

Filed On Behalf Of:

C4 Therapeutics, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

C4 THERAPEUTICS, INC.

Petitioner

v.

FOGHORN THERAPEUTICS, INC.

Patent Owner

PGR No.: To Be Assigned

U.S. Patent No. 11,560,381

DECLARATION OF STEVAN W. DJURIC, Ph.D.

UNDER 37 C.F.R. §1.68 AND §42.53(a)

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	SCOPE OF WORK AND SUMMARY OF OPINIONS	5
III.	TECHNOLOGY TUTORIAL	6
IV.	FILE HISTORY OF THE '381 PATENT	13
V.	CLAIMS OF THE '381 PATENT	16
VI.	CLAIM CONSTRUCTION	27
VII.	SUMMARY OF MY EXPERT OPINIONS	34
VIII.	DETAILED DISCUSSION OF MY EXPERT OPINIONS	40
1.	Lack of Written Description	42
a.	Interpretation of the Modular “Linker” Structure in the '381 Patent Claims	42
b.	Interpretation of the Modular “B” Degradation Moiety in the '381 Patent Claims	51
c.	Misleading Statements to the USPTO during Prosecution Regarding Scope of Linker	54
d.	Interpretation of the Modular “A” BRD9 Binding Moiety in the '381 Patent Claims and Additional Misrepresentation to the USPTO	58
e.	Use of the Term “Optionally Substituted” in the '381 Patent Claims	63
f.	Incorporation of Infinite Loops in the '381 Patent Claims	72
g.	Content of Specification and Data Provided in the '381 Patent Specification is Inadequate to Support the Breadth of the Claims	76
h.	The '381 Patent Claims are Indefinite under 112(b)	96
2.	The '381 Patent Claims Are Not Enabled	96

a.	There is No Synthesis of Any of the Claimed Compounds in the Specification.....	99
b.	Consideration of the Factors for Enablement	101
3.	Anticipation.....	103
IX.	LEGAL STANDARDS	130
A.	Burden of Proof.....	130
B.	Preponderance of the Evidence.....	130
C.	The Written Description Requirement.....	131
D.	The Enablement Requirement.....	135
E.	Indefiniteness of Patent Claims	137
F.	Anticipation (Novelty)	138
X.	CONCLUSION	142

I, Stevan W. Djuric, Ph.D., hereby declare as follows:

I. INTRODUCTION

1. My name is Stevan W. Djuric, Ph.D. I am the President of Discovery Chemistry and Technology Consulting LLC. My Curriculum Vitae is provided as Attachment 1 to my Declaration.

2. I have been retained by Knowles Intellectual Property Strategies, LLC on behalf of C4 Therapeutics, Inc. (“C4T” or “Petitioner”) as an independent expert to provide my opinions on the claimed subject matter in U.S. Patent No. 11,560,381 (the “’381 Patent”) (Ex.1001).

3. I received my B.Sc. in Chemistry (1976) and my Ph.D. in Organic Chemistry (1979) from the University of Leeds, England. I was a Post-Doctoral Research Fellow at Ohio State University (1980-1981) before starting my pharmaceutical research career. I have specialized in the area of organic chemistry and in particular pharmaceutical chemistry for forty-four years since obtaining my Ph.D. I have worked both in academic and industrial environments.

4. I was a senior scientist at Abbott, Inc. and its successor Abbvie, Inc. from 1996-2019 with positions of increasing responsibility, culminating in my role as the Vice President, Discovery Chemistry and Technology, Global Pharmaceutical Research and Head of their Global Medicinal Chemistry Leadership

Team, where I was responsible for a group of about 150 internal scientists and over 100 external scientists.

5. I was a Distinguished Research Fellow at Abbvie from 2015-2019, which is the highest ladder of scientific achievement at the company. I was also a member of the governing Scientific Advisory Board (highest level scientific Board at Abbvie).

6. During my tenure at Abbott/Abbvie, I with my team were responsible for the discovery of one marketed drug (Zotarolimus, an immunosuppressant currently licensed to Medtronic for use in its vascular stent), and a drug/medical device combination (a foscarbidopa/foslevodopa pump for the treatment of advanced Parkinson's Disease) currently in final stages of approval at the U.S. FDA. Teams I have directly supervised have also been responsible for the discovery of two other compounds in human clinical trials—a LTB₄ receptor antagonist (at Searle) and a DPP4 inhibitor (at Abbott).

7. Abbvie created a major targeted protein degradation initiative in its Discovery Chemistry and Technology team in 2018. I submitted the first proposal to Abbvie management to start the program. As part of this initiative, I was responsible for the medicinal chemistry aspect of the Abbvie collaboration with Calico Life Sciences (founded by Alphabet) to create drugs to treat age-related diseases. This collaboration, which started in 2014, has produced more than 20

early-stage programs, and includes research and development on protein degrading compounds that can address diseases of aging.

8. At Abbvie, I led a team of discovery chemistry researchers in the field of heterobifunctional protein degradation. We designed and evaluated complex large molecular weight pharmaceutical compounds for their ability to degrade proteins involved in various diseases.

9. Prior to my role as VP of Discovery Chemistry, I was the Senior Director of Discovery Chemistry and Technology and Head of the Abbvie Global Medicinal Chemistry leadership team.

10. I have well over 100 peer reviewed scientific publications and am the co-author of numerous review articles, posters, and presentations on a wide variety of pharmaceutical topics. I am also a listed inventor on a number of patent filings in the pharmaceutical area.

11. I am or have been a member of numerous editorial boards and a reviewer for a number of high-level journals, including the Journal of the American Chemical Society, Journal of Organic Chemistry, Journal of Medicinal Chemistry, ACS Medicinal Chemistry Letters (of which I am an Associate Editor), Organic Letters, Tetrahedron, and BioOrganic & Medicinal Chemistry, among others.

12. I am also a member of the faculty in the School of Pharmacy at the University of Kansas, and I have held an adjunct faculty position in the School of Pharmacy at High Point University, N.C.

13. I currently consult for a number of biopharmaceutical companies and sit on several Scientific Advisory Boards, both domestic and international.

14. I understand that C4 Therapeutics, Inc. is challenging the granted patent claims of the '381 Patent as Petitioner in a Post Grant Review ("PGR") proceeding at the Patent Trial and Appeal Board ("PTAB"), and that it is asking the PTAB to cancel claims 1-12 of the '381 Patent on the grounds of violation of 35 U.S.C. §112(a) and (b) and 35 U.S.C. §102. These laws have been explained to me, as discussed in Section IX below.

15. I also provided a Declaration to support a Petition for a PGR of U.S. Patent No. 11,414,416 (the "'416 Patent"), filed on May 1, 2023 (PGR2023-00029), that was likewise assigned to Patent Owner ("PO") of the '381 Patent, in which Petitioner challenged the issued claims of the '416 Patent on the same grounds of 35 U.S.C. §112(a) and (b) and 35 U.S.C. §102. I am told that in response, PO filed a statutory disclaimer of the '416 Patent. The '381 Patent is a continuation of the '416 Patent with broader claims.

16. I provide this Declaration based on personal knowledge, as well as my expert industrial and academic experience in the protein degradation field specifically, and my work generally, in the area of pharmaceuticals drug discovery.

17. I am being compensated for my time at a rate of \$800 per hour. My compensation does not depend on my opinions, conclusions, or the outcome of this proceeding. I am over 21 years old and competent to provide this Declaration.

II. SCOPE OF WORK AND SUMMARY OF OPINIONS

18. I have been asked by counsel for Petitioner to act as an independent expert to provide a tutorial for PTAB on the field of intracellular protein degradation, which I do in Section III below.

19. I have also been asked to consider and provide my opinions on certain topics related to the '381 Patent, including:

(i) How a person of ordinary skill in the art ("POSA") should be defined for the '381 Patent (which I describe in Section VI below);

(ii) How the POSA would interpret the claims of the '381 Patent (which I address in Section VI below);

(iii) Whether the written description of the '381 Patent indicates that the inventors had possession of the full scope of the subject matter claimed (which I conclude in Section VIII-1 below it does not);

(iv) Whether the claims of the '381 Patent are definite and capable of providing notice to a POSA of potential infringing activity (which I conclude in Section VIII-1h below they are not);

(v) Whether the claims of the '381 Patent are enabled across their full scope (which I conclude in Section VIII-2 they are not);

(vi) Whether the subject matter of the claims of the '381 Patent are fully described in its priority application (which I conclude in Section VIII-3 it is not);

(vii) What teachings and data are provided by WO2021/178920 (the C4T "'920 PCT Publication") (Ex.1010) that are relevant to the '381 Patent claims (which I describe in Section VIII-3);

(viii) Whether the '920 PCT Publication would be considered a first adequate disclosure of the claims of the '381 Patent if the '381 Patent is not entitled to its priority filing dates (which I affirm in Section VIII-3 below).

III. TECHNOLOGY TUTORIAL

20. Protein degradation is a highly regulated and essential process that maintains cellular homeostasis. The selective identification and removal of damaged, misfolded, or excess proteins is achieved via the ubiquitin-proteasome pathway ("UPP"). The UPP is central to the regulation of almost all cellular

processes, including antigen processing, apoptosis, cell cycling, DNA transcription and repair, differentiation and development, immune response and inflammation. Covalent attachment of multiple ubiquitin molecules by an E3 ubiquitin ligase enzyme to a terminal lysine residue of a protein to be degraded marks the protein for proteasomal processing, where the protein is digested into small peptides and eventually into its constituent amino acids, which subsequently are recycled as building blocks for new proteins. Defective proteasomal degradation has been linked to a variety of clinical disorders including cancer, abnormal cellular proliferation, and cardiovascular disease, among others. This process is illustrated in Figure 1 below, provided by Petitioner, and which I agree with.

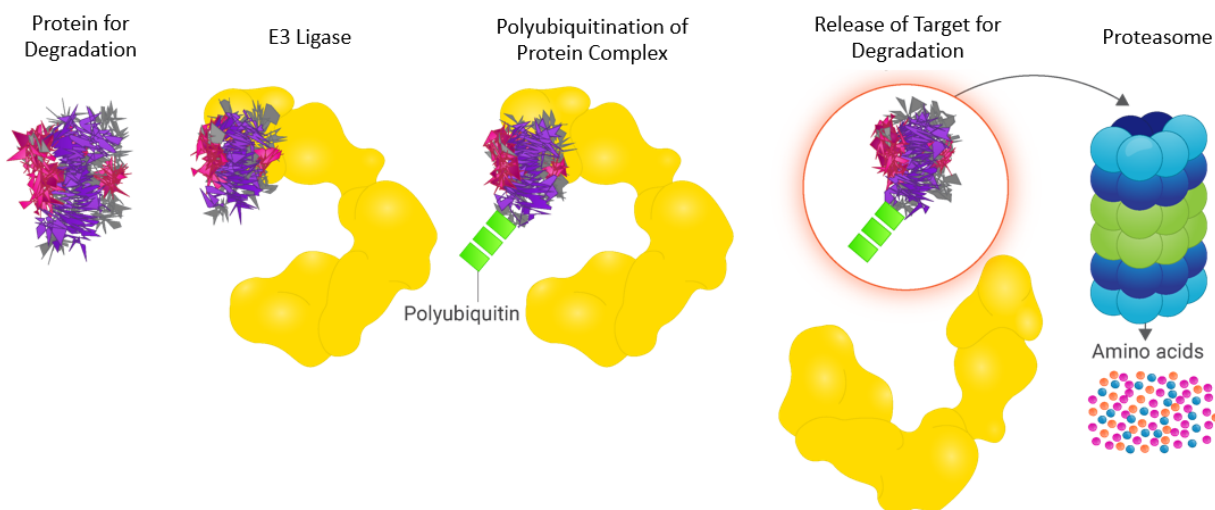


FIG. 1

21. Cereblon is the enzyme receptor component of the multi-protein complex cullin 4-RING E3 ligase that is relevant to the '381 Patent claims. In

successive reactions, a polyubiquitin chain is created by the cereblon-containing E3 ligase on the target protein. The polyubiquitin tail serves as a recognition marker for the proteasome, which degrades the tagged protein into its amino acid components for recycling.

22. As illustrated in Figures 2 and 3 below (provided by Petitioner, and which I agree with), research has been advanced to try to hijack this complex UPP process by designing molecules that bring together the two necessary parts for ubiquitinating the targeted protein – the E3 ligase enzyme and the target protein to be ubiquitinated. This “heterobifunctional” compound (also called a “BiDAC” degrader) is a three-component compound that consists of 1) a binding ligand to a protein to be degraded (“target protein ligand”), 2) a linker, and 3) a binding ligand to an E3 ligase enzyme, such as cereblon, that ubiquitinates the protein (“cereblon binder”).

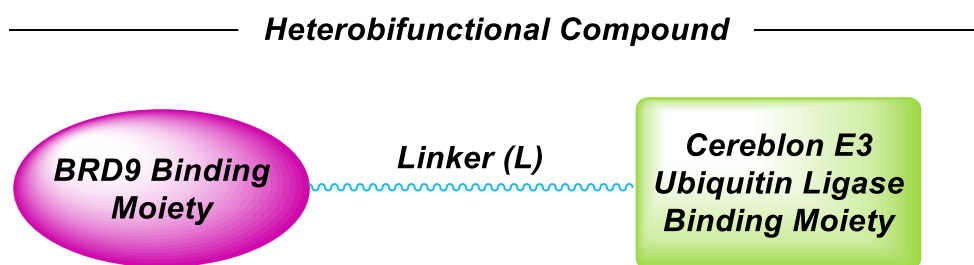


FIG. 2

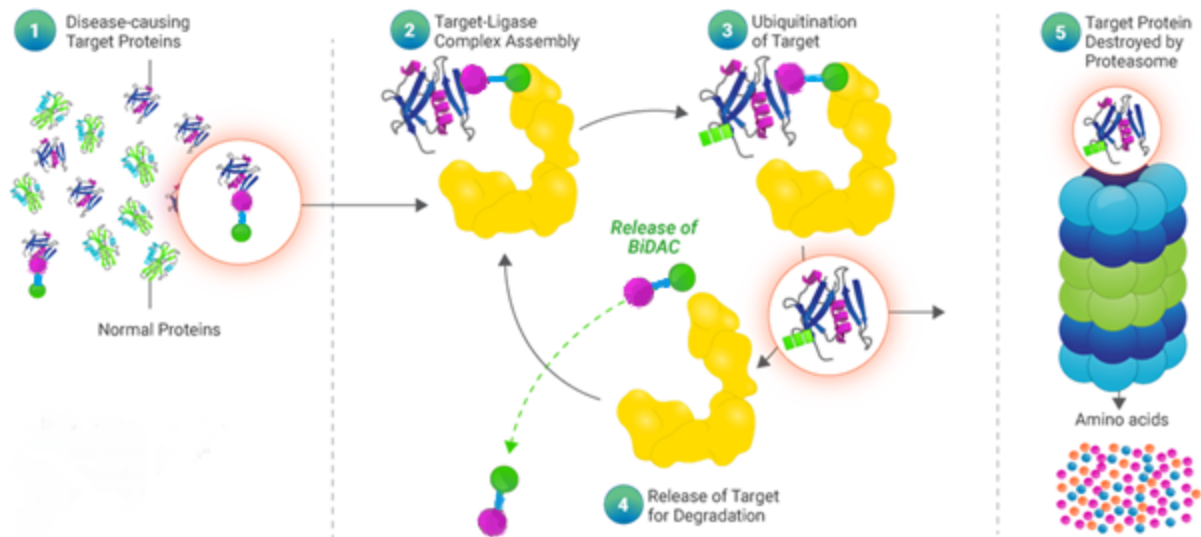


FIG. 3

23. The BAF protein complex is a multi-subunit chromatin remodeling unit that plays an important role in genomic regulation. BAF complex mutations occur in a number of human diseases, particularly cancer.

24. Bromodomain containing proteins (BRD) such as BRD9 are proteins that recognize acetylated lysine residues such as those on the N-terminals of histones. BRDs are evolutionarily conserved and are present in diverse nuclear proteins. Bromodomain containing proteins have a number of functions that mediate transcription and coactivation, and thus are involved in cellular proliferation.

25. As shown in Figure 4 below (provided by Petitioner and which I agree with), the cBAF complex (i.e., canonical, or naturally occurring, BAF) includes a protein referred to as SMARCB1, which is a tumor suppressing protein.

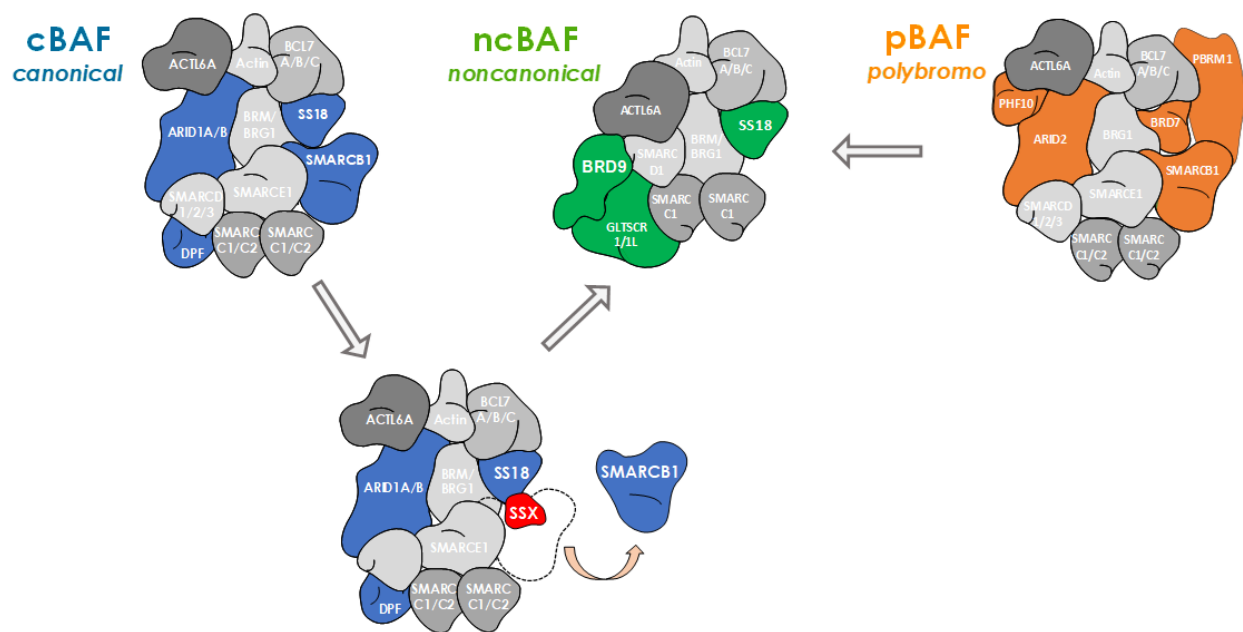


FIG. 4

26. During the development of certain cancers, SMARCB1 becomes ejected from the cBAF complex which results in a ncBAF (i.e., noncanonical, or non-normal, BAF). When SMARCB1 is eliminated from cBAF, the protein BRD9 becomes part of the protein complex. A similar process can occur from pBAF (polybromoBAF). In cells where this process has occurred, chromatin remodeling is dependent on ncBAF.

27. Since BRD9 is present in ncBAF but not cBAF or pBAF, this provides an opportunity to target the ncBAF complex with a therapeutic compound that binds to BRD9 and degrades it.

28. Specifically, in the cancer synovial sarcoma, there is an SS18-SSX protein fusion that ejects SMARCB1, causing cBAF to convert to ncBAF. The presence of ncBAF results in dysfunctional and aberrant chromatin remodeling, which can lead to an oncogenic state. Synovial sarcoma and other SMARCB1-perturbed cancers thus have a non-natural lethal dependency on BRD9 in the ncBAF complex. Because BRD9 is present in the ncBAF but not the cBAF or pBAF, the aberrant ncBAF complex can be selectively targeted in these cancer cells with a therapeutic compound that binds to BRD9 and degrades it (Brien et. al., “Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma.” *Elife.*, 2018, Nov. 15;7:e41305) (Ex.1016¹). BRD9 is also involved in the aberrant replication of acute myeloid leukemia cells, and can be selectively targeted in these cancers as well (Hohmann et. al., Sensitivity and Engineered Resistance of Myeloid

¹ I certify that Exhibit 1016 is a true and correct copy of Brien et al., Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma. *Elife.* 2018 Nov 15;7:e41305.

Leukemia Cells to BRD9 Inhibition, Nature Chemical Biology, 12, 672-679 (2016)) (Ex.1017²).

29. While this BRD9 therapeutic highjacking process seems straightforward, it is not. The process is full of three-dimensional complexities, whole-body biology, and uncertainties. Many potential heterobifunctional compounds fail after *in vitro* or *in vivo* testing for a variety of reasons. These include: (i) the inability to create an effective three component (i.e., ternary) structure architecture with the target protein and the E3 ligase to accomplish polyubiquitination and then degradation; (ii) strength of binding to the protein and to the E3 ligase; (iii) bulk or electronic interference by drug substituent groups with critical binding pockets; (iv) lipophilicity of the compound (potentially leading to increased rates of clearance and metabolism); (v) rate of clearance of free drug which is also affected by metabolism; (vi) polar surface area; (vii) aqueous solubility; (viii) volume of distribution; (ix) off-target degradation; (x) insufficient cell permeability (which can be highly dependent on physicochemical properties); (xi) insufficient tissue selectivity; and (xii) toxicity to a non-targeted tissue (e.g., heart or liver).

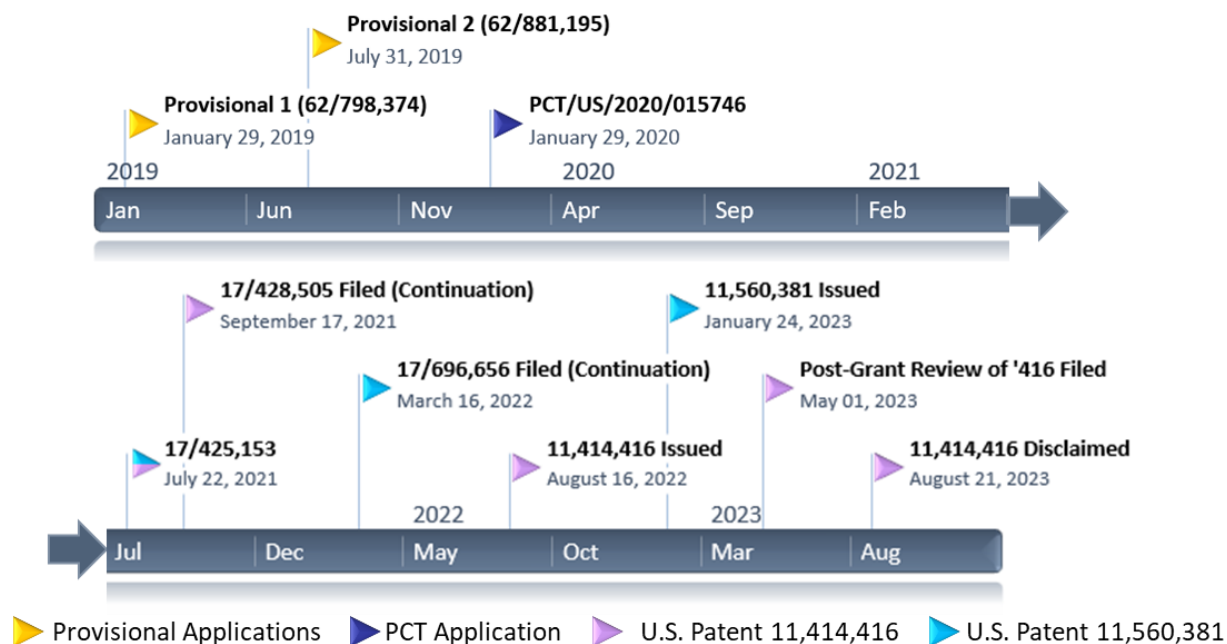
² I certify that Exhibit 1017 is a true and correct copy of Hohmann et. al., Sensitivity and Engineered Resistance of Myeloid Leukemia Cells to BRD9 Inhibition, Nature Chemical Biology, 12, 672-679 (2016).

30. As one of my expert specialties is the evaluation of ADME (absorption, distribution, metabolism, and excretion) properties of drug candidates, I am aware of the high bar that these “beyond the rule of 5” (i.e., compounds that do not follow Lipinski’s Rule of 5 for a well-behaved pharmaceutical compound) heterobifunctional compounds must achieve to progress to drug approval and use in humans, and that I have seen drug candidates fail for reasons cited above.

IV. FILE HISTORY OF THE ’381 PATENT

31. PO filed U.S. Patent Application No. 17/696,656 with the U.S. Patent and Trademark Office (hereinafter “USPTO”) with a Track One Request on March 16, 2022 (hereinafter the “’656 application”) (Ex.1002). The ’656 application is a continuation of U.S. Patent Application No. 17/478,505, filed with the USPTO on September 17, 2021 (issued as U.S. Patent No. 11,414,416) (Ex.1003), which is a continuation of U.S. Patent Application No. 17/425,153, filed with the USPTO on July 22, 2021 (Ex.1004), which is a national phase of PCT/US2020/015746, filed with the U.S. Receiving Office January 29, 2020 (Ex.1005), which claims the benefit of U.S. Provisional Application No. 62/881,195, filed with the USPTO on July 31, 2019 (Ex.1006); and U.S. Provisional Application No. 62/798,374, filed with the USPTO on January 29, 2019 (Ex.1007). The priority timeline is illustrated below, along with the issuance and disclaimer of the parent ’416 Patent.

Patent Owner (Foghorn Therapeutics) Timeline



32. The Decision Granting the Request for Prioritized Examination (Track 1) was issued by the USPTO on May 4, 2022 (Ex.1002,65-69).

33. The USPTO issued a Non-Final Office Action on May 19, 2022 (Ex.1002, 50-64). The Examiner rejected then pending claims 1-10 under 35 U.S.C. §102 as anticipated by Remillard et al., *Angewandte Chemie, International Edition* (2017), 56(21), 5738-5743 (Ex.1019) and Rao et.al., CN 108690020 (Ex.1020).

34. The Patent Office did not raise any rejections of the presented claims under 35 U.S.C. §112 or question the right to claim the benefit of priority to the '656 application's priority documents based on the presented claims.

35. PO filed a Response to the Non-Final Office Action with a Terminal Disclaimer over the '416 Patent Claims on June 16, 2022 (Ex.1002,24-63). PO amended Claim 1 to add the definition that p is 0 or 1, and to add dependent claims 11 and 12, dependent on claims 1 and 10, respectively, to define p as 1. I discuss PO's Response to Office Action below in Section VIII-1c "Misleading Statements to the USPTO during Prosecution."

36. A Notice of Allowance issued on June 29, 2022 (Ex.1002,7-21). Applicant paid the issue fee on July 12, 2023 (Ex.1002,2-20).

37. The '656 application issued as U.S. Patent No. 11,560,381 on January 24, 2023 (Ex.1002,1).

V. CLAIMS OF THE '381 PATENT

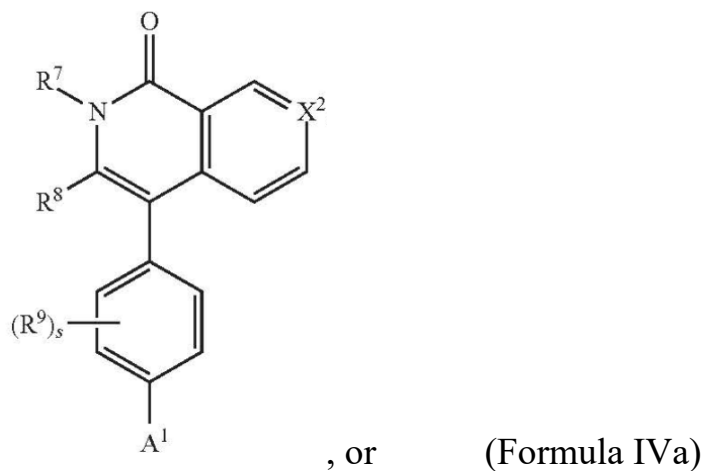
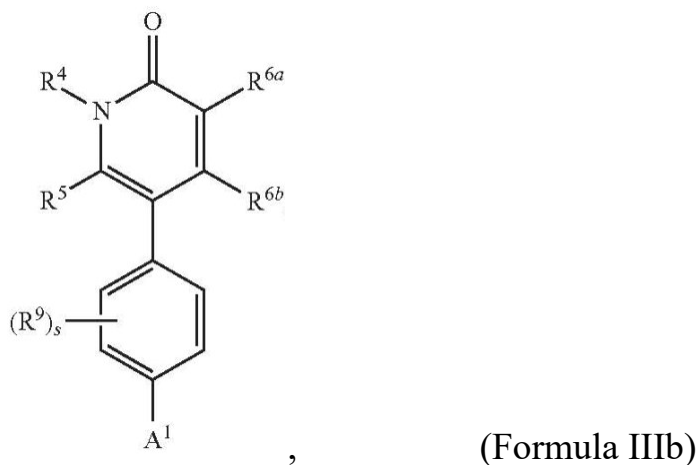
38. The claims of the '381 Patent are as follows.

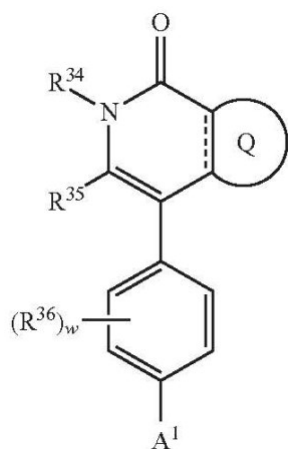
Claim 1 - A compound having the structure of Formula I:



wherein

A is:





(Formula IX)

wherein

A^1 is a bond between A and L;

s and w are, independently 0, 1, 2, 3, or 4;

R^4 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_{10} carbocyclyl,

R^5 is H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl;

R^{6a} is H, halogen, cyano, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

R^{6b} is H, halogen, cyano, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or R^{6a} and R^{6b} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl or optionally substituted C_2 - C_9 heteroaryl;

R^7 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_{10} carbocyclyl;

R^8 is H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl;

each R^9 is, independently, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

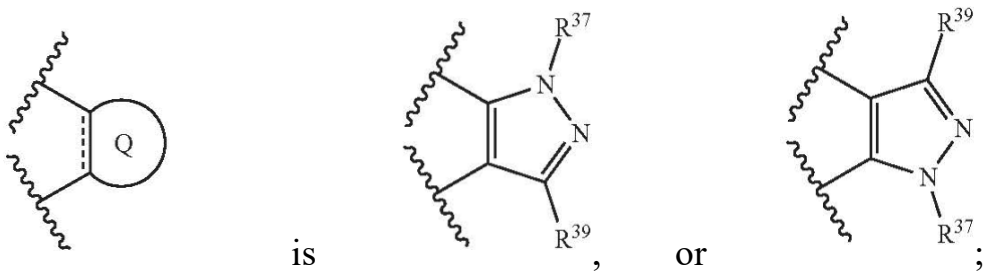
X^2 is N or CR^{10b} ;

R^{10b} is H, halogen, hydroxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

R³⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

R³⁵ is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₆ carbocyclyl, or optionally substituted C₆-C₁₀ aryl;

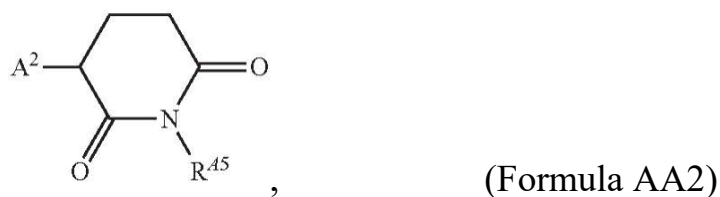
each R³⁶ is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;



R^{37} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl; and

R^{39} is H, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_6 - C_{10} aryl;

B is:

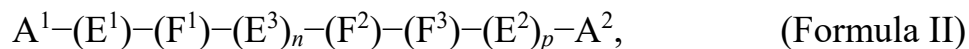


wherein

A^2 is a bond between B and L; and

R^{45} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

L is:



wherein

A^1 is a bond between the linker and A;

A² is a bond between B and the linker;

n is 0 or 1;

p is 0 or 1;

each of E¹ and E² is, independently, O, S, NR^N, optionally substituted C₁₋₁₀ alkylene, optionally substituted C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C_{2-C10} polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene;

E³ is optionally substituted C_{1-C6} alkylene, optionally substituted C_{1-C6} heteroalkylene, O, S, or NR^N;

each R^N is, independently, H, optionally substituted C₁₋₄ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl; and

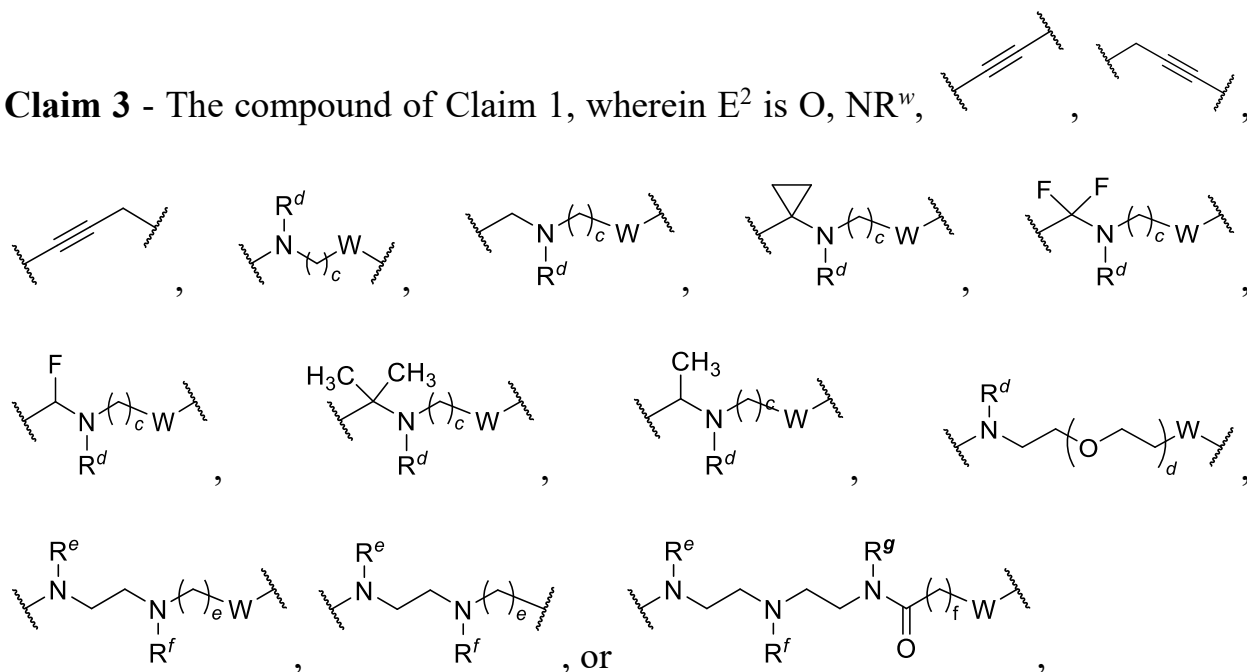
each of F¹, F², and F³ is, independently, optionally substituted C_{3-C10} carbocyclylene, optionally substituted C_{2-C10} heterocyclylene, optionally substituted C_{6-C10} arylene, or optionally substituted C_{2-C9} heteroarylene,

or a pharmaceutically acceptable salt thereof. (Ex.1001,502-503³).

Claim 2 - The compound of Claim 1, wherein E¹ is —CH₂—. (*Id.*,503).

³ Citation is to Exhibit page number.

Claim 3 - The compound of Claim 1, wherein E² is O, NR^w,



wherein

c is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

d is 0, 1, 2, or 3;

e is 0, 1, 2, 3, 4, 5, or 6;

f is 0, 1, 2, 3, or 4;

R^d is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

R^e is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

R^f is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

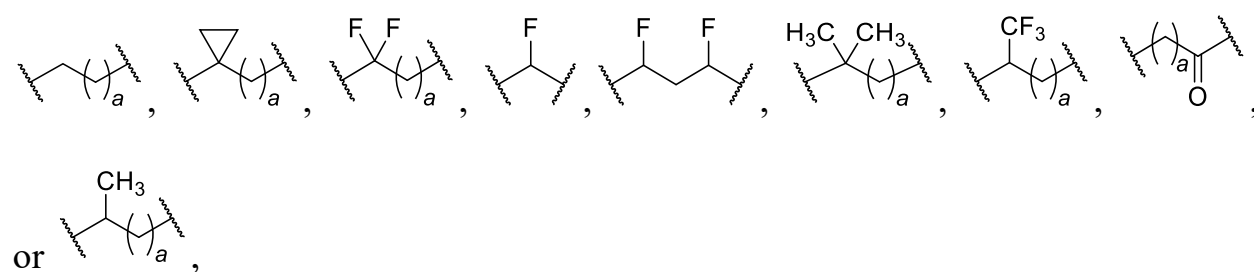
R^g is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl; and

W is O or NR^w , wherein R^w is H or optionally substituted C_1 - C_6 alkyl. (*Id.*).

Claim 4 - The compound of claim 3, wherein E^2 is $—NR^N—$. (*Id.*).

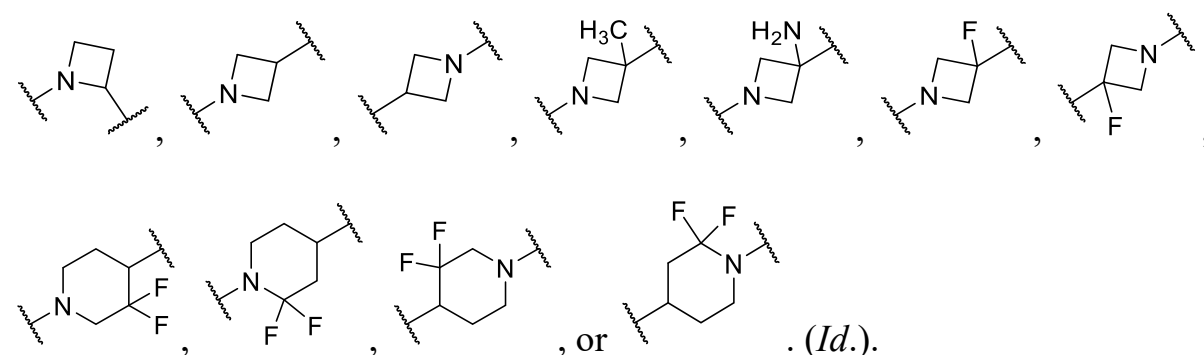
Claim 5 - The compound of claim 4, wherein E^2 is $—NH—$. (*Id.*).

Claim 6 - The compound of Claim 1, wherein n is 1 and E^3 is

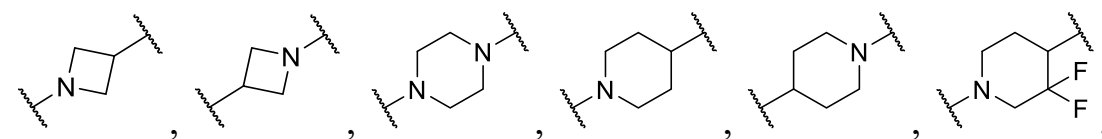


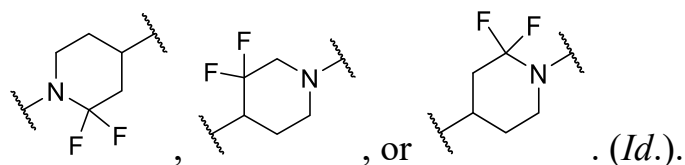
where a is 0, 1, 2, 3, 4, or 5. (*Id.*,503-504).

Claim 7 - The compound of Claim 1, wherein F^1 is



Claim 8 - The compound of Claim 1, wherein F^2 is

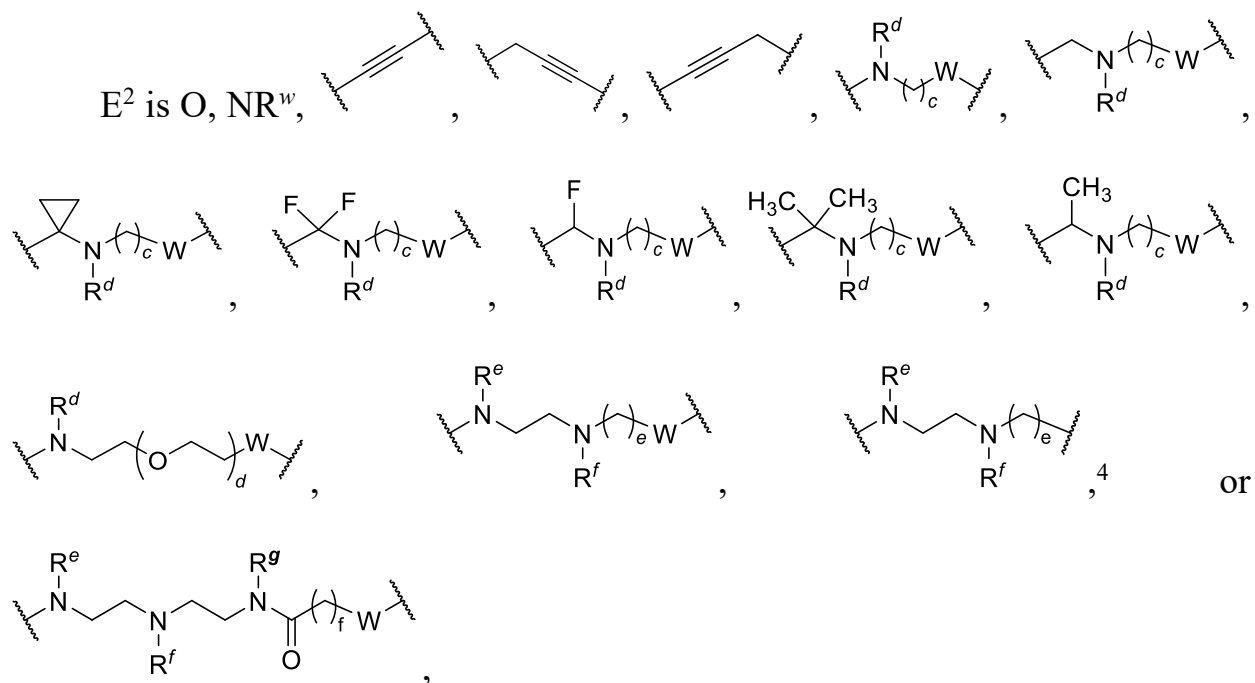




Claim 9 - The compound of Claim 1, wherein F³ is optionally substituted C₆-C₁₀ arylene. (*Id.*).

Claim 10 - The compound of Claim 1, wherein:

E¹ is —CH₂—;



⁴ I note that there is a publication error in the patent where R^d in the second to last structure of E² was R^e in the allowed claim set. There is no effect on scope because R^d and R^e have the same definitions. In the claim listing above I provide the structure

wherein

c is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

d is 0, 1, 2, or 3;

e is 0, 1, 2, 3, 4, 5, or 6;

f is 0, 1, 2, 3, or 4;

R^d is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

R^e is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

R^f is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

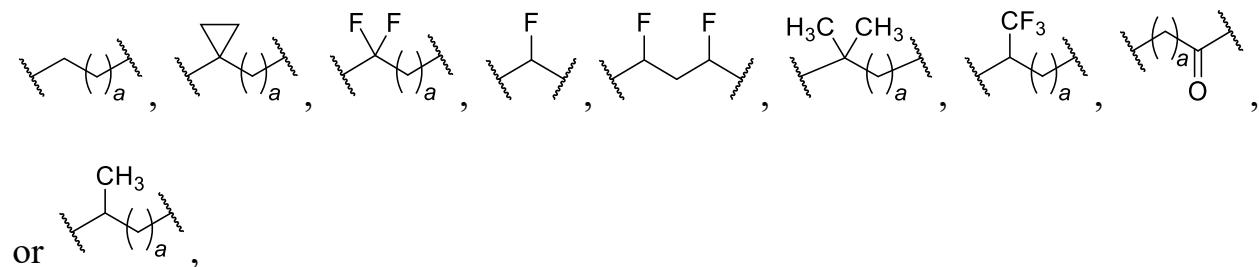
R^g is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

W is O or NR^w , wherein R^w is H or optionally substituted C_1 - C_6 alkyl;

n is 0 or 1;

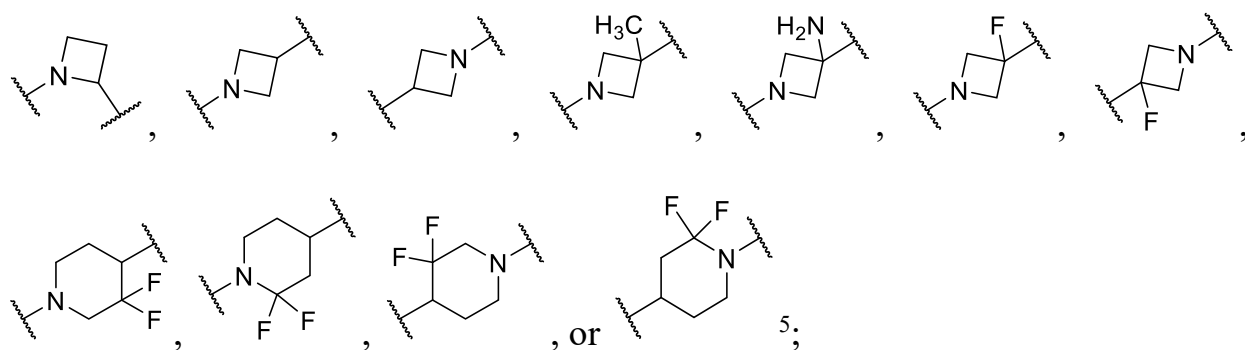
of the allowed moiety (*See* Ex.1002,38). I've been told that the PO has not corrected this error.

E³ is



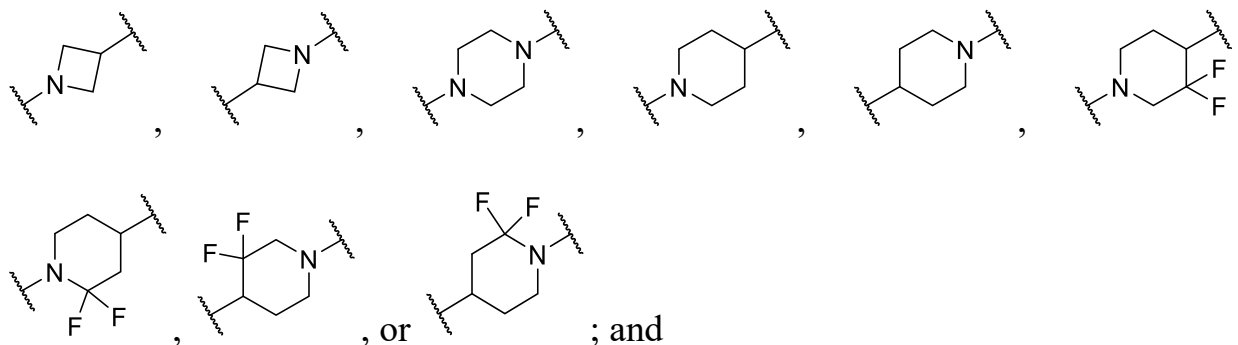
where a is 0, 1, 2, 3, 4, or 5; and

F¹ is



⁵ I note that there is a publication error in the patent where the last structure of F¹ is a difluoro-piperazine instead of the difluoro-piperidine of the allowed claims. In the claim listing above I provide the structure of the allowed moiety (*See* Ex.1002,38). I've been told that the PO has not corrected this error.

F² is



F³ is optionally substituted C₆-C₁₀ arylene. (*Id.*,504-505).

Claim 11 - The compound of Claim 1, wherein p is 1. (*Id.*).

Claim 12 - The compound of Claim 10, wherein p is 1. (*Id.*).

VI. CLAIM CONSTRUCTION

39. I understand claim construction focuses primarily on the “intrinsic evidence,” which consists of the claims themselves, the specification, and the file history. I understand that claim terms must be interpreted specifically in light of how the terms are used in the specification, not in a vacuum. I am also told that statements in the file history made by PO about a claim term cannot override or be inconsistent with the use of that term, or how a POSA would view that term, based on the specification as a whole.

40. I understand that an “independent claim” sets out the broadest scope of the claimed invention. An independent claim typically begins with the word

“a.” In the ’381 Patent only Claim 1 is independent while claims 2-12 are dependent claims.

41. I understand that a “dependent claim” is narrower than the claim from which it depends. A dependent claim includes each limitation of the claim it depends on and one or more additional limitations which narrow the scope of the claim. A dependent claim can be dependent on either an independent claim or another dependent claim.

42. I have been asked to provide my opinion on how a POSA would construe, or interpret, the following claim terms of the ’381 Patent based on the ’381 Patent specification:

- (i) Optionally Substituted;
- (ii) C₆-C₁₂ Aryl;
- (iii) C₆-C₁₀ Arylene; and
- (iv) B” and “AA2”.

“Optionally Substituted”

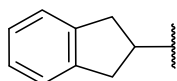
43. I discuss the term “optionally substituted” at length in Section VIII-1e and Section VIII-1f below and will not repeat it here. In summary, my conclusion is that the term “optionally substituted” as used in the ’381 Patent without being accompanied by a very precise definition such as a reference to a closed set of substituents in a claim, does not provide adequate notice to a POSA because the term

does not specifically describe what the substituents can be or where they are to be linked to the base molecule. It opens the molecule to unbounded speculation and possibilities. In the '381 Patent, in general, when a molecule is “optionally substituted,” a POSA cannot determine the molecule’s size, lipophilicity, toxicity, stability, or functionality, nor would it be possible to know how to make or use it.

44. It is not appropriate nor expected by a POSA for a party to use the term “optionally substituted” to construct any compound or moiety at will that is not actually described in a definite formula.

“C₆-C₁₂ Aryl”

45. Aryl is defined in column 440, lines 24-29 as “an aromatic mono- or polycarbocyclic radical of, e.g., 6 to 12, carbon atoms having at least one aromatic ring.” (Ex.1001, 236). The definition of aryl includes “phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl,” however, the attachment point is not specified. (*Id.*). Thus, one aspect of the uncertainty is where the attachment point on polycyclic aryl groups can be. For example, does an indanyl attached through the non-aromatic ring fall within the claim term “aryl”?



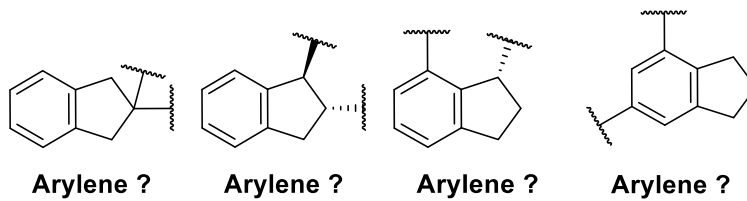
Aryl ?

Because the attachment points on “aryl” are capable of two different interpretations, for the purpose of this analysis I take the broader interpretation and consider that the

attachment point can be through any ring in the multi-ring system, given that the definition is not otherwise limited.

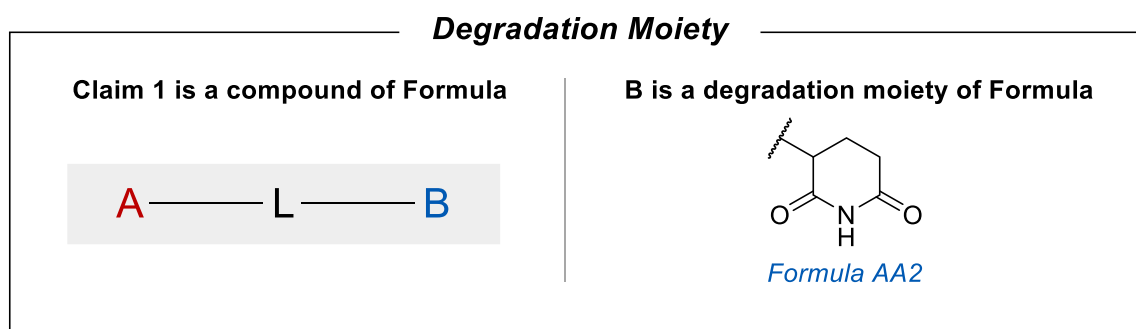
“C₆-C₁₀ Arylene”

46. The specification does not provide a definition of “arylene” or “C₆-C₁₀ arylene.” The specification teaches that when the suffix “ene” is added to the end of the term, that means the moiety is in the divalent state (see for example, ’381 Patent, col. 439, line 67 “an alkylene is a divalent alkyl group”; col. 440, lines 5-6 “an alkenylene is a divalent alkene group”) (Ex.1001,236). However, when the term aryl is defined (*see* col.440,1.24-29), it refers to an aromatic mono- or polycarbocyclic radical, of e.g., 6 to 12 carbon atoms having at least one aromatic ring. (*Id.*). The definition of aryl includes “phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl,” however, the attachment point is not specified. (*Id.*). This lack of clarity is further compounded by the divalent nature of arylene. For example, it is not clear which attachment points of indanyl are included within the term C₆-C₁₀ arylene.



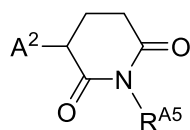
Interpretation of “B” and “AA2” by a POSA

47. I have also been asked to consider how a POSA would interpret “B” as used in the ’381 Patent claims. “B” is referred to in Claim 1. (Ex.1001,503). “B” is defined by PO in column 1, line 46, as a “degradation moiety.” (*Id.*,17). The specification states that “In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.” (*Id.*,50; col.68,1.50-51). In col. 68, lines 52-53, the specification states that the ubiquitin ligase binding moiety can be a cereblon ligand. (*Id.*). The term “degradation moiety” is defined in col. 448, lines 33-37 as “a moiety whose binding results in degradation of a protein, e.g., BRD9. (*Id.*,240). In one example, the moiety binds to a protease or a ubiquitin ligase that metabolizes the protein, e.g., BRD9.” (*Id.*).



48. Claim 1 specifically defines “B” as “Formula AA2.” (Ex.1001,503). According to the specification, this means that Formula AA2 is the degradation moiety (*see* col.68, lines 65-66 which defines degradation moiety Formula “Y” (*id.*,50); col. 71, lines 1-2 wherein Y can be Formula “Z” (*id.*,52); col.

71, lines 16-17, wherein Z can be Formula “AA0” (*id.*); col. 72, lines 10-11 wherein AA0 is Formula “AA” (*id.*); and then col. 73, lines 13-14, wherein AA can be Formula “AA2” (*id.*,53)) which is the cereblon binding moiety. AA2 has the structure below, wherein A² is defined as the bond between the degradation moiety and the modular Linker (col.69,1.12-13 (*id.*,51)) and R^{A5} is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl (col.973,1.16-17) (*id.*,503).

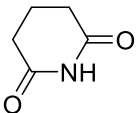


Formula AA2

49. I note that in col. 68, lines 65-66 of the '381 Patent it indicates that the degradation moiety “includes” the structure of Formula Y (*id.*,50). The term “includes” is in itself ambiguous because it doesn’t indicate what is missing or where it would be placed. And the term “includes” would appear to lack meaning when applied to Formula AA2, which is presented as a completed simple structure that is covalently bound to the linker.

50. I refer below to Table 1, which provides the CRBN Binding Kd included in the Declaration of Christopher G. Nasveschuk (Ex.1018,¶16). This table indicates that structure AA2, wherein R^{A5} is hydrogen, binds to cereblon with a Kd of 230 micromolar.

Table 1

Structure	CRBN Binding -FP assay Kd (μM)
	230

51. I agree with Dr. Nasveschuk that it would be very difficult to administer enough heterobifunctional drug to a human to reach a concentration of 230 micromolar of the moiety AA2 in the target human cells. (*See id.*, ¶17). A POSA would thus not consider this structure to be an effective cereblon binder. It is only when AA2 is bound to a second chemical moiety that it becomes a cereblon binder that might work to form a ternary structure in a human. Further, that is not how it is defined in the '381 Patent. A² is the bond between B and linker, and linker is not defined in the '381 Patent as contributing to the degradation of the protein.

52. I also refer to paragraph 20 of the Nasveschuk Declaration which states that Petitioner uses heterobifunctional molecules wherein R^{A5} is not hydrogen, for example methyl, as a “null” comparator. In other words, according to Dr. Nasveschuk, any substituent other than hydrogen or a cleavable moiety at R^{A5} substantially nullifies the activity of the heterobifunctional molecule. (Ex.1018, ¶20).

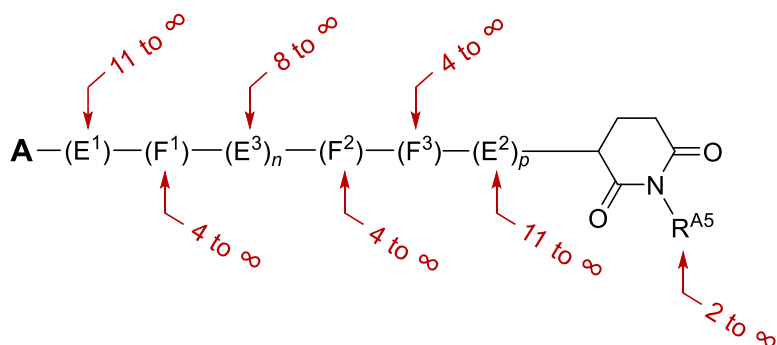
My experience is consistent with Dr. Nasveschuk's on this point. Therefore, based on both my experience, knowledge, and training as well as Dr. Nasveschuk's, substituents other than hydrogen or a cleavable moiety for R^{A5} on the formula AA2 cereblon binder would be considered non-operational and not useful.

VII. SUMMARY OF MY EXPERT OPINIONS

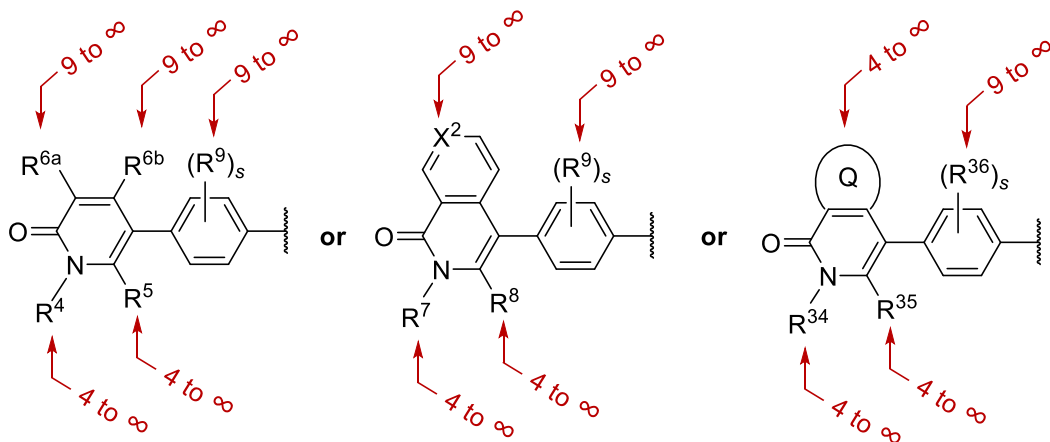
53. Given the complexity of the chemistry and the chemical formulas that are considered in my Declaration, I start out by summarizing my conclusions using the illustrations for clarity.

54. **Point 1** of my conclusion is that the '381 Patent Claims purport to present compounds that are constructed of open-ended optionally substituted building blocks such that the compounds are incomprehensible because any substituent can be located on any of the modular components in any location, leading to an unknown number and content of compounds that is impossible to visualize. By definition, there is inadequate support in the specification for a boundless array of compounds. Further, each optional substituent can be substituted with further optional substituents because the optional substituents themselves individually embed optional substituents, which leads to infinite loops (referred to below with the infinity sign (∞)).

Open-Ended Optional Substituents Leads to Infinite Loops



wherein A is

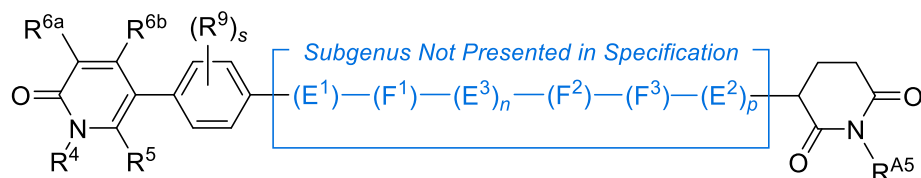


- ♦ Layers of optional substituents leads to boundless non-sensical structures
- ♦ At least 119 uses of "optionally substituted" in Claim 1
- ♦ Impossible to know the scope of the claimed compounds

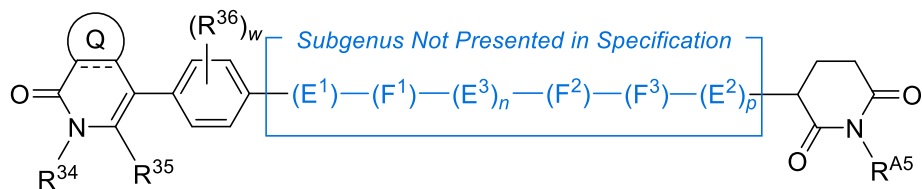
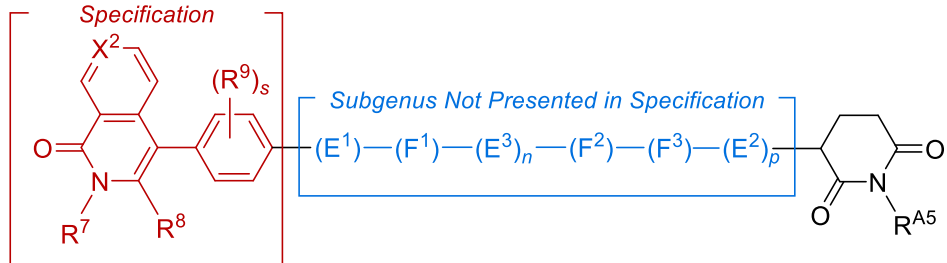
55. **Point 2** of my conclusion is that the genus of compounds presented in Claim 1 was not disclosed as is anywhere in the specification. This is because the Linker formula used in the claims is not found anywhere in the specification and was not a listed Linker subgenus (See Ex.1001,17 (col.2)). In addition, Formula IVa as presented in Claim 1 was also not presented anywhere in

the specification. Therefore, the claims are not supported by the description in the specification.

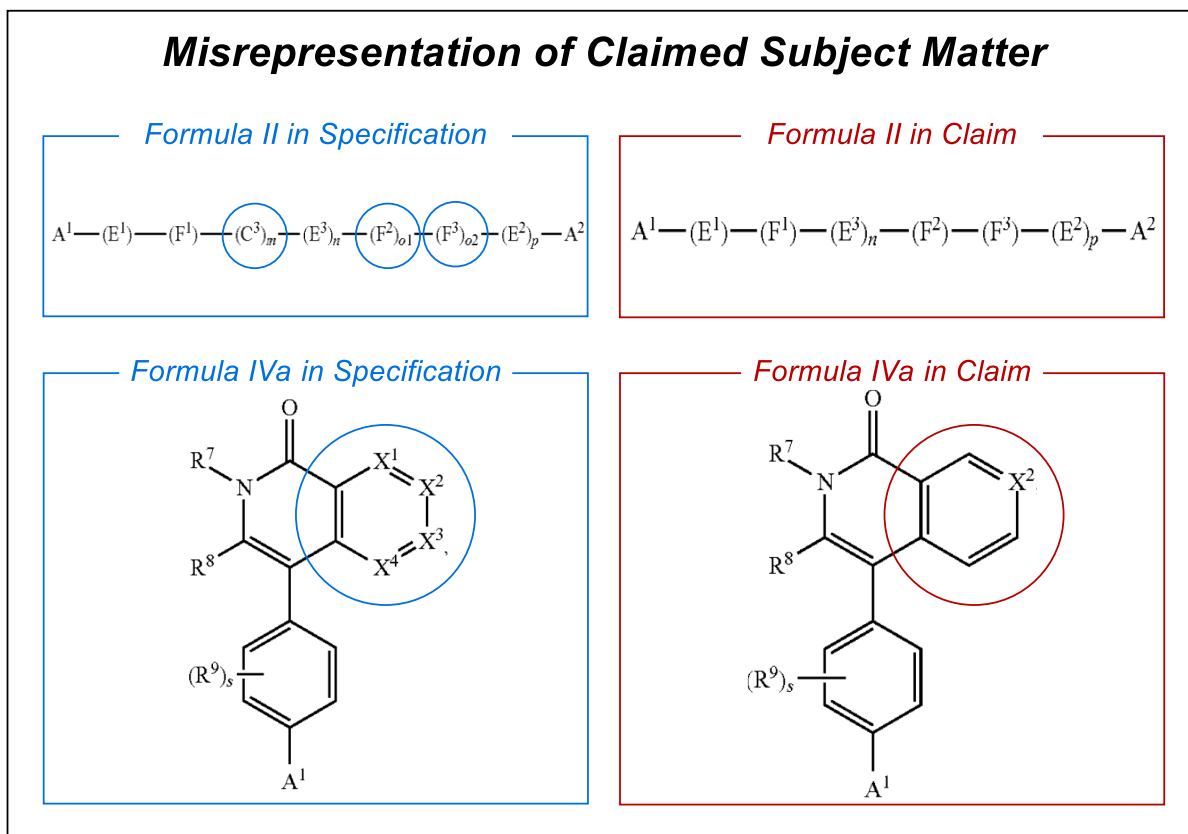
Genus as presented in Claim 1 was not presented anywhere in the specification



Subgenus Not Presented in Specification



56. **Point 3** of my conclusion is that there are misrepresentations in the issued claims. Formula IVa in Claim 1 is different from Formula IVa in the specification. Formula II in Claim 1 is different from Formula II in the specification. Formula IVa and Formula II in Claim 1 are not found in the specification even though they incorrectly use numbers of chemical structures found in the specification. This is misleading to the reader because when reference numbers such as “Formula IVa” and “Formula “II” are used in a claim, the reader assumes they refer to structures drawn and supported in the specification, which is not true in this case.



57. **Point 4** of my conclusion is that there are no compounds drawn or tested in the specification that are covered by Claim 1. I base my conclusion on PO's description of each individual modular unit of the claimed compound and its function. According to my review of the specification, and I think a POSA would agree, the Linker module (i) is required to include an F¹, F², and F³, and ii) none of F¹, F², and F³ can be phthalimide or its analog (*see* Section VIII-1b). Whether phthalimide is allowed to be in the claimed structures is critical because out of the 489 compounds synthesized in the '381 patent, 467 compounds included phthalimide or an analog thereof. The 22 remaining compounds do not include the claimed Linker.

Table 2

Example compounds containing a phthalimide or an analog thereof.*	467
Example compounds which do not include a phthalimide or an analog thereof and do not include the claimed Linker.	22
Total number of example compounds drawn.	489

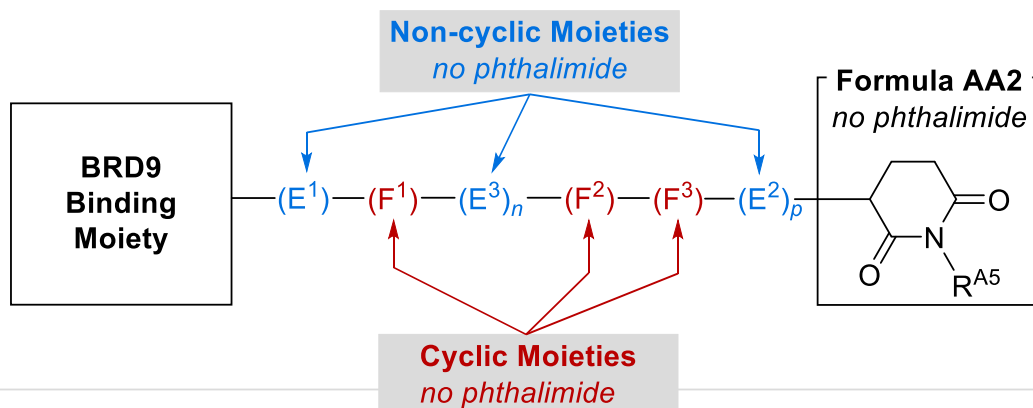
*See Attachment 2 for the definition of "phthalimide or analog thereof."

58. In Claim 1, F¹, F², and F³ is defined as independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene.

The reason why F¹, F², and F³ cannot include phthalimide or its analog is because (i) none of the descriptions or drawn examples of F¹, F², and F³ in the specification that span over 30 columns (cols.12-43) include a phthalimide or its analog; and (ii) none of the definitions of carbocyclylene, heterocyclylene, arylene or heteroarylene include any reference to phthalimide or its analog. Further, the required E¹, and optional E² and E³ (the other components of the Claimed Linker) cannot be a phthalimide or its analogue because they are defined as non-cyclic moieties.⁶ Likewise the B module, which is defined in Claim 1 is limited to Formula AA2, which also does not have a phthalimide or its analog. Thus, to fall under the claims of the '381 Patent, the full compound structure must have a linker with F¹, F², and F³, but no phthalimide or analog structure in the compound.

⁶ E¹ and E² is, independently, O, S, NR^N, optionally substituted C₁₋₁₀ alkylene, optionally substituted C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C_{2-C10} polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene; and E³ is optionally substituted C_{1-C6} alkylene, optionally substituted C_{1-C6} heteroalkylene, O, S, or NR^N (Ex.1001,503).

No Compounds in Claim 1 are Drawn or Tested in the Specification



■ Definition of F^1 , F^2 , and F^3 is C_3 - C_{10} carbocyclylene, optionally substituted C_2 - C_{10} heterocyclylene, optionally substituted C_6 - C_{10} arylene, or optionally substituted C_2 - C_9 heteroarylene (Ex.1001, col 973)

■ Definitions of carbocyclene (Ex.1001, col 440), heterocyclene (Ex.1001, col 441), arylene (Ex.1001, col 440), and heteroarylene (Ex.1001, col 441) in the specification do not refer to phthalimide or its analog

■ None of the descriptions or drawn examples of F^1 , F^2 , and F^3 in the specification (spanning over 30 columns (Ex.1001, col 12-43)) include a phthalimide or its analog

■ Therefore, claimed compounds do not include a phthalimide or its analog

VIII. DETAILED DISCUSSION OF MY EXPERT OPINIONS

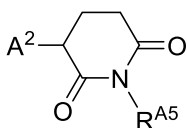
59. Based on my review of the '381 Patent, the person of ordinary skill in the art ("POSA") would be defined as a person with (a) a Ph.D. in chemistry, medicinal chemistry, biochemistry, or a closely related discipline in the pharmaceutical area or (b) an M.S. degree in chemistry, medicinal chemistry,

biochemistry, or a closely related discipline, with at least four years of practical experience in the field of drug discovery in the area of pharmaceutical compounds.

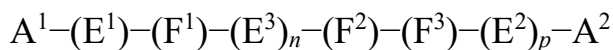
60. In my opinion, a POSA would conclude that Claim 1 of the '381 Patent defines a chemical structure in a modular fashion made of distinct subsections. Because the compound is defined modularly, a POSA would consider each modular component individually to try to understand the metes and bounds of Claim 1.

61. I conclude that the '381 Patent claims have insufficient written description and enablement support based on the '381 Patent specification, which I summarize here and discuss in more detail below.

- (a.) Specifically, Claim 1 is drawn modularly to a chemical compound of the formula: A-L-B (Ex.1001,502; col.971,1.6).
- (b.) A is one of three listed BRD9 binding moiety structures (*id.*; col.971,1.9-50).
- (c.) B is a degradation moiety limited to Formula AA2 (*id.*, 53; col.73,1.5-14), which is a simple glutarimide moiety.



- (d.) L (Linker) is defined modularly in the Claim as



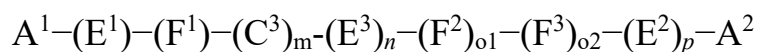
wherein A¹ is a bond between the Linker and A, and A² is a bond between B and the Linker, n is 0 or 1, and p is 0 or 1 (*id.*,503; col.973,1.20-30). I have to refer to the claims for the definition of Linker, and not the '381 Patent specification, because I do not find this Linker structure in the specification.

1. Lack of Written Description

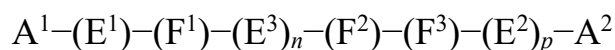
a. Interpretation of the Modular “Linker” Structure in the '381 Patent Claims

62. In my opinion, there is a lack of written description support for the claimed Linker structure in the '381 Patent specification. After a careful review, I do not see the '381 Patent claimed Linker definition listed anywhere in the specification. I conclude it was first presented in Claim 1 in U.S.S.N. 17/696,656, filed March 16, 2022. (Ex.1002,558). After reviewing the priority PCT application and claims (Ex.1005), I also do not see this specific modular form of Linker as presented in Claim 1 of the '381 Patent. Despite calling the claimed Linker “Formula II” there is no matching Linker in the specification, and Formula II as recited in the specification is much broader.

Formula II in the specification is:

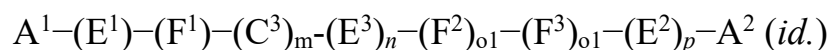


Formula II in the claims is:

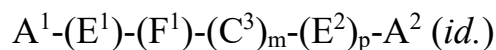


63. The claimed Linker structure requires the presence of at least E¹, F¹, F², and F³. The '381 Patent, in col. 1-2 provides a genus (Formula II) and numerous subgenres (Formulas IIa-g) defining the Linker and none of these subgenres require all of the F¹, F², and F³ moieties. (Ex.1001,17)

(a.) Formula II in the specification is a broad genus that encompasses a very large number of variations:⁷



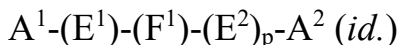
(b.) Formula IIa is a subgenus:



⁷Formula II actually covers an infinite number of variations because of the inclusion of the term “optionally substituted” (see Section VIII-1e below) which includes an infinite loop (see Section VIII-1f below). However, even if I ignore “optionally substituted” the Formula II subgenus still contains over 633,600 possible subgenres from which 1 subgenus was selected in Claim 1. I come to this number by multiplying the number of classes of substituents that each variable covers. For example, for the purposes of showing the large number of combinations optionally substituted C₁-C₆ alkyl is only counted as one group despite including many different moieties of alkyl. 15 values of E¹ x 4 values of F¹ x 4 values of C³ x 11 values of E³ x 4 values of F² x 4 values of F³ x 15 values of E² = 633,600.

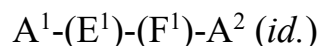
Formula IIa does not include F^2 or F^3 . It also differs from the Linker in Claim 1 in that E^3 is missing and C^3 can be present.

(c.) Formula IIb is a subgenus:



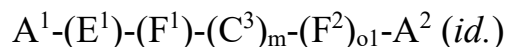
Formula IIb does not include F^2 or F^3 , and also omits E^3 .

(d.) Formula IIc is a subgenus:



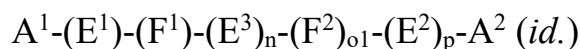
Formula IIc does not include F^2 or F^3 and also omits E^3 or E^2 .

(e.) Formula IId is a subgenus:



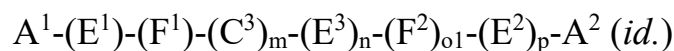
Formula IId does not have F^3 , F^2 is optional, C^3 is optional, and it does not have E^2 or E^3 .

(f.) Formula IIe is a subgenus:



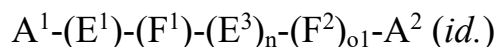
Formula IIe does not have F^3 and F^2 is optional.

(g.) Formula IIg is a subgenus:



Formula IIg does not have F^3 , F^2 is optional, and C^3 is optionally present.

(h.) Formula IIh is a subgenus:



Formula IIg does not have F³, F² is optional, and does not have E².

64. Therefore, none of the subgenuses described in the '381 Patent include F² and F³ as required moieties as set forth in the claimed Linker. In PO's response to Office Action dated June 16, 2022, PO argued to the Patent Office that the novelty of the claims is based on the fact that F² and F³ are both required (See Section VIII-1c below) (Ex.1002,40-46). Thus, the point of novelty argued to the Patent Office is not found in any of the subgenuses presented by PO in the '381 Patent specification as filed. It was added well after the asserted effective filing dates of the '381 Patent (Exs.1003-1009), and was actually first filed when Claim 1 was first presented on March 16, 2022 (Ex.1002,557-576).

65. I am baffled by the inconsistency between the asserted Formula II in Claim 1 and a very different Formula II in the specification. I am more perplexed by the fact that Formula II as presented in Claim 1 is not in the specification at all, and therefore appears to be an after-the-fact manufactured Formula without support.

66. I also have reviewed the priority PCT application (PCT/US2020/015746, Ex.1005), filed on January 29, 2020, and do not see the actual Linker presented in Claim 1 of the '381 Patent. In fact, the claims of the PCT application recite the subgenuses found in col. 2 of the '381 Patent, referenced

above, that do not cover the Linker subgenus in Claim 1, which requires both F² and F³.

67. Thus, PO's asserted point of novelty in the Linker (F² directly bonded to F³ with a required F¹) lacks specific written description in the Linker description in the specification and is thus new matter added after the priority dates, including the PCT filing date.

68. The '381 Patent, from col. 2, lines 66-68 to col. 68, line 49, provides detailed instructions to the POSA how to construct the Linker (Ex.1001,17-50). A POSA would study this section to try to learn how to create a Linker according to the claimed invention.

69. For the purposes of my analysis, I focus on F¹, F² and F³. Claim 1 specifies that "each of F¹, F² and F³ is, independently, optionally substituted (which as I describe below, is open-ended and impossible to interpret; see Section VIII-1e below) C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene" (Ex.1001,502; col.973,1.43-45). I am told these terms have to be interpreted in light of the teaching of and use in the specification, not in a vacuum.

70. The explanations of F¹, F² and F³ in the '381 Patent begin at col. 13, line 65 and go through col. 43, line 45 (*id.*,23-38). Thus the '381 Patent provides

fully 30 columns of text and structures to explain how to interpret and use F¹, F² and F³.

71. The description starts out by stating “In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₃-C₁₀ carbocyclylene” (*id.*, 23; col.13, l.66-68). It then provides embodiments and examples of carbocyclylene structures (*id.*; col.14,l.1-59).

72. Thereafter, the '381 Patent states “In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heterocyclylene” (Ex.1001; col.14, l.61-62). The '381 Patent specification continues by providing examples of C₂-C₉ heterocyclylenes (*id.*,23-28; col.14,l.63-col.23,l.29). Every example of a heterocyclylene provided in these 9 columns is a monocyclic, polycyclic (*id.*,23; col.14,l.65) or a bridged heterocyclic compound.⁸

73. The '381 Patent specification then provides individual examples of embodiments of F¹, F² and F³ from col. 23, line 32 to col. 26, line 46, all of which

⁸ Despite the definition of “heterocyclyl” in col. 441, lines 46-58 (Ex.1001,237), none of the examples of F¹, F² and F³ in the explanatory text (*Id.*,23-28; col.14-col.23) are heterocyclic compounds fused to an aryl compound. I also note that there are no examples in the definition of heterocyclyl in col. 441 that is a phthalimide or an analog thereof (see Attachment 2) nor in the col. 14-23 text.

are monocyclic heterocyclic moieties (*id.*,28-29). The '381 Patent specification then continues at col. 26, line 52 through col. 42, lines 19 with examples of bicyclic and fused saturated heterocyclic compounds. (*Id.*,29-37).

74. The '381 Patent then indicates that “In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heteroarylene” (Ex.1001,37-38; col.42,1.37-col.43,1.30). I note that the examples provided are all five-membered rings and none of these heteroarylene groups include a phenyl or a fused aryl.

75. The '381 Patent follows with examples of fully drawn Linker structures, which run from col. 44, line 1 through col. 68, line 49 (*id.*,38-50). Therefore, the '381 Patent provides fully 24 columns of fully drawn exemplary divalent Linker structures. Of all of these structures:

(a) None has a phthalimide or an analog thereof (i.e., the phthalimide in Formula A or A1-A10, which for clarity are provided in Attachment 2) in the Linker, despite the fact that 467 of the 489 examples of fully drawn Degradar compounds have a phthalimide or an analog thereof linked directly to the glutarimide.

(b) This is very strong evidence that the drawn cereblon binding degradation moieties (“B”) with phthalimide or an analog thereof directly linked to glutarimide fall exclusively under the degrader of Formula A and

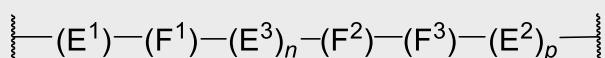
subgenuses Formulas A1-A10 (discussed further below), not under Formula AA2 as exclusively used in issued Claim 1.

76. As explained above, to fall under the definition of Linker in Claim 1, the Linker has to have two cyclic groups directly connected (F^2 and F^3) and a third cyclic group that does not have to be directly connected to the other two (F^1).

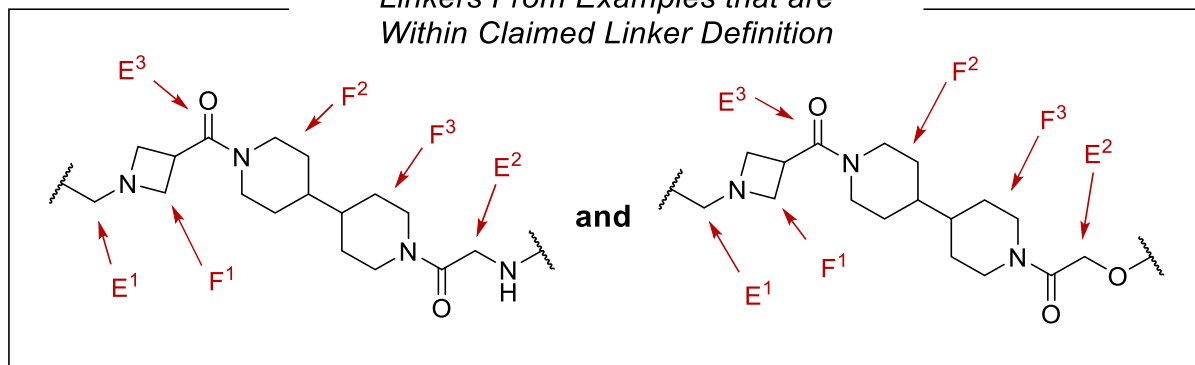
77. In my opinion, the specification teaches a POSA through exemplification that the phthalimide or analogs (Attachment 2) exclusively falls within the definition of “B” not Linker. I conclude this has to be the case based on the teaching in the specification.

78. I see only two examples of Linkers out of 223 structures in 22 columns of examples that fit the definition of Linker in the issued claims (the last structure in col. 48 and the first structure in col. 49) (*id.*, 40-41).

Linker Definition in Granted Claims



Linkers From Examples that are Within Claimed Linker Definition

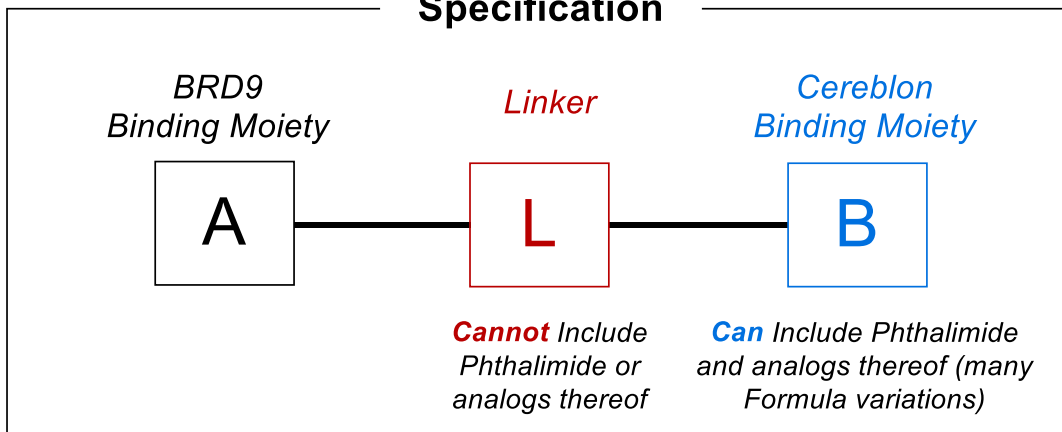


In my opinion, two examples of Linkers that fall within the definition of Linker in Claim 1 is woefully inadequate to support the claimed large subgenus of Linkers to establish that PO had written description possession of the broad modular Linker as defined in Claim 1.

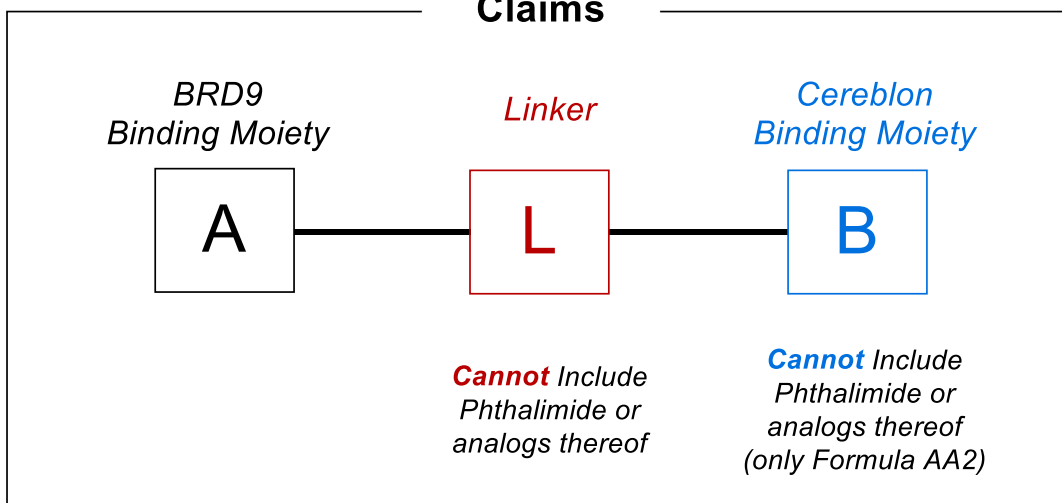
79. In addition, using the same analysis, based on my review, none of the 489 drawn degrader structures in the entire '381 Patent fall under the scope of Claim 1, due to the restrictions in the Linker structure, and the fact that the modular moiety "B" is limited to Formula AA2. Again, in my opinion, the exemplification of no structure out of 489 is of course woefully insufficient to support the metes and bounds of such broad claims as found in the '381 Patent.

The Compound Defined by A, L, B Modules in the Specification vs. Claim 1

Specification



Claims



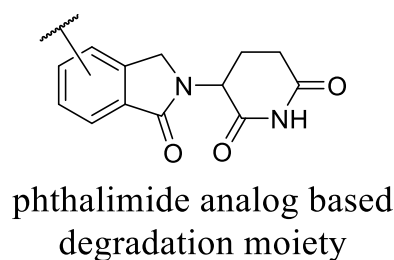
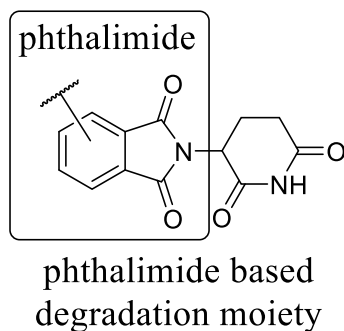
For phthalimide or analogs thereof see Attachment 1, Djuric Declaration

b. Interpretation of the Modular “B” Degradation Moiety in the ’381 Patent Claims

80. The ’381 Patent specification describes a large number of formulas and subformulas corresponding to the modular “degradation moiety” portion of the molecule including Formulas Y, Y1, Y2, Z, AA0, AB, AC, AA1,

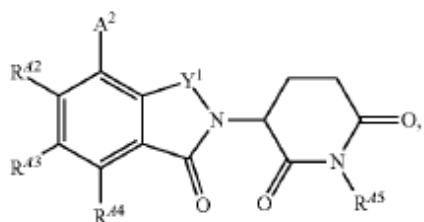
AB1, AC1, AA2, AA3, AA4, A, A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, B, B1, B2, B3, B4, C, D, E, FA, FA1, FB, FB1, F1, F2, and G (Ex.1001,50-63; cols 68-93). Of these over three dozen different degradation moiety formulas, the Claims of the '381 Patent are limited to Formula AA2. There are no blazemarks in the '381 Patent leading the POSA to the selection of Formula AA2 instead of other degradation moiety formulas, and thus the selection of Formula AA2 lacks written description in the specification.

81. The vast majority of drawn, synthesized, and tested molecules in the '381 Patent have a phthalimide based degradation moiety or an analog thereof

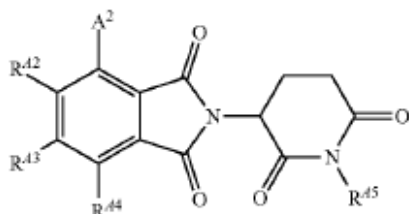


For example starting at column 130, compounds D1-D333, D335-D355, D359, D372-D373, D376, D385-D386, D398, D406, D413, D415, D418, D436, D445-D446, DD2, DD8, and DD11 all contain phthalimide based degradation moieties and compounds D356-D358, D360-D371, D374-D375, D377-D380, D387, D396-D397, D399-D405, D407-D412, D414, D416-D417, D419-D429, D431, D433-D435, D437-D444, D447-D470, and DD4 all contain phthalimide analog based degradation moieties (Ex.1001,81-230; cols.130-427).

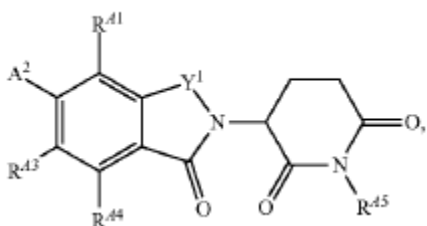
82. Formulas A, A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, and the more than a dozen subgenuses thereof described in cols. 77-81 (Ex.1001,55-57) are related to the phthalimide containing compounds described in the '381 Patent and analogs thereof. A POSA would be led to these formulas instead of Claimed Formula AA2 based on the teachings of the '381 Patent because these formulas correspond to drawn structures in the application. It is abundantly clear to me, and it would be to a POSA, from the '381 Patent specification that the inclusion of a phthalimide or analog structure comes from the modular "B" degradation moiety, not the Linker structure.



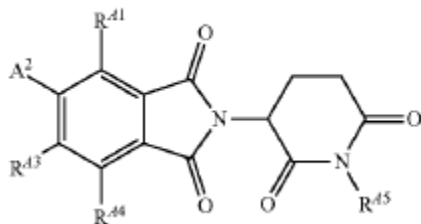
Formula A1



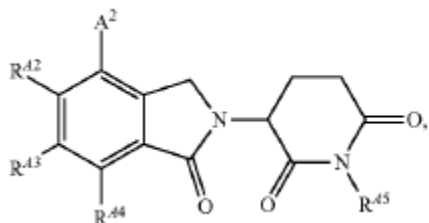
Formula A2



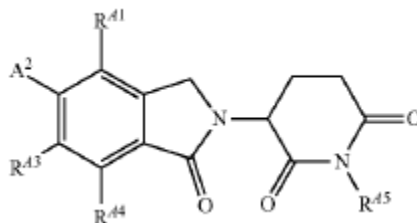
Formula A3



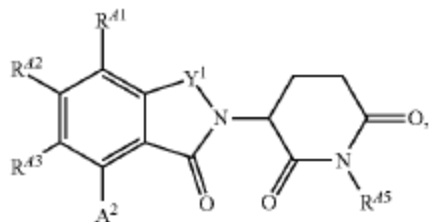
Formula A4



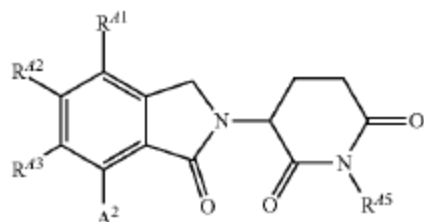
Formula A5



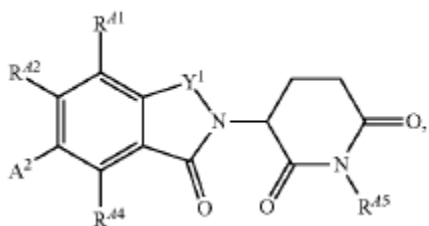
Formula A6



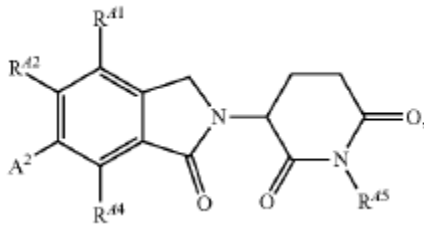
Formula A7



Formula A8



Formula A9



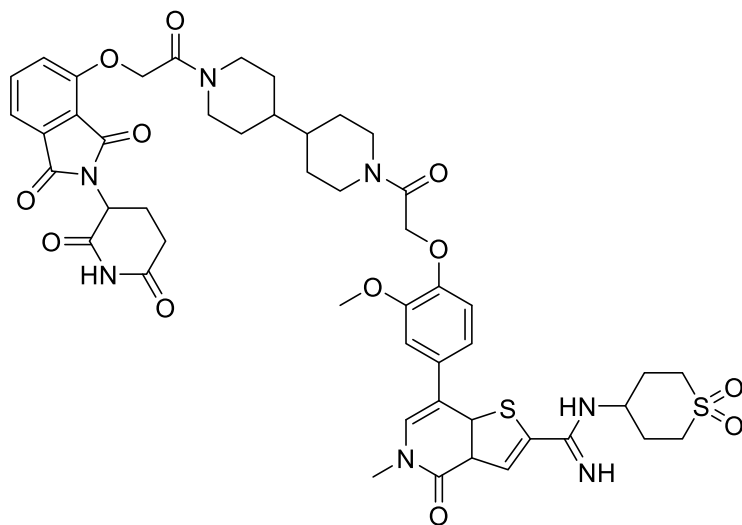
Formula A10

c. Misleading Statements to the USPTO during Prosecution Regarding Scope of Linker

83. The USPTO issued a Non-Final Office Action on May 19, 2022, (Ex.1002,50-64). The Examiner rejected then pending claims 1-10 under 35 U.S.C. §102 as anticipated by Remillard et al., *Angewandte Chemie, International Edition* (2017), 56(21), 5738-5743 (Ex.1019) and Rao et.al., CN 108690020 (Ex.1020).

84. In my opinion, in responding to the rejection, PO presented arguments that were inconsistent with the written description of the claimed subject matter in the specification.

85. The chemical structure in Remillard cited by the Examiner is:



(Ex.1002,53-54).

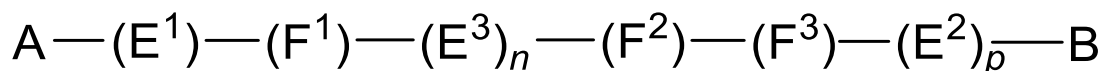
86. Referring to the Remillard structure, PO stated:

Quite simply, this linker [i.e., the Linker in '381 Patent Claim 1] does not cover the linker in the compound of Remillard, as the presently claimed linker requires two consecutive cyclic moieties F^2 and F^3 bonded to E^2 or directly⁹ to **A** through A^2 . In contrast, the compound of Remillard includes a single phthalimide connected directly to A on one side and to hydroxyacetyl moiety on the other side. Thus Remillard's molecule does not include two consecutive cyclic moieties, F^2 and F^3 , bonded to E^2 or directly to A through A^2 , as presently claimed. (bracketed information added, emphasis removed) (Ex.1002,41).¹⁰

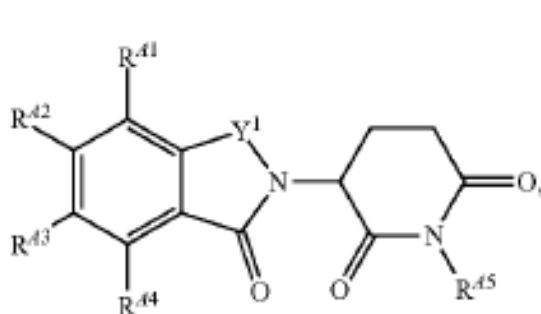
⁹ I note that this is a typographical error made by PO where they referred to "A" when they should have referred to "B".

¹⁰ The same analysis was applied to the Rao structures.

87. The reference to “A” was a typographical error that should have referenced “B”, as E² is connected to the degradation moiety “B” (cereblon binding moiety), not the BRD9 binding moiety “A”. Notwithstanding, PO represented that phthalimide is F³, a component of the modular Linker, in the chemical formula without any stated or inherent written description support in the specification for this assertion (*see* Section VIII-1b). Based on my review, this position is wholly unsupported by the specification.



88. On the contrary, phthalimide is part of the degradation moiety “B” in the ’381 Patent, which is Formula A (*see generally* Formulas A1-A10).

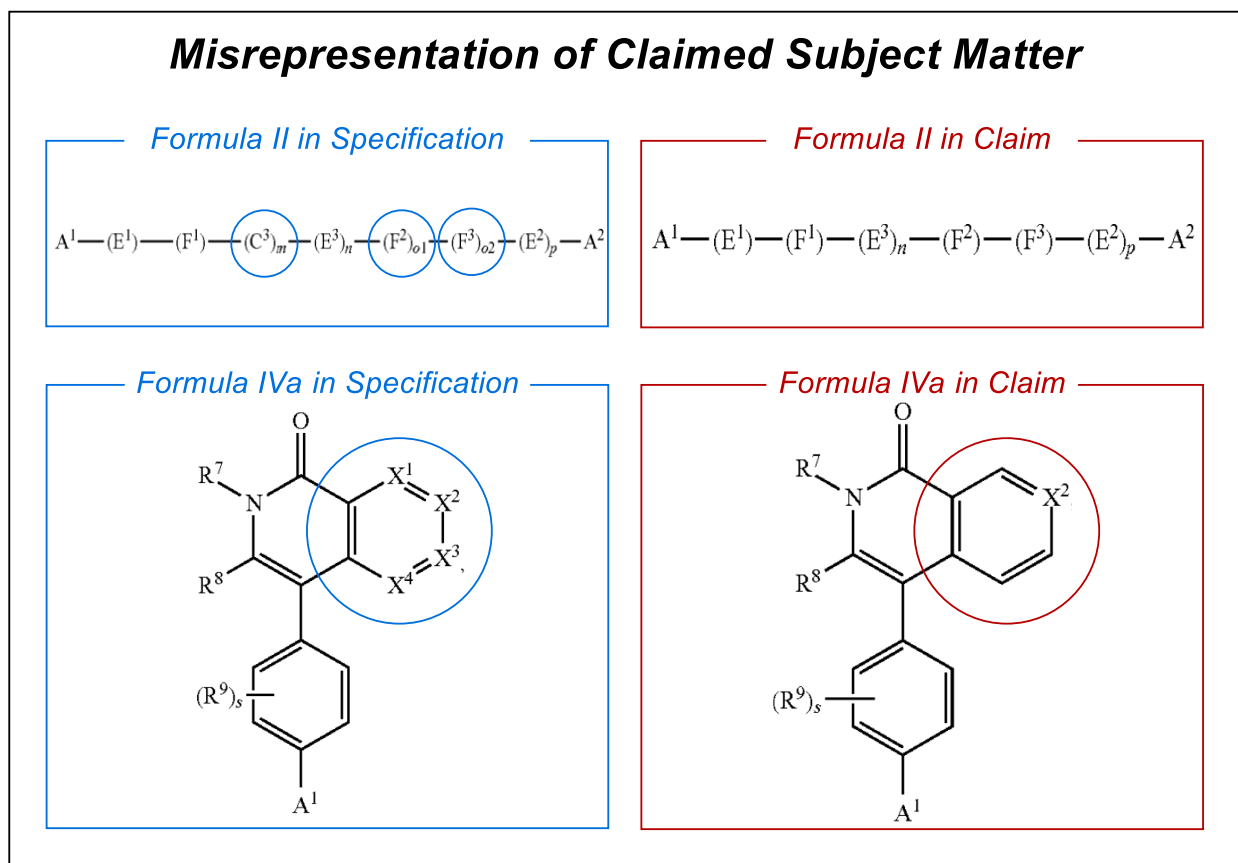


89. There are no examples of phthalimide in the Linker in the entire ’381 Patent specification (Section VIII-1a). Claim 1 requires Formula AA2 to be the degradation moiety, not Formula A. The difference between Formula AA2 and

Formula A is that Formula AA2 does not include phthalimide or an analog thereof and Formula A does.

90. The PO also failed to alert the Examiner that “Formula II” as recited in Claim 1 is a different Formula than the structure named Formula II in the specification (*see* Section VIII-1a) and was never previously drawn.

91. The PO also failed to alert the Examiner that “Formula IVa” as recited in Claim 1 is a different Formula than the structure named Formula IVa in the specification (*see* Section VIII-1b) and does not exist in the specification.

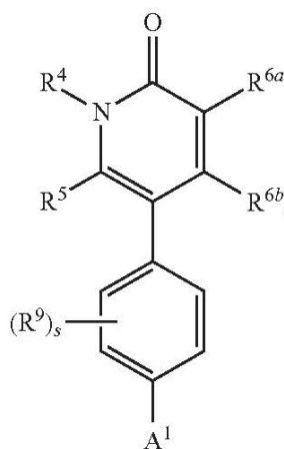


92. The misrepresentation of the interpretation of the modular segments of the claimed compounds is not trivial or inconsequential. It determines which compounds fall under the scope of Claim 1 for infringement purposes.

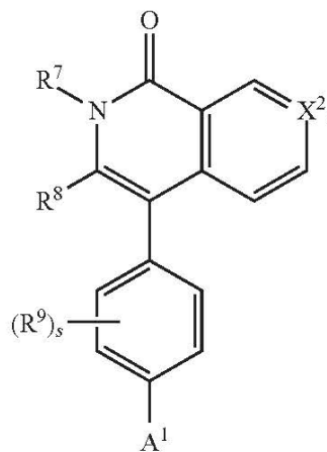
d. Interpretation of the Modular “A” BRD9 Binding Moiety in the ‘381 Patent Claims and Additional Misrepresentation to the USPTO

93. Claim 1 of the '381 Patent provides three structures for modular moiety "A" of Formula I, which is the moiety that binds to BRD9.

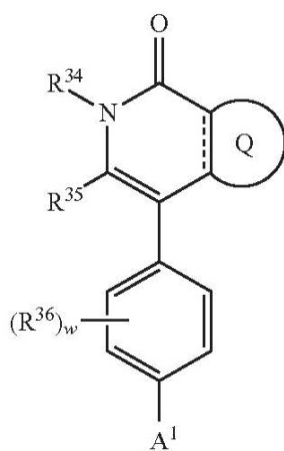
A is:



(Formula IIb),



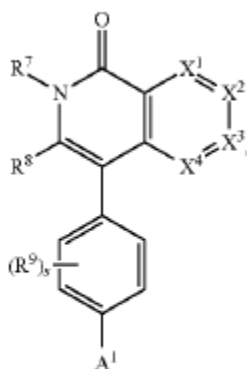
(Formula IVa), or



(Formula IX),

94. Claim 1 refers to Formula IVa, however, Formula IVa in the specification is a different moiety than the one presented in Claim 1 (Ex.1001,71-72; col.110,1.65-col.111, 1.16):

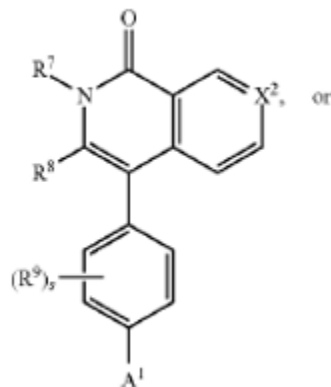
In some embodiments, A includes the structure of Formula IVa:



Formula IVa

or a pharmaceutically acceptable salt thereof.

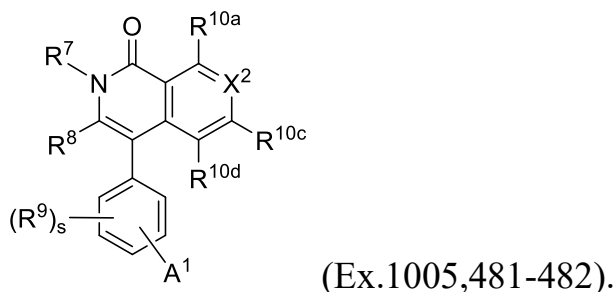
95. Each of X^1 , X^3 , and X^4 can be N or CR^{10a} , CR^{10c} , or CR^{10d} respectively. This structure covers dramatically more compounds than Formula IVa of Claim 1, shown below.



Formula IVa :

96. Despite searching the entire '381 Patent specification, I did not find any representation of the revised Formula IVa as found in Claim 1.

97. Looking to the asserted PCT priority document, the multiply dependent PCT claims 226, and 230-231 describe a subgenus of the formula:

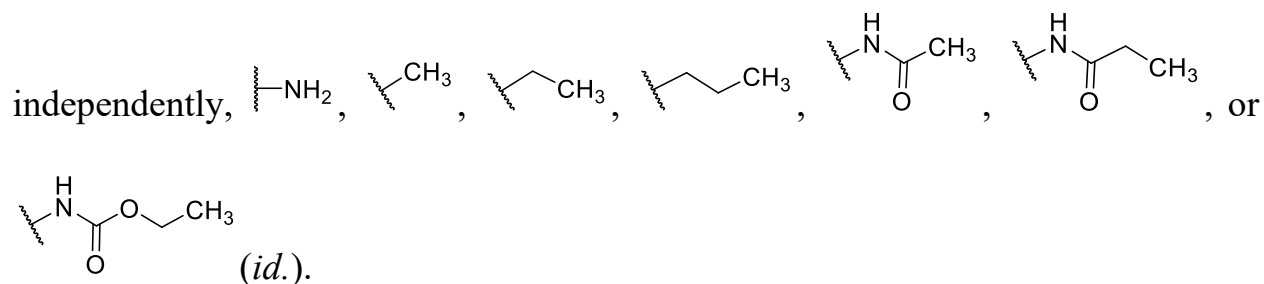


98. However, I have been informed that according to U.S. case law, the use of multiple dependent claims to arrive at a subgenus does not support that subgenus in the absence of other blaze marks.

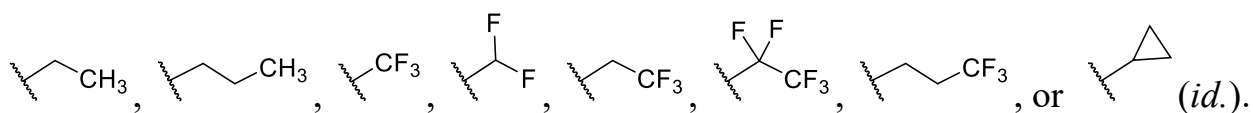
99. Even if, *arguendo*, the PCT claims supported a subgenus of compounds as shown above, which in my opinion they do not, claims 246-255 do not properly define R^{10a}, R^{10c}, and R^{10d} as hydrogen as recited in Claim 1 of the '381 Patent (*id.*,483-484). PCT claims 247-255, each of which recites hydrogen as one of several possible options depends from claim 246, which does not recite hydrogen as a possible selection, as shown below (*id.*).

246. The compound of any one of claims 225 to 245, wherein each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted amino (*id.*).

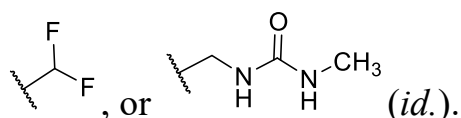
247. The compound of claim 246, wherein each of R^{10a} , R^{10b} , R^{10c} and R^{10d} is



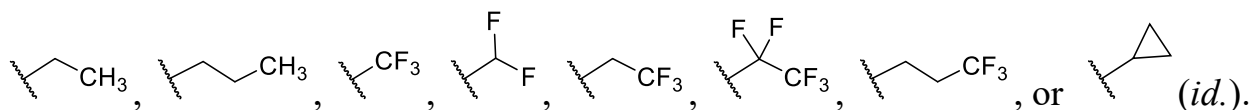
248. The compound of claim 246, wherein R^{10a} is H, F, cyano, ,



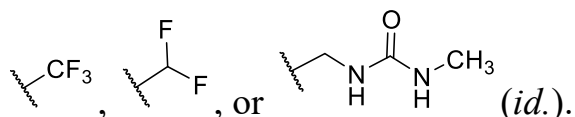
249. The compound of claim 246, wherein R^{10a} is H, F, cyano, , ,



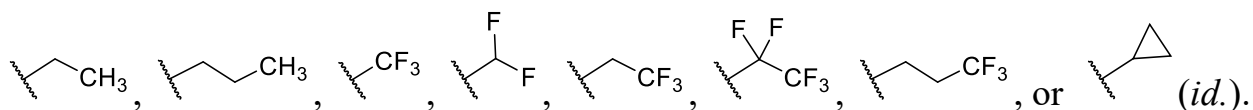
250. The compound of claim 246, wherein R^{10b} is H, F, cyano, ,



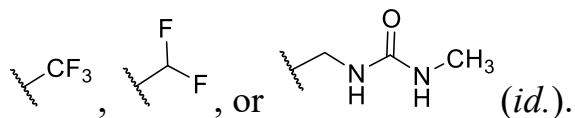
251. The compound of claim 246, wherein R^{10b} is H, F, cyano, ,



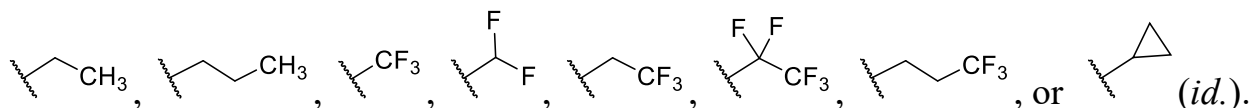
252. The compound of claim 246, wherein R^{10c} is H, F, cyano ,



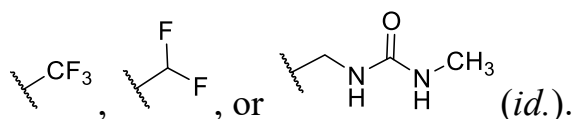
253. The compound of claim 246, wherein R^{10c} is H, F, cyano, ,



254. The compound of claim 246, wherein R^{10d} is H, F, cyano, ,



255. The compound of claim 246, wherein R^{10d} is H, F, cyano, ,



100. Therefore, I conclude that there is insufficient written description support for Formula IVa as presented in Claim 1.

e. Use of the Term “Optionally Substituted” in the ’381 Patent Claims

101. In addition to the numerous written description issues that I have identified above in Claim 1, the POSA would not be able to interpret the claims of the ’381 Patent at all, because they are indefinite, vague, and without clear bounds for the reason that the ’381 Patent claims use the term “optionally substituted” multiple times in each issued claim, and this term is inadequately defined and boundless in the ’381 Patent specification.

102. According to my count, PO used the term “optionally substituted” at least 119 times in Claim 1 (*see* Table 3 below), and in Claim 3, the term was used 121 times (*see* Ex.1001,502-503). In addition to the fact that a chemical compound with that many variations would be literally impossible for a POSA to visualize, the term “optionally substituted” as defined in the specification is open-ended and thus non-sensical and incapable of any meaning.

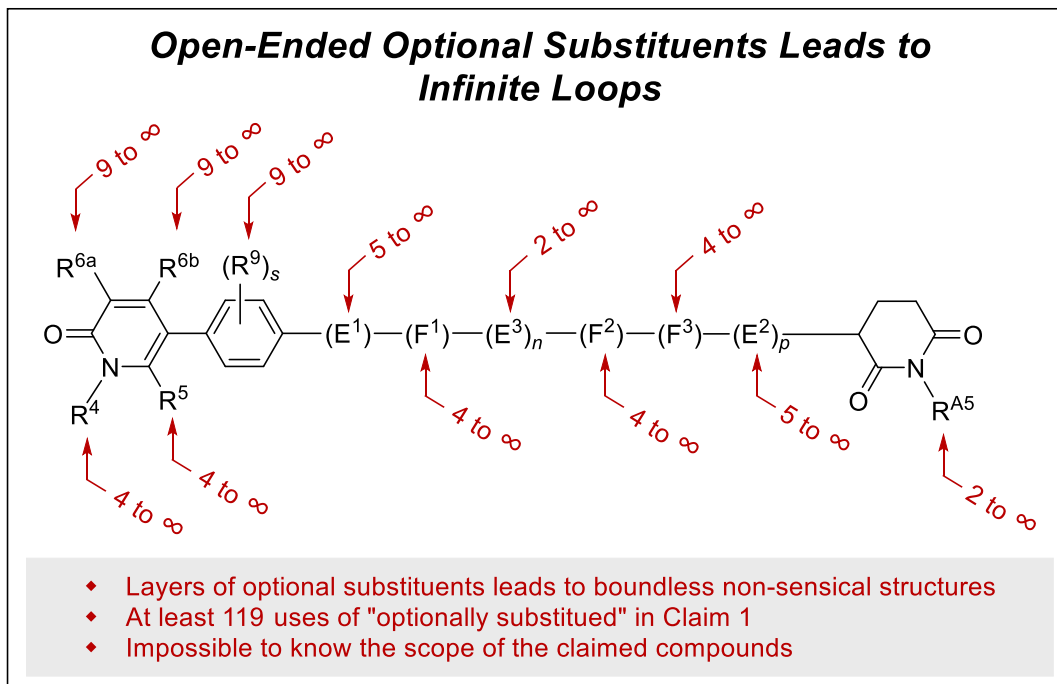
TABLE 3

Claim	Times “optionally substituted” is used in claim
1	R^4 – 4 times; R^5 – 4 times; R^{6a} – 9 times; R^{6b} – 9 times; R^{6a} and R^{6b} together – 2 times; R^7 – 4 times; R^8 – 4 times; R^9 – at least 9 times; ¹¹

¹¹ The compound of Claim 1 can contain as many as four R^9 substituents because variable “s” is 0, 1, 2, 3, or 4 and each of these up to four R^9 substituents is independently selected. Thus, the claims include at least 9 recitations of optionally substituted in R^9 but can include more recitations depending on the selection of variable “s.”

	R^{10b} – 9 times; R^{34} – 4 times; R^{35} – 4 times; R^{36} – at least 9 times; R^{37} – 2 times; R^{39} – 2 times; R^{A5} – 2 times; E^1 – 5 times + 6 times through R^N ; E^2 – 5 times + 6 times through R^N ; E^3 – 2 times + 6 times through R^N ; F^1 – 4 times; F^2 – 4 times; F^3 – 4 times. Total: at least 119 times (Ex.1001,502-503)
2	Depends on Claim 1. E^1 is defined as CH_2 Total: at least 108 times (<i>id.</i>)
3	Depends on Claim 1. E^2 is separately defined. at least 108 times from Claim 1 W – 1 time (through R^w); R^d – 3 times; R^e – 3 times; R^f – 3 times; R^g – 3 times; Total: at least 121 times (<i>id.</i>)
4	Depends on claim 3. E^2 is defined as NR^N Total: at least 116 times (<i>id.</i>)

5	Depends on claim 4. E ² is defined as NH Total: at least 110 times (<i>id.</i>)
6	Depends on Claim 1. E ³ is separately defined. Total: at least 111 times (<i>id.</i>)
7	Depends on Claim 1. F ¹ is separately defined. Total: at least 115 times (<i>id.</i>)
8	Depends on Claim 1. F ² is separately defined. Total: at least 115 times (<i>id.</i>)
9	Depends on Claim 1. F ³ is optionally substituted C ₆ -C ₁₀ arylene. Total: at least 116 times (<i>id.</i>)
10	Depends on Claim 1. Total: at least (119 – 11 (E¹) + at least 13 (from W, R^d, R^e, R^f, and R^g) – 11 (E²) – 8 (E³) – 8 (both F¹ and F²) – 3 (F³)) = at least 91 times (<i>id.</i>,504-504)
11	Depends on Claim 1. Wherein p is 1. Total: at least 119 times (<i>id.</i>,505)
12	Depends on Claim 10. Wherein p is 1. Total: at least 91 times (<i>id.</i>)



103. The claims of the '381 Patent do not provide notice to a POSA of whether compounds of interest would infringe the claims of the '381 Patent, which is important to third parties in structuring drug discovery and development activities.

104. In my opinion, the term "optionally substituted" as used in the '381 Patent does not provide adequate notice to a POSA because the term does not specifically describe what the substituents can be or where they are to be linked to the base molecule. It opens the molecule to unbounded speculation and possibilities. In general, when a molecule in the '381 Patent is "optionally substituted," a POSA cannot determine the molecule's size, lipophilicity, toxicity, stability, or functionality, nor would it be possible to know how to make or use it.

105. The term “optionally substituted” is used many times in every claim of the ‘381 Patent. The term as used in the ‘381 Patent does not provide any limitations and in my opinion it does not adequately inform a POSA what the compound actually is, because an infinite number of possibilities would be allowable or at least have to be considered.

106. Thus, in my opinion, the term “optionally substituted” in the ‘381 Patent is incapable of claim construction because it is meaningless and unbounded as defined and used in the specification.

107. I note that the ‘381 Patent specification has not one but two definitions of the term “optionally substituted” and I have studied both of them (Ex.1001,235-237). In my opinion, there are a multitude of reasons why, as used by PO, the ‘381 Patent’s claimed compounds are undefined, indefinite and meaningless to a POSA. I conclude a POSA would be given insufficient guidance from the claims, as interpreted in view of the specification, to know whether a compound would be infringing, because it would be impossible to know what the claimed compounds are, or if they are even possible.

108. Not only are both provided definitions of “optionally substituted” boundless, they are even inconsistent in the boundless state. For example, in col. 438, line 48 to col. 439, lines 1-5 (Ex.1001,235-236), the ‘381 Patent provides a first definition of “optionally substituted” as:

Herein a phrase of the form “optionally substituted X” (e.g., optionally substituted alkyl) is intended to be equivalent to “X, wherein X is optionally substituted” (e.g., “alkyl, wherein said alkyl is optionally substituted”). It is not intended to mean that the feature “X” (e.g., alkyl) per se is optional. As described herein, certain compounds of interest may contain one or more “optionally substituted” moieties. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent, e.g., any of the substituents or groups described herein. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

Emphasis added.

109. According to my reading of the col. 438-439 definition of “optionally substituted,” a compound that is “optionally substituted” can have a substituent at every position on the compound where a hydrogen exists and with any

substituent for example a substituent “described herein” (but without saying where “herein” is or how it is described). Further, the substituents don’t need to be the same because any combination is allowed.

110. In addition, the combinations of substituents are only “preferably” stable. Stability is not required. Also, the resulting compound is only “preferably” chemically feasible. It is surprising to me that neither stability nor chemical feasibility is required. And the stability of the “optionally substituted” compound can be altered, as long as not “substantially altered” (emphasis added; wherein the term “substantially” is not defined and thus not bounded), when subjected to conditions to allow for their production, detection, recovery, purification or use. I don’t see any interpretation of this paragraph that would make sense to a POSA. This is not capable of definite meaning.

111. I next compared the first definition of optionally substituted at col. 438, line 48 to col. 439, lines 1-5 (*id.*,235-236) to a second definition I found in the ’381 Patent specification of “optionally substituted” provided in col. 442, lines 48-64 (*id.*,237) in the ’381 Patent:

The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. **Substituents include, for example: alkyl (e.g., unsubstituted and**

substituted, where the substituents include any group described herein, e.g., aryl, halo, hydroxy), aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH₂ or mono- or dialkyl amino), azido, cyano, nitro, oxo, sulfonyl, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Emphasis added.

112. This second col. 442 definition of “optionally substituted” adds to the confusion a POSA already faces about this term when used as is in a claim. In this alternative definition, it names all of the functional groups that are defined in the Claim 1 other than amino (and wherein polyethylene glycol referred to in Claim 1 is a heteroalkyl group), so in that respect it is not significantly different in scope from the col. 438-439 definition of “optionally substituted.” However, this alternative definition has its own set of myriad problems. As a first example, in the col. 442 definition, the specification purportedly teaches that a chemical moiety “when substituted, will generally have 1 to 4 substituents.” (*Id.*). Again, this is open ended because the term “generally” doesn’t mean “absolutely.” Further, nothing in the specification provides a pointer to which chemical moieties are to be substituted,

so the “when substituted” term is without context. Second, in the col. 442 definition, the specification teaches that when substituted, there will generally be 1 to 4 substituents (*id.*), but doesn’t say where on the chemical moieties these substituents will or should be located. Third, all of the purported substituents listed in col. 442 do not constitute concrete guidance because the lists are not bounded (“Substituents include, for example”) (emphasis added) (*id.*).

f. Incorporation of Infinite Loops in the ’381 Patent Claims

113. There is another very serious and in fact fatal problem with the col. 442 definition of “optionally substituted.” The definitions provided in the ’381 Patent result in “infinite loops” where chemical definitions refer to other definitions which then loop back to the first definition. This creates the known chemical problem of a purportedly boundless or infinite molecule. As an example, “optionally substituted alkyl” may be substituted with another optionally substituted substituent (*id.*,237). Examples of substituents in col. 442 include alkyl, which may be substituted (*id.*,237). This creates a fatal mistake. For example, alkyl optionally substituted with a first optionally substituted alkyl creates a problem wherein the first optionally substituted alkyl can also be optionally substituted with a second alkyl, which can be optionally substituted with a third alkyl which can be optionally substituted again and again and again, to infinity. This dilemma can be applied to all

of the optional substituents in col. 442 that refer to “e.g., unsubstituted and substituted.” (*See id.*). Worse, the optional substituents are boundless so any substituent can be used including unnamed substituents. For example, the substitution of an amino on a hydroxyl that is subsequently substituted with a thiol and then another amino or hydroxyl, etc.

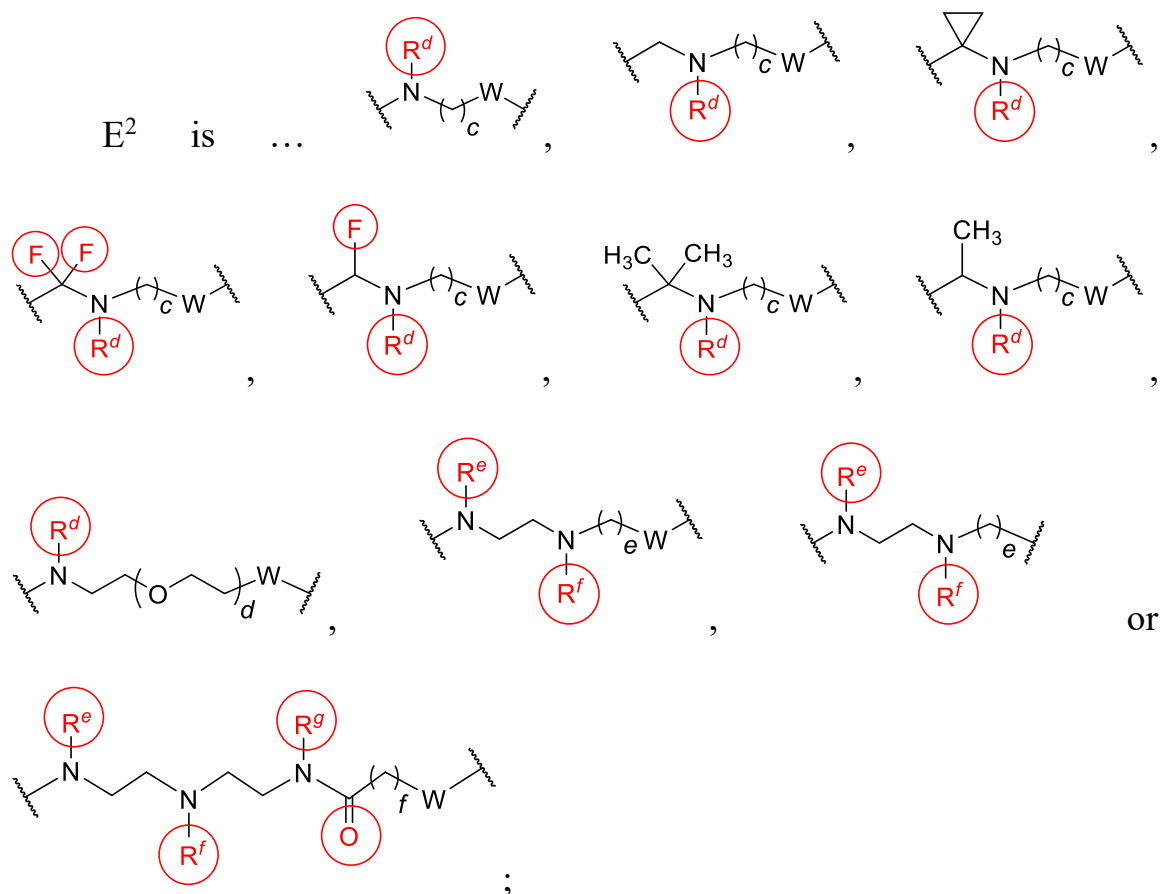
114. In this declaration I refer to the looping nature of “optional substituent” as an “infinite loop” because when one optional substituent is placed on the molecule that substituent can be substituted with another which can in turn be substituted with another and another, etc. The optional substituent ultimately covers an infinite amount of chemical space because there is no limitation on how many iterations of optional substituents attached to optional substituents that the term “optionally substituted” covers.

115. This infinite loop is necessary for dependent claims 3 and 10 to be properly dependent on Claim 1. The definitions of E² in claims 3 and 10 are only properly dependent on Claim 1 if you consider the term “optionally substituted C₁-C₁₀ heteroalkylene” to include optional substitutions that are in turn optionally substituted. (*Id.*,503). Here is the explanation (with yellow highlighting for emphasis):

Claim 1:

Each of E¹ and E² is, independently, O, S, NR^N, optionally substituted C₁₋₁₀ alkylene, optionally substituted C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C₂₋₁₀ polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene (*id.*, 503);

Claim 3 and Claim 10:



wherein

R^d, R^e, R^f, and R^g are each independently H, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or optionally substituted C₃₋₆ carbocyclyl (*id.*).

For Claim 3 and Claim 10 to be properly dependent, these E² groups must be optionally substituted C₁₋₁₀ heteroalkylene with random substituents including for example R^d, R^e, R^f, and R^g. In Figure 5, optional substituents in two of these E² groups are identified.

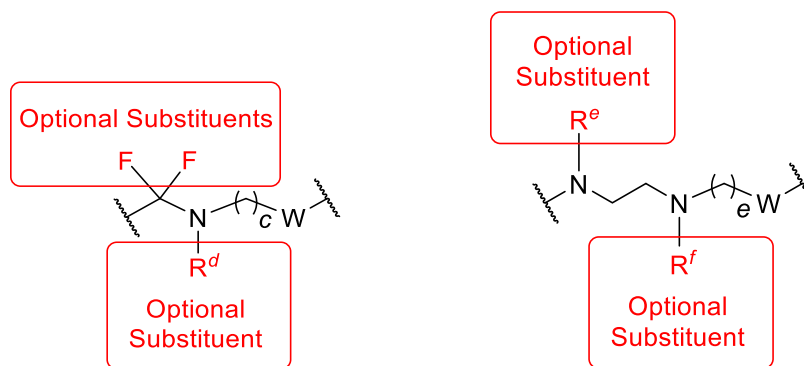


FIG. 5

And the optional substituents R^d, R^e, and R^f in turn are defined to include optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, and optionally substituted C₃₋₆ carbocyclyl. Thus, as shown in Figure 6, PO's own claims use the infinite loop of optional substituents where a 1st layer of optional substituents can be subsequently substituted by a 2nd layer of optional substituents which can then again be optionally substituted infinitely.

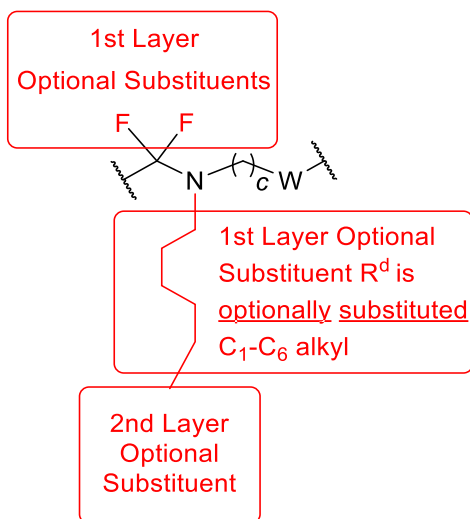


FIG. 6

116. I must conclude that the term “optionally substituted” as used in Claims 1-12 is incapable of clear interpretation, or construction, and includes infinite loops, and therefore is vague and indefinite. In addition, every term in the challenged Claims 1-12 that includes this term is likewise boundless, vague, indefinite, and incapable of construction.

**g. Content of Specification and Data Provided in the '381 Patent
Specification is Inadequate to Support the Breadth of the Claims**

117. I reviewed the twelve Figures provided by the '381 Patent. These Figures present data for only two compounds (Compounds 1 and 2) (Ex.1001,4-15). However, neither Compound 1 nor Compound 2 fall within the claims of the '381 Patent. They are both published prior art compounds. See Example 2, col. 473, lines 7-10 (*id.*,253), where Compound 1 is defined as a compound first appearing in

Remillard, et al, Degradation of the BAF Complex Factor BRD9 by Heterobifunctional Ligands. Angew. Chem Int Ed Engl. 56(21):5738-5743 (2017) (Ex.1019¹²) and Example 3 (*id.*,253-254), which defines Compound 2 as a BRD9 ligand first published in Martin, et al, Structure-Based Design of an in Vivo Active Selective BRD9 Inhibitor. J. Med. Chem. 59(10):4462-4475 (2016) (Ex.1021¹³).

118. The Detailed Description starts in col. 454. (Ex.1001,243). In columns 454-461, the patent has broad language about pharmaceutical uses and combinations. (*See id.*,243-247).

119. The Examples start in col. 462 (*id.*,247). Example 1 merely provides data that sgRNA (single guide RNA) against human BRD9 in synovial sarcoma cells can inhibit cell growth (*id.*,247-252). It provides data for 470 RNA sequences (filling over 10 columns of space) that are completely irrelevant to the invention, because no RNA sequences are in the described broad general formulas

¹² I certify that Exhibit 1019 is a true and correct copy of Remillard, et al, Degradation of the BAF Complex Factor BRD9 by Heterobifunctional Ligands. Angew. Chem Int Ed Engl. 56(21):5738-5743 (2017).

¹³ I certify that Exhibit 1021 is a true and correct copy of Martin, et al, Structure-Based Design of an in Vivo Active Selective BRD9 Inhibitor. J. Med. Chem. 59(10):4462-4475 (2016).

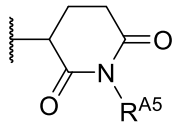
of the '381 Patent, much less the claimed compounds (*id.*,502-505). Further, it had already been published in the literature that degrading BRD9 can kill cancer cells prior to the priority date of the '381 Patent so that was already known. (Ex.1019).

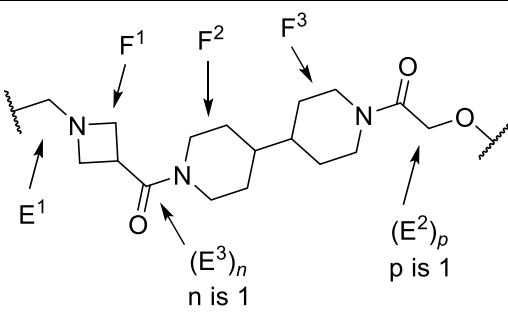
120. Example 2 provides data on the 2017 prior art BRD9 degrader compound (Compound 1) that depletes BRD9 protein in synovial sarcoma cells (FIGS. 2-4). (*Id.*,253; 4-6). Example 3 provides data for the prior art BRD9 degrader Compound 1 along with a ligand for BRD9 that does not degrade BRD9 (Compound 2) (FIGS. 5-7). (*Id.*,253-254;7-9). Examples 4 and 5 also provide data for the inhibition of synovial sarcoma cells with prior art compounds (FIGS. 8-13). (*Id.*, 254;10-15). Example 6 describes BRD9 as a component of the SS18-SSX containing BAF complex (FIG. 14) (which was already known as of the priority date (*see* Ex.1016: Gerard Brien et. al., “Targeted Degradation of BRD9 Reverses Oncogenic Gene Expression in Synovial Sarcoma,” eLife, 2018, 7 (e41305)) (*id.*,264;16).

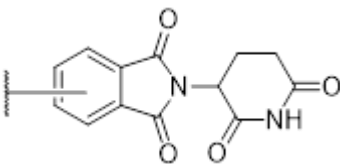
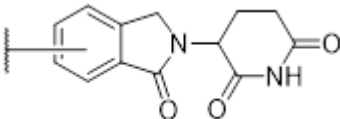
121. Examples 7-85 (spanning over 300 columns) provide syntheses of compounds, **none** of which fall within the issued claims (*id.*,254-404). Example 86 assesses the ability of compounds to inhibit BRD9 in a competitive binding assay, **none** of which fall within the scope of the issued claims (*id.*,404-406). Example 87 provides data on the ability of compounds to degrade a tagged-BRD9 fusion protein in a synovial sarcoma cell, **none** of which fall within the scope of the issued claims (*id.*,406-410). I have been provided with Table 4 below that shows the number of

species drawn, synthesized or tested in the '381 Patent that fall within the scope of the granted claims. As indicated, every box is a "0." I have reviewed Table 4, compared it to the '381 Patent specification and confirmed that these representations are accurate.

Table 4

Claim	Drawn	Made	Data	Note
1	0	0	0	A compound of Claim 1 has the following general formula: $A-(E^1)-(F^1)-(E^3)_n-(F^2)-(F^3)-(E^2)_p-B,$ wherein B is  1) Among all compounds D1-D474 and DD1-DD16 described in the '381 Patent, only compound D6 (<i>see</i> Ex.1001,83) contains the structural motif $-(E^1)-(F^1)-(E^3)_n-(F^2)-(F^3)-(E^2)_p-$ in the linker portion of the molecule and even this compound does not include a Formula AA2 moiety:

Claim	Drawn	Made	Data	Note
				 Although compounds D280, D281, D291, D300, D301, and D302 contain the three required ring moieties F¹, F², F³ in the linker (<i>see id.</i>,177,180,182), they are connected in such a way that the resulting linker does not fall with the definition of the linker of Claim 1. The linker in these 6 compounds may be described as follows: –(E¹)–(F¹)–(F²)–CH₂–(F³)–(E²)_p– in D280 and D300, or –(E¹)–(F¹)–(F²)–CH₂O–(F³)–(E²)_p– in D281 D291, D301 and D302. Neither linker falls within the linker definition of Claim 1. Therefore, only the linker of D6 falls under the definition of the linker in Claim 1.

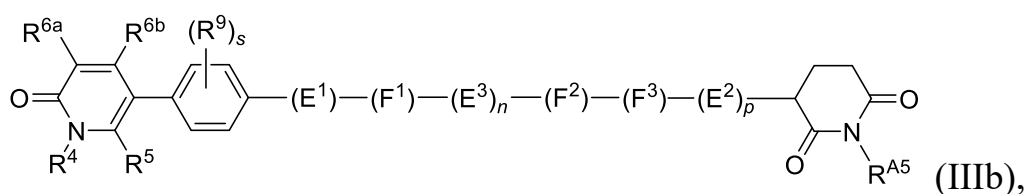
Claim	Drawn	Made	Data	Note
				2) Most of the compounds among compounds D1-D474 and DD1-DD16 contain glutarimide directly attached to phthalimide or the phthalimide analog where one carbonyl is replaced with CH₂:  or  This phthalimide-glutarimide moiety does not fall within the definition of the degradation moiety B (Formula AA2) of Claim 1. Compounds D382, D383, D388, D389, D390, DD1, and D474 do not even contain a glutarimide (<i>see id.</i>, 204-206, 199, 230, respectively). Therefore, none of the compounds D1-D474 and DD1-DD16 falls within the scope of

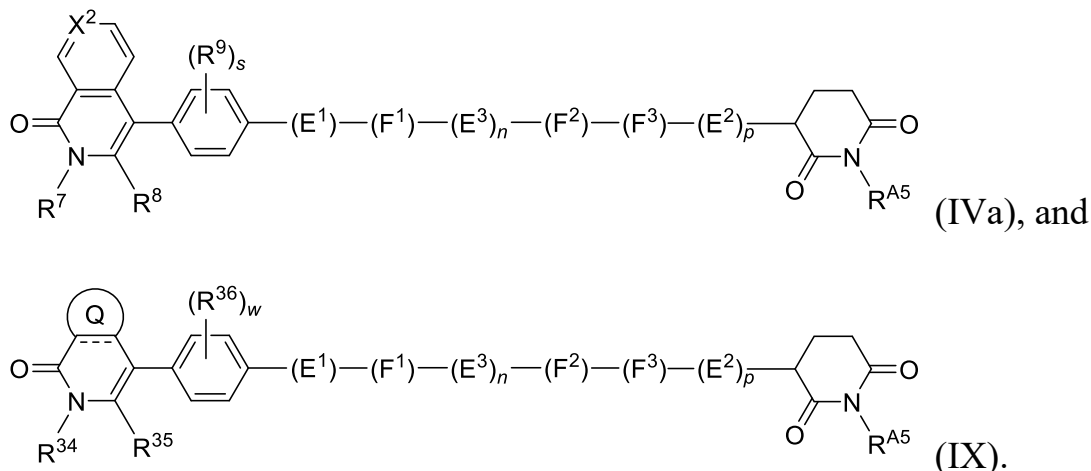
Claim	Drawn	Made	Data	Note
				Claim 1 because either they do not contain the linker or the degradation moiety as defined in Claim 1, or do not contain both. For example, although compound D6 contains the linker covered by Claim 1 (<i>see id.</i> ,83), it does not contain the moiety B as defined in the claim, and, therefore, is not within the scope of claim as whole.
2	0	0	0	The claim is directed to the compound of Claim 1, wherein E ¹ is –CH ₂ –.
3	0	0	0	The claim is directed to the compound of Claim 1, wherein E ² is limited to narrower defined group of moieties.
4	0	0	0	The claim is directed to the compound of claim 3, wherein E ² is limited to –NR ^N –.
5	0	0	0	The claim is directed to the compound of claim 4, wherein E ² is limited to –NH–.

Claim	Drawn	Made	Data	Note
6	0	0	0	The claim is directed to the compound of Claim 1, wherein n is 1 and E ³ is limited to narrower defined groups.
7	0	0	0	The claim is directed to the compound of Claim 1, wherein F ¹ is limited to a narrower group of cyclic moieties encompassed by the term C ₂₋₁₀ heterocyclylene.
8	0	0	0	The claim is directed to the compound of Claim 1, wherein F ² is limited to a narrower group of cyclic moieties encompassed by the term C ₂₋₁₀ heterocyclylene.
9	0	0	0	The claim is directed to the compound of Claim 1, wherein F ³ is limited to optionally substituted C ₆ -C ₁₀ arylene.
10	0	0	0	The claim is directed to the compound of Claim 1, wherein E ¹ is -CH ₂ -; E ² is defined as in claim 3; n is 0 or 1;

Claim	Drawn	Made	Data	Note
				E^3 is defined as in claim 6; F^1 is defined as in claim 7; F^2 is defined as in claim 8; and F^3 is optionally substituted C_6-C_{10} arylene.
11	0	0	0	The claim is directed to the compound of Claim 1, wherein: p is 1.
12	0	0	0	The claim is directed to the compound of Claim 10, wherein: p is 1.

122. For convenience, Formulas IIIb, IVa, and IX of Claim 1 can be drawn as follows.





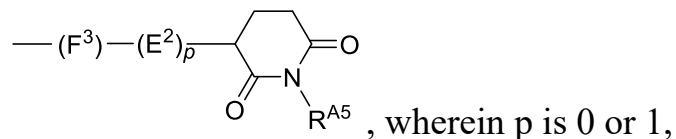
123. These formulas do not cover a single compound drawn in the '381 Patent specification, Tables 1A to 1E. The reasons for this observation are as follows.

124. As defined in Claim 1, each of E¹ and E², independently, is -O-, -S-, -NR^N-, optionally substituted C₁-C₁₀ alkylene, optionally substituted C₂-C₁₀ alkenylene, optionally substituted C₂-C₁₀ alkynylene, optionally substituted C₂-C₁₀ polyethylene glycol, or optionally substituted C₁-C₁₀ heteroalkylene. (Ex.1001,503).

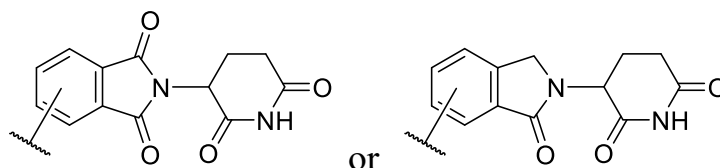
125. As further defined in Claim 1, each of F¹, F², and F³ is, independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene (*id.*).

126. It follows from the definitions of F³ and E² that the structures in Claim 1 do not fit the drawn structures of compounds D1-D333, D335-D371, DD2, DD4, DD8, DD10, D372-D381, D384-D387, D396-D429, D431, D433-D468,

D470, D474, DD11-DD16 in the specification of the '381 Patent (*id.*). For example, fragment $-(F^3)-(E^2)_p-B$ of formula:



cannot form a phthalimide structure, even when p is 0:



either of which is present in most of the compounds presented in Tables 1A to 1E of the '381 Patent specification (compounds D1-D333, D335-D371, DD2, DD4, DD8, DD10, D372-D381, D384-D387, D396-D429, D431, D433-D468, D470, D474, DD11-DD16) (*id.*,81-232). Additionally, the non-phthalimide '381 Patent drawn compounds DD1, D382, D383, and D388-D390 do not even contain the required

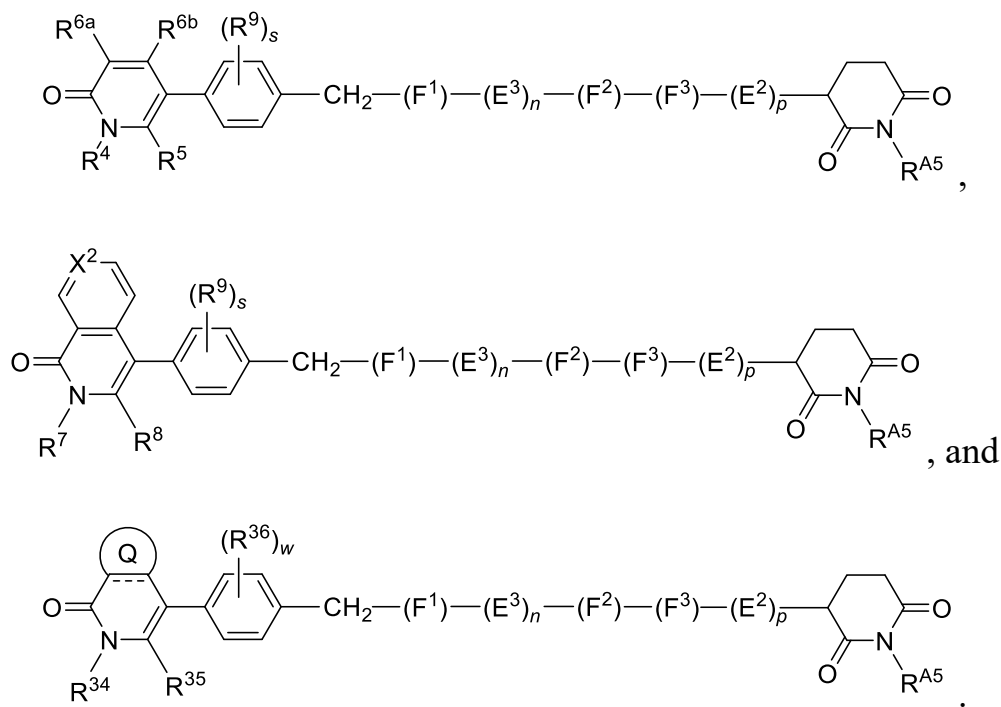
glutarimide moiety . Compounds D334, DD1, DD3, DD5, DD6, DD7, DD9, D382-D383, D391-D395, D430, D432, and D471-D473 also do not fall within the genus of the Claim 1 formula because they do not contain the linker as claimed in Claim 1 ($-A^1-(E^1)-(F^1)-(E^3)_n-(F^2)-(F^3)-(E^2)_p-A^2-$).

127. I conclude that there is not a single compound within the claimed genus described in the '381 Patent specification. Therefore, Formula I in Claim 1 of

the '381 Patent does not cover even a single compound described in the '381 Patent specification (*id.*, 81-232, Tables 1A to 1E). Claims 2-12 similarly do not cover a single disclosed structure in the '381 Patent.

Claim 2

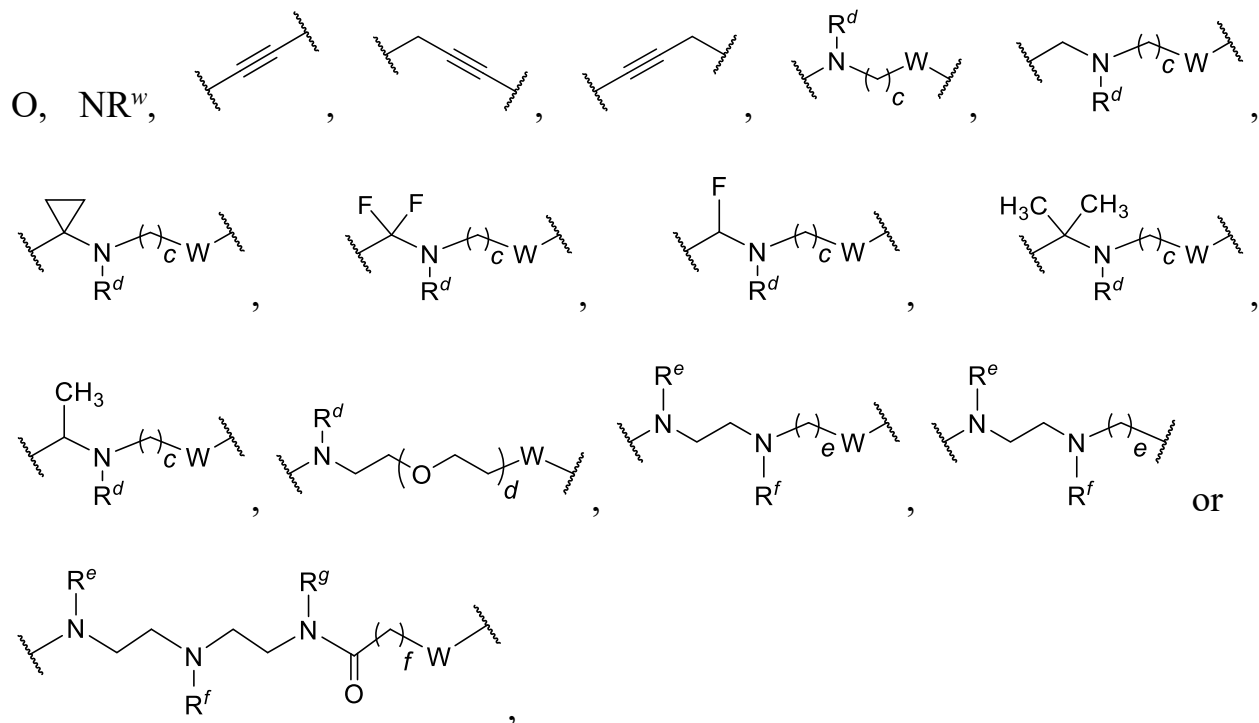
128. Claim 2 is directed to the compound of Formula I of Claim 1 with the only limitation that variable E^1 is CH_2 . Therefore, with this limitation, compounds of claim 2 can be represented by the following structures:



129. For the reasons presented when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent specification (*id.*, Tables 1A to 1E).

Claim 3

130. This claim is directed to the compound of Formula I, in which variable E^2 is limited to a narrower subset of non-cyclic groups. Specifically, E^2 is



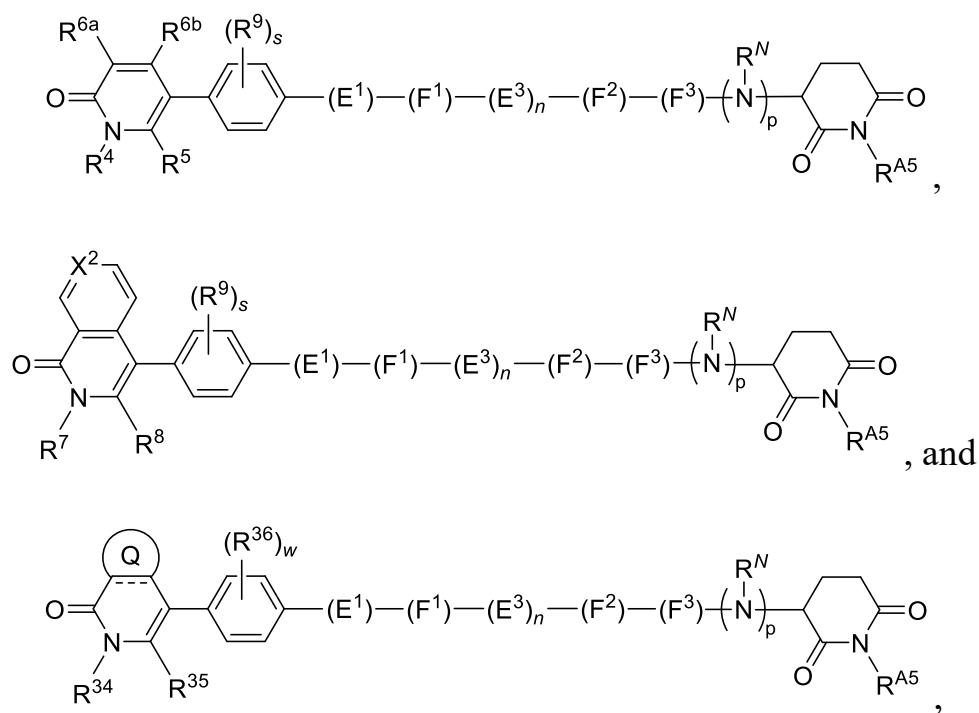
wherein W is O or NR^w , and wherein R^w is H or optionally substituted C_1 - C_6 alkyl (Ex.1001,503).

131. Claim 3 demonstrates PO's use of optional substituents on optional substituents and the open-ended nature of this term. For example, the last structure of E^2 is a heteroalkylene with five optional substituents (R^e , R^f , R^g , oxo, and NR^w). And these substituents (except oxo) in turn are each optionally substituted.

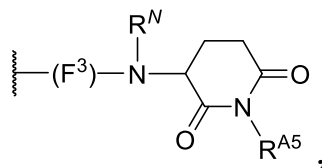
132. For the reasons presented when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent specification (*id.*,81-232, Tables 1A to 1E).

Claim 4

133. Claim 4 is directed to the compound of claim 3, in which variable E^2 is further limited to $-NR^N-$, and, therefore, compound of claim 4 may be represented by the structures:



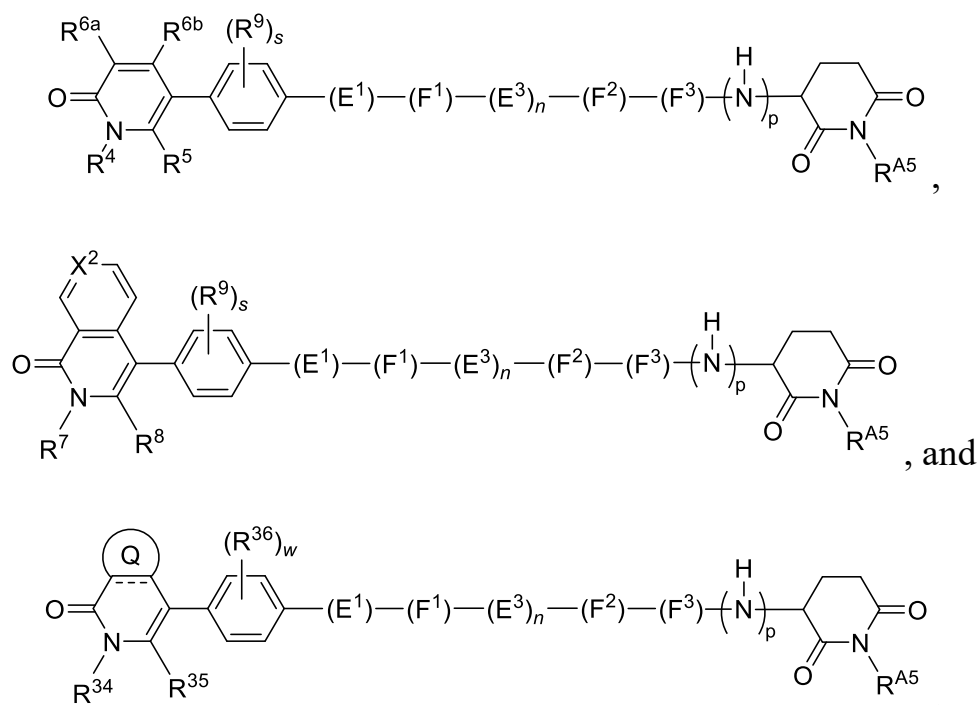
where R^N is H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl (Ex.1001,503). None of the compounds of the '381 Patent contain fragment



in which a cyclic fragment F^3 is linked to the glutarimide through a linking nitrogen.

Claim 5

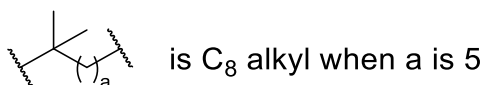
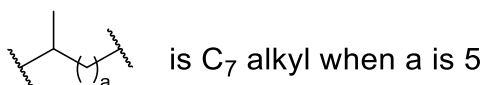
134. Claim 5 is directed to the compound of claim 4, in which variable E^2 is further limited to $-NH-$ (Ex.1001,503), and Formula I may be represented by the structures:



135. Therefore, Formula I as limited in claim 5 does not cover a single compound described in the '381 Patent specification.

Claim 6

136. Claim 6 is directed to the compound of Claim 1, in which variable n is 1 and variable E^3 is further limited to a narrower subset of substituted or unsubstituted C_1 - C_6 alkylene (Ex.1001,503-504). These “narrower” C_1 - C_6 alkylene moieties include moieties with more than six carbons demonstrating PO’s use of an optionally substituted alkylene substituted with an alkyl and making their recitations of length nearly meaningless.



137. Formula I as limited in claim 6 does not cover even a single compound described in the '381 Patent specification.

Claim 7

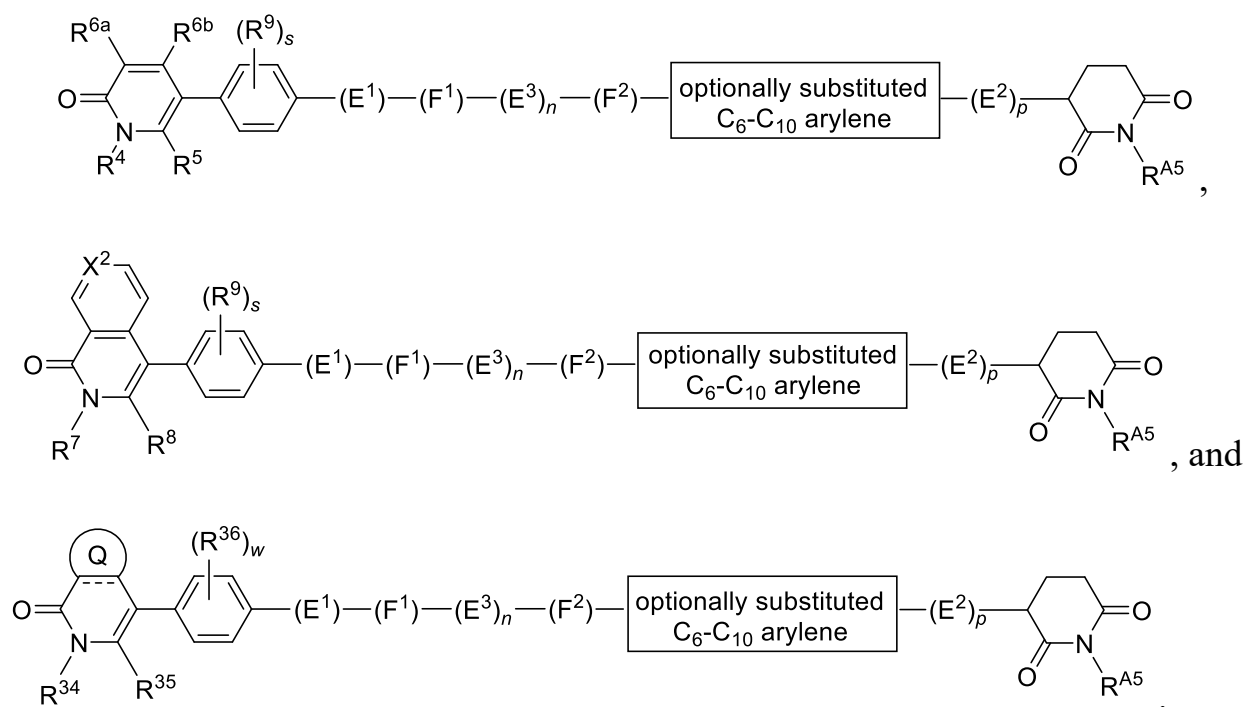
138. Claim 7 is directed to the compound of Claim 1, in which variable F^1 is further limited to a narrower subset of substituted or unsubstituted 4- or 5-membered heterocyclic moieties with one nitrogen heteroatom: azetidiny1 or piperidiny1 (Ex.1001,504). Formula I, as limited in claim 7 does not cover a single compound described in the '381 Patent specification.

Claim 8

139. Claim 8 is directed to the compound of Claim 1, in which variable F^2 is further limited to a narrower subset of substituted or unsubstituted 4- or 5-membered heterocyclic moieties with one or two nitrogen heteroatom(s): azetidiny, piperidinyl, or piperazinyl (*id.*). Formula I as limited in claim 8 does not cover a single compound described in the '381 Patent specification.

Claim 9

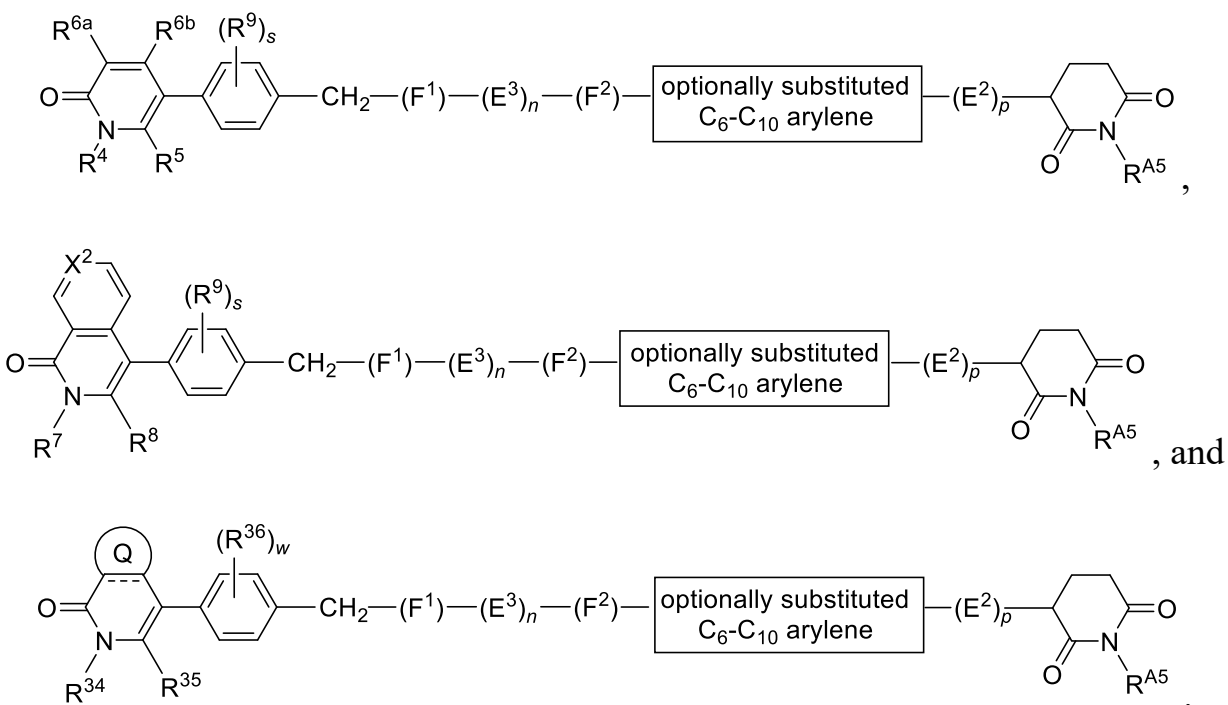
140. Claim 9 is directed to the compound of Claim 1, in which variable F^3 is further limited to optionally substituted C_6 - C_{10} arylene (*id.*). and Formula I may be represented by the structures:



141. Formula I as limited in claim 9 does not cover a single compound described in the '381 Patent specification.

Claim 10

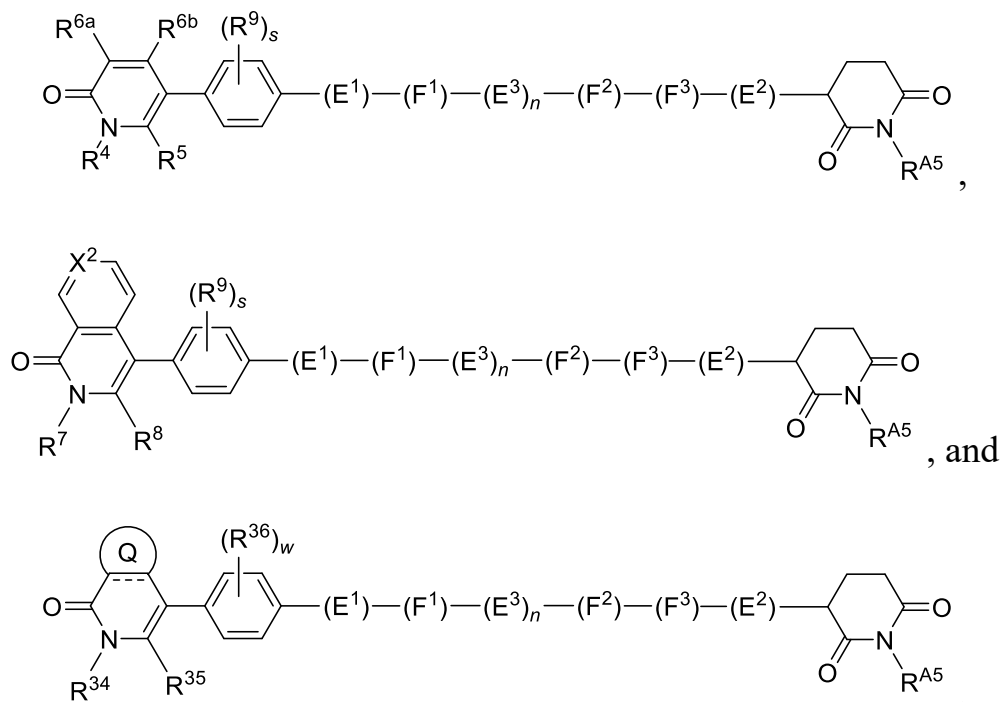
142. Claim 10 is directed to the compound of Claim 1, in which variable E¹ is limited to CH₂, variable E² is “limited” as described in claim 3, variable E³ is limited as described in claim 6, variable F¹ is limited to specific heterocycles as described in claim 7, variable F² is limited to specific heterocycles as described in claim 8, and variable F³ is limited to optionally substituted C₆-C₁₀ arylene, (Ex.1001,504-505):



143. Formula I as limited in Claim 10 does not cover a single compound described in the '381 Patent specification.

Claim 11

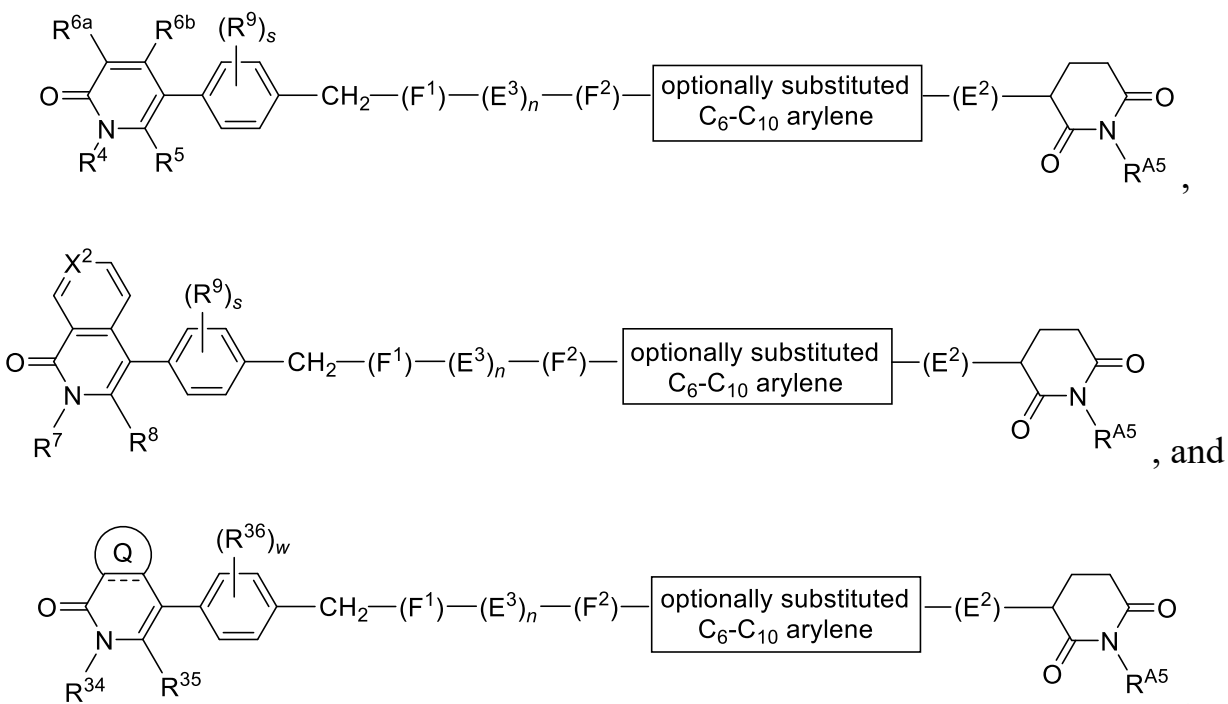
144. Claim 11 is directed to the compound of Claim 1, in which variable p is 1. (Ex.1001,505)



145. Formula I as limited in Claim 11 does not cover a single compound described in the '381 Patent specification.

Claim 12

146. Claim 12 is directed to the compound of Claim 10, in which variable p is 1 (*id.*).



147. Formula I as limited in Claim 12 does not cover a single compound described in the '381 Patent specification. Furthermore, there is no disclosure in the specification combining these specific chemical moieties or any guidance or blaze marks to a POSA to the many selections and combinations in this claim.

148. On the basis that the '381 Patent specification does not draw, make or test a single compound that falls within the scope of the issued '381 Patent claims, nor does the specification combine the elements of the subgenus of Claim 1 into one formula in the specification, and based on my understanding of the law on written description, I must reach the conclusion that the '381 Patent specification

does not provide an adequate written description for the POSA of the claimed subject matter.

149. My opinion on the lack of written description for the claims of the '381 Patent is even more solidified by reference to the multitude of nebulous “optionally substituted” references in the claims which lack meaningful metes and bounds.

h. The '381 Patent Claims are Indefinite under 112(b)

150. For the reasons referred to above in Section VIII-1e and Section VIII-1f, I conclude that a POSA would not be able to identify the metes and bounds of the term “optionally substituted” as used in all of the claims of the '381 Patent, and thus would not be placed on notice whether activities would be infringing. For that reason, I conclude that claims 1-12 are invalid as indefinite.

151. Also for the reasons referred to above in Section VI, I conclude that if the Board does not construe the terms “C₆-C₁₂ Aryl” and “C₆-C₁₀ Arylene” to allow for attachment points at either the aromatic or non-aromatic moiety, it is my opinion that a POSA would be confused by these terms and would be incapable of construing them in a definite manner, rendering the terms indefinite.

2. The '381 Patent Claims Are Not Enabled

152. The claims of the '381 Patent are not enabled across their full scope for the reasons set out below, including that there are no included syntheses

or biological data for any of the claimed compounds. More importantly, it is not possible to know how to make or use compounds in claims that are inadequately defined and have boundless terms.

153. I have studied Examples 86 and 87 of the '381 Patent specification. (Ex.1001,404-410). In my opinion, a POSA would conclude that the PO sets a threshold for utility for the claimed BRD9 degraders as having an IC₅₀ activity of not more than 1 micromolar ("μM") in at least one of the only two biological examples in the specification, Example 86 and Example 87. (*See id.*).

154. Example 86 measured the ability of a test compound to biochemically inhibit BRD9 bromodomain in a competition binding assay (col.775,1.57-59) (*id.*,404). In col. 777, lines 9-12, PO stated that "As shown by the results in Table 4, a number of compounds of the present disclosure exhibit an IC₅₀ value of <1 μM for BRD9 binding, indicating their affinity for targeting BRD9." (*id.*). This teaches the POSA two things: (i) not all of the compounds in the '381 Patent have affinity for targeting BRD9; and (ii) the threshold binding activity for a useful compound is set by PO at an IC₅₀ value of <1 μM using its assay.

155. Example 87 refers to the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay (*id.*,406-410). In col. 780, lines 10-15, PO states that "As shown by the results in Table 5A, Table 5B and Table 5C, a number of compounds of the

present disclosure exhibit an IC_{50} value of $<1 \mu M$ for the degradation of BRD9, indicating their use as compounds for reducing the levels and/or activity of BRD9 and their potential for treating BRD9-related disorders” (*id.*,406). I conclude that this teaches a POSA that (i) not all of the compounds work to reduce the level of BRD9 or have potential for treating BRD9-related disorders and (ii) the threshold for potential utility to treat BRD9-related disorders is benchmarked by PO at an IC_{50} value of $<1 \mu M$ in that degradation assay.

156. Together, Examples 86 and 87 confirm that PO was aware at the filing date that not all of the described compounds would work for the intended function—treating a BRD9 mediated medical disorder in a human, and that the threshold for expectation of activity is $< 1 \mu M$ in these assays.

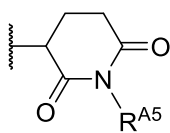
157. Because **none** of the compounds that fall within the issued claims were tested, there can be no reasonable expectation whether they would work for the intended function or not. And even if some of them would, there was no way to know which would and which would not. Therefore, the '381 Patent specification is not enabling to a POSA for the claimed compounds.

158. Further compounding the problem is that the claimed compounds can have any number of unspecified “optional substituents.” It is simply impossible for me or a POSA to determine whether any of the claimed compounds would act as intended to degrade BRD9 in a human.

a. There is No Synthesis of Any of the Claimed Compounds in the Specification.

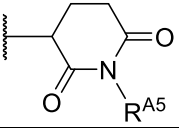
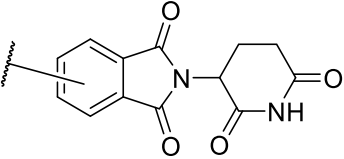
159. The specification does not provide sufficient detail to teach a POSA how to make the claimed compounds across the scope of the claims. In fact, as discussed extensively above in Section VIII-1, the scope of the claimed invention has no set boundaries and includes an infinite number of compounds because of the repeated use of the term “optionally substituted” in the claims. A skilled artisan would require infinite experimentation to make and use compounds across an infinite scope. Thus, the specification does not enable the synthesis of the claimed compounds across the scope of the claims.

160. A detailed synthetic procedure is provided for fewer than a fourth of the drawn molecules (D1 to D74) (*see id.*, 265-397). And, even when synthetic methods are provided, the synthesis is for compounds that aren’t covered by the claims and often these compounds differ in several structural motifs from the limitations required by the ’381 Patent claims (see Table 5 below). For example,



focusing on the and Linker moieties every molecule except D6 with a detailed synthesis differs in both moieties.

Table 5

	Moiety	
Compound Number		$-(F^1)-(E^3)_n-(F^2)-(F^3)-(E^2)_p$
D1 to D74	Not covered by the claims of the '381 Patent due to the presence of  in the compounds	Not covered, except compound D6

161. However, even if a POSA concludes that it would have been routine to make compounds falling within the claims where there are no optional substituents, it is impossible that a POSA could conclude that it would be routine to make a virtually infinite number of compounds with an unspecified variety of substituents.

162. The synthesis of compounds D75-D476 and DD1-DD16 are not described and instead the specification states that they were prepared by analogy to the described syntheses of D1 to D74 using appropriate starting materials (*see id.*, 382, 385, 393, 394, 404). These compounds are also not covered by the claims of the '381 Patent.

b. Consideration of the Factors for Enablement

163. Application of the following factors, which I have been advised are used to determine whether the specification is enabling, demonstrates the lack of enablement as described below when the continuously used vague and open-ended term “optionally substituted” is used in the claim analysis:

- (i) The quantity of experimentation necessary.

The claims cover a vast and unbounded number of molecules. The quantity of experimentation necessary to enable a POSA to make and use compounds across an infinite scope is an infinite amount of experimentation.

- (ii) How routine any necessary experimentation is in the relevant field.

The necessary experimentation is beyond routine experimentation for medicinal chemistry because the compounds in the claims are not sufficiently defined. As noted in the claim construction Section VI the claims do not even exclude compounds which are unstable. And of course, it would take infinite experimentation to test the utility of an infinite number of compounds as fall within the claims when the scope of “optional substituents” are considered.

- (iii) Whether the patent discloses specific working examples of the claimed invention.

The patent doesn't describe a single working example for the synthesis or biological activity of a claimed compound, much less an "optionally substituted" claimed compound.

(iv) The amount of guidance presented in the patent.

The guidance of the specification is primarily focused on the synthesis and use of BRD9 degraders with phthalimide based cereblon binders which are not covered by the claims. There is not a single drawn, synthesized, or tested compound in the patent which is covered by the claims.

(v) The nature and predictability of the field.

The field of BRD9 degraders is complex and unpredictable. Small changes can create profound differences in activity. The claims include dozens of optional substituents and there an unbounded number of compounds covered which would require synthesis and testing to determine if their optional substituents were appropriate.

(vi) The level of ordinary skill.

As discussed in Section VI a POSA would have either a Ph.D. or a Masters degree and four years of relevant industry experience. However, there is no level of training that would enable a POSA to make and use an infinite list of compounds. Likewise, it would be impossible to predict whether they would work for the

intended function. The claims cover compounds of potentially infinite size, which exceeds the level of ordinary skill.

(vii) The scope of the claimed invention.

As discussed in Section VIII-1 the scope of the invention is unbounded because the multiple uses of “optional substituent” in the claims. And the scope can be considered infinite because of the infinite loop problem.

164. All seven of the factors above weigh in favor of finding the claims invalid for lack of enablement over the full scope of the granted claims.

3. Anticipation

165. As discussed in detail in Section VIII-1 above, PCT/US2020/015746 (the “’746 PCT Application”) (Ex.1005), and even the parent application U.S.S.N. 17/425,153 (Ex.1004) of the ’381 Patent fail to adequately describe the presently claimed combinations of elements. Thus, the claims are not entitled to a priority date earlier than March 16, 2022, which is when PO filed the claims of the ’381 Patent with the USPTO in U.S.S.N. 17/696,656 (Ex.1002,137-563).

166. In fact, the claims should also not be entitled to the priority date of March 16, 2022, because I am told that even if each element of a generic compound may be individually described in the specification, there is a deficiency

of the lack of adequate written description if the combination itself is not presented in a clear form.

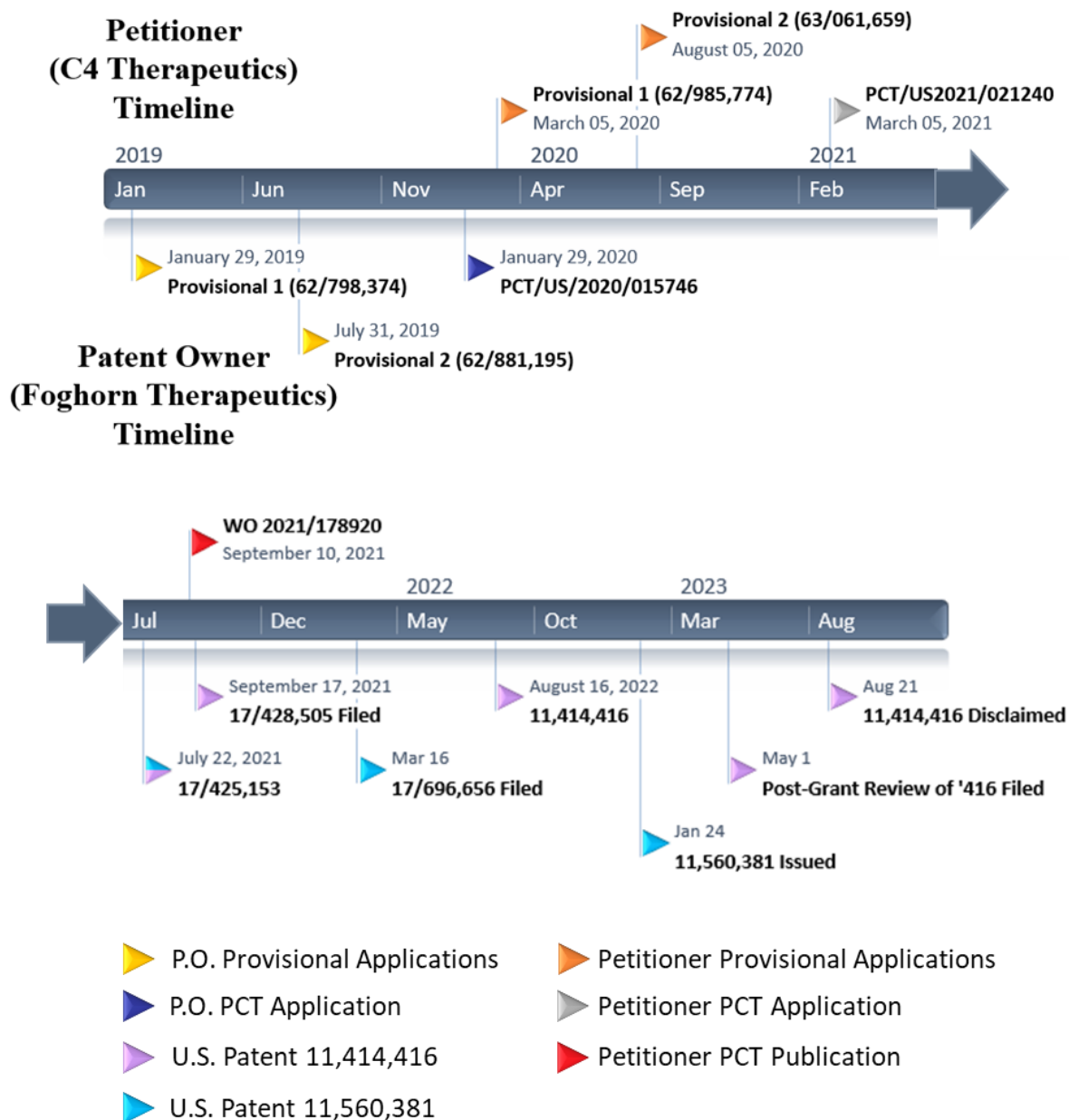
167. I understand that even if PO were to amend its claims in the PGR to remove all of the “optionally substituted” references, the claims would still be invalid based on my understanding that the written description requirement forbids post-hoc cherry-picking of elements in the specification to create a genus that was not presented as the specific claimed genus combination at the filing date and further, no drawing, synthesis or data are provided for any of the claimed compounds in any event, even without consideration of the term “optionally substituted.”

168. In my opinion, intervening patent publication WO2021/178920 (the “’920 PCT Publication” (Ex.1010) is a novelty destroying reference to claims 1-12 of the ’381 Patent (for example, see Table 6 and Table 7 below).

169. I am told that a claim is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. And that, when a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.

170. I provide below another timeline that includes both the PO’s priority dates and the priority dates of Petitioner’s ’920 PCT Publication (Ex.1010) that will be discussed further below. While I understand that the ’746 PCT

Application claims priority to two additional United States provisional applications (U.S. Provisional Application Nos. 62/798,374 (Ex.1007) and 62/881,195 (Ex.1006)), for purposes of my analysis I have been asked to consider the '746 PCT Application as the relevant priority document in this case, and whether the '746 PCT Application meets the written description and enablement requirements of 35 U.S.C. § 112(a). I understand that if the '746 PCT Application does not meet the written description and enablement requirements of § 112(a), then the '381 Patent cannot claim the benefit of its filing date.

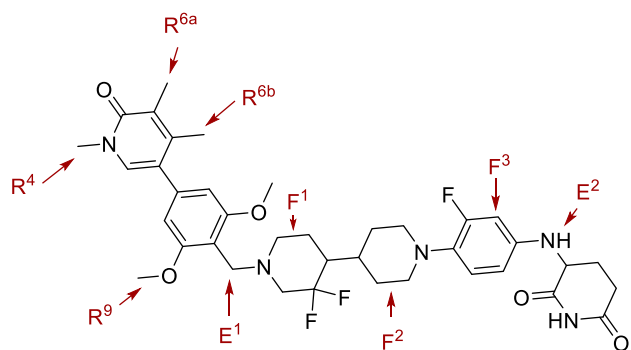
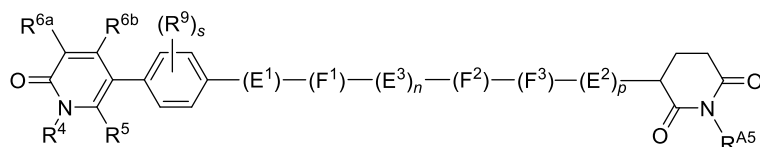


171. WO2021/178920 (Ex.1010) was published on September 10, 2021 (*id.*,1). The '920 PCT Publication was filed as PCT/US2021/021240 (The “C4T ’240 Application”) (Ex.1011) on March 5, 2021. The '920 PCT Publication describes over a dozen molecules that are within the scope of at least one claim of the '381 Patent. This includes for example C4T compounds 70, 172, 176, 182, 184,

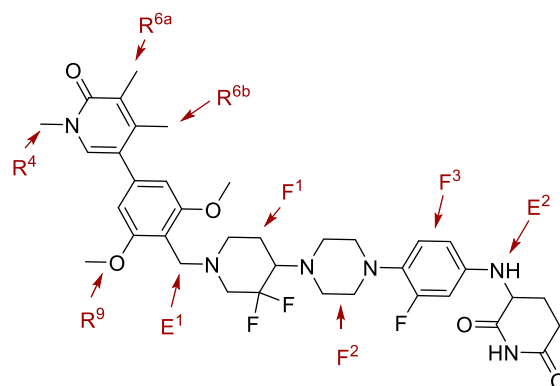
185, 187, 188, 195, 198, 206, 225, 231, 251, and 265 (see structures and citations in Table 6 below). I note that Dr. Nasveschuk confirms that these compounds were synthesized and tested under his direction and supervision, according to the procedures provided in the C4T '920 PCT Publication. (Ex.1018, ¶¶9-14). Each of the described compounds exhibited a DC₅₀ of less than 100 nM.

Table 6

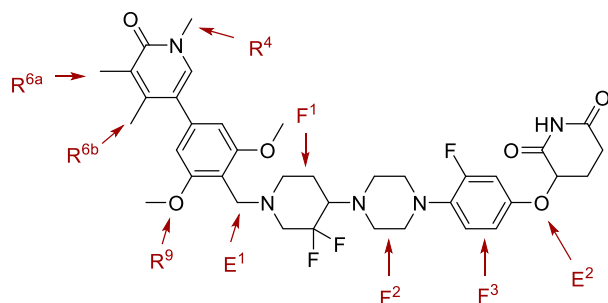
For Formula I where A is Formula IIIb:



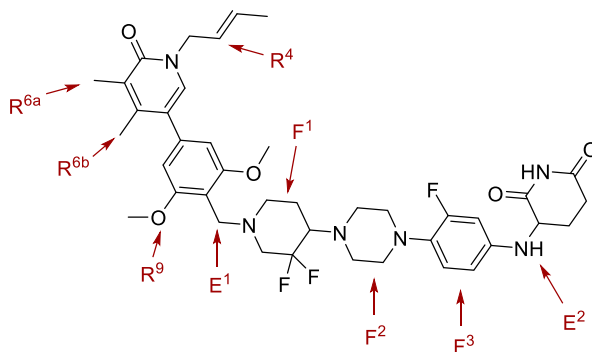
C4T Compound 198 Ex. 1010 at 711



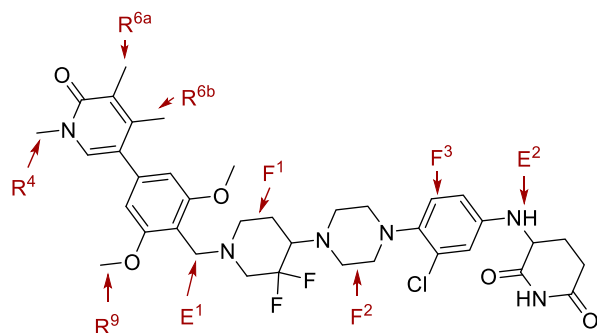
C4T Compounds 172-176 Ex. 1010 at 704-705



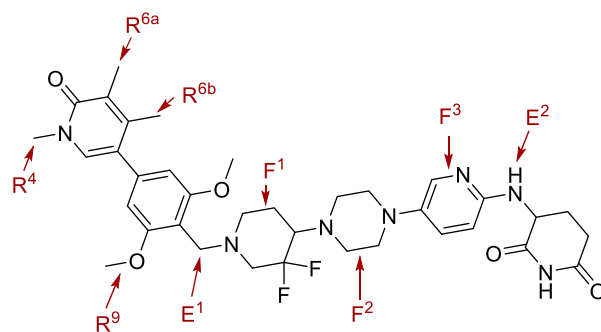
C4T Compound 251 Ex. 1010 at 724



C4T Compound 265 Ex. 1010 at 728

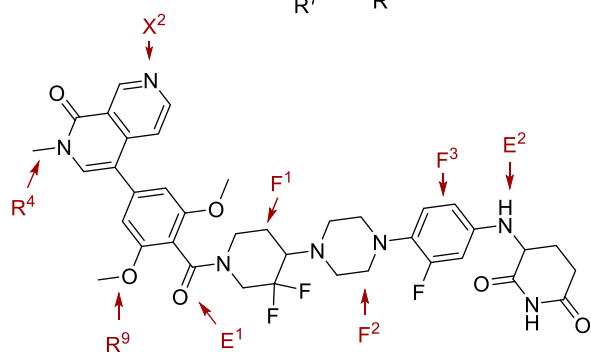
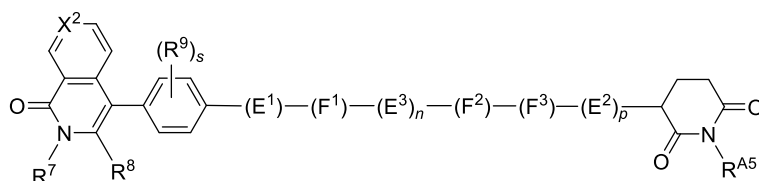


C4T Compound 187 Ex. 1010 at 708

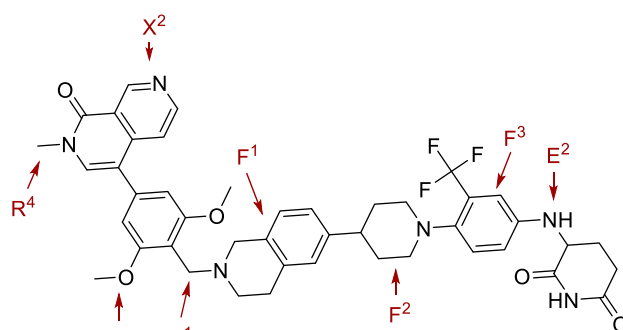


C4T Compound 195 Ex. 1010 at 710

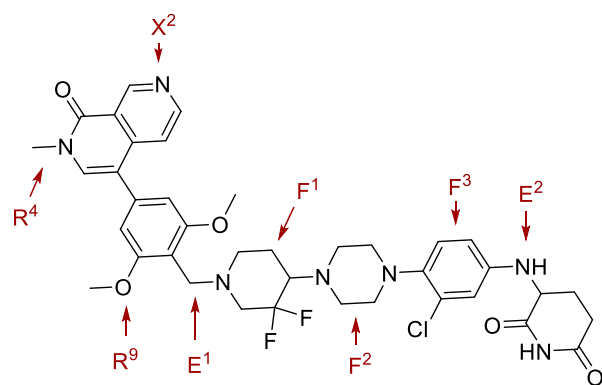
For Formula I where A is Formula IVa:



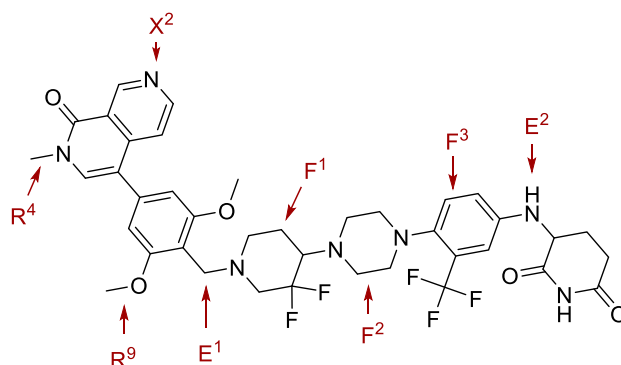
C4T Compound 225 Ex. 1010 at 717



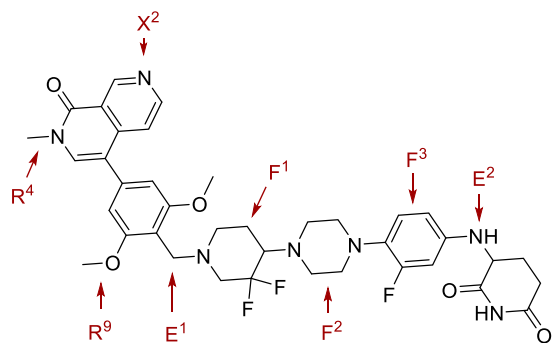
C4T Compound 231 Ex. 1010 at 719



C4T Compound 188 Ex. 1010 at 708

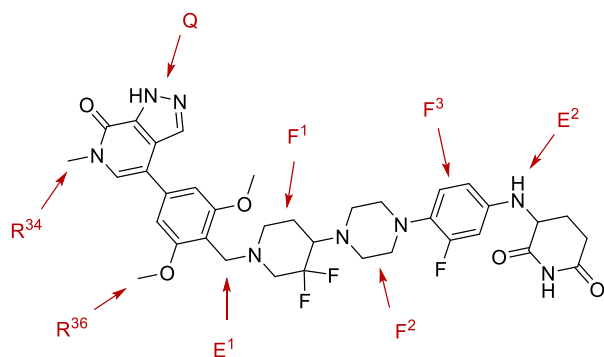
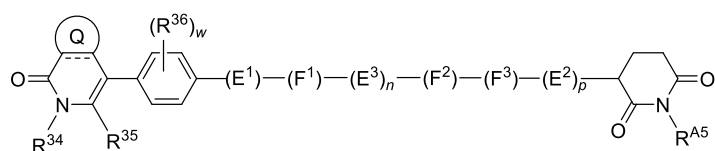


C4T Compound 185 Ex. 1010 at 707

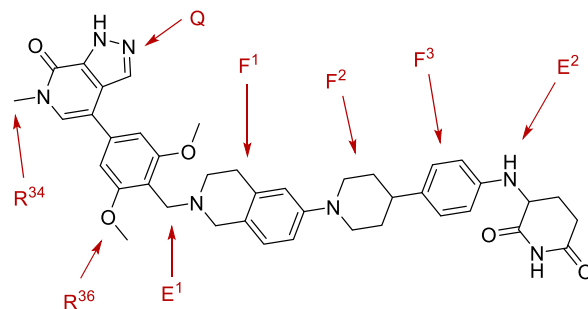


C4T Compound 184 Ex. 1010 at 707

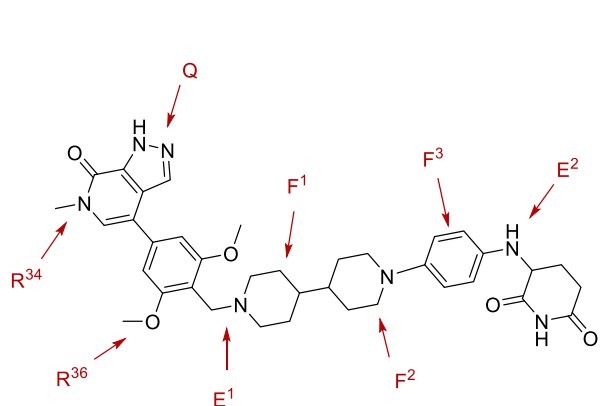
For Formula I where A is Formula IX:



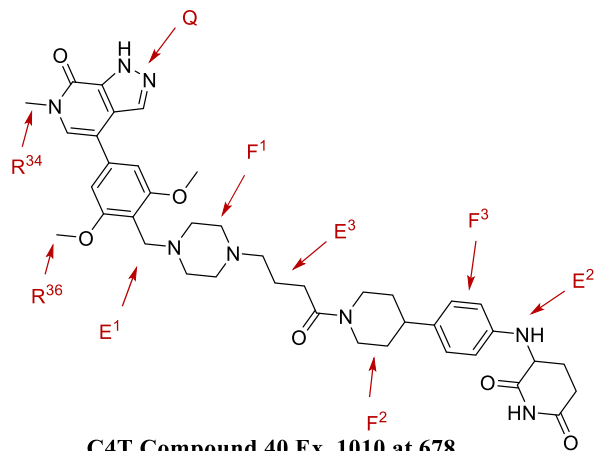
C4T Compound 182 Ex. 1010 at 707



C4T Compound 206 Ex. 1010 at 713



C4T Compound 70 Ex. 1010 at 679



C4T Compound 40 Ex. 1010 at 678

172. The C4T '920 PCT Publication provides NMR characterization, mass spectra characterization, and BRD9 protein degradation data for each of the compounds described above. (See Ex.1010, 411-412, 528-531, 533-536, 539, 556, 568-570, 579, 596-600, 620-624, 649-650, 678-704, 707, 708, 710, 711, 713, 717, 719, 724, and 728). In fact, the '920 PCT Publication provides the synthesis and data for over a dozen compounds that fall within the claims of the '381 Patent. This is in sharp contrast to the specification of the '381 Patent which does not provide synthesis or data on a single compound in its issued claims.

173. The following Table 7 matches the compounds of the '920 PCT Publication (Ex.1010) to the claims which they anticipate in the '381 Patent.

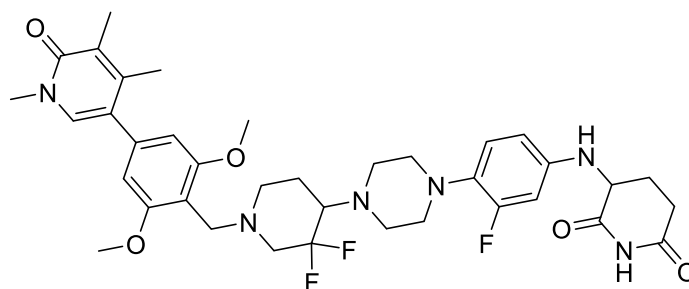
Table 7

US Patent No. 11,560,381 Claim	Compound from C4T '920 PCT Publication (Ex. 1010)
1	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 710-711, 713, 717, 719, 724, 728).
2	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 231, 251, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 710-711, 713, 719, 724, 728).
3	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, 265. (<i>See id.</i> , 671,

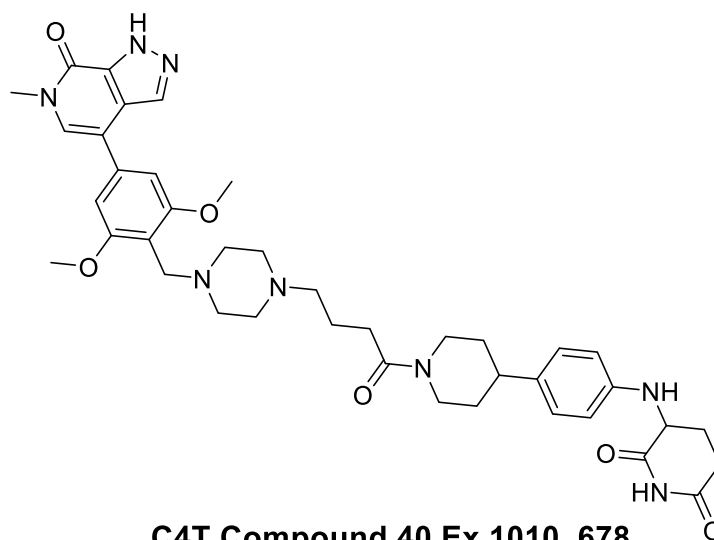
	679, 704-705, 707-708, 710-711, 713, 707, 719, 724, 728).
4	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 710-711, 713, 717, 719, 728).
5	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 710-711, 713, 717, 719, 728).
6	C4T Compounds 40 (<i>See id.</i> , 671).
7	C4T Compounds 172-176, 182, 184-185, 187-188, 195, 198, 225, 251, 265. (<i>See id.</i> , 704-705, 707-708, 710-711, 717, 724, 728).
8	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 710-711, 713, 717, 719, 724, 728).
9	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 198, 206, 225, 231, 251, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 711, 713, 717, 719, 724, 728).
10	C4T Compounds 172-176, 182, 184-185, 187-188, 198, 251, 265. (<i>See id.</i> , 704-705, 707-708, 711, 724, 728).
11	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 710-711, 713, 717, 719, 724, 728).

12	C4T Compounds 172-176, 182, 184-185, 187-188, 198, 251, 265. (<i>See id.</i> , 704-705, 707-708, 711, 724, 728).
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174. C4T Compound 172 reads on every claim of the '381 Patent except claim 6. Claim 6 is anticipated by C4T Compound 40.



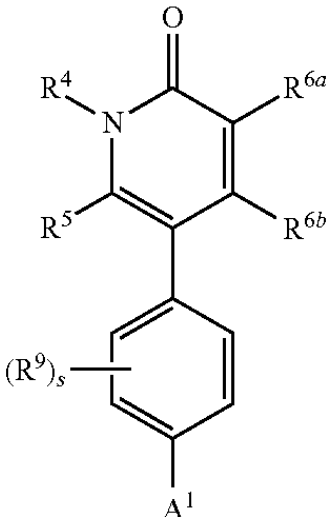
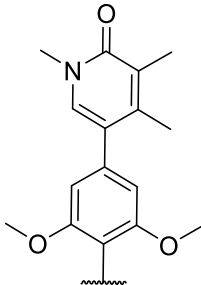
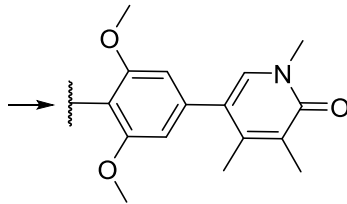
C4T Compound 172 - Ex.1010, 704



C4T Compound 40 Ex.1010, 678

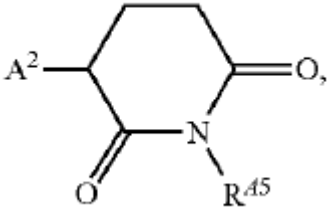
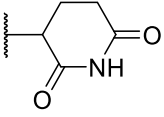
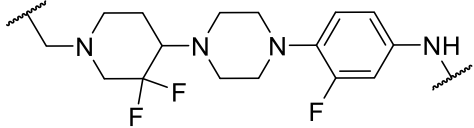
175. In the table below the selection of variables for each substituent in the claims of the '381 Patent is provided which when combined cover C4T Compound 172 or C4T Compound 40.

Table 8

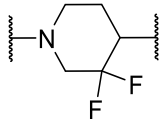
Claim 1	
A compound having the structure of Formula I: A-L-B	
'381 Patent	Cmp 172 ('920 PCT)
A is 	Reads on the corresponding moiety  of C4T Compound 172 as follows
A¹ is bond between A and L	The A¹ bond is in the same location 
R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally	Methyl is subset of optionally substituted C₁-C₆ alkyl

substituted C ₁ -C ₆ heteroalkyl, or optionally substituted C ₃ -C ₁₀ carbocyclyl;	
R ⁵ is H, halogen, optionally substituted C ₁ -C ₆ alkyl, optionally substituted C ₁ -C ₆ heteroalkyl, optionally substituted C ₃ -C ₁₀ carbocyclyl, or optionally substituted C ₆ -C ₁₀ aryl;	H is hydrogen
R ^{6a} is H, halogen, cyano, optionally substituted C ₁ -C ₆ alkyl, optionally substituted C ₁ -C ₆ heteroalkyl, optionally substituted C ₃ -C ₁₀ carbocyclyl, optionally substituted C ₂ -C ₉ heterocyclyl, optionally substituted C ₆ -C ₁₀ aryl, optionally substituted C ₂ -C ₉ heteroaryl, optionally substituted C ₂ -C ₆ alkenyl, optionally substituted C ₂ -C ₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino	Methyl is subset of optionally substituted C ₁ -C ₆ alkyl
R ^{6b} is H, halogen, cyano, optionally substituted C ₁ -C ₆ alkyl, optionally substituted C ₁ -C ₆ heteroalkyl, optionally substituted C ₃ -C ₁₀ carbocyclyl, optionally substituted C ₂ -C ₉ heterocyclyl, optionally substituted C ₆ -C ₁₀ aryl,	Methyl is subset of optionally substituted C ₁ -C ₆ alkyl

optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or R^{6a} and R^{6b} together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl or optionally substituted C₂-C₉ heteroaryl;	
each R⁹ is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino	Methoxy is subset of optionally substituted C₁-C₆ heteroalkyl
s is 0, 1, 2, 3 or 4	2

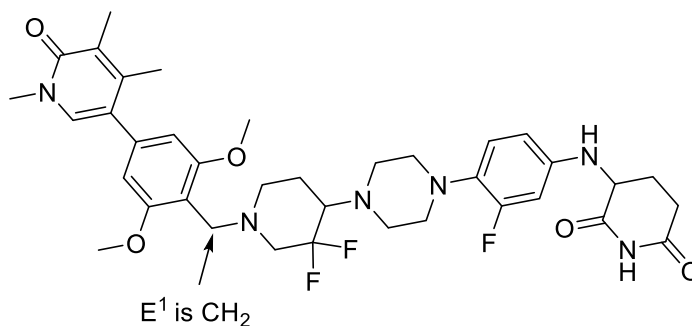
B is 	Reads on the corresponding moiety  of C4T Compound 172 as follows
A^2 is a bond between B and L	The A^2 bond is in the same location
R^{45} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;	H is hydrogen
L is $A^1-(E^1)-(F^1)-(E^3)_n-(F^2)-(F^3)-(E^2)_p-A^2$	Reads on the corresponding moiety  of C4T Compound 172 as follows
p is 0 or 1	p is 1
n is 0 or 1	n is 0
E^2 is, independently, O, S, NR^N, optionally substituted C_{1-10} alkylene, optionally substituted	 is a NR^N

C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C_{2-C10} polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene; NR^N is, independently, H, optionally substituted C₁₋₄ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl;	
F³ is, independently, optionally substituted C₃ - C₁₀ carbocyclylene, optionally substituted C₂ - C₁₀ heterocyclylene, optionally substituted C_{6-C10} arylene, or optionally substituted C_{2-C9} heteroarylene,	is an optionally substituted C_{6-C10} arylene
F² is, independently, optionally substituted C₃ -C₁₀ carbocyclylene, optionally substituted C₂ -C₁₀ heterocyclylene, optionally substituted	is an optionally substituted C₂ -C₁₀ heterocyclylene

C ₆ -C ₁₀ arylene, or optionally substituted C ₂ -C ₉ heteroarylene,	
F ¹ is, independently, optionally substituted C ₃ -C ₁₀ carbocyclylene, optionally substituted C ₂ -C ₁₀ heterocyclylene, optionally substituted C ₆ -C ₁₀ arylene, or optionally substituted C ₂ -C ₉ heteroarylene,	 is an optionally substituted C ₂ -C ₁₀ heterocyclylene
E ¹ is, independently, O, S, NR ^N , optionally substituted C ₁₋₁₀ alkylene, optionally substituted C ₂₋₁₀ alkenylene, optionally substituted C ₂₋₁₀ alkynylene, optionally substituted C ₂ -C ₁₀ polyethylene glycol, or optionally substituted C ₁₋₁₀ heteroalkylene;	 is an optionally substituted C ₁₋₁₀ alkylene

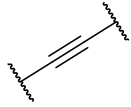
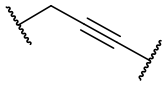
Claim 2

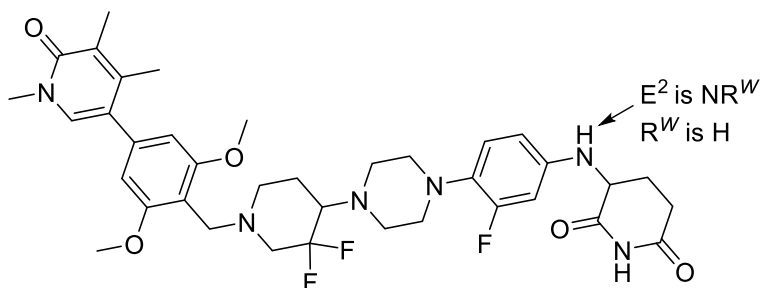
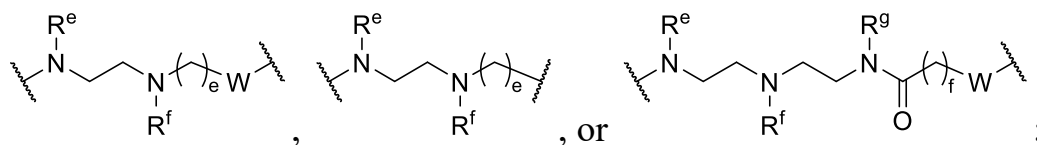
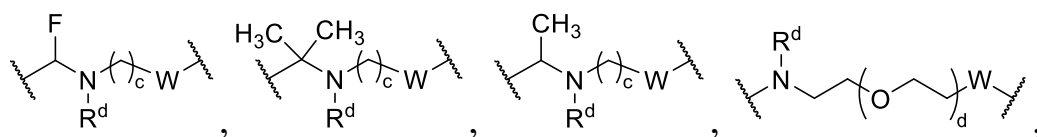
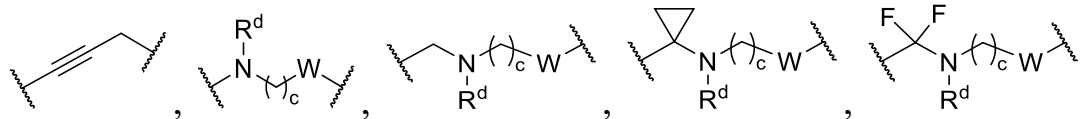
The compound of Claim 1, wherein E¹ is -CH₂-.



C4T Compound 172

Claim 3

The compound of Claim 1, wherein E² is O, **NR^W**, , ,



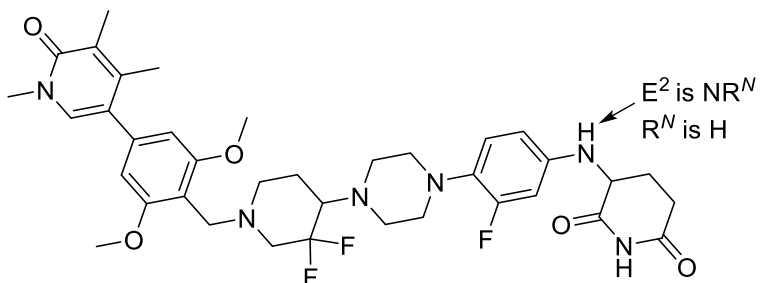
C4T Compound 172

Claim 4

The compound of claim 3, wherein E² is -NR^N-.

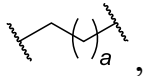
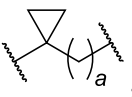
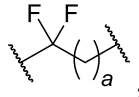
Claim 5

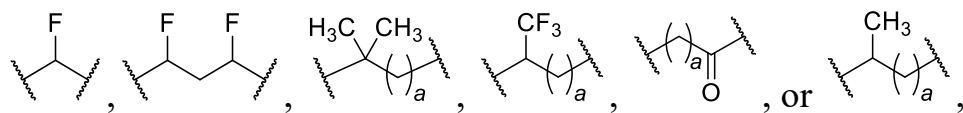
The compound of claim 4, wherein E² is -NH-.



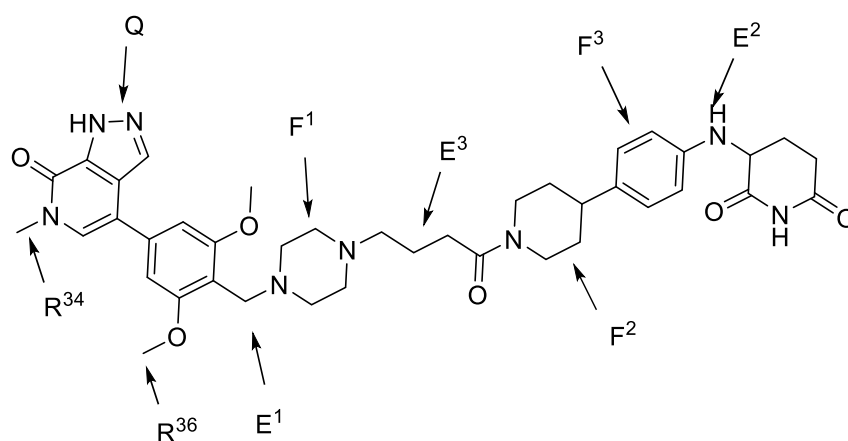
C4T Compound 172

Claim 6

The compound of Claim 1, wherein n is 1 and E³ is , , ,



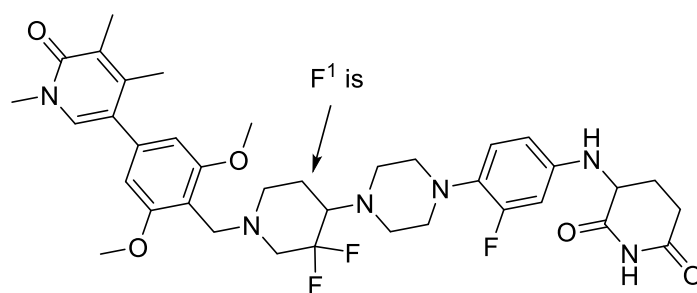
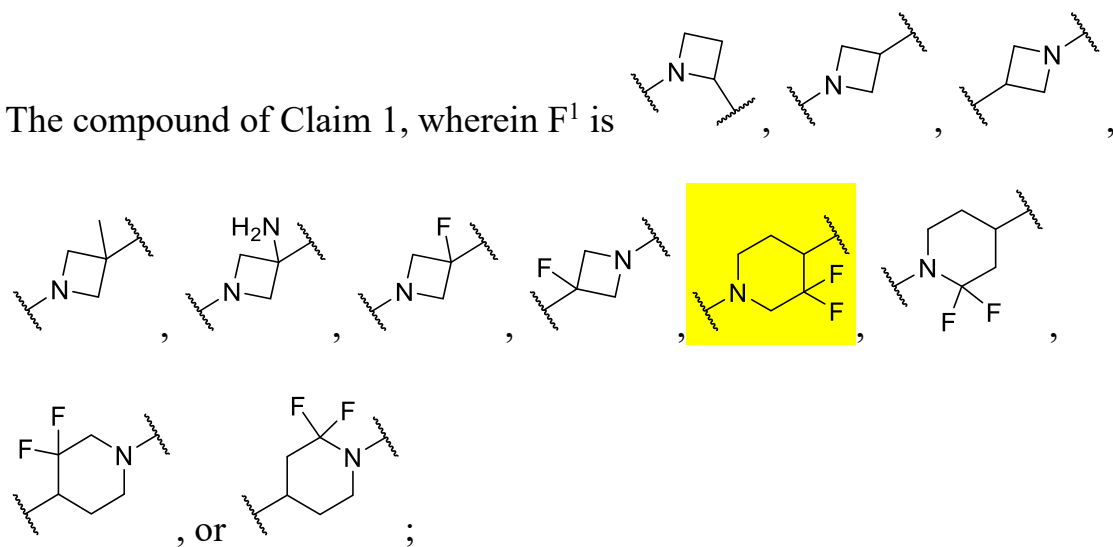
where a is 0, 1, 2, 3, 4, or 5.



C4T Compound 40

Claim 7

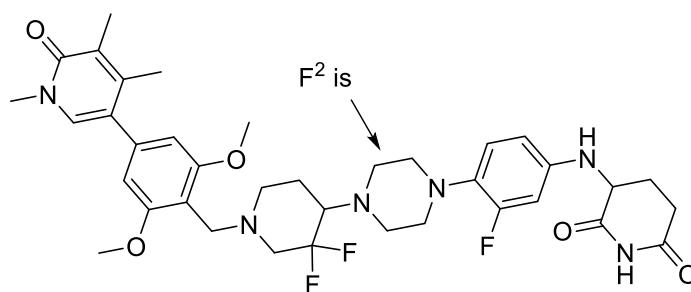
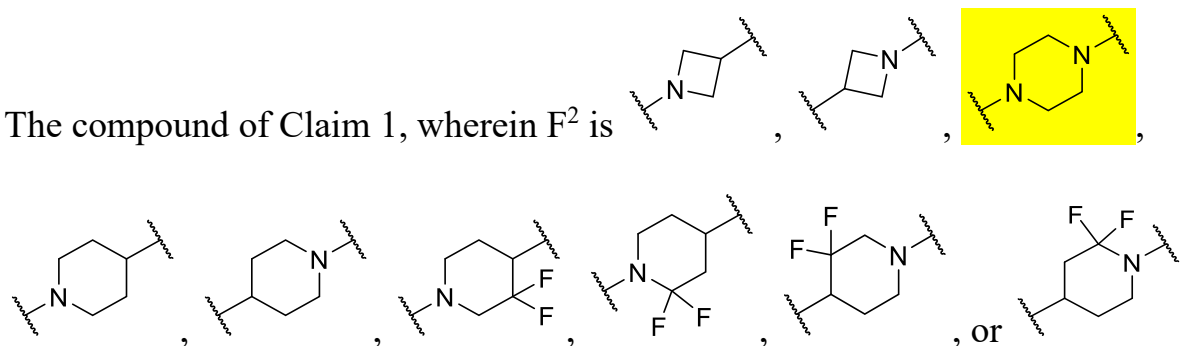
The compound of Claim 1, wherein F¹ is



C4T Compound 172

Claim 8

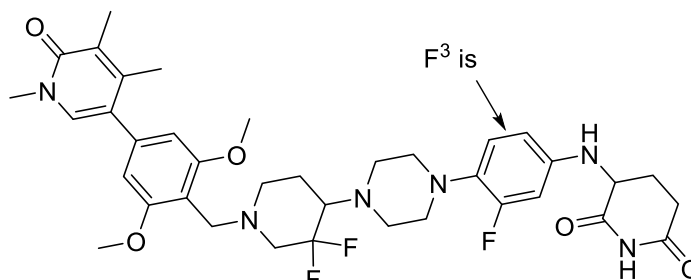
The compound of Claim 1, wherein F² is



C4T Compound 172

Claim 9

The compound of Claim 1, wherein F³ is optionally substituted C₆-C₁₀ arylene.

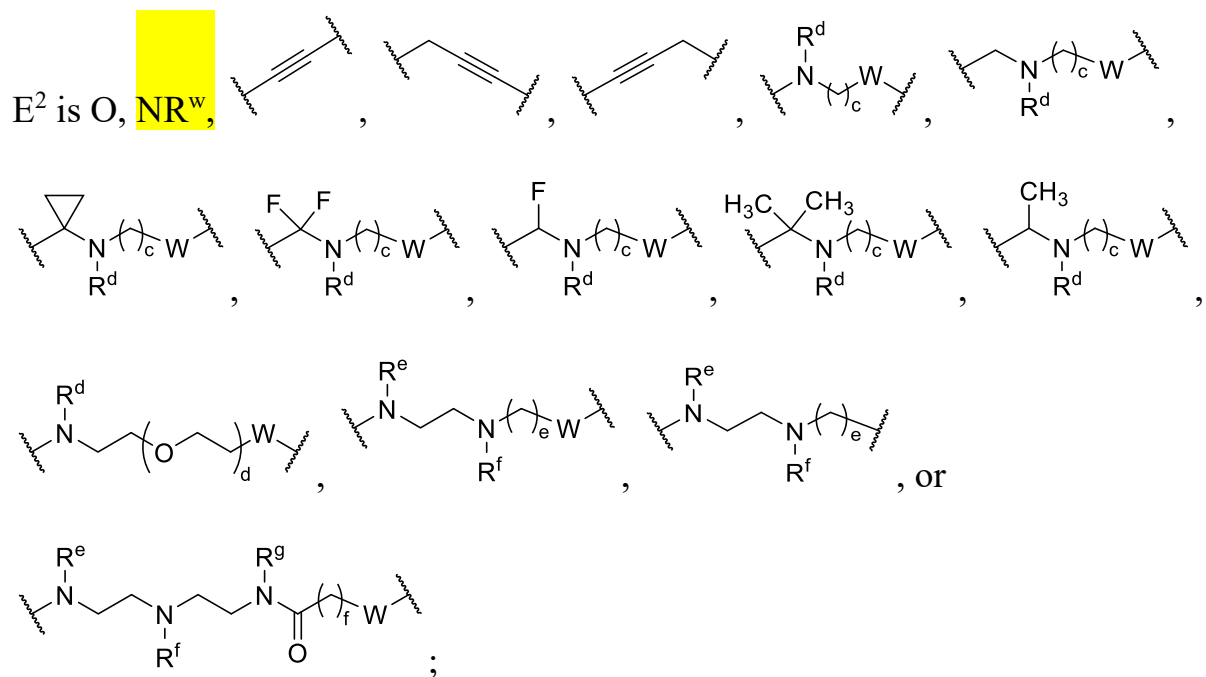


C4T Compound 172

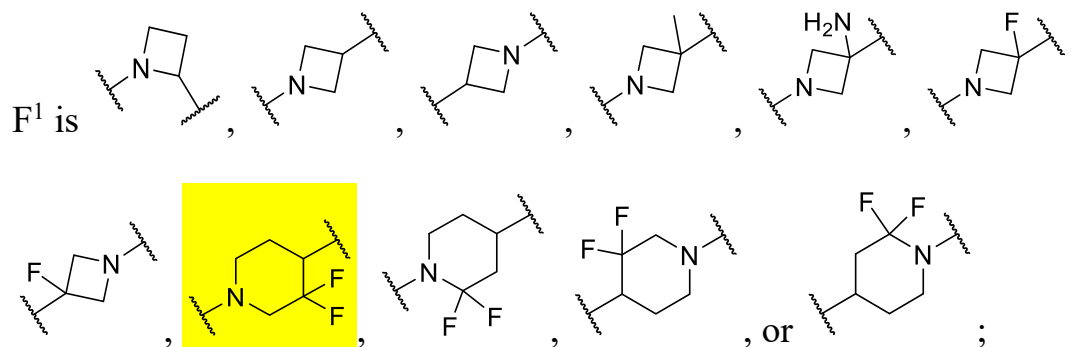
Claim 10

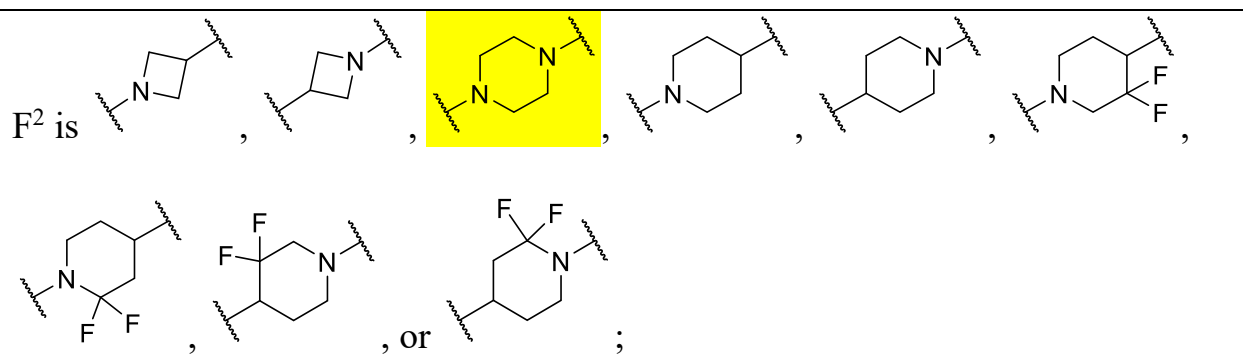
The compound of Claim 1, wherein

E¹ is -CH₂-;

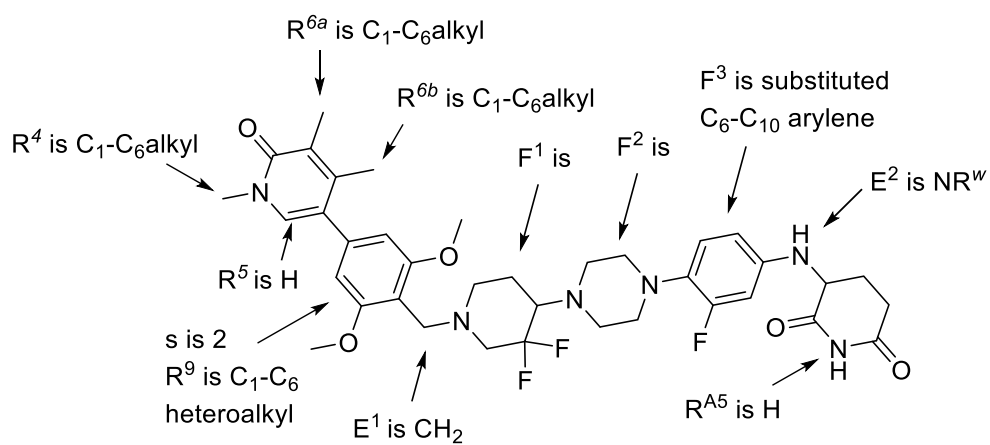


n is 0 or 1;





F^3 is optionally substituted C_6-C_{10} arylene;



C4T Compound 172

The compound of Claim 1, wherein p is 1.

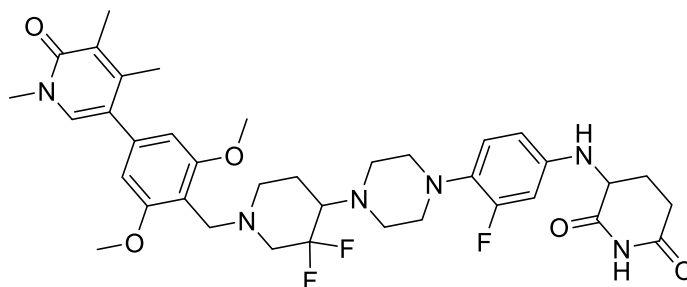


The compound of Claim 10, wherein p is 1.



C4 Therapeutics, Inc.
Exhibit 1014 Page 129 of 200

assays and experiments beyond the DC₅₀ determination (Ex.1010, 13-16; 758-775 (Figures 1-24)).



C4T Compound 172 - Exh. 1010 at 704

177. Figure 1 demonstrates that C4T Compound 172 has a strong effect on tumor volume in an *in vivo* mouse synovial sarcoma xenograft model (*id.*,13 (1.27-29); 758 (FIG. 1)).

178. Figure 2 and Figure 3 demonstrate that C4T Compound 172 selectively degrades BRD9 with respect to BRD7 and BRD4 (*id.*,14 (1.1-6); 758 (FIG. 2); 759 (FIG. 3)).

179. Figure 4 is a confluence graph that demonstrates the dose response effect (inhibition) on the growth of Yamato synovial sarcoma cells by C4T Compound 172 (*id.*,14 (1.7-9); 759 (FIG. 4)). Figure 5 provides pharmacokinetic (PK) data for C4T Compound 172 in an *in vivo* mouse synovial sarcoma xenograft model (*id.*,14 (1.10-13); 760 (FIG. 5)).

180. Figure 6 provides PK data for C4T Compound 172 in another *in vivo* mouse synovial sarcoma xenograft model (*id.*,14 (1.13-16); 760 (FIG. 6)). Figure 7 and Figure 8 demonstrate the dose dependent response of tumor volume

and body weight change after administration of C4T Compound 172 in an *in vivo* mouse xenograft model (*See id.*,14 (1.17-23); 761 (FIG. 7 & FIG. 8)).

181. Figure 9 demonstrates the tolerability of C4T Compound 172 in an *in vivo* mouse synovial sarcoma PDX-model (*id.*,14 (1.26-28; 762 (FIG. 9)). Figures 10A and 10B provide dose prediction models for human *in vivo* dosing of C4T Compound 172 (*id.*,14 (1.27-31); 763-764 (FIG. 10A & FIG. 10B)).

182. Figure 11 demonstrates that C4T Compound 176 selectively degrades BRD9 with respect to BRD7 and BRD4 (*id.*,15 (1.2-5); 765 (FIG. 11)). Figures 12 and 13 demonstrate the dose dependent effect of C4T Compound 172 *in vivo* in two different mouse xenograft models (*id.*,15 (1.6-13); 765-766 (FIG. 12 & FIG. 13)).

183. Figure 14 provides the protein level of BRD9 in synovial sarcoma tumors at different time points after administration of a single dose of C4T Compound 172 (*id.*,15 (1.14-16); 766 (FIG. 14)). Figure 15 provides protein degradation data for C4T Compound 176 in four different cancer cell lines including a human rhabdoid tumor cell line, a soft tissue sarcoma cell line, and two synovial sarcoma cell lines (*id.*,15 (1.17-21); 767 (FIG. 15)).

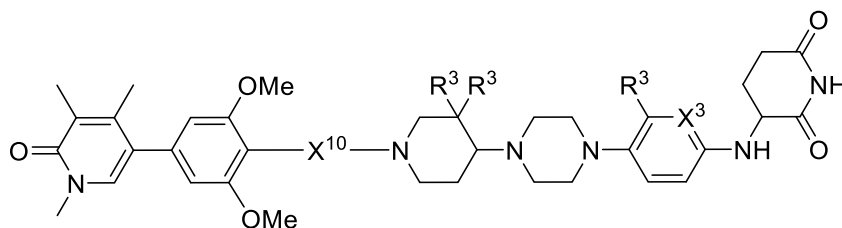
184. Figure 16 is a confluence graph that demonstrates the dose response effect (inhibition) on the growth of Yamato synovial sarcoma cells by C4T Compound 176 (*id.*,15 (1.22-25); 768 (FIG. 16)). Figure 17 demonstrates the lack of

BAF wildtype growth inhibition in the presence of C4T Compound 176 in a SW982 cell line (*See id.*,15 (1.26-28); 769 (FIG. 17)).

185. Figure 18 provides pharmacokinetic (PK) data for C4T Compound 176 in an *in vivo* mouse synovial sarcoma xenograft model (*id.*,15 (1.29-31); 770 (FIG. 18)). Figures 19 and 20 provide tumor PD data for C4T Compound 176 at various concentrations after oral once daily administration to mice (*id.*,16 (1.1-7); 770-771 (FIG. 19 & FIG. 20)).

186. Figures 21 and 22 demonstrate the efficacy and tolerability of C4T Compound 176 at various concentrations in an *in vivo* mouse synovial sarcoma CDX model (*See id.*,16 (1.8-13); 772-773 (FIG. 21 & FIG. 22)). Figures 23 and 24 demonstrates the efficacy and tolerability of C4T Compound 176 at various concentrations in a PDX model (*id.*,16 (1.14-19); 774-775 (FIG. 23 & FIG. 24)).

187. The C4T '920 PCT Publication also includes several genus formulas that anticipate the claims of the '381 Patent. For example, on pages 62 and 63 of the C4T '920 PCT Publication there are at least five formulas that read on the claims of the '381 Patent (*id.*,64-65). For example, the following formula from the '920 PCT Publication reads on each and every limitation of claims 1, 3-5, and 8-12 of the '381 Patent.



Ex. 1010 at 64

188. In total there are over a dozen compounds and at least five formulas described in the C4T '920 PCT Publication that anticipate at least one claim of the '381 Patent.

IX. LEGAL STANDARDS

A. Burden of Proof

189. I understand from counsel that a post-grant review may be instituted if Petitioner shows that it is more likely than not that at least one claim of the challenged patent is unpatentable. I understand Petitioner bears the ultimate burden of proving that the challenged claims are unpatentable by a preponderance of the evidence.

B. Preponderance of the Evidence

190. I understand that preponderance of the evidence means that the evidence must establish that it is more likely than not that a challenged claim is unpatentable for lack of written description or enablement, or if the claims are indefinite, anticipated, or rendered obvious. I am also told that preponderance of the

evidence means that there is a greater than 50% chance that the challenged claim is invalid.

C. The Written Description Requirement

191. I am told that 35 U.S.C. §112(a) says:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

192. I understand that the patent applicant has one year from its first provisional priority application filing to file a “non-provisional” U.S. application or a PCT international application that designates the U.S. I understand that the term patent “specification” refers to the full application and the claims as originally filed in a provisional application or a U.S. non-provisional or PCT international application. The specification does not necessarily include patent claims that were filed in a later continuing application after the priority dates unless it is shown that the specification complies with the written description and enablement requirements

for those continuation claims.¹⁴ I understand from counsel that a later filed patent claim is only supported by the written description of a patent specification if the specification reasonably conveys to the POSA that the inventor had possession of the full scope of the claimed subject matter as of the filing date.

193. Thus, the term “later filed claim” as it is used in this Declaration refers to a patent claim that is filed in a continuing application after the priority dates of the patent application, which may consist of one or more provisional applications and the U.S. non-provisional or PCT application filed within one year.

194. I am also told that to establish that the inventors had possession of the claimed invention, the specification must describe the invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. I understand that compliance with the written description requirement is essentially a fact-based inquiry that will depend on the nature of the invention. In this case, it is my opinion that the chemical

¹⁴ I am also told that under the U.S. written description requirement, even an original claim in a provisional or U.S. non-provisional application may not have written description support if the full patent description does not provide adequate support for the claim, with a sufficient and representative number of drawings, compounds, figures, and data.

structures and the underlying biology are complex and unpredictable, and therefore a high-level of detail is needed in the specification to show possession.

195. I am told that a claim that is merely obvious in view of the specification does not have written description support.

196. I am told that a claim to a combination of elements must be supported by a description of that combination in the specification, not merely a description of individual elements.

197. I am advised by counsel that where a claim recites a specific combination of variables, the specification must direct the POSA to that specific combination. I understand that a broad genus that merely includes the elements of the combination is not sufficient to satisfy the written description requirement. I further understand that, in the context of patent claims on chemical compounds, a claim to a particular subgenus is not adequately supported where the specification discloses only a broader genus and fails to sufficiently describe the subgenus. I understand that, analogizing the disclosure to a forest (a large genus of trees), and the claim to a few trees (a sub-genus of the forest), the written description must provide “blaze marks” directing and pointing out to the POSA the claimed invention (i.e., the few trees) out of the broader disclosure (i.e., the forest).

198. I am further informed by counsel that, when the claimed invention is a genus or subgenus, to show possession of the invention the

specification must set forth either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can visualize or recognize the genus and members of the genus. The representative species in the specification must reflect the full scope of the genus, and not just a cluster in one part of the genus.

199. I have also been told that under U.S. patent law, new matter cannot be introduced into a patent application after its asserted priority filing dates. This serves to prevent a patent applicant from adding information that goes beyond the subject matter originally filed. Therefore, if new claims are added that do not find clear support in the priority specification, then new matter has been added to the application.

200. I understand from counsel that the number and breadth of species described in the specification must establish that the applicant possessed the metes and bounds, i.e., the full scope, of the genus so that one of ordinary skill in the art can recognize the members of the genus. I also understand that when there is substantial variation within a genus, the applicant must describe a sufficient variety of species to reflect this variation. I understand that for inventions in an unpredictable art, such as the field of therapeutic protein degradation, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one or a small number of species within the genus, or

even species that do not fairly represent all corners of the genus and within. It follows that it the disclosure of no compounds that fall under the granted claims cannot satisfy the written description requirement.

201. I am told that even where an applicant's specification lists each element in a claimed combination, the patent specification must also support the particular claimed combination of elements. Therefore, in reviewing the '381 Patent, I looked for both the individual elements as well as whether they were combined in the specification (not including the claim) in the manner depicted in the claims later added.

D. The Enablement Requirement

202. I have also been informed by counsel that the enablement requirement of 35 U.S.C. §112(a) mandates that the specification of a patent must teach the POSA how to make and use the full scope of the claimed subject matter without undue experimentation. I understand that whether experimentation is undue is a conclusion reached by weighing many factual considerations, including (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. I

understand that these factors are illustrative and not mandatory, and that some factors may be more important than others depending on the circumstances.

203. I have further been informed by counsel that the “how-to-use” prong of the enablement requirement under 35 U.S.C. §112(a) incorporates as a matter of law the requirement under 35 U.S.C. §101 that the specification adequately disclose a practical utility, or use, for the claimed invention. I also understand from counsel that showing that only part of a genus would work for the intended purpose is not sufficient to meet the utility requirement when the POSA would not reasonably believe the entire genus would have the stated use based on the limited disclosure.

204. I understand from counsel that to meet the how-to-use requirement, the specification must establish that the claimed invention achieves its intended purpose. In this case that would mean that the compounds covering the full scope of the '381 Patent claims can degrade BRD9 in a therapeutically useful manner on administration to a human.

205. I am also told that in the unpredictable arts, especially those that involve new and incompletely understood technology, the specification is required to give more guidance to one of ordinary skill in the art to enable the full scope of the claims. It is my opinion that targeted protein degradation is a relatively new and incompletely understood technology, certainly as of the filing date of the '381 application.

206. I understand from counsel that it is the specification, not the knowledge of one of ordinary skill in the art, that must supply the novel aspects of an invention to meet the enablement requirement.

E. Indefiniteness of Patent Claims

207. I am told that 35 U.S.C. §112(b) states:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

208. I have also been informed that the claims of a patent must particularly point out the claimed subject matter so that the metes and bounds, or the scope, is clearly defined to the POSA. This “definiteness” requirement serves the policy goal of affording the public clear notice of what is claimed, to place them on notice of what is forbidden without a license from the patentee and what is still open to them. I understand that claims are in compliance with §112(b), if viewed in light of the specification and prosecution history, they adequately inform a POSA of the scope of the invention with reasonable certainty.

209. I have been told that in certain circumstances, a claim is indefinite if it is so expansive that the POSA cannot determine the metes and bounds of the claimed invention. I understand that sometimes a claim defines a chemical compound using one or more “Markush” groups, which are claims that recite a list

of alternative useable members, and as is the case here, a chemical structure with substituents defined by variables. Where a Markush claim encompasses a massive number of distinct alternative members, I understand that the claim is indefinite under § 112(b) if a POSA cannot determine its metes and bounds due to an inability to identify all of the compounds defined by the Markush group(s).

210. Specifically, I understand that a claim is indefinite when the boundaries of the protected subject matter are not clearly delineated and the scope is unclear. For example, I understand that a genus claim to a chemical compound that could be interpreted in such a way that it is not clear whether a chemical species is covered would be indefinite (e.g., because there is more than one reasonable interpretation of what species are included in the claim).

F. Anticipation (Novelty)

211. I understand that patent protection may be granted for any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof. I understand that a patent or other publication must first qualify as prior art before it can be used to invalidate a patent claim. I understand that the law provides categories of information that constitute prior art that may be used to anticipate (i.e., novelty destroy) or render obvious patent claims. To be prior art to a particular patent, a reference must have been made, known, used, published,

patented, or described in a patent application by another, before the priority date of the patent at issue. I also understand that a POSA is presumed to have knowledge of the relevant prior art as of the priority date. I have reviewed the teachings of the prior art with the understanding of a POSA. I have also reviewed the '381 Patent and relevant portions of the patent's file history with this understanding.

212. I understand from counsel that for a prior art reference to anticipate a patent claim, all of the limitations of the claim must be disclosed in a single prior art reference. I also understand that if any claim limitation is missing from the prior art reference, then the prior art reference does not anticipate that claim but might render it obvious. I further understand that it is improper to rely upon additional prior art to supply any claim limitations that are missing from the allegedly anticipating prior art reference. I understand that documents and materials that qualify as prior art can be used to render a claim unpatentable as novelty destroyed (i.e. anticipated) under 35 U.S.C. §102.

213. I also understand that to qualify as prior art, a reference must predate the priority date of the challenged claim. In forming my opinions and conclusions, I have been informed by counsel that to claim the benefit of an earlier-filed priority application, the earlier-filed application must meet the written description and enablement requirements of 35 U.S.C. §112 for the claimed subject matter.

214. I understand from counsel that the “effective filing date” of a patent claim is the actual filing date of the patent, unless the patent properly claims the benefit of an earlier filing date from a parent application that discloses the claimed invention in compliance with the written description and enablement requirements.

215. It is my understanding that patents, published patent applications, and other printed publications that were published before the effective filing date of a patent can be prior art to a patent in a post-grant review proceeding.

216. I understand that the first step in comparing prior art to patent claims is to properly construe the claims to determine claim scope and meaning. I discuss claim construction in Section VI.

217. I understand that, once the claims of a patent have been properly construed, the second step in determining anticipation under 35 U.S.C. §102 requires a comparison of the properly construed claim language to the prior art on a limitation-by-limitation basis.

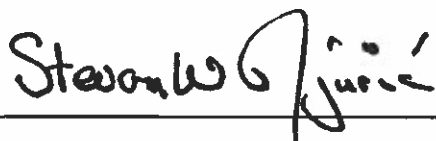
218. I understand that a prior art reference “anticipates” a claim (i.e., is novelty destroying), and thus renders the claim unpatentable, if each and every element of a challenged claim are disclosed in that prior art reference, either explicitly or inherently (i.e., necessarily present or implied).

219. I further understand that the disclosure of a species in the prior art may anticipate a later-claimed genus if the species meets all of the limitations of (i.e. falls within) the genus. I am informed that, in order to anticipate, the prior art disclosure must be enabling for what it teaches.

X. CONCLUSION

220. Based on my review of the matters described herein and based on my experience, knowledge, and training in the field of pharmaceutical drug discovery, including heterobifunctional protein degradation, it is my opinion and conclusion that at least one claim of the '381 Patent is invalid under 35 U.S.C. §112 and §102. In fact, it is my opinion and conclusion that all of claims 1-12 of the '381 Patent are invalid under these statutes.

221. In accordance with 37 C.F.R. §1.68, I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001). All statements made of my own knowledge are true and all statements made on information and belief are believed to be true.

A handwritten signature in black ink, reading "Stevan W. Djuric", written over a horizontal line.

Stevan W. Djuric, Ph.D.

A handwritten date "10-19-23" in black ink, written over a horizontal line.

Date

ATTACHMENT 1

STEVAN W. DJURIC, Ph.D.
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New Bern, NC 28562
847-226-6768
DCaTconsultingLLC@gmail.com

PROFESSIONAL EXPERIENCE

DISCOVERY CHEMISTRY AND TECHNOLOGY CONSULTING LLC

President

- 12 Retained Consultancies

ABBVIE INC (2013- 2019)

Vice President, Discovery Chemistry and Technology (2017-19)

- Responsible for a group of ~150 internal scientists and >100 external FTEs.
- Multimillion-dollar budget.
- Areas covered- medicinal chemistry, HTC, HTE, TPD, SBDD, cheminformatics, analytical chemistry, chemical biology/chemical proteomics. Chemistry automation and robotics.

Distinguished Research Fellow (2015-19)

- Awarded title in recognition of career scientific achievements – highest level of AbbVie scientific ladder.

Senior Director, Discovery Chemistry and Technology (2013-17)

- Responsible for centralized lead optimization, hit to lead, high throughput chemistry, library design and construction groups at AbbVie.

- Also responsible for High Throughput Purification, Structural chemistry including Chemical proteomics and Structural Biology (incl FBDD) groups and the Drug Sample Room ~ 125 scientists in total
- Responsible for Discovery Chemistry outsourcing activities (~\$7MM budget) ~80+ indirect FTEs
- Oversight of chemistry efforts that delivered small molecule clinical candidates ABBV-2222, ABBV-2851, ABBV-3067, ABBV-2737. ABBV-3221, ABBV-3748, ABBV-168, ABBV-951 and Immunology ADCs ABBV-3373 and ABBV-154.
- Discovery of ABBV-951. Currently being evaluated for Phase 3 POC in Parkinson's Disease patients.
- Discovery of ABBV-2222. Achieved Phase 2 POC for target engagement in Cystic Fibrosis patients.

Head of AbbVie Global Medicinal Chemistry Leadership Team (2013-2019)

- October 2013 - awarded AbbVie President's Award for leading the team that designed and implemented the AbbVie best in class library production system SWIFT (synthesis with integrated flow technology).

ABBOTT LABORATORIES (1996-2013)

Senior Director, Medicinal Chemistry Technologies and Structural Chemistry (2008-2013)

- Responsible for High throughput chemistry/parallel synthesis, hit to lead, library design and construction groups at Abbott. Also responsible for High

Throughput Purification, Structural chemistry, and Structural Biology (incl FBDD) groups. ~75 scientists and the Drug Sample Room. Responsible for Discovery Chemistry outsourcing activities (~\$7MM budget) ~80+ indirect FTEs.

Head, Global Medicinal Chemistry Leadership Team (2010-2013)

- Responsible for leading a senior medicinal chemistry group charged with establishing best chemistry practices and technology and communication initiatives throughout Abbott worldwide.
- June 2010 awarded Abbott President's Award for accomplishments involving the corporate File Enhancement Initiative.
- September 2008 awarded Abbott President's Award for the discovery of ZotarolimusTM.

Director, Medicinal Chemistry Technologies and Structural Chemistry (2002-2008)

- Responsible for parallel synthesis, hit to lead, library construction groups at Abbott. Also responsible for High Throughput Purification and Structural chemistry groups. Group size ~ 68 scientists
- Responsible for the Abbott corporate file enhancement initiative 2004-2008. Budget of \$25MM

Senior Project Leader, Diabetes and Obesity Research (2001-2002)

- Responsible for Glucagon Antagonist and Dipeptidyl Peptidase-IV inhibition programs and Hit to Lead activities in the Abbott/Millennium collaboration. Led a group of 20-40 chemists and biologists.
- Project Leader for the team that identified the DPP-IV inhibitor ABT-279

which was approved for clinical development (October 2004). FIM in January 2006.

Volwiler Associate Research Fellow (2001)

Senior Project Leader, Antibacterial Macrolide and Quinolone Projects (1999-2001)

- Responsible for Abbott efforts in the Macrolide and Quinolone areas. Led a group of 30 chemists.
- Identified the novel ketolide antibiotic ABT-281 which was approved for development (2002) and subsequently selected for outlicencing.

Senior Project Leader, Novel Antibacterial Drug Discovery (1998-1999)

- Responsible for the new antibacterial discovery program at Abbott. Led a group of 42 chemists and biologists.

Project Leader, Immunological Diseases Research (1996-1998)

- Responsible for the Immunosuppressants project at Abbott. Led a group of 25 chemists and biologists.
- Identified two novel rapamycin based immunosuppressants ABT-507 and ABT-578 approved for development for the treatment of rheumatoid arthritis. ABT-578, now ZotarolimusTM, This compound is used as the anti-restenotic agent on Medtronic Endeavour stent which is marketed in Europe and the USA
- Identified a novel class of NFAT Transcription Factor regulators which operate via a non-calcineurin inhibitory mechanism. Lead compound A-285222.0 evaluated in primate heart transplant paradigm at Stanford

University. Publication on this work led to ~100 citations in the scientific literature.

RHONE-POULENC RORER RESEARCH AND DEVELOPMENT (1993 - 1996)

Director, Inflammation and Bone Metabolism Chemistry

- Responsible for Inflammation Chemistry and Bone Metabolism Chemistry programs at RPR, USA, including budget, salary administration and recruiting. Led group of 25 chemists. During two-year tenure:
- Identified novel, selective type IV Phosphodiesterase inhibitor, RPR 122147 which was selected for development for the treatment of rheumatoid arthritis and asthma.

SEARLE RESEARCH AND DEVELOPMENT (1981-1993)

Fellow (1991 - 1993)

Group Leader II (1988 - 1991)

- Youngest appointed Research Fellow at Searle. Directed two Inflammation Programs, LTB₄ Receptor Antagonists and Leukotriene A₄ Hydrolase Inhibitors. Led a group of 13 chemists and acted as interim Biology Program leader.
- Identified and developed first Leukotriene B₄ receptor antagonist SC-41930 to reach Phase II clinical trials.

- Identified and developed second generation LTB4 antagonist SC-53228 with superior pharmacodynamic (PD) and pharmacokinetic (PK) profiles relative to SC-41930. Compound selected for development (1993).
- Group identified and developed prototype Leukotriene A4 hydrolase inhibitor SC-57461A. Compound showed excellent PD and PK profiles in Cottontop Tamarin paradigm of ulcerative colitis. First LTA4-H inhibitor to be advanced into development (1994).

Research Scientist II (1986 - 1988)

Research Scientist I (1984 - 1986)

- Member of Searle cardiovascular diseases antithrombotic program.
- Designed and synthesised prostacyclin analog SC-34450 which was recommended for development status as antithrombotic agent for application in renal dialysis (1987).

Research Investigator (1981 - 1984)

- Member of the Searle cardiovascular diseases antihypertensives/antiarrhythmics team. Identified two new patentable series of antiarrhythmic agents.

SCIENTIFIC EXTRACURRICULAR OFFICES AND/OR APPOINTMENTS HELD

- Editorial Board, ACS Medicinal Chemistry Letters, 2017-2019
- Associate Editor, ACS Medicinal Chemistry Letters, 2020-2023
- Member of NIH Molecular Probes Initiatives Reviewer Panel 2010-2013

- Editorial Advisory Board, The Journal of Molecular Diversity, 2008-2012
- Member of US-Japan Saito Award Committee, (committee consists of top academic and industrial medicinal chemists) 2008-2012
- Editorial Advisory Board, The Journal of Medicinal Chemistry 2006-2010, 2016-present
- Advisory Board Member, Drug Discovery Technology Europe 2005-2007, IBC Conferences, London UK, March 2005 and 2006.
- Executive Advisory Board, University of Kansas 2005-2015
- Adjunct Professor of Chemistry, Department of Medicinal Chemistry, The University of Kansas, Kansas, 2005-present
- Member of the Editorial Advisory Board – Current Medicinal Chemistry 2004-present
- Member of the Editorial Board - Current Pharmaceutical Design 2000-2010
- Member of Editorial Board for Current Opinion in Anti-inflammatory and Immunomodulatory Drugs 1998-2002
- Editor - Antiinflammatory and Antiallergy issues of Current Pharmaceutical Design 1997-2000
- Reviewer – Organic Letters, 1999-present
- Reviewer - Tetrahedron, 1993-2000
- Reviewer - BioOrganic and Medicinal Chemistry Letters, 1992-present.
- Reviewer – BioOrganic and Medicinal Chemistry 2005- present

- Reviewer – Tetrahedron Letters, 2000-present
- Reviewer – Organic Process Research and Development, 2017-present
- Reviewer Journal of Combinatorial Chemistry/ACS Combinatorial Sciences 2008-2019
- Section Editor and Reviewer - Expert Opinion in Therapeutic Patents, (Anti-inflammatories section), 1992-1998
- Reviewer - Journal of the American Chemical Society, Journal of Organic Chemistry, and Journal of Medicinal Chemistry, 1993-present.
- Member - American Chemical Society, Organic and Medicinal Chemistry Division, 1980-present.
- Co-organiser and chair of the Annual Midwest Inflammation Research Association Meeting, Chicago, Illinois 1997-1998
- Program Committee, Chicago Section of the American Chemical Society, 1989-1990.

MANAGEMENT COURSES

- 1996 Completed “Managing diversity” course for senior management at Abbott Laboratories
- Completed “Executive presentation skills” program for senior management at Abbott Laboratories
- 2000 Completed Performance Management Modules I and II for Abbott Senior management
- 2000-2013 Completed numerous high level Discovery senior management

training courses

EDUCATION

Post-Doctoral Research, OHIO STATE UNIVERSITY, Columbus, OH
(1980-1981) In collaboration with Professor P.D. Magnus

Ph.D., Organic Chemistry, UNIVERSITY OF LEEDS, Leeds, England
(1976-1979) Supervisor: Professor F.G. Holliman

BSc. (Hons) Chemistry, UNIVERSITY OF LEEDS, Leeds, England
(1972-1976) 1st Class (Highest class of degree in G.B.) 2nd in year.

PERSONAL

Married with two children. British (U.S.A. Permanent Visa Holder).
Hobbies include soccer, running, music, chess and gardening.

PUBLICATIONS

1. Talaty, N , Sawicki, J, Johnson, RW, Nacham, O and Djuric, SW Recent Developments in the Application of Analytical Spectrometric Techniques to Support Next-Generation Synthesis and Screening, ACS MedChem Letters in press (2023)
2. Sawicki, James W., et al. "Rapid analytical characterization of high-throughput chemistry screens utilizing desorption electrospray ionization mass spectrometry." Reaction Chemistry & Engineering 4.9 (2019): 1589-1594
3. Tu, N. P., Dombrowski, A. W., Goshu, G. M., Vasudevan, A., Djuric, S. W., & Wang, Y. (2019). High-Throughput Reaction Screening with Nanomoles of

Solid Reagents Coated on Glass Beads. *Angewandte Chemie*, 131(24), 8071-8075.

4. Ruggeri, Michele, Amanda W. Dombrowski, Stevan W. Djuric, and Ian Richard Baxendale. "Photochemical Flow Synthesis of 3 - Hydroxyazetidines." *ChemPhotoChem* 3, no. 12 (2019): 1212-1218.
5. Ruggeri, M., Dombrowski, A. W., Djuric, S. W., & Baxendale, I. R. (2020). Rearrangement of 3-hydroxyazetidines into 2-oxazolines. *The Journal of Organic Chemistry*, 85(11), 7276-7286.
6. Garner, A. L., & Djuric, S. W. (2021). RNA: Opening New Doors in Medicinal Chemistry, a Special Issue. *ACS Medicinal Chemistry Letters*, 12(6), 851-853.
7. Accelerated multi-reagent copper catalysed coupling reactions in micro droplets and thin films, Iyer, Kiran; Yi, Jing; Bogdan, Andrew R.; Talaty, Nari; Djuric, Stevan W.; Cooks, R. Graham, *Reaction Chemistry & Engineering* (2018), Ahead of Print
8. Pd-PEPPSI-IPent-SiO₂: A Supported Catalyst for Challenging Negishi Coupling Reactions in Flow Price, Gregory A.; Hassan, Abbas; Chandrasoma, Nalin; Bogdan, Andrew R.; Djuric, Stevan W.; Organ, Michael G. *Angewandte Chemie, Int.Edition* (2017), 56(43), 13347-13350
9. Are We There Yet? Applying Thermodynamic and Kinetic Profiling on Embryonic Ectoderm Development (EED) Hit-to-Lead Program Wang, Ying; Edalji, Rohinton P.; Panchal, Sanjay C.; Sun, Chaohong; Djuric, Stevan W.;

Vasudevan, Anil. *Journal of Medicinal Chemistry* (2017), 60(20), 8321-8335.

10. Expedient Diels-Alder cycloadditions with ortho-quinodimethanes in a high temperature/pressure flow reactor Tsoung, Jennifer; Wang, Ying; Djuric, Stevan W. *Reaction Chemistry & Engineering* (2017), 2(4), 458-461.
11. Integrated Platform for Expedited Synthesis-Purification-Testing of Small Molecule Libraries Baranczak, Aleksandra; Tu, Noah P.; Marjanovic, Jasmina; Searle, Philip A.; Vasudevan, Anil; Djuric, Stevan W. *ACS Medicinal Chemistry Letters* (2017), 8(4), 461-465.
12. *Journal of Medicinal Chemistry, Technological Advances: Highlights 2015-2016*. Djuric, Stevan W.; Meanwell, Nicholas A. *Journal of Medicinal Chemistry* (2017), 60(1), 1-3.
13. Synthesis of Fused Pyrimidinone and Quinolone Derivatives in an Automated High Temperature and High Pressure Flow Reactor. Tsoung, Jennifer; Bogdan, Andrew R.; Kantor, Stanislaw; Wang, Ying; Charaschanya, Manwika; Djuric, Stevan W. *Journal of Organic Chemistry* (2016)
14. Automated library synthesis of cyclopropyl boronic esters employing diazomethane in a tube-in-tube flow reactor Koolman, Hannes F.; Kantor, Stanislaw; Bogdan, Andrew R.; Wang, Ying; Pan, Jeffrey Y. Djuric, Stevan W. *Organic & Biomolecular Chemistry* (2016), 14(27), 6591-6595.

15. High-Temperature Boc Deprotection in Flow and Its Application in Multistep Reaction Sequences Bogdan, Andrew R.; Charaschanya, Manwika; Dombrowski, Amanda W.; Wang, Ying; Djuric, Stevan W. *Organic Letters* (2016), 18(8), 1732-1735
16. Continuous flow Negishi cross-couplings employing silica-supported Pd-PEPPSI- IPr precatalyst. Price, Gregory A.; Bogdan, Andrew R.; Aguirre, Ana L.; Iwai, Toshiyuki; Djuric, Stevan W.; Organ, Michael G. *Catalysis Science & Technology* (2016), 6(13), 4733-4742
17. Nucleophilic aromatic substitution of heterocycles using a high-temperature and high-pressure flow reactor. Charaschanya, Manwika; Bogdan, Andrew R.; Wang, Ying; Djuric, Stevan W. *Tetrahedron Letters* (2016), 57(9), 1035-1039.
18. Tandem Click-Suzuki reactions in a novel flow reactor incorporating immobilized and exchangeable reagents, Tu, Noah P.; Sarris, Kathy; Djuric, Stevan W. *RSC Advances* (2015), 5(7), 4754-4757.
19. Roth, G. P.; Stalder, R.; Long, T. R.; Sauer, D. R.; Djuric, S. W. *J. Flow Chem.* (2013) 3, 34-40.
20. Hit to Lead optimization of a novel class of squarate-containing polo-like kinase inhibitors, Zhang, Qingwei; Xia, Zhiren; Mitten, Michael J.; Lasko, Loren M.; Klinghofer, Vered; Bouska, Jennifer; Johnson, Eric F.; Penning, Thomas D.; Luo, Yan; Giranda, Vincent L.; Djuric, S.W et al *Bioorganic & Medicinal Chemistry Letters* (2012), 22(24), 7615-7622.

21. Contribution of indazolinone tautomers to kinase activity_Vasudevan, Anil; Verzal, Mary K.; Villamil, Clara I.; Stewart, Kent D.; Abad-Zapatero, Cele; Oie, Tetsuro; and Djuric, Stevan W. *Bioorganic & Medicinal Chemistry Letters* (2012), 22(14), 4502-4505.
22. An integrated synthesis-purification system to accelerate the generation of compounds in pharmaceutical discovery, Hochlowski, Jill E.; Searle, Philip A.; Tu, Noah P.; Pan, Jeffrey Y.; Spanton, Stephen G.; Djuric, Stevan W. *Journal of Flow Chemistry* (2011), 1, 56-61
23. Small molecule library synthesis using segmented flow, Thompson, Christina M.; Poole, Jennifer L.; Cross, Jeffrey L.; Akritopoulou-Zanze, Irini; Djuric, Stevan W. *Molecules* (2011), 16, 9161- 9177.
24. Scaffold oriented synthesis. Part 4: Design, synthesis and biological evaluation of novel 5-substituted indazoles as potent and selective kinase inhibitors employing heterocycle forming and multicomponent reactions , Akritopoulou- Zanze, Irini; Wakefield, Brian D.; Gasiecki, Alan; Calvin, Douglas; Johnson, Eric F.; Kovar, Peter; Djuric, Stevan W. *Bioorganic & Medicinal Chemistry Letters* (2011), 21(5), 1480-1483
25. Scaffold oriented synthesis. Part 3: Design, synthesis and biological evaluation of novel 5-substituted indazoles as potent and selective kinase inhibitors employing [2+3] cycloadditions . Akritopoulou-Zanze, Irini; Wakefield, Brian D.; Gasiecki, Alan; Calvin, Douglas; Johnson, Eric F.; Kovar, Peter; Djuric, Stevan W. *Bioorganic & Medicinal Chemistry Letters* (2011), 21(5), 1476-1479

26. LOPHTOR: a convenient flow-based photochemical reactor Anil Vasudevan, Clara Villamil, Jonathan Trumbull, Jeff Olson, David Sutherland, Jeff Pan, Stevan Djuric Tetrahedron Letters, (2010), 51(31), 4007-4009
27. A facile and practical one-pot 'catch and release' synthesis of substituted guanidines. Wang, Ying; Sauer, Daryl R.; Djuric, Stevan W. Tetrahedron Letters (2009), 50(36), 5145-5148.
28. Synthesis of substituted fused pyridines, pyrazines, and pyrimidines by sequential Ugi/inverse electron demand Diels-Alder transformations. A kritopoulou-Zanze, Irini; Wang, Ying; Zhao, Hongyu; Djuric, Stevan W.. Tetrahedron Letters (2009), 50(42), 5773-5776.
29. A flexible synthesis of privileged structural motifs using the Ollis-Sweeney ammonium ylide rearrangement. Alan F Gasiecki, Jeffrey L Cross, Rodger F. Henry, Vijaya Gracias, and Stevan W Djuric, Tetrahedron Letters (2008), 49(44), 6286-6288.
30. Scaffold oriented synthesis. Part 2: Design, synthesis, and biological evaluation of pyrimido-diazepines as receptor tyrosine kinase inhibitors. Vijaya Gracias, Zhiqin Ji, Irini Akritopoulou-Zanze, Cele Abad-Zapatero, Jeffrey R Huth, . Danying Song, Philip J Hajduk, Eric F Johnson, Keith B Glaser, Patrick A Marcotte, Lori Pease, Nirupama B Soni, Kent D Stewart, Steven K Davidsen, Michael R Michaelides, and Stevan W Djuric, Bioorganic & Medicinal Chemistry Letters (2008), 18(8), 2691-2695.

31. Concise Construction of Novel Bridged Bicyclic Lactams by Sequenced Ugi/ RCM/Heck Reactions. Timothy P Ribelin, Andrew S Judd, Irini Akritopoulou- Zanze, Rodger F Henry, Jeffrey L Cross, David N Whittern, and Stevan W Djuric. *Organic Letters* (2007), 9(24), 5119-5122.
32. Topography-biased compound library design: the shape of things to come? Irini Akritopoulou-Zanze, James T Metz, and Stevan W Djuric, *Drug Discovery Today* 12(21&22), 948-952 (2007).
33. Synthesis of Novel and Uniquely Shaped 3-Azabicyclo[4.2.0]octan-4-one Derivatives by Sequential Ugi/[2+2] Ene-Enone Photocycloadditions. Irini Akritopoulou-Zanze, Alan Whitehead, Jan E Waters, Rodger F Henry, and Stevan W Djuric, *Organic Letters* 9(7), 1299-1302 (2007).
34. Synthesis of substituted 3,4-dihydroquinolin-2(1H)-one derivatives by sequential Ugi/acrylanilide [6pi]-photocyclizations. Irini Akritopoulou-Zanze, Alan Whitehead, Jan E Waters, Rodger F Henry, and Stevan W Djuric, *Tetrahedron Letters* 48(20), 3549-3552 (2007).
35. Zotarolimus, a Novel Sirolimus Analogue With Potent Anti-proliferative Activity on Coronary Smooth Muscle Cells and Reduced Potential for Systemic Immunosuppression. Yung-Wu Chen, Morey L Smith, Michael Sheets, Steve Ballaron, James M Trevillyan, .; Sandra E Burke, Teresa Rosenberg, Cindy Henry, Rolf Wagner, Joy Bauch, Kennan Marsh, Thomas Fey, Gin Hsieh, Donna Gauvin, Karl W Mollison, George W Carter, and Stevan W Djuric, *Journal of Cardiovascular Pharmacology* 49(4), 228-235

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36. 1,4-Dihydroindeno[1,2-c]pyrazoles with acetylenic side chains as novel and potent multitargeted receptor tyrosine kinase inhibitors with low affinity for the hERG ion channel. Juergen Dinges, Daniel H Albert, Lee D Arnold, Kimba L Ashworth, Irini Akritopoulou-Zanze, Peter F Bousquet, Jennifer J Bouska, George A Cunha, Steven K Davidsen, Gilbert J Diaz, Djuric, Stevan W et al Journal of Medicinal Chemistry 50(9), 2011-2029 (2007).
37. An expeditious and convenient synthesis of acylsulfonamides utilizing polymer- supported reagents. Ying Wang, Kathy Sarris, Daryl R Sauer, and Stevan W Djuric, Tetrahedron Letters 48(30), 5181-5184 (2007).
38. An expedient route to diaza-spirocycles utilizing a sequential multicomponent α -aminoallylation/ring-closing metathesis strategy. Vijaya Gracias, Alan F Gasiecki, Joel D Moore, Irini Akritopoulou-Zanze and Stevan W Djuric, Tetrahedron Letters 47(50), 8977-8980 (2006).
39. Synthesis of fused imidazole rings by sequential van Leusen/C-H bond activation. Vijaya Gracias, Alan F Gasiecki, Thomas G Pagano, and Stevan W Djuric 47(50), 8873-8876. (2006).
40. A post aza Baylis-Hillman/Heck coupling approach towards the synthesis of constrained scaffolds. Anil Vasudevan, Pei-San Tseng, and Stevan W Djuric, Tetrahedron Letters 47(48), 8591-8593 (2006),
41. Discovery of 2-[4-{2-(2S,5R)-2-Cyano-5-ethynyl-1-pyrrolidinyl]-2-oxoethyl] amino]- 4-methyl-1-piperidinyl]-4-pyridinecarboxylic Acid

(ABT-279): A Very Potent, Selective, Effective, and Well-Tolerated Inhibitor of Dipeptidyl Peptidase-IV, Useful for the Treatment of Diabetes. David J Madar, Hana Kopecka, Daisy Pireh, Hong Yong, Zhonghua Pei, Xiaofeng Li, Paul E. Wiedeman, Stevan W Djuric, et al. *Journal of Medicinal Chemistry* 49(21), 6416-6420 (2006).

42. 1,4-Dihydroindeno[1,2-c]pyrazoles as novel multitargeted receptor tyrosine kinase inhibitors. Juergen Dinges, Kimba L Ashworth, Irini Akritopolou-Zanze, Lee D Arnold, Steven A Baumeister, Peter F Bousquet, George A Cunha, Steven Davidsen, Stevan W Djuric, Vijaya J Gracias, Michael R Michaelides, Paul Rafferty, Thomas J Sowin, Kent D Stewart, Zhiren Xia, and Henry Q. Zhang, *Bioorganic & Medicinal Chemistry Letters* 16(16), 4266-4271 (2006).

43. Efficient Pd-catalyzed synthesis of 2-arylaminopyrimidines via microwave irradiation. Henry Q Zhang, Zhiren Xia, Anil Vasudevan, and Stevan W Djuric. *Tetrahedron Letters* 47(28), 4881-4884 (2006)

44. A simple and efficient one step synthesis of benzoxazoles and benzimidazoles from carboxylic acids. Ying Wang, Kathy Sarris, Daryl R Sauer, and Stevan W Djuric, *Tetrahedron Letters* 47(28), 4823-4826 (2006).

45. Synthesis of fused imidazo-pyridine and -azepine derivatives by sequential van Leusen/Heck reactions. Xenia Beebe, Vijaya Gracias, and Stevan W Djuric, *Tetrahedron Letters* 47(19), 3225-3228 (2006).

46. A simple and efficient one step synthesis of 1,3,4-oxadiazoles utilizing polymer- supported reagents and microwave heating. Ying Wang, Daryl R. Sauer and Stevan W. Djuric., *Tetrahedron Letters*, 47(1), 105-108 (2006).
47. Synthesis of fused triazolo-imidazole derivatives by sequential van Leusen/ alkyne–azide cycloaddition reactions. Vijaya Gracias, Daria Darczak, Alan F. Gasiiecki and Stevan W. Djuric. *Tetrahedron Letters*, 46(52), 9053-9056 (2005).
48. Synthesis of fused imidazo azepine derivatives by sequential van Leusen/enyne metathesis reactions. Vijaya Gracias, Alan F. Gasiiecki and Stevan W. Djuric. *Tetrahedron Letters*, 46(52), 9049-9052 (2005).
49. Rapamycin analogs with reduced systemic exposure. Rolf Wagner; Karl W Mollison.; Luping Liu; Cynthia L Henry; Teresa A Rosenberg; Nwe Bamaung; Noah Tu; Paul E Wiedeman; Yatsun Or; Jay R Luly; Benjamin C Lane; James Trevillyan; Yung-Wu Chen; Thomas Fey; Gin Hsieh; Kennan Marsh; Merrill Nuss; Peer B Jacobson; Denise Wilcox; Richard P Carlson; George W Carter and Stevan W Djuric. *Bioorganic & Medicinal Chemistry Letters* 15(23), 5340-5343 (2005).
50. Synthesis of Fused Bicyclic Imidazoles by Sequential Van Leusen/Ring-Closing Metathesis Reactions. Vijaya Gracias, Alan F Gasiiecki and Stevan W Djuric. *Organic Letters* 7(15), 3183-3186 (2005).
51. Design, synthesis and structure-activity relationships of 6-O-arylpropargyl diazalides with potent activity against multidrug-resistant *Streptococcus pneumoniae*. Yong, Hong; Gui Gu, Yu; Clark, Richard F.; Marron,

Thomas; Ma, Zhenkun; Soni, Niru; Stone, Gregory G.; Nilius, Angela M.; Marsh, Kennan; Djuric, Stevan W. *Bioorganic & Medicinal Chemistry Letters* 15(10), 2653-2658, (2005),

52. Rapid and Efficient Synthesis of 1,2,4-Oxadiazoles Utilizing Polymer-Supported Reagents under Microwave Heating. Ying Wang; Reagan L Miller; Daryl R Sauer and Stevan W Djuric. *Organic Letters* 7(5), 925-928, (2005).

53. A versatile synthesis of fused triazolo derivatives by sequential Ugi/alkyne- azide cycloaddition reactions. Irini Akritopoulou-Zanze, Vijaya Gracias and Stevan W. Djuric, *Tetrahedron Letters*, 45(46), 8439-8441 (2004).

54. Synthesis of Diazepinones via Intramolecular Transamidation. Anil Vasudevan,; Clara I Villamil, and Stevan W Djuric. *Organic Letters* 6(19), 3361-3364 (2004)

55. Cloning and characterization of the glucagon receptor from cynomolgous monkey. Teresa McNally; Nelson D Grihalde.; Terry M Pederson,; Christopher A Ogiela,.; Stevan W Djuric,.; Christine A Collins; Chun W Lin, and Regina M Reilly, *Peptides (New York, NY, United States)* 25(7), 1171-1178 (2004)

56. Synthesis and antibacterial activity of novel bifunctional macrolides. Irini Akritopoulou-Zanze, Kathleen M Phelan; Thomas G Marron; Hong Yong,; Zhenkun Ma,; Greg G Stone; Melissa M Daly; Dena M Hensey; Angela M Nilius; and Stevan W.Djuric, *Bioorganic & Medicinal Chemistry Letters*

14(14), 3809-3813 (2004)

57. Synthesis and antibacterial activity of 6-O-arylpropargyl-9-oxime-11,12-carbamate ketolides. , Xenia Beebe; Fan Yang,; Mai H Bui,.; Michael J Mitten; Zhenkun Ma; Angela M.Nilius; and Stevan W Djuric. *Bioorganic & Medicinal Chemistry Letters* 14(10), 2417-2421 (2004)
58. Synthesis of novel fused isoxazoles and isoxazolines by sequential Ugi/INOC reactions. Irini Akritopoulou-Zanze,; Vijaya Gracias; Joel D Moore; and Stevan W Djuric. *Tetrahedron Letters* 45(17), 3421-3423 (2004)
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Title: High Throughput Synthesis and Purification Platforms: Key components of the Abbott Drug Discovery Engine

Drug Discovery Technology, Europe 2005, March 2005 London, UK.

Title: The Role of The Chemist in Fueling the Pharmaceutical Discovery Engine

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2005 Title: The Role of The Chemist in Fueling the Pharmaceutical Discovery Engine

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