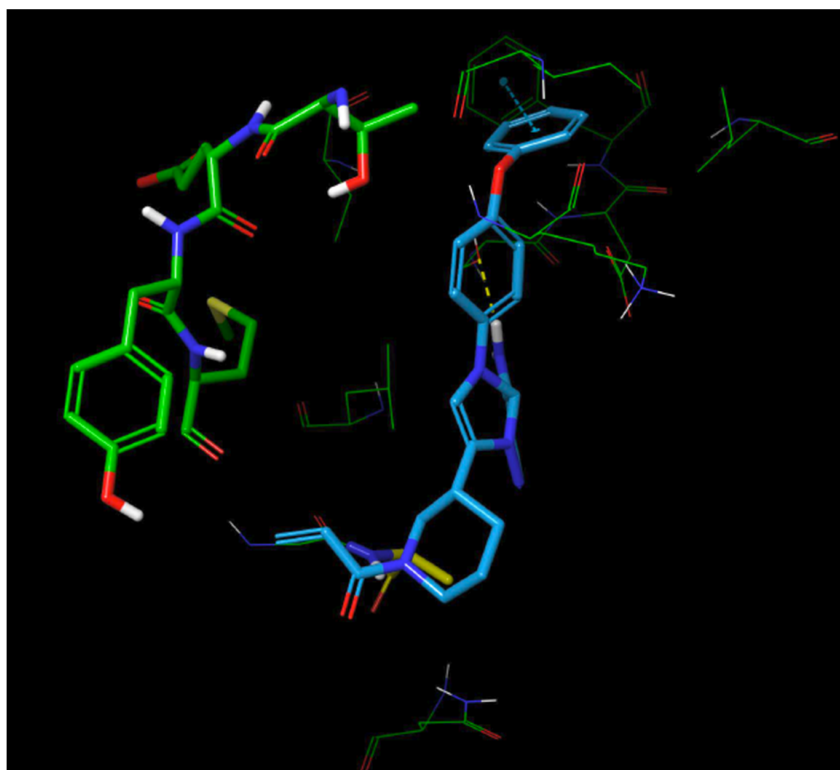


EX1001, 62:44-63:21

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

152. While Structure E4 properly oriented the phenoxyphenyl to bind Btk's back pocket, Structure E4 was not at all tolerated in the binding site of Btk, did not form any H-bonds to Btk's hinge region, and did not properly orient the linker-warhead to covalently bind Cys481 (even the best docking pose had the linker-warhead significantly displaced from the vicinity of Cys481). In my opinion, Structure E4 does not dock well at least in part because it does not have one of the

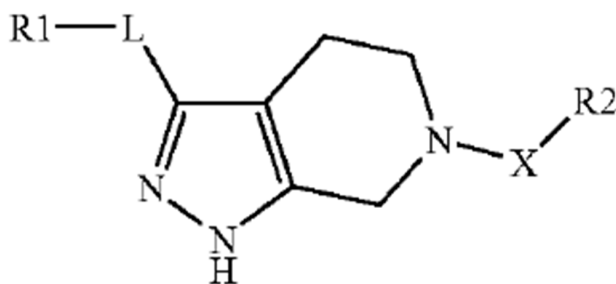
aromatic nitrogens that is present in ibrutinib and forms a H-bond with Btk's hinge region. Moreover, the "butterfly" conformation of the structure due to its sp^3 hybridized carbon favoring a tetrahedral geometry leads to an unfavorable steric clash that displaces the ligand from the adenine binding region. Below is the docking pose of Structure E4 with attached substituents with the most negative Glide docking score (-7.4).



EX1149.001

(4) 820 Patent (EX2023), Formula I

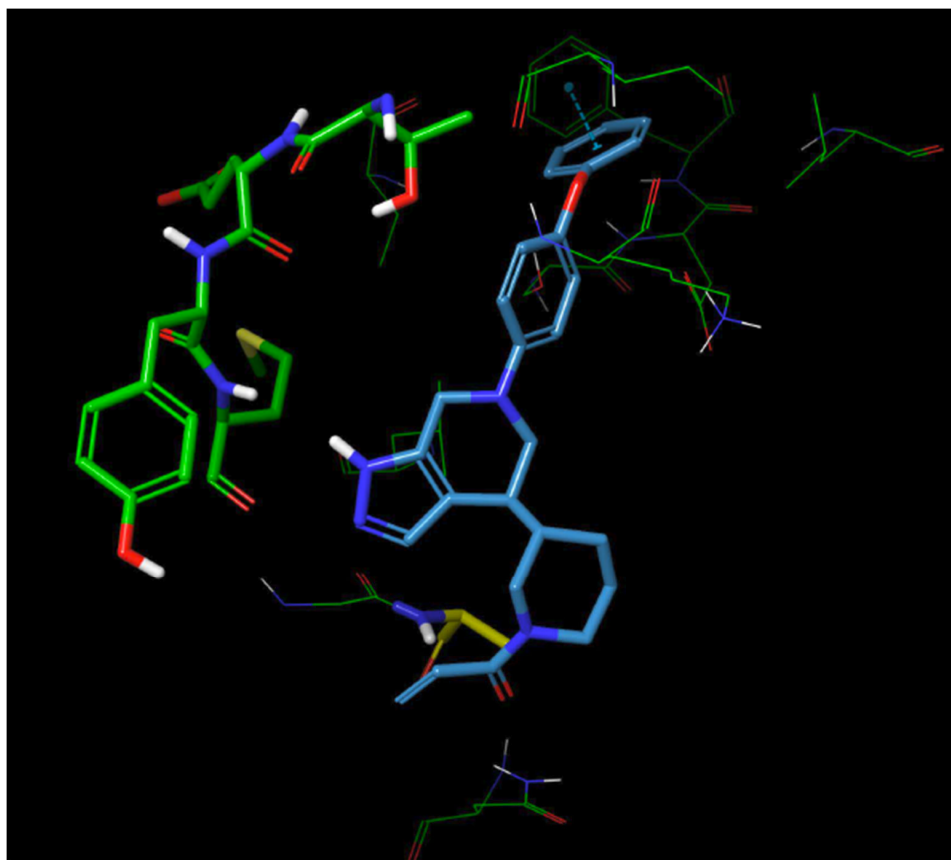
153. Formula I of the 820 Patent comprises a non-biaryl Z'-scaffold (a non-aromatic 6-membered ring fused to an aromatic 5-membered ring), as shown below:



EX2023, 1:65-2:6

154. In my opinion, a POSA would recognize that the 5-membered ring (pyrazole group) would almost certainly be the hinge binder moiety on the scaffold and form H-bonds to Btk's hinge region with the pyrazole NH forming a H-bond to Glu475 C=O and the pyrazole N forming an H-bond to Met477 NH. Based on this concept, the phenoxyphenyl was attached to the 6-membered ring (piperidine) nitrogen and the linker-warhead was attached to the unsubstituted carbon of the piperidine meta to the piperidine nitrogen. The chirality of the carbon was varied, and the warhead was incorporated both meta and para within the linker-warhead ring. The Glide docking poses that resulted from this approach were unfavorable for binding to Btk with the best Glide score being -7.4. The phenoxyphenyl docked correctly and the linker-warhead was able to position as well in the vicinity of Cys481. However, making these binding interactions significantly distorted the ability of the pyrazole to bind proximal to the hinge region and form appropriate H-bonds. Thus, it is my opinion that the 820 Patent (EX2023), Formula I structure

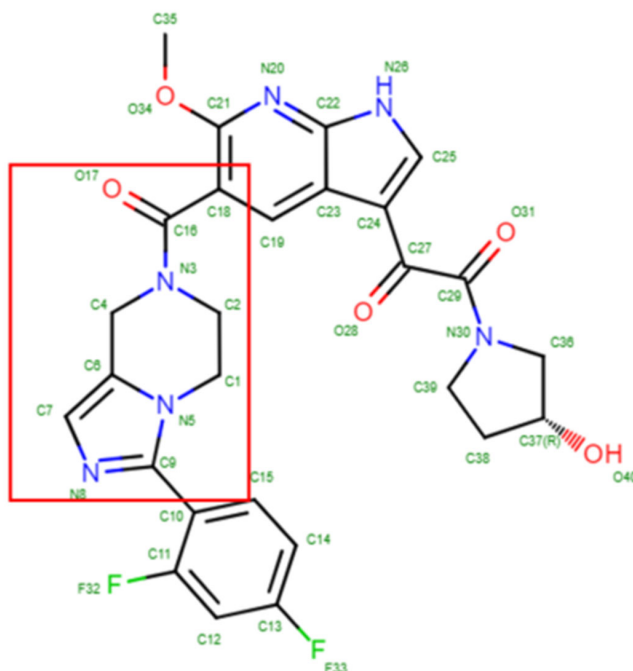
does provide any guidance that would lead one to the zanubrutinib structure or any non-biaryl Z'-scaffold. Note that I also evaluated adding an NH₂ group to the pyrazole (similarly to ibrutinib), but this resulted in a poorer docking score versus not adding the NH₂ group.



EX1150.001

(5) PDB: 2QD9

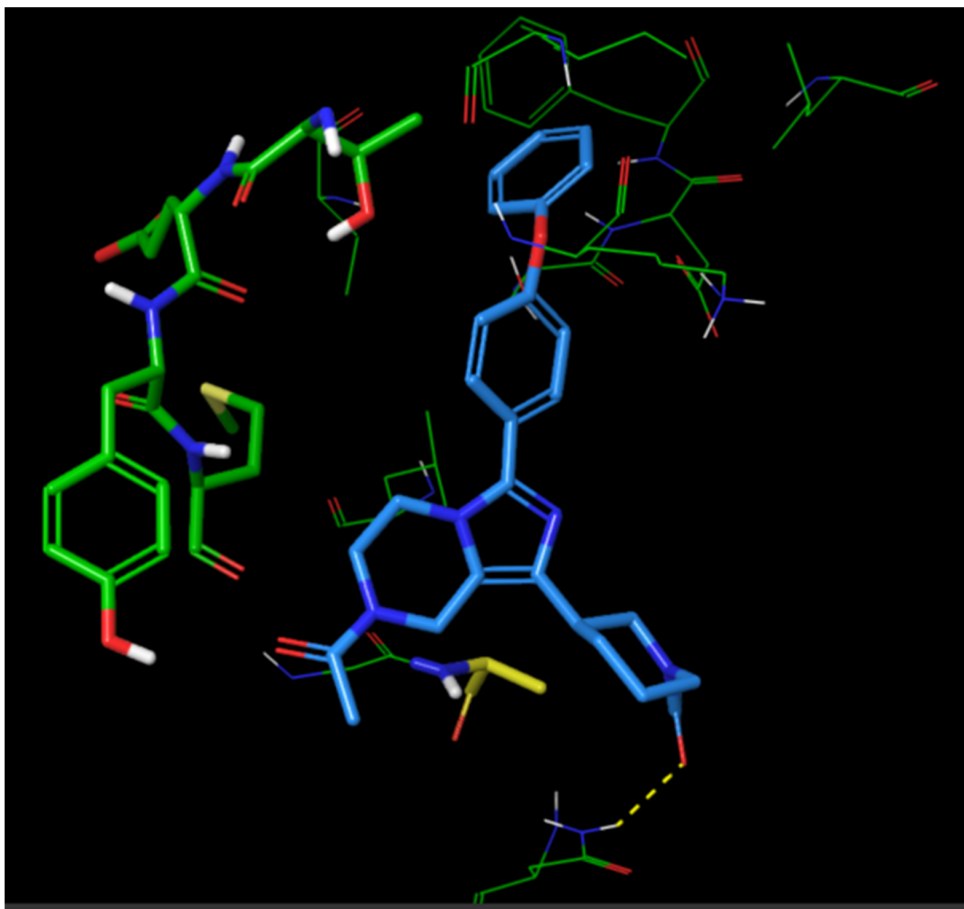
155. The structure of 2QD9 obtained from the PDB is shown below:



EX1153.003

156. For 2QD9, I truncated to the 5:6 fused heterocyclic ring system (imidazopiperazine core) except I kept the carbonyl (as an acetyl group) since it is the hinge binder, forming the H-bond to the NH of Met109 in p38, which is the equivalent residue to Met477; the truncated structure used for docking is boxed in red, above. I added the linker-warhead to the C7 position of the 5-membered ring, and added the phenoxyphenyl to the C9 position of the 5-membered ring. Note that the difluorophenyl group of the 2QD9 ligand binds to the back pocket of p38 so attaching the phenoxyphenyl at this position would be consistent with that observation.

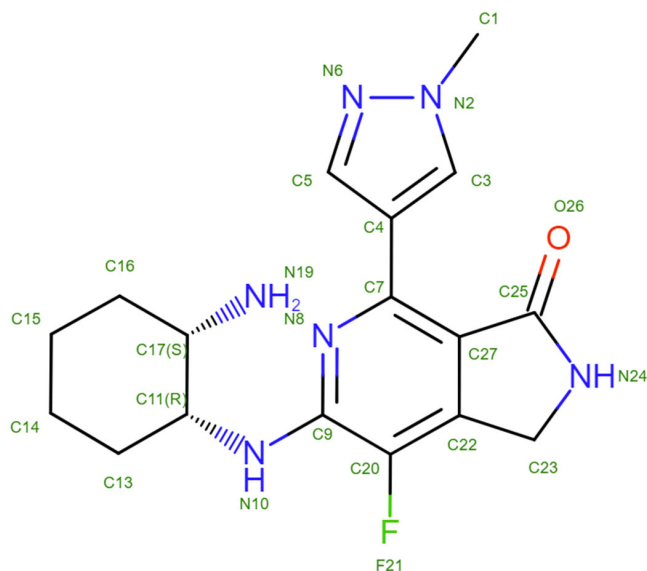
157. 2QD9 had a poor Glide docking score (-7.5) with no H-bonding to the hinge region of Btk. Below is the docking pose of the 2QD9 Z'-scaffold with the attached substituents with the most negative Glide docking score (-7.5). The phenoxyphenyl docked correctly and the linker-warhead was able to position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



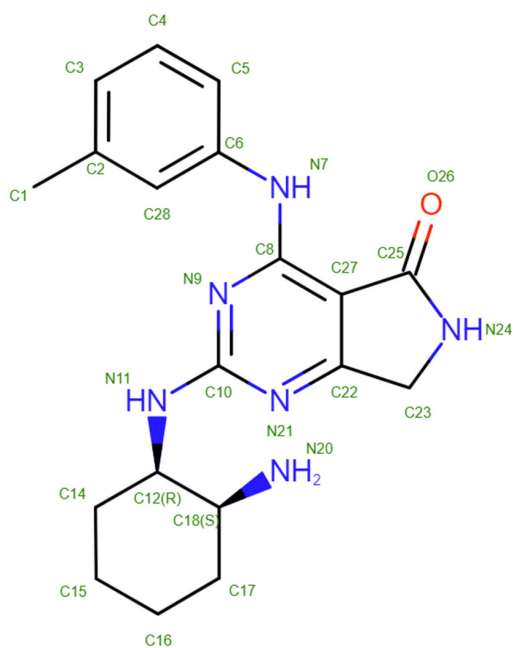
EX1151.001

(6) PDB: 5TR6 and 5TT7

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

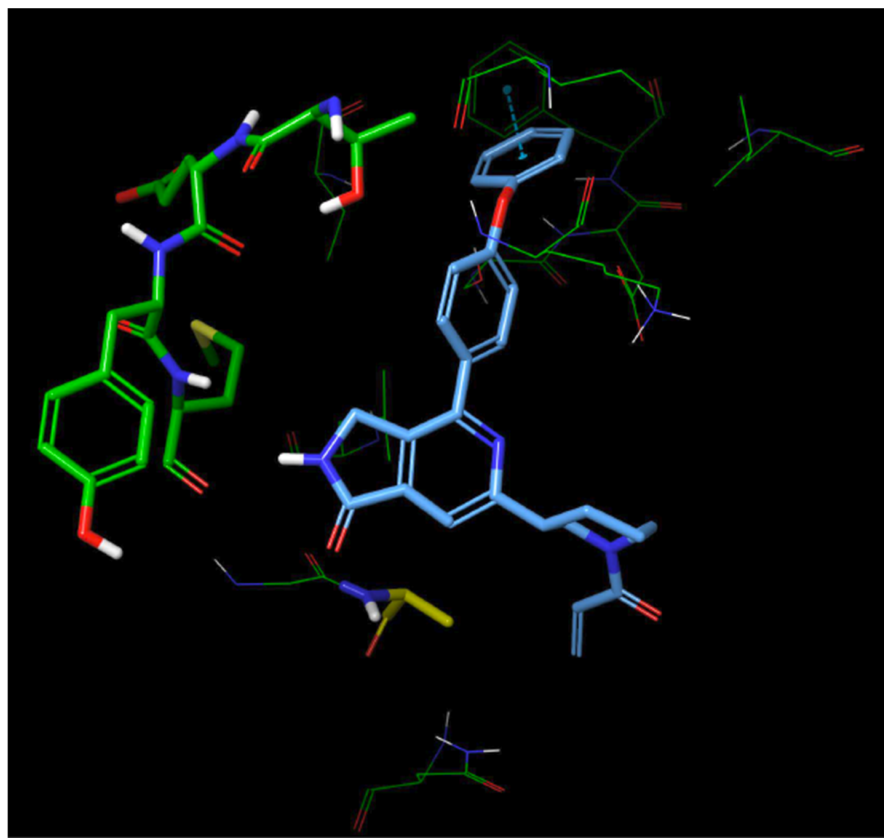
**EX1154.003**

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

**EX1155.003**

160. 5TR6 and 5TT7 have similar 5:6 fused heterocyclic ring systems with the exception of one additional nitrogen in 6-membered ring of the 5TT7 structure (pyridine vs. pyrimidine). I used the 5TR6 structure for docking and truncated to the core aza-oxindole, which forms H-bonds with the hinge region. I opted to transpose the pyridine nitrogen to the adjacent ring position and then added the phenoxyphenyl and linker-warhead both at ortho positions to the pyridine ring nitrogen.

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



EX1152.001

VII. CLAIM CONSTRUCTION

162. I understand that Dr. Eck applies certain claim constructions for the following terms as defined in the specification: irreversible BTKI, optionally substituted, substituted, fused, heterocyclic, heterocycle, ring, and ring system. EX2010, ¶¶120-122. I have used these definitions throughout my analysis.

VIII. RESPONSE TO DR. ECK'S ASSERTIONS REGARDING WRITTEN DESCRIPTION

A. The Specification Does Not Provide Written Description Support for the Claimed Irreversible BTKIs

1. Independent Claims 1 and 8

163. Dr. Eck contends that the specification provides adequate written description support for the claimed irreversible BTKIs. EX2010, Section X. I disagree. In my opinion, the specification fails to provide sufficient written description support for the Challenged Claims as of 2010/2011 or as of 2020. Further, a POSA in 2010/2011 or in 2020 would not have been able to visualize or recognize all of the structurally diverse claimed BTKIs that irreversibly inhibit Btk. The specification does not show that the inventors discovered or possessed any compounds other than ibrutinib that perform the claimed function of irreversibly inhibiting Btk or covalently binding Cys481 of Btk. Therefore, there is no verbatim disclosure of any other BTKI that satisfies the Structural Limitations and irreversibly inhibits Btk or covalently binds Cys481, including zanubrutinib. Notably, Dr. Eck admitted that the inventors of the 803 Patent did not possess the structure of zanubrutinib. EX1110, 58:7-10.

164. In response to Dr. Eck's written description opinions, the discussion below analyzes what a POSA reading the specification would have understood with respect to various structural components of the claimed BTKIs (*i.e.*, linker-warhead,

phenoxyphenyl, and Z'-scaffold). In my opinion, whether and how a compound satisfying the Structural Limitations will irreversibly inhibit Btk depends on the overall structure and bioactive orientation of the compound within the Btk's kinase domain, including the arrangement and interrelationship of the various structural components.

a) No Common Structural Features for the Claimed Irreversible BTKIs

165. Dr. Eck contends that the Challenged Claims include common structural features that bind within Btk's hinge region. EX2010, Section X.A.2. I disagree. As explained below, the specification does not provide common structural features for the full scope of structurally diverse BTKIs that satisfy the Functional Limitation of irreversibly inhibiting Btk or covalently binding Cys481 or another residue of Btk, including zanubrutinib.

(1) Linker-Warhead

166. Dr. Eck contends that the specification "teaches the importance of irreversible binding to Cys481 for selectivity to BTK" and "that the linker-warhead forms the covalent bond to Cys481." EX2010, ¶132 (citing EX1001, 45:56-60, 46:10-12). The specification, however, does not disclose that the linker-warhead will necessarily result in all compounds satisfying the Structural Limitations covalently binding Cys481. *See supra* Section V.B.1.

167. Dr. Eck contends that a POSA would have understood that the claimed linker-warhead would result in covalently binding Cys481 and thus would selectively and irreversibly inhibit Btk. EX2010, ¶¶133-134 (citing EX1060, EX2111, EX2001, EX1077). Each of the references that Dr. Eck relies on, however, provides little information beyond what was disclosed in the specification of the 803 Patent.

168. *First*, Pan’s (EX1060) teachings were limited and show that testing is required to determine binding of a target kinase. *See supra* Sections VI.A.3, VI.B.5.

169. *Second*, the 742 Publication (EX2111) does not describe structural features of the claimed linker-warhead that result in covalently binding Btk.

170. *Third*, Marcotte (EX2001) lacks the claimed linker-warhead and only includes a general description of binding cysteine.

171. *Fourth*, the BTKI disclosed in Zhang (EX1077) is ibrutinib. Further, Zhang only provides a general description of binding cysteine.

172. Dr. Eck also contends that “[l]ater data confirmed what a POSA reading the ’803 Patent in 2011 would have understood about the importance of the linker-warhead.” EX2010, ¶136 (citing EX1076 and EX1053). However, Guo (EX1053) is a 2019 article regarding zanubrutinib, and Zhang (EX1076) is a 2021

reference regarding ibrutinib. Such “[l]ater data” does not inform what a POSA would have understood in 2010/2011.

(2) Orientation of Linker-Warhead

173. Dr. Eck contends that the specification discloses that the linker-warhead can approach Cys481 from different trajectories. *See* EX2010, ¶¶137-141. Not so. *See supra* Section V.B.1. The claimed linker-warhead alone is not sufficient to determine whether a compound will covalently bind. Rather, whether a compound will irreversibly inhibit Btk depends on the holistic structure of the compound. Further, whether the linker-warhead will properly orient and covalently bind Cys481 is controlled by the Z'-scaffold and would not have been predictable as of 2010/2011. *See supra* Section V.B.1. Further, even if the linker-warhead is oriented such that it is near Cys481, there is no guarantee that it will satisfy the more specific and precise geometry and distance requirements to allow for the chemical reaction involving nucleophilic addition of the cysteine thiol to the Michael acceptor acrylamide. EX1157; EX1158.

174. Dr. Eck contends that Marcotte shows that Cys481 adopts two orientations and is relatively solvent-exposed. EX2010, ¶139. The structures disclosed in Marcotte, however, lack the claimed linker-warhead. Further, the fact that Cys481 may adopt two orientations does not indicate to a POSA all possible

directions from which the claimed linker-warhead of the structurally diverse BTKIs of the Challenged Claims will approach Cys481.

175. Dr. Eck contends that Table 3 in Pan (EX1060) shows that irreversible BTKIs with different orientations, warheads with different lengths, or different linkers all covalently bind Btk. EX2010, ¶139. Dr. Eck also contends that Guo (EX1053) discloses that the linker-warhead could approach Cys481 from different directions. EX2010, ¶141. First, Guo was published in 2019 and therefore not available to a POSA in 2011. Further, in my opinion, chirality unpredictably impacts Btk binding activity, which is supported by the fact that Guo discloses that the R and S-isomers of zanubrutinib have different IC₅₀ values. Specifically, the R-isomer of zanubrutinib had a higher IC₅₀ value (11nM) compared to the S-isomer (0.30nM), representing a 37-fold difference in potency. The chirality of the linker-warhead is critical to the overall structure and bioactive orientation of the BTKI, and the chirality of the linker-warhead must cooperate with the other structural components of the BTKI (*i.e.*, the hydrophobic moiety and Z'-scaffold) in order for the linker-warhead to align with the Cys481 at a proper angle and distance to enable the covalent reaction.

176. I understand that Dr. Eck modeled ibrutinib and its S isomer because he was “curious to see the impact of the inversion of the stereocenter on the

confirmation of the compound and its ability to juxtapose the warhead with cysteine 481 of BTK” and was “struck by how similarly it could position the warhead in spite of the inversion of the stereochemistry.” EX1110, 117:3-18. The fact that Dr. Eck was “struck” by these results further supports my opinion that it would be generally difficult to visualize or recognize how the chirality of a compound impacts its Btk binding activity and thus a POSA would not have been able to visualize or recognize all of the structurally diverse claimed compounds that irreversibly inhibit Btk.

(3) Phenoxyphenyl

177. Dr. Eck contends that a POSA would have understood that the phenoxyphenyl is important for potency and selectivity in Btk binding and that the claimed BTKIs must orient the hydrophobic moiety to bind within Btk’s back pocket. EX2010, ¶¶142-143 (citing EX2001, EX1052, and EX1060). The specification, however, does not disclose that the phenoxyphenyl will necessarily result in all compounds satisfying the Structural Limitations binding Btk’s back pocket. *See supra* Section V.B.2. Further, the hydrophobic moiety alone is not sufficient to determine whether a compound will covalently bind Btk. Rather, whether a compound will irreversibly inhibit Btk depends on the holistic structure of the compound and proper orientation of the phenoxyphenyl is controlled by the Z’-scaffold. *See supra* Section V.B.2.

(4) Z'-Scaffold

178. Dr. Eck contends that the specification describes the structural features of the claimed Z'-scaffolds and a POSA would have understood that the Z'-scaffolds need to allow the fixed linker-warhead and phenoxyphenyl to properly orient to bind Btk. EX2010, ¶¶145, 150. The specification, however, does not disclose that the structurally diverse Z'-scaffolds will necessarily result in 1-3 H-bonds with Btk's active site or properly orient the fixed substituents. *See supra* Section V.B.3. Further, as Dr. Eck agreed, there are factors other than forming the H-bonds and properly orienting the claimed phenoxyphenyl and linker-warhead, including electrostatics, Van der Waals interactions, and an overall binding site shape complementarity between the ligand and protein across the entire Btk active site, that impact whether and how a compound will bind and irreversibly inhibit Btk. *See* EX1110, 156:15-157:14, 158:18-159:3, 160:2-21.

179. Dr. Eck contends that Formula E refers to the understanding that diverse structures would bind in the active site of Btk and reflects the structure-function relationship for the hinge-binding region of the claimed BTKIs. EX2010, ¶147. I disagree for the reasons described above. *See supra* Section V.B.3. Further, while Dr. Eck did not model any of the Formula E cores, Structures E2-E4 docked poorly when I modeled them in Glide. *See supra* Section VI.C.2.c).

180. Dr. Eck relies on Akritopoulou-Zanze (EX2028) to support his opinion that a POSA would have understood that ATP-competitive kinase inhibitors make 1-3 H-bonds with the kinase region. EX2010, ¶¶147-148. However, a POSA reading Akritopoulou-Zanze would have understood that whether a compound can bind and inhibit Btk depends on the holistic structure of the compound; it is more than just predicting whether a Z'-scaffold can form H-bonds with the hinge region. *See supra* Section VI.A.4.

181. Dr. Eck relies on references to support his opinion that diverse heterocyclic Z'-scaffolds were capable of making hinge interactions, including partially saturated or non-biaryl Z'-scaffolds. EX2010, ¶148. However, the references on which Dr. Eck relies provide limited, if any, information regarding whether and how the structurally diverse compounds satisfying the Structural Limitations would both interact with the hinge region and irreversibly inhibit Btk. *See supra* Sections VI.A.4, VI.A.5.a)-c), VI.B.1, VI.B.3.

182. Dr. Eck contends that the need for the linker-warhead to be oriented generally toward Cys481 would limit the scope of acceptable Z'-scaffolds. *See* EX2010, ¶151. Dr. Eck, however, fails to describe how the scope would be limited and what are the metes and bounds of acceptable Z'-scaffolds. In my opinion, the

fact that the linker-warhead must be oriented toward Cys481 does not predictably limit the scope of acceptable Z'-scaffolds.

183. Similarly, Dr. Eck opines that the phenoxyphenyl would need to be oriented to allow for binding, which would limit the scope of acceptable Z'-scaffolds. *See id.*, ¶152. Again, Dr. Eck fails to describe how the scope would be limited and what are the metes and bounds of acceptable Z'-scaffolds. In my opinion, the fact that the phenoxyphenyl would need to be oriented to allow for binding does not predictably limit the scope of acceptable Z'-scaffolds.

**(5) Modeling Is Not Predictive of Irreversible
Inhibition of Btk and Amounts to Trial-and-Error**

184. Dr. Eck contends that a POSA would have used docking to aid in identifying irreversible BTKIs, which would have allowed a POSA to visualize the Z'-scaffolds that satisfy the need for forming H-bonds to Btk's hinge region and the ability for the phenoxyphenyl to occupy Btk's back pocket and the linker-warhead to covalently bind Cys481. *Id.*, ¶153. However, the specification does not mention modeling at all. Further, the references that Dr. Eck relies on and modeling capabilities available in 2010/2011 or in 2020 do not undercut the unpredictability of the art. *See supra* Sections VI.A.1-4, VI.B.1-5. Modeling would not have allowed a POSA to visualize or recognize the full scope of BTKIs that satisfy the Structural Limitations and irreversibly inhibit Btk for the reasons described below.

185. While the specification only discloses that a single BTKI, ibrutinib, irreversibly inhibits Btk, Dr. Eck agrees that the claimed Z'-scaffolds encompass billions of structures. *See* EX1110, 42:21-43:18, 46:11-47:6. I understand that PO has criticized Dr. Showalter's calculations, and that Dr. Showalter has concluded that even when accounting for PO's criticisms the Structural Limitations are still broadly directed to at least 4 million species. EX1105, ¶¶31-35. In my opinion, under either calculation, modeling would not have allowed a POSA to visualize or recognize the full scope of BTKIs that satisfy the Structural Limitations and irreversibly inhibit Btk.

186. As explained above, modeling is not predictive of either general Btk binding or irreversible inhibition. *See supra* Sections VI.C.1, VI.C.2.b). Thus, a POSA would also have to run biological assays to measure inhibition of Btk and determine whether each and every structure will irreversibly inhibit Btk. *See supra* Section VI.C.1.

187. Even if modeling were predictive, it would amount to trial-and-error as explained below.

188. First, a POSA would need to generate a library of compounds that satisfy the Structural Limitations. As explained above, modeling in 2011 would not have allowed a POSA to use a computer to generate all compounds that satisfy a pre-

specified set of structural parameters, including a library of all compounds that satisfy the Structural Limitations. *Supra* Section VI.C.1.

189. Creating that library would be a complex task and hindsight exercise because the specification does not even disclose the definition of the Z'-scaffold. The Structural Limitations encompass both *known and unknown* Z'-scaffolds and evaluating all of the claimed Z'-scaffolds would require evaluating *known and unknown* structures, which Dr. Eck acknowledged would take a "significant amount of time," which he has not tried to estimate or determine how to execute. EX1110, 128:3-129:6, 129:13-16, 129:23-130:3. In order to model Z'-scaffolds that were unknown in 2011, a POSA would first need to visualize or recognize each and every unknown Z'-scaffold that satisfies the claimed Z'-scaffold, which would include drawing each of these Z'-scaffolds. For each of the known and unknown Z'-scaffolds, a POSA would then need to visualize all the possible locations where the claimed phenoxyphenyl and linker-warhead could attach. Dr. Eck struggled to identify at which locations the claimed fixed substituents could or could not be attached to known Z'-scaffolds, which supports my opinion that the process is complex. *See* EX1110, 75:25-77:13, 90:23-93:25.

190. Second, a POSA would have to prepare each conceived compound from the library for docking using a modeling tool such as LigPrep. *Supra* Section VI.C.1.

191. Finally, a POSA would need to evaluate the modeling results for each compound. According to Dr. Eck, a POSA would need to generate and evaluate the five best docking poses for each compound using visual inspection along with the corresponding docking scores to assess whether modeling suggests that that compound would irreversibly inhibit Btk. *See* EX1110, 132:12-20, 133:5-15, 134:10-136:19 (Dr. Eck testifying that analyzing whether modeling results suggest that a given structure will productively irreversibly inhibit Btk requires analyzing both the docking pose and docking score and comparing that docking score with structurally similar molecules that irreversibly inhibit Btk), 152:6-153:2. This is consistent with my approach to modeling compounds. In my experience, evaluating the poses and scores for each docked compound could not have been automated on a computer in 2011. Indeed, as Dr. Scott admits, large scale structure-based virtual screening was not developed in 2011. *See supra* Section VI.C.1.

(6) Hinge-Binding Was Unpredictable in 2010/2011

192. Dr. Eck contends that hinge-binding was predictable based on the knowledge in the art in 2011. *See* EX2010, Section X.A.3.a. I disagree. In my opinion, hinge-binding, particularly the potential for a specific scaffold to show hinge-binding to a specific kinase, was unpredictable based on the state of the art and modeling did not undercut this unpredictability in 2010/2011 or in 2020.

193. Dr. Eck contends that Dr. Showalter did not consider Marcotte (*see* EX2010, ¶154), but Marcotte does not demonstrate that the hinge-binding of the diverse claimed Z'-scaffolds was predictable. *See supra* Section VI.A.1.

194. Dr. Eck contends that Ghose (EX1052) shows that changing the substitution pattern of Z' predictably affects the orientation of the inhibitor in the kinase domain and the distinct orientations of the Z'-scaffold are due to structural differences among different specific kinases, not changes in substitution pattern of the Z'-scaffold. *See* EX2010, ¶¶155-157. As described above, Ghose supports that empirical studies (synthesis and testing) would be required to determine the binding activity of any given structure. *See supra* Section VI.B.2. Further, Table 2 of Ghose discloses various molecules that are structurally similar, but project their substituents at different orientations, in part driven by the fact that the hinge region interaction fixes how the substituents orient.

195. Dr. Eck contends that Dr. Showalter did not address how Ghose reports diverse fused heterocyclic ring systems that productively bind the hinge region. EX2010, ¶165. However, the structures disclosed in Ghose that Dr. Eck relies on (scaffolds 30, 31, 33, 37, and 39) do not satisfy the claimed Z'-scaffolds. Thus, any information disclosed in Ghose relating to these structures has no bearing on a POSA's ability to visualize or recognize the full scope of structurally diverse

compounds satisfying the Structural Limitations that would interact with the hinge region and irreversibly inhibit Btk. Ghose also does not provide any guidance to a POSA regarding where to attach the claimed linker-warhead and phenoxyphenyl to the Z'-scaffolds. Moreover, as explained above, Ghose cautions that the knowledge-based drug discovery disclosed in the article is not suitable for routine prediction. *See supra* Sections VI.A.2, VI.B.2.

196. Dr. Eck contends that Garuti (EX1049) explains how to select an appropriate structure to allow for covalent bonding and teaches the importance of H-bonding for selecting a Z'-scaffold. *See* EX2010, ¶158. Dr. Eck also contends that Garuti “teaches that ‘important parameters’ include ‘the corrected orientation of the Michael acceptor toward the cysteine and a short distance’ to the cysteine side chain” and “explains that hinge-binding interactions place the warhead in the correct position to bind with the cysteine residue of the kinase.” *Id.* (quoting EX1049.001). Garuti, however, does not disclose how modifications to the Z'-scaffold impact covalent binding. As explained above, the claimed linker-warhead is not sufficient alone to determine whether a compound will covalently bind to Btk. *See supra* Section VIII.A.1.a)(2). The only disclosure relating to H-bonding that Dr. Eck points to in Garuti is that “these inhibitors first reversibly interact with the ATP-binding site of the kinase domain and form hydrogen bonding with the hinge region.”

EX1049.001. This disclosure, however, relates to reversible inhibitors not irreversible inhibitors.

197. Dr. Eck contends that the 432 Publication (EX1036) shows that structures falling within the claim scope have potent IC₅₀ values ranging from 1-30 nM. *See* EX2010, ¶159. Note that the structures in the 432 Publication have a Z'-scaffold that is closely related to the ibrutinib Z'-scaffold, differing by a single nitrogen to carbon change in which the NH₂-pyrimidine of ibrutinib is modified to an NH₂-pyridine. The 432 Publication was not published until May 2020 and therefore not available to a POSA in 2011. Further, the 432 Publication does not disclose how modifications to the Z'-scaffold impact covalent binding. In my opinion, even the varied IC₅₀ values of these structures supports the unpredictability of whether the structurally diverse compounds satisfying the Structural Limitations will irreversibly inhibit Btk.

198. Dr. Eck contends that “neither Pan nor Honigberg shows that there was a ‘limited understanding’ of the structure-function relationship.” EX2010, ¶160. Not so.

199. Specifically, Dr. Eck contends that Pan (EX1060) reports a potential covalent bond between inhibitor and Btk and confirms irreversibility by testing. *See* EX2010, ¶160 (citing EX1060.001-002). While the Structural Limitations

encompass structurally diverse compounds, Pan only discloses structures with the Z'-scaffold of ibrutinib. Further, Pan provides little information regarding these limited structures. For example, Pan does not mention how an irreversible inhibitor may bind to Btk's back pocket or hinge region or form H-bonding.

200. Dr. Eck also contends that Honigberg (EX1055) reports preclinical data relating to ibrutinib. *See* EX2010, ¶161. Honigberg, however, does not disclose how modifications to the Z'-scaffold impact covalent binding. First, Honigberg is limited to ibrutinib. Further, similarly to Pan, Honigberg does not mention Btk's back pocket, H-bonding, or Btk's hinge region.

201. Dr. Eck contends that nothing about the crystallography data for Btk-ibrutinib and Btk-zanubrutinib disclosed in Brullo (EX1044) or Zhang 2021 (EX1076) supports that Btk inhibition is highly unpredictable. *See* EX2010, ¶¶162-164. I disagree. Neither Brullo nor Zhang 2021 disclose how modifications to the Z'-scaffold impact covalent binding. Further, Brullo and Zhang 2021 were both published in 2021 and therefore not available to a POSA in 2011.

202. Zhang 2021 discloses an X-ray crystal structure of Btk-ibrutinib, which involves two H-bonds with Btk residues. *See* EX1076.006 (Fig. 3). In addition to these H-bonds, Zhang 2021 discloses that the Z'-scaffold of ibrutinib forms other complicated interactions with Btk residues. *See* EX1076.005.

203. Despite having the same linker-warhead and phenoxyphenyl, the crystallography data in Brullo shows that zanubrutinib and ibrutinib have distinct interactions with Btk because of their different Z'-scaffolds and linkers. For example, the two BTKIs have distinct Z'-scaffold orientations in the binding site of Btk's kinase domain, different H-bonds formation with the hinge region, and zanubrutinib's warhead has a H-bond with an adjacent water molecule and Asn484 residue (unlike ibrutinib). *See* EX1044.004 (Fig. 2, Panels C and D). As described earlier, ibrutinib's H-bonding to Met477 NH of the hinge region is accomplished by an aromatic nitrogen that is part of its Z'-scaffold whereas zanubrutinib's H-bonding to Met477 NH is via a carboxamide that is attached to the Z'-scaffold. *See supra* Section VI.A.6. Zanubrutinib also projects into a second hydrophobic pocket that is not occupied by ibrutinib. The vector approach of the linker-warhead to Cys481 is also distinct. The fact that Brullo indicates that zanubrutinib and ibrutinib "share similar bioactive conformations" within Btk's active site and are "mainly stabilized by similar interactions," does not undermine the fact that the two compounds have distinct orientations, H-bonds, and multiple different binding interactions within the Btk active site.

204. There has been a difference of opinion regarding whether zanubrutinib forms two or three H-bonds with the hinge region of Btk. *See, e.g.,* EX1044.003-

005 (reporting two H-bonds); EX1053.005 (reporting three H-bonds); EX1076.018 (same). Dr. Eck contends that this difference of opinion does not arise “from actual differences in scientific opinion, but likely from differences in defaults used to define hydrogen bonds in the software used to analyze and illustrate the interactions.” EX2010, ¶163. To the extent that such differences arise from differences in software, this supports my opinion that a POSA may obtain different modeling results depending upon the modeling software used. As described earlier, this difference in opinion on the presence of a third H-bond for zanubrutinib arises because it is long in distance to form an H-bond (2.5 angstroms in the X-ray structure), and this would create additional unpredictability when modeling zanubrutinib as whether this would be a favorable or unfavorable interaction. *See supra* Section VI.A.6.

205. Dr. Eck disagrees that zanubrutinib’s binding mode was unpredictable because “Petitioner, using structural data and tools that were widely available to a POSA in June 2011, accurately predicted the binding mode of a compound having zanubrutinib’s hinge-binding elements, phenoxyphenyl, and linker.” EX2010, ¶165 (citing EX2039); *see also* EX2010, ¶164 (same). EX2039, however, is a 2019 reference. Dr. Eck provides no support for his opinion that the structural data and tools used “were widely available to a POSA in June 2011.”

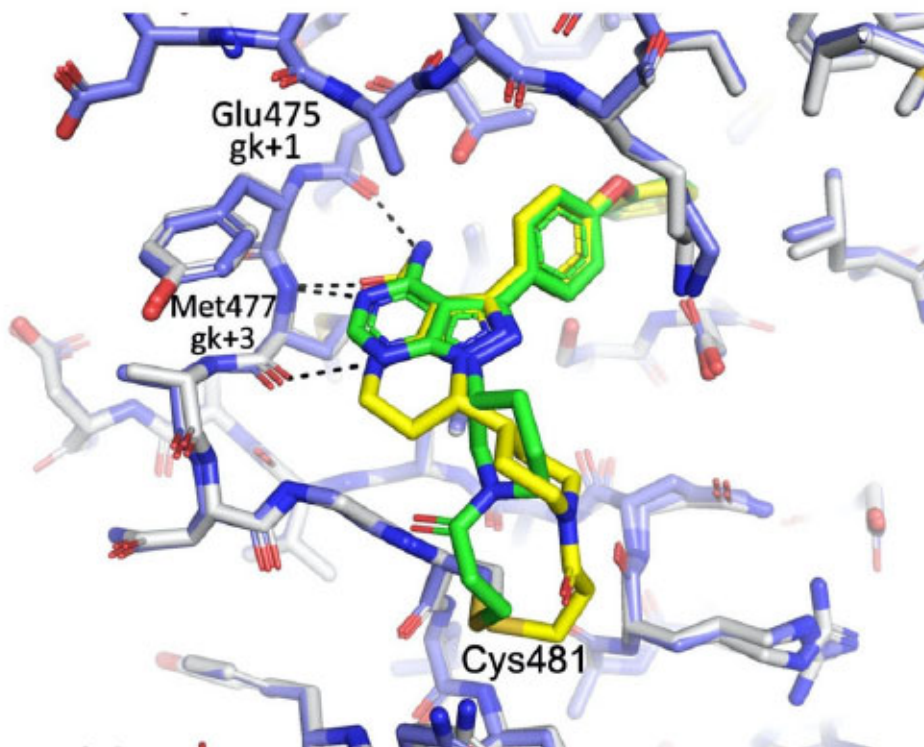
(7) The Specification's Description of Irreversible Inhibitors is Limited

206. Dr. Eck contends that zanubrutinib is an adenine mimic like ibrutinib and that Dr. Showalter's analysis of genus diversity that is not represented by the specification focuses on irrelevant differences between ibrutinib and zanubrutinib. EX2010, Section X.A.3.b(1)-(2); *see also* EX2010, ¶¶96-102. I disagree. In my opinion, the specification's description of irreversible BTKIs is limited – at most, it shows that ibrutinib, which comprises a biaryl Z'-scaffold that forms the same H-bonds and occupies the same space as adenine, irreversibly inhibits Btk. And as Dr. Eck admitted, the inventors did not possess zanubrutinib, which comprises a non-biaryl Z'-scaffold. EX1110, 58:7-10.

207. Dr. Eck contends that a POSA would use the term “adenine mimic” to refer to “hinge binding scaffolds that mimic the interactions of the adenine portion of ATP” and zanubrutinib is an adenine mimic. EX2010, ¶¶167-169; *see also id.* ¶92. Dr. Eck appears to contend that zanubrutinib is an adenine mimic because it forms H-bonds with the same Btk residues as adenine, namely GK+3 Met477 and GK+1 Glu475. EX1110, 167:1-10. While zanubrutinib competes with ATP, as does any competitive inhibitor of any target kinase, zanubrutinib's hinge-binding pattern does not mimic adenine's hinge binding pattern. Compared to adenine (and ibrutinib), zanubrutinib forms distinct H-bonds to Btk using both a primary amide

group and piperidine NH versus an NH₂-pyrimidine ring and its Z'-scaffold occupies a different space within the binding site. *See supra* Section VI.A.6.

208. Dr. Eck also contends that the aromaticity of the fused 5:6 membered rings of zanubrutinib is not relevant to whether it is an adenine mimetic and that ibrutinib and zanubrutinib have “largely overlapping placement in three-dimensional space.” EX2010, ¶¶94, 168. I disagree. A POSA would recognize that the non-biaryl nature of the zanubrutinib Z'-scaffold is a significant change from the biaryl scaffolds of adenine and ibrutinib that would lead to unpredictable binding, given that the kinase active site is optimized to bind the biaryl adenine scaffold. Additionally, in my opinion, while the phenoxyphenyl groups of zanubrutinib and ibrutinib overlap, their linker-warheads project at different angles and their distinct Z'-scaffolds have significant non-overlapping regions. The 6-membered ring non-aromatic carbons of zanubrutinib do not overlap at all with any atoms of the 6-membered pyrimidine ring of ibrutinib and zanubrutinib's 5:6 fused heterocyclic rings bind roughly perpendicular to those of ibrutinib, as shown below:



EX2010, ¶94

209. While ibrutinib's Z'-scaffold is biaryl and includes the hinge binding nitrogen ring atom, zanubrutinib's Z'-scaffold is non-biaryl and the hinge binding element is not any nitrogen ring atom, but rather the amide substituent. Zanubrutinib's non-biaryl Z'-scaffold is non-planar, more hydrophobic, and occupies a larger space in Btk's kinase domain. In particular, the 6-membered saturated ring of the Z'-scaffold occupies a different space in the domain than the 6-membered rings of ibrutinib and adenine. EX1003, ¶61; EX2010, ¶92 n.9. Post-priority crystal structures reveal that, consequently, one of its ring N atoms

(piperidine NH) forms a third H-bond with the carbonyl oxygen of Met 477. *Id.* A POSA in 2011 could not have predicted how the location of the 6-membered saturated ring of the Z'-scaffold would have impacted H-bonding.

210. The fact that the authors of Guo (EX1053) stated that the “five approved BTK inhibitors all have similar hinge binding to ATP” and Zhang 2021 discloses that “[t]o 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” does not change my opinion that zanubrutinib forms distinct H-bonds to Btk and occupies a different space compared to adenine. EX2010, ¶168 (quoting EX2020.0002, EX1076.005). Notably, EX2020 was published in 2023 and therefore not available to a POSA in 2011. Further, the authors of EX2020 and Zhang 2021 (EX1076) did not dispute that zanubrutinib forms distinct H-bonds to Btk and occupies a different space compared to adenine. In my opinion, these differences in hinge-binding and the overall orientation of zanubrutinib are due to its distinct Z'-scaffold core. In 2011, a POSA would not have been able to envision zanubrutinib's structure and orientation and predict that it would irreversibly inhibit Btk.

211. Dr. Eck contends that as of 2011, there were reported fused heterocyclic hinge-binding scaffolds with one non-aromatic ring. EX2010, ¶168 (citing EX2028,

EX2023, EX2026, EX1052). The only scaffold that Dr. Eck relies on that satisfies the claimed Z'-scaffold is Formula I of the 820 Patent (EX2023). However, as explained above, the 820 Patent provides limited, if any, information to a POSA regarding whether and how the structurally diverse compounds satisfying Structural Limitations would interact with the hinge region and irreversibly inhibit Btk. *See supra* Section VI.A.5.a). Dr. Eck testified that a POSA would not “immediately recognize” that the Formula I scaffold would form appropriate H-bonds with the hinge region and appropriately orient the fixed substituents and would instead perform modeling on Formula I, which would include determining where to attach the claimed phenoxyphenyl and linker-warhead. *See* EX1110, 91:2-93:25. Nevertheless, Dr. Eck did not attempt to perform such modeling as he described. When I modeled the Formula I scaffold with the claimed linker-warhead and hydrophobic moiety attached, however, the structure docked poorly. *See supra* Section VI.C.2.c)(4).

212. Dr. Eck contends that the “central focus” of a POSA identifying BTKIs for use in the claimed method is the ability to form appropriate H-bonds with Btk’s hinge region and properly orient the phenoxyphenyl and linker-warhead. EX2010, ¶171. However, experimentation would have been required to determine the full scope of claimed BTKIs as Dr. Eck describes. Further, as Dr. Eck acknowledged,

there are binding interactions other than forming the H-bonds and properly orienting the claimed phenoxyphenyl and linker-warhead that impact whether and how a compound will irreversibly inhibit Btk. EX1110, 156:15-157:14, 158:18-159:3, 160:2-21.

213. Dr. Eck also contends that differences in the saturation state of ibrutinib and zanubrutinib are not relevant to whether a Z'-scaffold would predictably bind to the hinge region. EX2010, ¶171. I disagree. The specification does not disclose any non-biaryl Z'-scaffolds that contain a non-aromatic, saturated ring. Rather, ibrutinib and all of the formulas and examples of Z'-scaffolds disclosed in the specification have two rings that are both unsaturated (I contend that E4 is a non-realistic structure and that the single non-aromatic carbon shown in it is a typographical mistake). The Z'-scaffold of zanubrutinib, on the other hand, has a non-aromatic, saturated 6-membered ring, causing the core to be non-planar, more hydrophobic, and occupy a larger space in Btk's kinase domain. Based on the specification and the state of the art in 2011, a POSA reading the 803 Patent would not have been able to predict whether or how a compound satisfying the Structural Limitations comprising with a saturated ring as part of the Z'-scaffold would bind to Btk's hinge region. In fact, the only Z'-scaffolds disclosed in the art as of June 2011 having a saturated ring and satisfy the claimed Z'-scaffold (Formula I of the

820 Patent and PDBs: 2QD9, 5TR6, and 5TT7) did not dock well. *See supra* Section VI.C.2.c).

214. Dr. Eck contends that a POSA would have known from the art that partially saturated hinge binding elements were capable of fitting into Btk's hinge region. EX2010, ¶171. The references that Dr. Eck relies on, however, provide limited, if any, information to a POSA regarding whether and how the structurally diverse compounds satisfying the Structural Limitations would interact with the hinge region and irreversibly inhibit Btk as described below. *See supra* Section VI.A.5.a) and VIII.A.1.a)(7).

215. Dr. Eck contends that EX2055 discloses a kinase inhibitor (PDB:2QD9) with a partially saturated Z'-scaffold. EX2010, ¶171. EX2055, however, discloses that 2QD9 is a p38alpha MAP kinase inhibitor, not a BTKI. 2QD9 also does not have the claimed linker-warhead or phenoxyphenyl. Further, as explained above, when I modeled this Z'-scaffold with the claimed linker-warhead and phenoxyphenyl attached, the structure docked poorly. *See supra* Section VI.C.2.c)(5).

216. Dr. Eck contends that EX2038 reports the design of new scaffolds for tyrosine kinase inhibitors and discloses a partially saturated scaffold. EX2010, ¶171.

The proposed new scaffolds in EX2038, however, do not satisfy the Z'-scaffold of the Challenged Claims.

217. Dr. Eck contends that EX2053 discloses an inhibitor with a partially saturated scaffold. EX2010, ¶171. EX2053, however, discloses a FGFR1 inhibitor, not a BTKI. Moreover, the scaffold does not satisfy the Z'-scaffold of the Challenged Claims.

218. Dr. Eck contends that EX2026 discloses BTKIs containing a partially saturated scaffold. EX2010, ¶¶171, 175. However, the claimed scaffolds in EX2026 (claims 1, formula I; claim 10, formula Ia) do not satisfy the Z'-scaffold of the Challenged Claims.

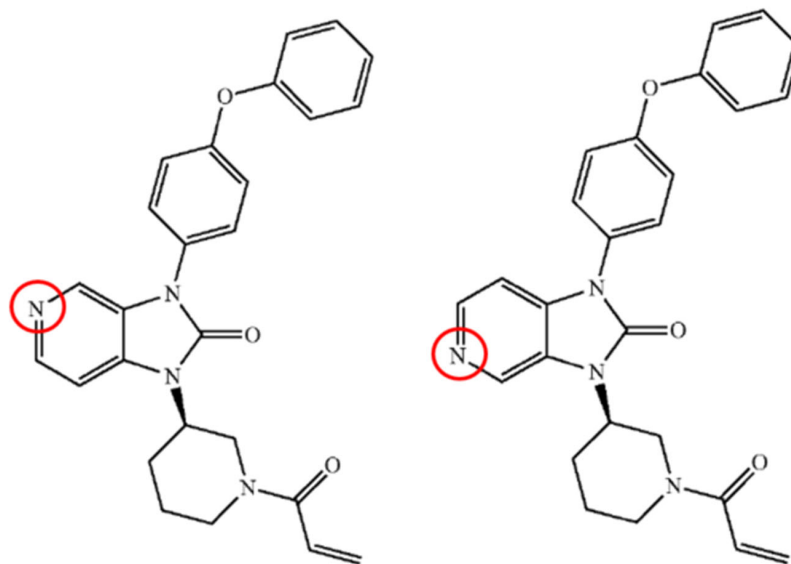
219. Dr. Eck relies on six PDB structures. EX2010, ¶173. Yet, none of the PDB structures that Dr. Eck relies on are BTKIs. Further, none of these structures comprise a core that satisfies the Z'-scaffold of the Challenged Claims. As noted above, Akritopoulou-Zanze (EX2028.0006, Fig. 7) showed that different hinge binding scaffolds have varying preferences for different kinases, and thus there is a lack of predictability of whether a scaffold that binds to one kinase with affinity will similarly bind with affinity to a different kinase (*i.e.*, Btk).

220. Dr. Eck contends that partially saturated scaffolds allow for productive H-bonds to the hinge. EX2010, ¶¶174-175 (relying on structures disclosed in

EX2049, EX2046, and EX2061). First, EX2049 did not publish until 2012, EX2046 did not publish until 2016, and EX2061 did not publish until 2016 and therefore were not available to a POSA in 2011. Further, PDB:4EKL, which is disclosed in EX2049, does not comprise a scaffold that satisfies the Z'-scaffold of the Challenged Claims. Further, as described above, the Z'-scaffolds disclosed in EX2046, namely PDB:5TR6 and PDB:5TT7, did not dock well. *See supra* Section VI.C.2.c)(6). Finally, Compound 14f disclosed in EX2061 (which is an article from 2016) does not comprise a scaffold that satisfies the Z'-scaffold of the Challenged Claims.

221. Dr. Eck contends that differences in the ring heteroatom patterns of the Z'-scaffold of zanubrutinib and ibrutinib are not determinative as to whether the Z' scaffold would predictably bind to the hinge region, and the relevance of these ring heteroatom patterns is limited as to whether Z'-scaffold allows for H-bonding and proper orientation of the claimed linker-warhead and phenoxyphenyl. EX2010, ¶176. Not so. The ring heteroatom patterns of the Z'-scaffold may generally impact whether and how a compound will bind and irreversibly inhibit Btk, which is demonstrated by the 446 Patent (EX2024). While Compounds 20 and 122 of the 446 Patent only differ in their ring heteroatom patterns in their Z'-scaffolds, these compounds have distinct IC₅₀ values. EX2024.0118-0119. Specifically, Compound 20 has an IC₅₀ value of 10-100 nM that a POSA would have understood means it is

active, while Compound 122 has an IC₅₀ value of 1,000-10,000 nM that a POSA would have understood means it is inactive. *Id.*



Compound 20 (left); Compound 122 (right) (annotated)

222. Dr. Eck contends that acalabrutinib “has a different heteroatom substitution pattern of its heterocyclic ring system as compared to ibrutinib.” EX2010, ¶177. The Z'-scaffold of acalabrutinib, like ibrutinib, has a close correspondence to adenine with respect to both chemical structure and how it orients in Btk's active site, and, as Dr. Eck notes, the same ring heteroatom and amine substitution form H-bonds to Btk's hinge region. *Id.* This does not change my opinion, however, that the ring heteroatom pattern unpredictably impacts whether and how a compound satisfying the Structural Limitations will bind Btk's hinge

region (as demonstrated above by Compounds 20 and 122 of the 446 Patent). Further, Dr. Eck's reliance on acalabrutinib is based on hindsight, and acalabrutinib has a different hydrophobic moiety and linker-warhead. As Dr. Eck admitted, there are things other than forming the H-bonds and properly orienting the claimed phenoxyphenyl and linker-warhead, such as electrostatics, complementarity, and Van der Waals interactions, that impact whether and how a compound will irreversibly inhibit Btk. EX1110, 156:15-157:14, 158:2-7, 158:18-159:3, 160:2-21. Electrostatic and hydrophobic interactions between the BTKI and Btk, as well as the desolvation of the BTKI upon binding to Btk, will be significantly affected by the ring heteroatom pattern.

223. Dr. Eck contends that the specification teaches heterocyclic Z'-scaffolds with different ring heteroatom patterns, pointing to the distinct ring heteroatom patterns of the eight Formula E structures. EX2010, ¶176. Notably, none of the formulas or examples in the specification have the same ring heteroatom pattern as zanubrutinib. Importantly, the substitution pattern of the Z'-scaffold of zanubrutinib (attachment points of the carboxamide, phenoxyphenyl, and linker-warhead) is also distinct from the substitution pattern of the Z'-scaffolds of ibrutinib and E1-E8. Further, the specification does not disclose that any compound other than ibrutinib will irreversibly inhibit Btk.

224. Dr. Eck contends that the placement of the phenoxyphenyl and linker-warhead of ibrutinib and zanubrutinib is not determinative of binding. EX2010, ¶178. Not so. The placement of the claimed phenoxyphenyl and linker-warhead impact whether and how a compound will bind Btk. As described above, while the phenoxyphenyl of zanubrutinib and ibrutinib overlap, their linker-warhead projects out at completely different angles and their distinct Z'-scaffolds do not overlap.

225. Dr. Eck contends that the difference in how the linkers in ibrutinib and zanubrutinib connect the Z'-scaffolds and warheads is irrelevant. EX2010, ¶179. Not so. As discussed above, the chirality of a BTKI impacts binding. *See supra* Section VIII.A.1.a)(2) (describing how zanubrutinib's R- and S-isomers have varied IC₅₀ values).

226. Dr. Eck contends that modeling would be used to determine Btk binding. EX2010, ¶179. I disagree with Dr. Eck's opinions regarding modeling. Modeling is not mentioned in the specification and does not reliably and accurately predict whether a compound will irreversibly inhibit Btk. *See supra* Sections VI.C.1, VIII.A.1.a)(5). Further, the only structure that Dr. Eck modeled that was known in 2011 is ibrutinib, and Dr. Eck's reliance on zanubrutinib is pure hindsight. *See supra* Section VI.C.2.a).

(8) Dr. Showalter Did Not Inflate the Breadth of Potential Z'-Scaffolds

227. Dr. Eck contends that Dr. Showalter inflated the breadth of potential Z'-scaffolds. EX2010, Section X.A.3.b(3). In my opinion, based on Dr. Showalter's calculations or alternative calculations, the scope of potential Z'-scaffolds is extremely broad and diverse. EX1003, Section VIII; EX1105, ¶¶31-35.

228. Dr. Eck contends that a POSA would have known that the linker-warhead needed to be oriented toward Cys481 and the phenoxyphenyl needed to be oriented to bind the back pocket. EX2010, ¶181. Dr. Eck, however, does not provide any opinion regarding how a POSA would have understood that this limits the scope of the Z'-scaffolds. In my opinion, such factors do not predictably limit the scope of the potential Z'-scaffolds. Dr. Eck did not provide an opinion regarding the size of the Z'-scaffolds comprised by compounds satisfying the Structural Limitations that would covalently bind Cys481. EX1110, 47:18-48:5. Notably, Dr. Eck has not tried to do that calculation and was unable to identify common structural features of such Z'-scaffolds. *See id.*, 47:18-48:5, 48:23-51:3.

229. Dr. Eck contends that a POSA would understand that the orientations and potential steric hindrance/clash resulting from substituents would limit scope of acceptable Z'-scaffolds. EX2010, ¶¶181-182. I understand that Dr. Eck does not

provide any opinion regarding how this limits the scope of the claimed Z'-scaffolds (or whether this would be predictable). EX1105, ¶30.

230. Dr. Eck again contends that a POSA would have known of the structural information disclosed in Marcotte to use in virtual docking and modeling of compounds that fall within the Structural Limitations of the Challenged Claims to predict irreversible inhibition. EX2010, ¶¶181-182. I disagree with Dr. Eck that docking with Marcotte to predict which Z'-scaffolds irreversibly inhibit Btk allows a POSA to visualize or recognize the full scope of claimed BTKIs. Based on Dr. Eck's logic, a POSA would have been required to model or dock structurally diverse compounds to determine whether the inventors were in possession of the full scope of the Challenged Claims. Even if modeling could be utilized, however, modeling does not accurately predict irreversible inhibition of Btk, and empirical testing would be required to determine whether a BTKI irreversibly inhibits Btk. *See supra* Sections VI.C.1.b), VIII.A.1.a)(5).

b) No Blaze Marks for Irreversible BTKIs

231. Dr. Eck contends that the specification provides sufficient blaze marks to the claimed genus. EX2010, Section X.B. I disagree.

232. Dr. Eck contends that the specification provides blaze marks to the fixed phenoxyphenyl and the linker-warhead. EX2010, ¶¶187, 190. Not so. The

specification does not describe that any species other than ibrutinib will irreversibly inhibit Btk and does not disclose that the phenoxyphenyl and linker-warhead will necessarily result in all compounds satisfying the Structural Limitations binding the back pocket. In fact, the specification does not disclose where the phenoxyphenyl binds or even mention Btk's hydrophobic back pocket, does not disclose structural features that result in covalently binding Btk, and does not expressly disclose that any compounds that satisfy the Structural Limitations of the Challenged Claims will bind Cys481, let alone from what direction(s) the linker-warhead will approach Cys481. *See supra* Sections V.B.1-2. Further, while the Challenged Claims do not require attaching the hydrophobic moiety to any particular position of the Z' structure, the specification does not disclose any BTKIs that have the hydrophobic moiety and linker-warhead attached to different rings of the Z' structure (like zanubrutinib).

233. Dr. Eck contends that the specification provides blaze marks to the Z'-scaffold, relying on Formula E. EX2010, ¶¶191-193. Not so. As described above, a POSA would have understood that the substituted fused biaryl moiety for the orb of Formula E would be limited to the seven biaryl cores (E1-E3 and E5-E8) and would not include the only non-biaryl core (Structure E4). *See supra* Section V.B.3. The specification does not disclose that any BTKIs containing these Z'-scaffolds,

other than ibrutinib, will bind the hinge region of Btk. *See supra* Section V.B.3. Therefore, the specification would not lead a POSA to use any non-biaryl scaffold or any other undisclosed biaryl Z'-scaffold.

234. Dr. Eck has not modeled any of the eight cores disclosed for Formula E and has not tried to determine how many compounds would meet the function of “bind[ing] to the active site of the kinase, including a tyrosine kinase.” EX1110, 60:5-18. To the extent that one subscribes to Dr. Eck’s opinion that modeling is predictive, a POSA reading the specification and performing modeling would conclude that three of the Formula E cores (E2-E4) dock poorly, including the only non-biaryl core disclosed in the specification (E4) and would not be inhibitors. *See supra* Sections VI.C.2.c)(1)-(3). Moreover, modeling suggests that none of the non-biaryl Z'-scaffolds Dr. Eck has pointed to and were known in 2011 could be appropriately substituted to both bind and irreversibly inhibit Btk. *See supra* Sections VI.C.2.c)(3)-(6).

235. Dr. Eck again relies on references to support his blaze marks opinions that provide limited relevant information, if any, for at least the reasons described above. EX2010, ¶¶192-193; *see supra* Sections VI.A.1-4, VI.A.5.b), VI.B1-3.

2. Dependent Claims

236. Dr. Eck contends that Dr. Showalter did not provide a separate analysis regarding the written description of the limitations recited in the dependent claims and therefore the dependent claims are fully described for all the same reasons as independent claims 1 and 8. EX2010, ¶194. I understand from Dr. Showalter's Declaration that the dependent claims do not reduce or appreciably reduce the number of species that satisfy the claimed Structural Limitations. EX1003, ¶¶222, 225, 227, 230. Therefore, it is my opinion that the dependent claims lack written description support in the specification for at least the same reasons as described with respect to claims 1 and 8.

IX. RESPONSE TO DR. ECK'S ASSERTIONS REGARDING ENABLEMENT

A. The Specification Does Not Provide Enabling Support for the Challenged Claims

237. Dr. Eck contends that the 803 Patent enables the use of the irreversible BTKIs of the Challenged Claims. EX2010, Section XI. In my opinion, however, the specification fails to provide enabling support for the Challenged Claims as of 2010/2011 or as of 2020 for at least the following reasons.

238. I understand from counsel that to satisfy the enablement requirement, the specification must teach a POSA how to make and use the *full scope* of the claimed invention without undue experimentation. I also understand from counsel,

however, that Dr. Scott and Dr. Eck have applied the wrong standard with respect to enablement because they did not consider whether a POSA would have been able to make and use the *full scope* of the claimed genus without undue experimentation. EX1110, 53:19-54:6, 124:17-125:2, 129:1-130:18; EX1117, 65:14-66:10.

239. In my opinion, the specification fails to teach a POSA how to make and use the full scope of the claimed invention without undue experimentation. A POSA would not know, without extensive trial and error testing, which of the structurally diverse species that meet the Structural Limitations would also satisfy the Functional Limitation of irreversibly inhibiting Btk by covalently binding Cys481 or another residue of Btk.

1. Independent Claims 1 and 8

**a) Amount of Direction or Guidance Presented,
Working Examples, Nature of the Invention**

240. Dr. Eck contends that these factors support that a POSA would have been able to make and use the full scope of the claimed irreversible BTKIs necessary for the claimed treatment method. EX2010, ¶¶198-202. I disagree.

241. Dr. Eck contends that the specification guides a POSA to the claimed phenoxyphenyl and linker-warhead and aligns with the SAR revealed in Marcotte. EX2010, ¶199. Dr. Eck also contends that the specification teaches the Z'-scaffold as the hinge-binding element and a POSA had a sophisticated understanding of the

Btk active site and the role of hinge binding based on the specification and state of the art. *Id.*, ¶¶200-201. As explained above, however, whether and how a compound will irreversibly inhibit Btk depends on the overall structure and bioactive orientation of the compound within the Btk's kinase domain, including the various structural components and their arrangement and interrelationship. The specification, however, does not provide guidance regarding how any structural change in the Z'-scaffold will impact whether and how a compound will irreversibly inhibit Btk. Based on the state of the art, a POSA would have understood that the SAR for unknown Z'-scaffolds would be unpredictable.

242. Dr. Eck contends that any testing and experimentation to confirm irreversible inhibition of Btk would be routine. EX2010 ¶199. As described below, in my opinion, such trial and error testing would have been extensive. Further, scaffold swapping and modeling would not have allowed a POSA to accurately predict whether a compound will irreversibly inhibit Btk and experimental testing would have been required to determine whether any given compound will irreversibly inhibit Btk. *See supra* Sections VI.B, VI.C.1, VI.C.2.b), VIII.A.1.a)(5).

243. In my opinion, these factors favor nonenablement.

b) Quantity of Experimentation

244. Dr. Eck contends that this factor supports that a POSA would have been able to make and use the full scope of the claimed irreversible BTKIs necessary for the claimed treatment method. EX2010, ¶¶203-215. I disagree.

245. In my opinion, under either Dr. Showalter's calculation or alternative calculations regarding the scope of the structurally diverse claimed Z'-scaffolds, extensive trial and error experimentation would have been required to practice the full scope of the Challenged Claims.

246. Dr. Eck contends that a POSA would have leveraged the structural information from Marcotte and used scaffold swapping or modeling tools which were available in June 2011. EX2010, ¶¶204-210. Scaffold swapping or modeling, however, would not have allowed a POSA to reliably and accurately predict whether a compound satisfying the Structural Limitations will irreversibly inhibit Btk. *See supra* Sections VI.B, VI.C.1, VI.C.2.b), VIII.A.1.a)(5).

247. Even if modeling could have been used, modeling the full scope of the structurally diverse claimed compounds satisfying the Structural Limitations alone would have required extensive efforts. *See supra* Section VIII.A.1.a)(5). As explained above, the Structural Limitations encompass both *known and unknown* Z'-scaffolds and evaluating the full scope of the compounds satisfying the Structural

Limitations would require evaluating *known and unknown* structures, which Dr. Eck acknowledged would take a “significant amount of time,” which he has not tried to estimate or determine how to execute. EX1110, 128:3-129:6, 129:13-16, 129:23-130:3. Dr. Eck contends that modeling a compound would have only taken “a matter of minutes.” EX2010, ¶209. Even so modeling the full scope of structurally diverse compounds satisfying the Structural Limitations still would have required extensive efforts. Specifically, modeling 4 million potential candidates would have taken over 7 years assuming each one could be modeled and evaluated in a single minute, and modeling billions would have taken far longer.

248. While Dr. Eck agrees that the Z'-scaffold could potentially encompass billions of structures, Dr. Eck has not tried to estimate how long it would have taken to actually prepare and dock the full scope of structurally diverse compounds satisfying the Structural Limitations. *See* EX1110, 42:21-43:18, 46:11-47:6, 125:8-19 (Dr. Eck testifying that he has not tried to estimate how long it would take to prepare and dock a million compounds, but it could not be done in a matter of minutes).

249. Even if modeling may have been able to provide some insight into whether a compound less likely to inhibit Btk, it would not have been able to accurately predict whether a compound in fact could irreversibly inhibit Btk.

Instead, additional, extensive testing would be required to determine whether the full scope of structurally diverse compounds satisfying the Structural Limitations would irreversibly inhibit Btk. *See supra* Section VI.C.1.b). Dr. Eck contends that a compound predicted to irreversibly inhibit by the use of modeling would have a “high probability of irreversibly inhibiting BTK in confirmatory biochemical testing.” EX2010, ¶210. Dr. Eck, however, provides no support for his opinion, except a single example, zanubrutinib. Although I disagree with Dr. Eck’s contention, even if true, this supports my opinion that additional experimental testing would have been necessary to accurately determine which compounds satisfying the Structural Limitations in fact irreversibly bind Btk.

250. Dr. Eck contends that mass spectrometry could be used to confirm the formation of a covalent complex between a candidate BTKI and Btk and fluorescent labeling could be used to assess selectivity and irreversible inhibition of Btk. EX2010, ¶¶212-213. However, extensive experimentation would have been required to perform mass spectrometry or fluorescent labeling to determine whether the full scope of structurally diverse compounds satisfying the Structural Limitations would irreversibly inhibit Btk.

251. Dr. Eck again contends that “the claim requirement that the compound be an irreversible BTKI imposes additional structural limitations” that would limit

the size and number of substitutions that a POSA would consider for the Z'-scaffold and a POSA would have understood that "additional substitutions of Z' would need to avoid steric clash with the BTK structure." EX2010 ¶¶208. However, I understand that Dr. Showalter disagrees with these criticisms, and even accounting for them, Dr. Showalter has concluded that the Structural Limitations are still broadly directed to at least 4 million species. EX1105, ¶¶31-35. In any event, my opinion that extensive testing is necessary is the same whether the Structural Limitations encompass potentially billions of or 4 million structurally diverse species. *Id.*

252. In my opinion, these factors favor nonenablement.

c) Breadth of the Claims

253. Dr. Eck contends that this factor supports that a POSA would have been able to make and use the full scope of the claimed irreversible BTKIs necessary for the claimed treatment method. EX2010, ¶¶216-222. I disagree.

254. In my opinion, even based on Dr. Showalter's alternative calculations, the scope of the Challenged Claims is extensive. EX1105, ¶¶31-35. While Dr. Scott and Dr. Eck did not provide any opinion regarding how many BTKIs fall within the scope of the Challenged Claims, Dr. Eck agreed that the claimed Z'-scaffold could potentially encompass billions of structures. *See* EX1110, 42:21-43:18, 46:11-47:6, 165:13-17.

255. Dr. Eck contends that “a POSA’s knowledge about the kinase hinge region in June 2011 from the ’803 Patent and art would limit the scope of acceptable compounds to those that have a Z’-scaffold that functions as a hinge-binding element and makes the necessary one to three H-bonds with the BTK hinge region.” EX2010, ¶218. Dr. Eck further suggests that modeling/docking would have been required to determine how these H-bonding interactions would have limited the scope. As described above, however, modeling the structurally compounds satisfying the Structural Limitations would have required extensive efforts, modeling is not predictive of whether a compound will in fact irreversibly inhibit Btk, and experimental testing would have been required. *See supra* Section IX.A.1.b).

256. Dr. Eck contends that a POSA would have understood the necessary orientation of the claimed linker-warhead and phenoxyphenyl and “a POSA would have further understood that these required substituents on Z’-scaffolds—and their orientations and the potential resulting steric hindrance—would limit the scope of acceptable Z’-scaffolds.” EX2010, ¶218; *see also id.*, ¶221. In my opinion, such considerations do not predictably limit the scope of acceptable Z’-scaffolds. Rather, extensive testing would have been required.

257. Dr. Eck contends that a POSA would have leveraged the structural information from Marcotte and used scaffold swapping or virtual docking and modeling. EX2010, ¶219. For the reasons explained above, however, these tools do not reliably and accurately predict whether any given compound will irreversibly inhibit Btk. Even if modeling could provide some insight into whether a compound is less likely to irreversibly inhibit Btk, a POSA would have been required to model all of the compounds satisfying the Structural Limitations in order to determine which one would be “ruled out.” *Id.*

258. In my opinion, this factor favors nonenablement.

**d) Unpredictability of the Art, State of the Prior Art,
Relative Skill of Those in the Art**

259. Dr. Eck contends that these factors support that a POSA would have been able to make and use the full scope of the claimed irreversible BTKIs necessary for the claimed treatment method. EX2010, ¶¶223-229. I disagree.

260. Dr. Eck contends that the SAR of BTKIs was well understood, and a POSA would have been aware of scaffold swapping. EX2010, ¶¶224, 227. I disagree that the SAR was well understood. Moreover, as described above, scaffold swapping would have required extensive trial and error and would not have accurately predicted whether a compound satisfying the Structural Limitations

comprising a known or unknown Z'-scaffold would irreversibly inhibit Btk. *See supra* Section VI.B.

261. Dr. Eck again contends that based on Marcotte a POSA would have had data to visualize BTKIs through virtual docking. EX2010, ¶¶224-225. However, the state of the art was unpredictable, including the use of modeling. *See supra* Section IX.A.1.b).

262. Dr. Eck again relies on the teachings of Ghose and Garuti. EX2010, ¶228. As described above, however, these teachings do not show that the nature of the invention was predictable. *See supra* Sections VI.A.2, VI.B.2, VIII.A.1.a)(6).

263. In my opinion, these factors favor nonenablement.

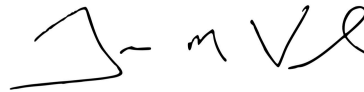
2. Dependent Claims

264. Dr. Eck contends that Dr. Showalter did not provide a separate analysis regarding the enablement of the limitations recited in the dependent claims and therefore the dependent claims are fully enabled for the same reasons as independent claims 1 and 8. EX2010, ¶232. I understand from Dr. Showalter's Declaration that the dependent claims do not reduce or appreciably reduce the number of species that satisfy the claimed Structural Limitations. EX1003, ¶¶260, 263, 266, 269. Therefore, it is my opinion that the dependent claims are not enabled for the same reasons as claims 1 and 8.

X. DECLARATION

265. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

DATED: October 30, 2024

A handwritten signature in black ink, appearing to read "J. M. Veal", written above a horizontal line.

James M. Veal, Ph.D.