

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.: PGR2024-00005

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

**PETITION FOR POST GRANT REVIEW OF
U.S. PATENT NO. 11,560,381**

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37 C.F.R. §42.8(b)(3)	1

37 C.F.R. §42.8(b)(4)	2
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PETITIONER’S LIST OF EXHIBITS

Exhibit No.	Document
1001	U.S. Patent No. 11,560,381
1002	File History of U.S. Patent No. 11,560,381
1003	U.S.S.N. 17/478,505
1004	U.S.S.N. 17/425,153
1005	PCT/US2020/015746
1006	U.S.S.N. 62/881,195
1007	U.S.S.N. 62/798,374
1008	US 2022-0098194 A1
1009	U.S.S.N. 17/541,035
1010	WO2021/178920
1011	PCT/US2021/021240
1012	U.S.S.N. 62/985,774
1013	U.S.S.N. 63/061,659
1014	Declaration of Stevan W. Djuric, Ph.D.
1015	Declaration of Kevin Sprott, Ph.D.
1016	Brien et al., Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma. Elife. 2018 Nov 15;7:e41305
1017	Hohmann et. al., Sensitivity and Engineered Resistance of Myeloid Leukemia Cells to BRD9 Inhibition, Nature Chemical Biology, 12, 672-679 (2016)
1018	Declaration of Christopher G. Nasveschuk, Ph.D.
1019	Remillard, et al, Degradation of the BAF Complex Factor BRD9 by Heterobifunctional Ligands. Angew. Chem Int Ed Engl. 56(21):5738-5743 (2017)
1020	Rao, et al., CN 108690020
1021	Martin, et al, Structure-Based Design of an in Vivo Active Selective BRD9 Inhibitor. J. Med. Chem. 59(10):4462-4475 (2016)
1022	Nasir, M. S. and Jolley, M. E., "Fluorescence Polarization: An analytical tool for Immunoassay and Drug Discovery," Combinatorial Chemistry & High Throughput Screening 2, 177-190 (1999)

1023	Z.X. Wang, An exact mathematical expression for describing competitive binding of two different ligands to a protein molecule. FEBS Lett 1995 Feb 27;360(2):111-4
1024	Sender et al., Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLOS Biology 14(8): e1002533 (2016)
1025	Katherine Luby-Phelps, Cytoarchitecture and Physical Properties of Cytoplasm: Volume, Viscosity, Diffusion, Intracellular Surface Area. International Review of Cytology, Volume 192, 1999, Pages 189-221

I. MANDATORY NOTICES (37 C.F.R. §42.8)

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

The real party-in-interest is Petitioner C4 Therapeutics, Inc.

B. Related Matters (37 C.F.R. §42.8(b)(2))

U.S. Patent No. 11,560,381 (“’381 Patent” or “’381”) is a continuation of U.S. Patent No. 11,414,416 (“’416 Patent”), which was the subject of PGR2023-00029. The ’416 Patent was statutorily disclaimed by PO.

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

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D. Service Information (37 C.F.R. §42.8(b)(4))

Please address all correspondence to the lead and back-up counsel at the above addresses. Petitioner consents to electronic service to the email addresses above.

E. Time for Filing Petition (37 C.F.R. §42.202)

The '381 Patent issued on January 24, 2023. (Ex.1001,1). This Petition is timely filed on or before the date that is nine months after the date of the grant of the patent (October 24, 2023). (*Id.*)

Consistent with 35 U.S.C. §325(d), the arguments presented in this Petition are not the same or substantially the same as any arguments presented or addressed by the Patent Office during prosecution (Ex.1002, 40-47, 50-62).

F. Payment of Fees (37 C.F.R. §§42.203(a) and 42.15(b))

Pursuant to 37 C.F.R. §42.203(a) and §42.15(b), the required fees are submitted with this Petition. If additional fees are due during this proceeding, the Office is authorized to charge Deposit Account No. 50-5834.

G. Grounds for Standing (37 C.F.R. §42.204(a))

Petitioner certifies under 37 C.F.R. §42.204(a) that the '381 Patent is available for PGR, and that Petitioner is not barred or estopped from requesting PGR to challenge the claims on the grounds identified in this Petition. Petitioner further certifies that the prohibitions of 35 U.S.C. §325(a) are inapplicable.

The '381 Patent is available for PGR because the claims have an effective filing date on or after March 16, 2013.

H. Identification of Challenged Claims and Relief (37 CFR §42.204(b))

Petitioner respectfully requests institution of a PGR of Claims 1-12 of the '381 Patent and cancellation of Claims 1-12 as unpatentable under 35 U.S.C. §112(a), §112(b), and §102(a)(1). It is more likely than not that at least Claim 1, and in fact Claims 1-12, are unpatentable in view of the following unpatentability grounds and prior art references.

Ground	Claims	Statutory Basis	Prior Art References
1	1-12	35 U.S.C. §112(a) – Lack of Written Description	
2	1-12	35 U.S.C. §112(b) – Indefinite	
3	1-12	35 U.S.C. §112(a) – Lack of Enablement	
4	1-12	35 U.S.C. §102(a)(1)	'920 PCT Publication (Ex.1010)

II. INTRODUCTION

C4 Therapeutics, Inc. (“Petitioner”) requests Post Grant Review (“PGR”) of claims 1-12 of U.S. Patent No. 11,560,381 to Ruppel et al., (“’381 Patent” or “’381”) (Ex.1001), owned by Foghorn Therapeutics, Inc. (“Patent Owner” or “PO”). This Petition establishes that it is more likely than not that at least one, and in fact all, of the claims of the ‘381 Patent are invalid.

Petitioner is a public company in Watertown, MA developing pharmaceutical compounds for degradation of disease-modulating proteins. It has two pharmaceutical heterobifunctional¹ protein degraders in human clinical trials (CFT8634 to degrade BRD9 and CFT1946 to degrade mutant BRAF) and a third has clearance to begin human clinical trials (CFT8919 to degrade mutant EGFR).

PO is a public pharmaceutical company in Cambridge, MA that is also developing one or more BRD9 heterobifunctional protein degraders for the treatment of cancer.

¹The term heterobifunctional compound or protein degrader as used herein refers to a three-component compound consisting of a binding ligand to a protein to be degraded, a linker and a binding ligand to cereblon, which is part of an E3 ligase enzyme ubiquitinating complex (Ex.1014, ¶68; FIGS. 2 and 3 below).

The '381 Patent is a continuation of U.S. Patent No. 11,414,416, which issued August 16, 2022. Petitioner submitted a Request for Post Grant Review of the '416 Patent May 1, 2023 (PGR2023-00029). On August 21, 2023, PO filed a statutory disclaimer of all the '416 Patent claims and notified the Board.

Petitioner supports this Petition with a Declaration from Stevan W. Djuric, Ph.D. (Ex.1014). Dr. Djuric was a senior scientist at Abbott and its successor Abbvie from 1996-2019 with positions of increasing responsibility, culminating in his role as the Vice President, Discovery Chemistry and Technology, Global Pharmaceutical Research and Head of its Global Medicinal Chemistry Leadership Team, where he was responsible for a group of about 150 internal scientists and over 100 external scientists (*id.*, ¶4).

Dr. Djuric was a Distinguished Research Fellow at Abbvie from 2015-2019, the highest ladder of scientific achievement at the company, and a member of its governing Scientific Advisory Board (highest level scientific Board at Abbvie) (Ex.1014, ¶5).

Abbvie created a major targeted protein degradation initiative in its Discovery Chemistry and Technology group in 2018. Dr. Djuric submitted the first proposal to Abbvie management to start the program. As part of this initiative, Dr. Djuric 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 degraders that can address diseases of aging (*id.*, ¶7).

Dr. Djuric has over 100 scientific publications and is the co-author of numerous review articles, posters, and presentations on a wide variety of pharmaceutical topics. He is also a listed inventor on a number of patent filings in the pharmaceutical area (Ex.1014, ¶10). Dr. Djuric is or has 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 he is an Associate Editor), Organic Letters, Tetrahedron, and Bioorganic & Medicinal Chemistry, among others (Ex.1014, ¶11).

Dr. Djuric received his BSc. in Chemistry and his Ph.D. in Organic Chemistry from the University of Leeds, England. He was a Post-Doctoral Research Fellow at Ohio State University before starting his pharmaceutical research career (*id.*, ¶3).

Petitioner also provides the Declaration of Kevin L. Sprott, Ph.D. (“Sprott Declaration”, Ex.1015), an expert in complex organic synthesis. Dr. Sprott carried out research under Professor Elias J. Corey, Nobel Laureate and Professor of Chemistry at Harvard University. Dr. Sprott is the Head of Tesova Drug Discovery Consulting, LLC. Dr. Sprott was a Co-Founder of Stablix, Inc. founded out of

Columbia Medical School to develop heterobifunctional compounds for stabilization of proteins to return their function. Dr. Sprott has led or contributed to ten developmental candidates and clinical stages assets across six biopharmaceutical companies.

Petitioner further supports this Petition with a Declaration from Christopher G. Nasveschuk, Ph.D. (Ex.1018), Senior Vice President of Chemical Sciences at C4 Therapeutics, Inc.

Like the '416 Patent claims (but even more so), the issued claims of the '381 Patent are a shockingly broad, undeserved land grab for a huge genus of compounds not placed in the possession of the public and an exclusionary interest in compounds PO did not invent as of its priority filing dates.

As described in detail below, and supported by the Declaration of Dr. Djuric, (Ex.1014), the '381 Patent claims enormous genres of heterobifunctional compounds, without a single claimed compound synthesized, tested, or evaluated in the patent (Ex.1014, ¶148). The claims represent an aspirational basket of compounds that the '381 Patent did not place in the possession of the Person of Ordinary Skill in the Art ("POSA") under the written description requirement of 35 U.S.C. §112(a).

The '381 Patent claims are also invalid as indefinite under 35 U.S.C. §112(b) because the metes and bounds of the claims cannot be determined by a POSA

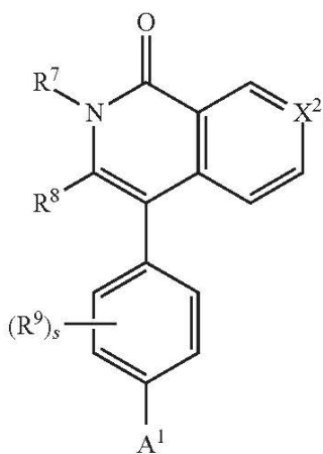
(*id.*, ¶¶150-151). Each of the '381 Patent claims includes the term “optionally substituted” (in fact each claim includes the term over eighty times when all of the embedded variables are considered (Table 3; Ex.1014, ¶102)), which, as discussed in the Declaration of Dr. Sprott, results in compounds that can have absurd structures, and some with a vast or even infinite number of substituents (*id.*, ¶¶101-105; Ex.1015, ¶¶19-21). For example, in Claim 1, the term “optionally substituted” is used over one hundred times (Ex.1014, ¶102).

The scope of the claimed compounds also exemplify the “infinite loop” fatal flaw sometimes seen in patent specification drafting that results in compounds that are not definable because they include unlimited substitutions and size (Ex.1014, ¶¶113-116). None of these “infinite loop” compounds were drawn or shown to exist by PO, certainly were not made (nor could many be made), and would not work for the intended purpose (*id.*; Ex.1015, ¶¶19-21). Because a POSA cannot determine the metes and bounds of the claims with reasonable certainty, the claims are indefinite, and thus invalid (Ex.1014, ¶¶116; Ex.1015, ¶19).

As supported in the Sprott Declaration (Ex.1015, ¶21), since the issued claims are boundless in scope and nonsensical, a POSA can draw almost any number of whimsical compounds that either could not be made or would not have stability to degrade a BRD9 protein.

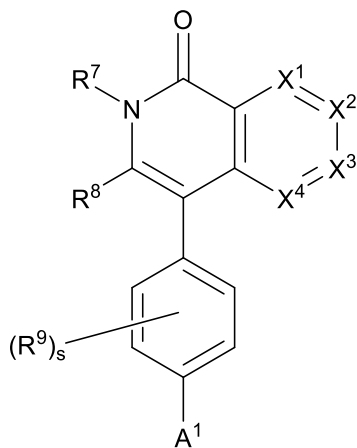
Further, the claims also violate the enablement requirement of §112(a), as the unclear, infinite, or boundless compounds were not (and cannot be) taught, drawn, made, or tested in the specification (Ex.1014, ¶¶152-164). The specification does not and cannot teach how to make and use the full scope of the “optionally substituted” compounds that purportedly fall within the claims (*id.*).

Additionally, and even more troubling, during PO’s attempt at this undeserved “land grab” there were at least three material misrepresentations made to the USPTO during prosecution. PO submitted a new claim set for prosecution to the USPTO in U.S.S.N. 17/696,656 (Ex.1002,557-562). In Claim 1, PO represented the structure below as Formula IVa.



Formula IVa

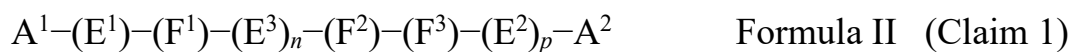
In fact, in the specification, Formula IVa is



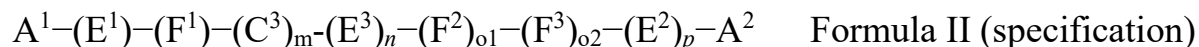
Formula IVa

The structure PO presented in Claim 1 for prosecution with the label “Formula IVa” is not found anywhere in the 420-page application (Ex.1014, ¶¶55, 56, 91-100). In this specification, filled with complex chemical formulas, it should not be up to the Examiner to uncover that the chemical structure presented in Claim 1 as Formula IVa is in fact not Formula IVa in the specification, and did not exist in the specification, thus lacking written description support.

PO did this not once but twice in Claim 1. Specifically, PO also labeled the linker structure in the claimed formula as “Formula II”. (Ex.1002,558).



In fact, Formula II is a very different structure in the specification as submitted. (*Id.*,137).



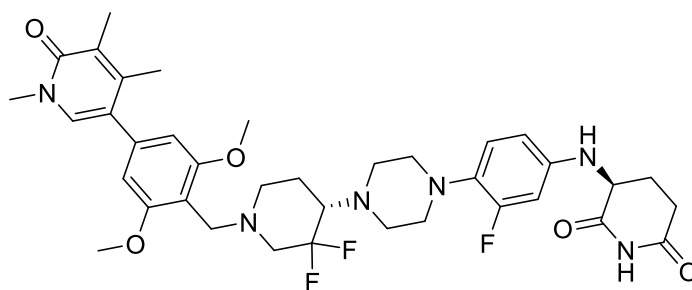
The purported Formula II presented in Claim 1 for prosecution is not found as a presented Linker Formula anywhere in the specification and thus lacks written description (Ex.1014,¶55). On the contrary, as described in Section VIII below and in the Declaration of Stevan Djuric (*Id.*,¶55), the specification lists Formulas IIa-IIg as the described subgenuses of Formula II (Ex.1001,17; col.2), none of which are the purported Formula II presented to the Examiner in Claim 1 as Formula II. In fact, PO, in its Response to Office Action in the file history (Ex.1002,40-47), stated that the claimed invention requires the presence of F^2 and F^3 , but no such requirement is found in either Formula II of the the specification or in any of the subgenus Formulas IIa-g in the specification (Ex.1014,¶64). Therefore, PO concocted the Linker formula it wanted (but which did not exist in the specification) and presented it as “Formula II” in Claim 1.

It would have been reasonable for the Examiner to accept these two representations of the PO at face value and assume that there was exact written description for the purported “Formula IVa” and purported “Formula II” as

presented in Claim 1. The Examiner should not have to check the truthfulness of every representation made by PO in the file history.

In sum, PO was not honest with the Examiner, which resulted in the allowance of the claims of the '381 Patent.

As described in detail below, because the '381 Patent claims are not entitled to any priority date earlier than their actual filing date of March 16, 2022 (and not that date either), the claims are also invalid as anticipated under 35 U.S.C. §102 over intervening PCT/US2021/021240 (“’240 Application” (Ex.1011)), filed March 5, 2021, and published September 10, 2021, as WO2021/178920 (“’920 PCT Publication” (Ex.1010)) by Nasveschuk, et al., and assigned to Petitioner C4 Therapeutics, Inc., with priority dates of March 5, 2020 (U.S.S.N. 62/985,774 (Ex.1012)) and August 5, 2020 (U.S.S.N. 63/061,659 (Ex.1013)), which was filed in the U.S. as U.S.S.N. 17/541,035 on Dec. 2, 2021 (Ex.1009). In fact, the intervening ’920 PCT Publication does something that the ’381 Patent fails to do—it actually draws, makes, and tests over a dozen species correctly encompassed by the ’381 Patent claims, including C4T’s oral BRD9 degrader currently in Phase I/II human clinical trials, CFT8634, thereby clearly anticipating the challenged unsupported ’381 Patent claims (Ex.1014, ¶¶171-176).



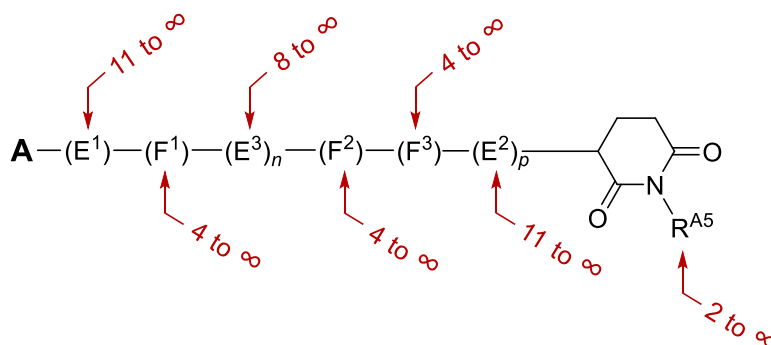
CFT8634

III. SUMMARY OF OPINIONS OF DR. DJURIC

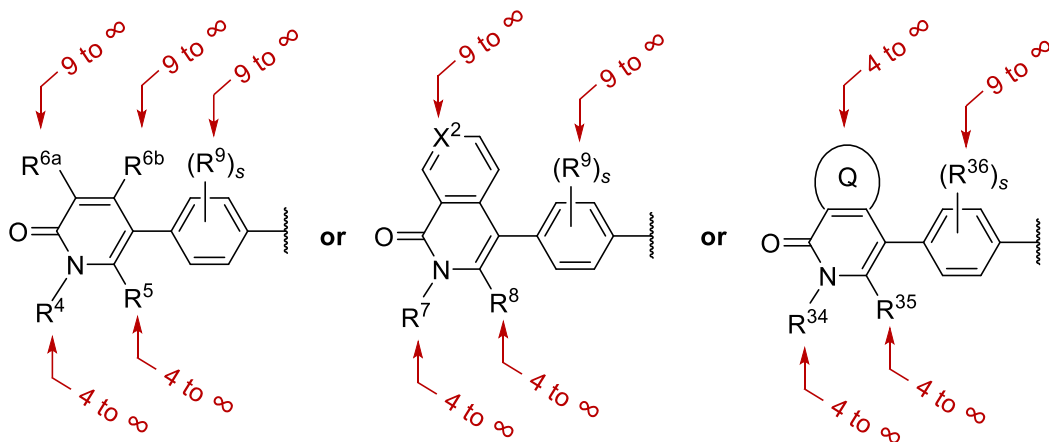
Given the complexity of the chemistry and the '381 claimed formulas addressed in this PGR, Dr. Djuric has provided expert testimony with a helpful illustrated summary of his conclusions for clarity. This can help guide the Board through this Petition.

Point 1 of Dr. Djuric's 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. (Ex.1014, ¶54). 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 (∞)). (*Id.*).

Open-Ended Optional Substituents Leads to Infinite Loops



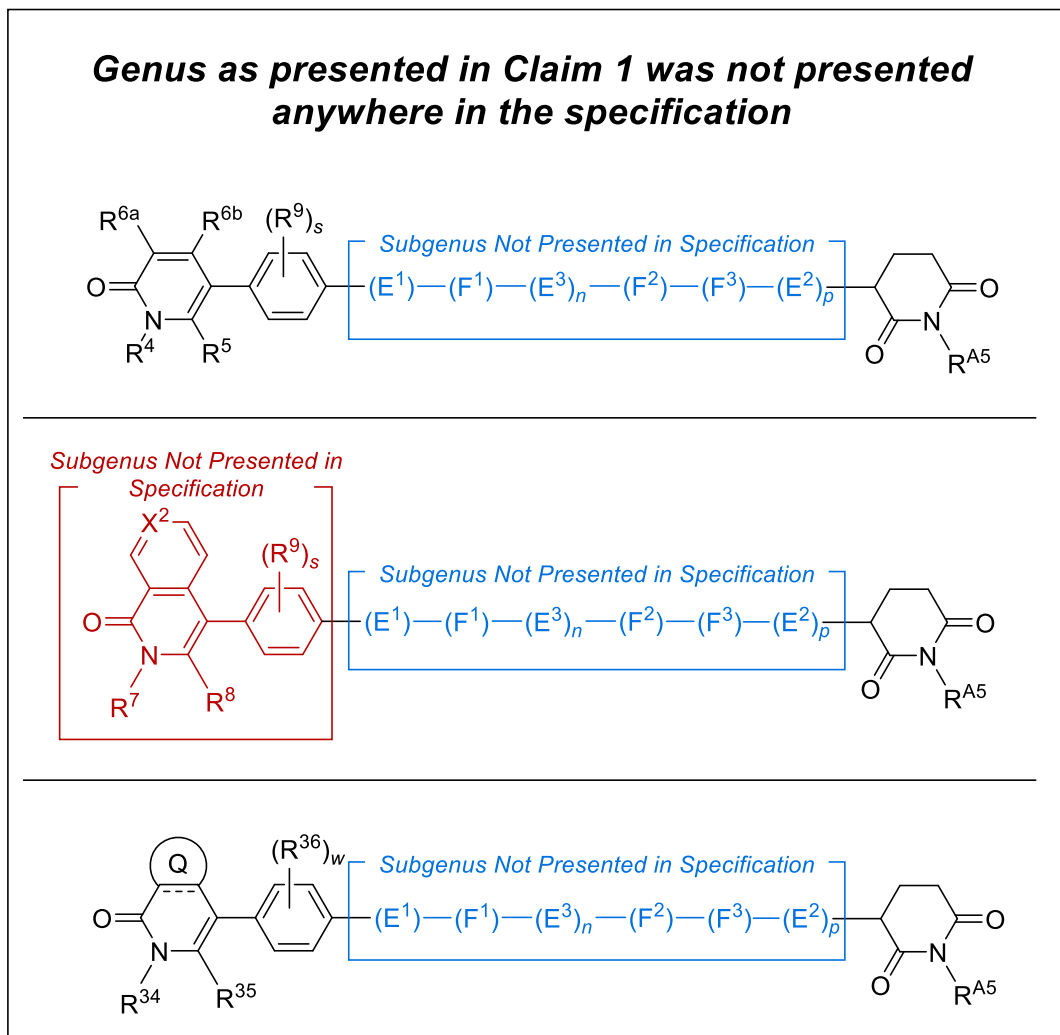
wherein A is



- ♦ 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

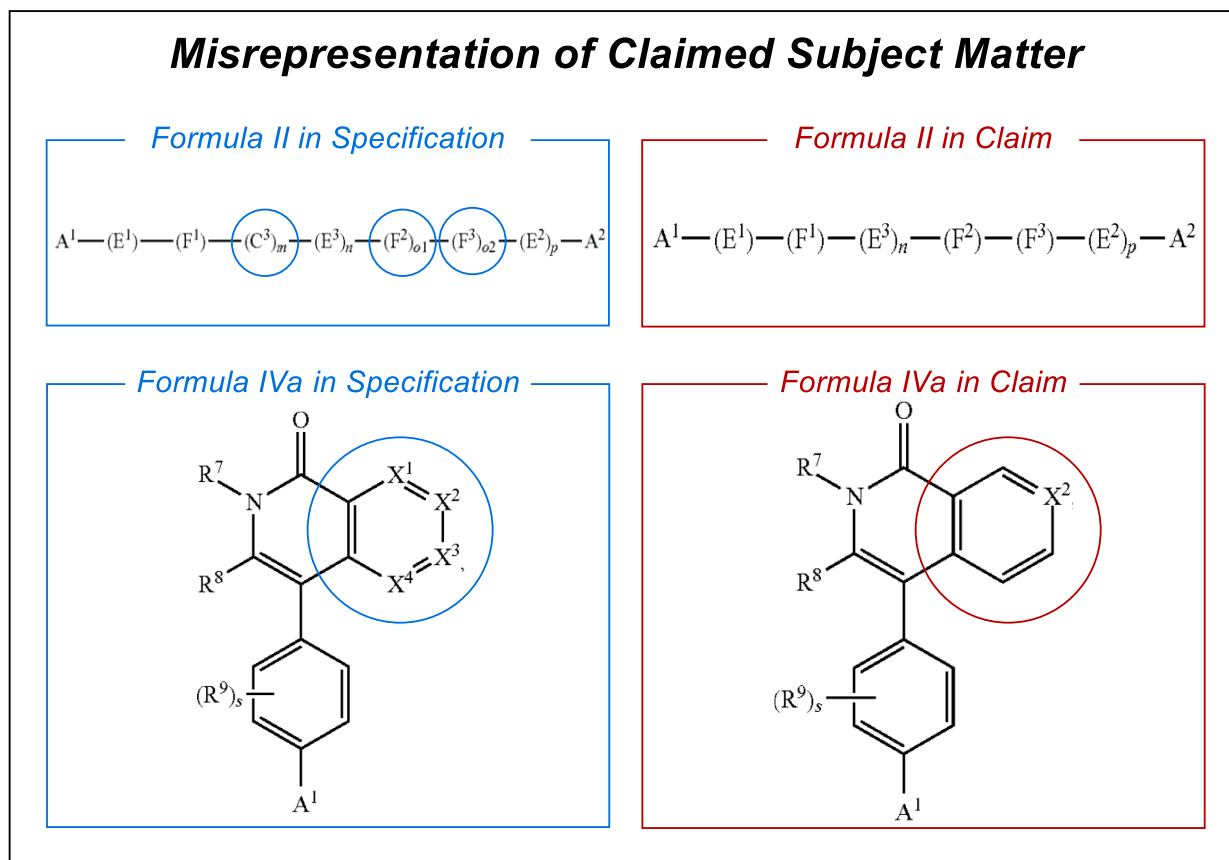
Point 2 of Dr. Djuric's conclusion is that the genus of compounds presented in Claim 1 was not disclosed as is anywhere in the specification. (*Id.*, ¶55). This is because the Linker formula used in the claims is not found anywhere in the specification and is not a listed Linker subgenus (*see* Ex.1002,17; col.2). In addition, the 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. (Ex.1014,¶55).



Point 3 of Dr. Djuric's conclusion is that there are misrepresentations in the issued claims. Formula IVa in Claim 1 is different from Formula IVa in the specification. (*Id.*,¶56). 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 formulas found in the

specification. (*Id.*). This is misleading to the reader (including the USPTO) 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. (*Id.*).



Point 4 of Dr. Djuric’s conclusion is that there are no compounds synthesized or tested in the specification that are covered by Claim 1. (*Id.*, ¶57). He bases his conclusion on PO’s description of each individual modular unit of the claimed compound and its function. (*Id.*). According to his review of the specification, and he thinks a POSA would agree, the Claimed 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 discussion below; and Appendix 2 with exemplary structures). 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 a phthalimide. (*Id.*). Of the 22 remaining, none include the claimed Linker. (*Id.*).

Table 1

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 Appendix 2 for the definition of “phthalimide or analog thereof.”

In Claim 1, F¹, F², and F³ are defined as independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene. (Ex.1001,502-503).

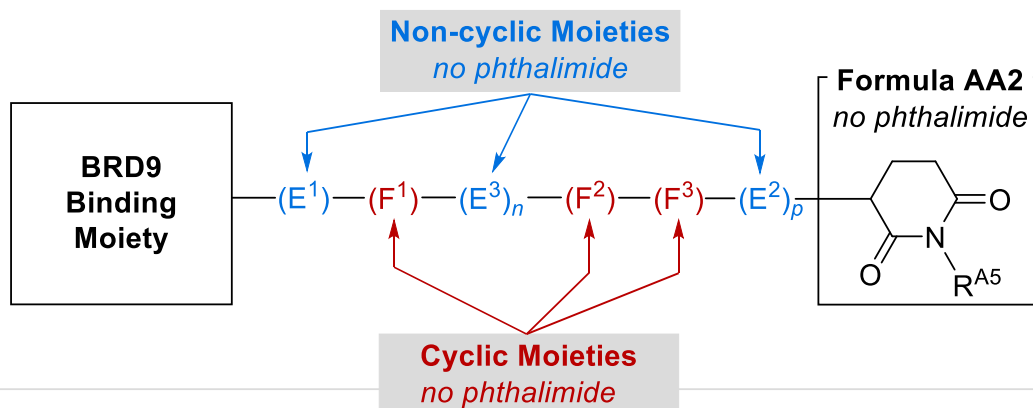
Dr. Djuric reasons that F¹, F², and F³ cannot include phthalimide or its analog because (i) none of the descriptions or drawn examples of F¹, F², and F³ in the specification that span over 30 columns (cols.12-43) include a phthalimide or its analog, and (ii) none of the definitions of carbocyclylene, heterocyclylene, arylene

or heteroarylene (see illustration below) include any reference to phthalimide or its analog. (Ex.1014;¶58). 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.² (*Id.*).

Likewise the B module, which as defined in Claim 1 is limited to Formula AA2, also does not have a phthalimide or its analog. (*Id.*). Thus, Dr. Djuric summarizes that to fall under the '381 Patent claims, the full compound structure must have a Linker with F¹, F², and F³, but no phthalimide or analog structure in the compound. (*Id.*).

² 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.

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



■ Definition of F¹, F², and F³ is C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ 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 F¹, F², and F³ 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*

IV. PROTEIN DEGRATION PRIMER

A. Basics of Heterobifunctional Compounds for Protein Degradation

Dr. Djuric has provided the following Protein Degradation Primer in Section III of his Declaration (Ex.1014, ¶¶20-30).

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. (*Id.*,¶20).

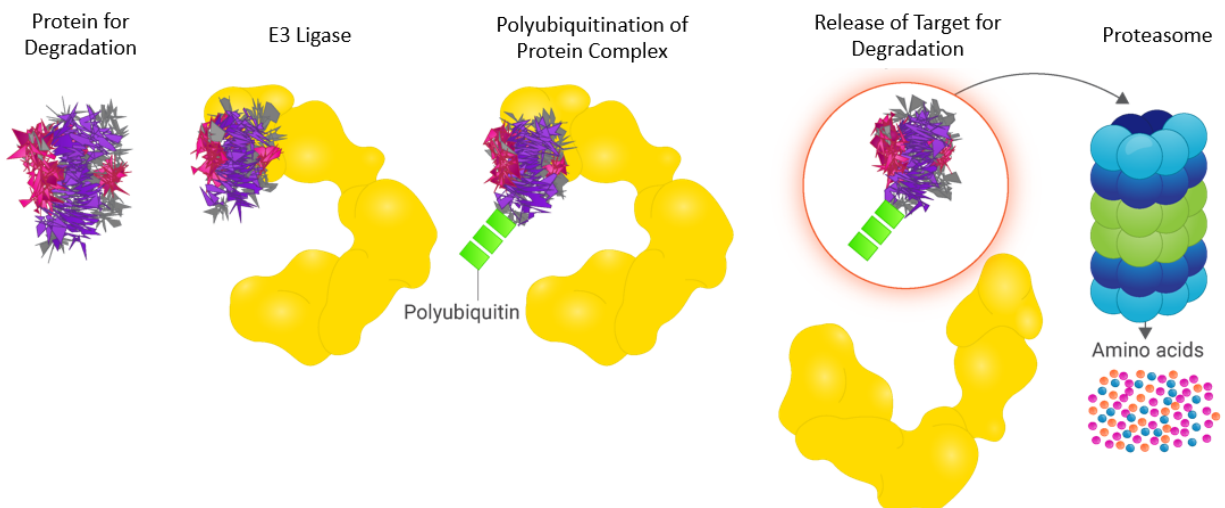


FIG. 1

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 (*id.*,¶21).

As illustrated in Figures 2 and 3 below, 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 (*id.*,¶22). 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”) (*id.*).

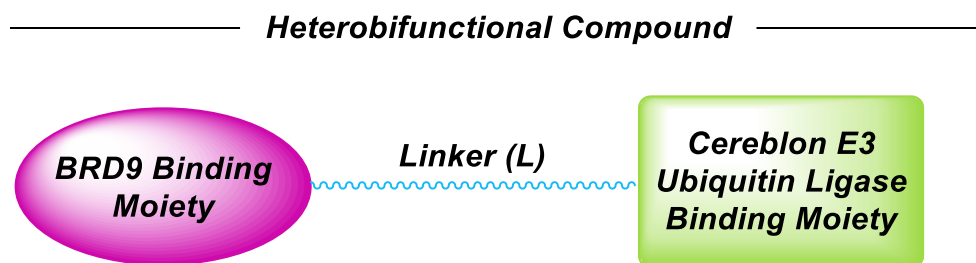


FIG. 2

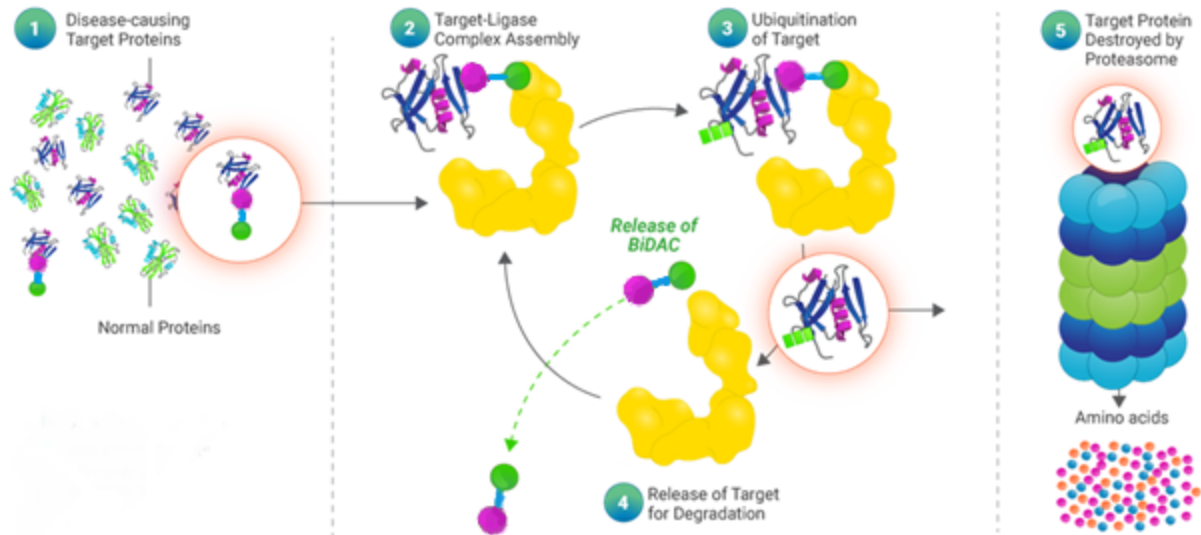


FIG. 3

B. The BAF Protein Complex and BRD9-Related Diseases

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 (*id.*,¶23)

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 (*id.*,¶24).

As shown in Figure 4 below, the cBAF complex (i.e., canonical, or naturally occurring, BAF) includes a protein referred to as SMARCB1, which is a tumor suppressing protein (*id.*,¶25).

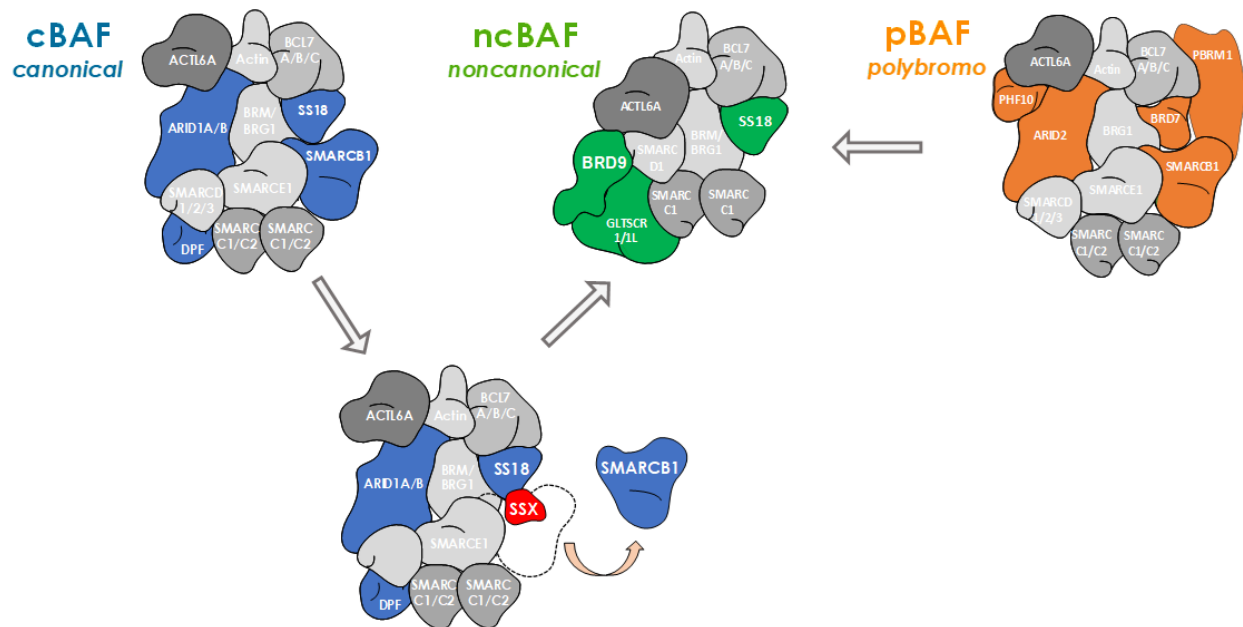


FIG. 4

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

The presence of BRD9 in ncBAF but not cBAF or pBAF, provides an opportunity to target the ncBAF complex with a therapeutic compound that binds to BRD9 and degrades it (*id.*,¶27).

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 ncBAF but not 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) (“Brien et al.”, Ex.1016). 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 Leukemia Cells to BRD9 Inhibition, *Nature Chemical Biology*, 12, 672-679 (2016)) (Ex.1017) (Ex.1014,¶28).

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) (Ex.1014, ¶29).

Dr. Djuric notes that one of his expert specialties is the evaluation of ADME (absorption, distribution, metabolism, and excretion) properties of drug candidates. He states that he is 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 he has seen drug candidates fail for reasons cited above (*id.*, ¶30).

V. PROSECUTION HISTORY

A. The Parent '153 Application

PO filed U.S.S.N. 17/425,153 on July 22, 2021 (“’153 Parent”; Ex.1004)). The ’153 Parent is a continuation of PCT/US2020/015746 (Ex.1005), filed with the U.S. Receiving Office on January 29, 2020; which claims the benefit of U.S. Provisional Application No. 62/881,195 (Ex.1006), filed July 31, 2019; and U.S. Provisional Application No. 62/798,374 (Ex.1007), filed January 29, 2019.

B. The '505 Continuation Application and the '416 Patent

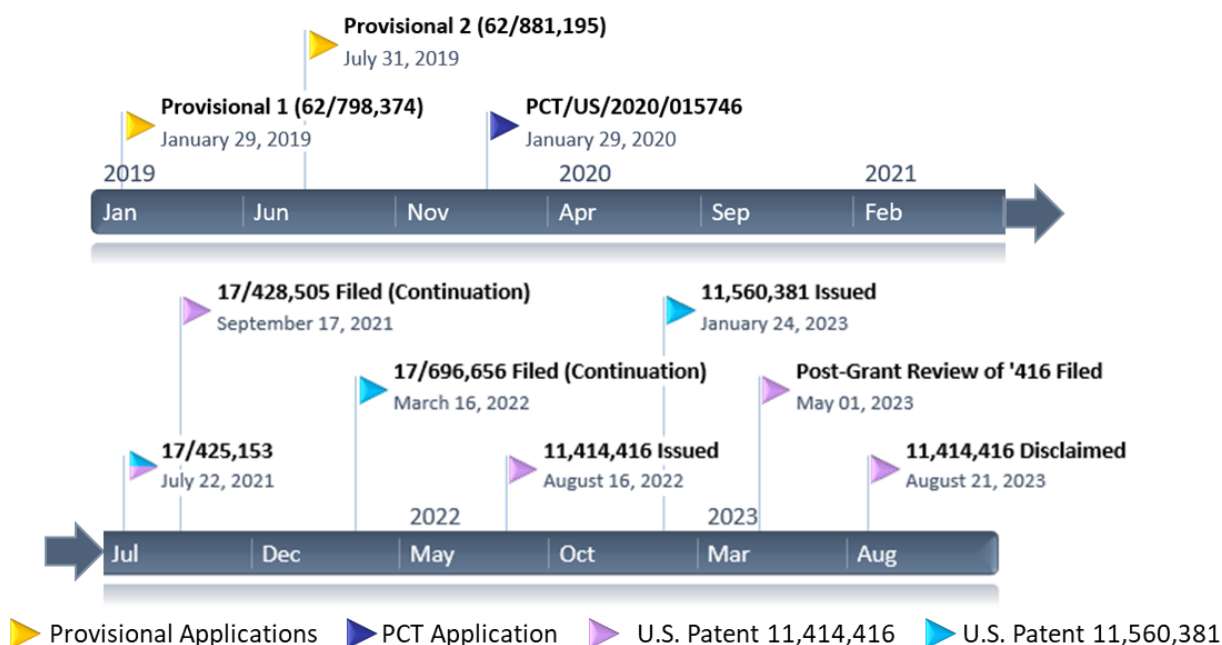
On September 17, 2021, PO filed a U.S. Track One application (U.S.S.N. 17/478,505; the “’505 Con”) (Ex.1003). The ’505 Con was granted with a first action allowance as U.S. Patent 11,414,416 (the “’416 Patent”) on August 16, 2022. Petitioner filed a Petition for Post Grant Review of the ’416 Patent (PGR2023-00029) on May 1, 2023. On August 21, 2023, PO disclaimed all the ’416 Patent claims.

C. The '656 Continuation Application and the '381 Patent

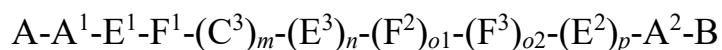
On March 16, 2022, PO filed a U.S. Track One application (U.S.S.N. 17/696,656; the “’656 Con”) (file history provided as Ex.1002). The USPTO issued a Non-Final Office Action on May 19, 2022, rejecting all claims over PO’s ’505 Con (nonstatutory double patenting rejection) and under §102 over Remillard et al., *Angewandte Chemie, International Ed.* (2017), 56(21), 5738-5743 (“Remillard et

al.”, Ex.1019), and Rao et al., CN108690020 (Ex.1020). (“Rao et al.”, Ex.1002,50-62). PO filed a Response to the Nonfinal Office Action on June 16, 2022, with a terminal disclaimer and added new claims 11-12. (*Id.*,29-47). On June 29, 2022, the USPTO issued a Notice of Allowance. (*Id.*,7-8). On January 24, 2023, the ’656 Con was issued as the ’381 Patent with Claims 1-12. (Ex.1001).

Patent Owner (Foghorn Therapeutics) Timeline



As issued, the ’381 Patent provides an extremely broad chemical formula that is defined by modular alphabet letters--a heterobifunctional compound that contains a BRD9 binding moiety (“A”), a degradation moiety (“B”) and a linker (“L”) that covalently links A and B. In this broad embodiment, the patent describes the following formula (where A¹ to A² is the linker):



These variables are broadly defined in col. 1 of the patent, with variations of broad and subgenus embodiments stretching all the way through col. 130 (Ex.1001,1-81). None of the genus or subgenres presented in the first 130 columns of the '381 Patent is the genus that was presented for prosecution or granted in the '381 Patent (Ex.1014,¶121). The '381 Patent then proceeds from col. 130 through col. 432, with no less than 300 columns of examples of compound species (Ex.1001,81-232). Fatally, not a single one of the compounds in the 300 columns of the patent fall within the issued claims of the '381 Patent (Ex.1014,¶121).

The '381 Patent purports to define chemical terminology in cols. 438-453 (*id.*,235-243), which where relevant will be addressed below.

The '381 Patent presents 14 Figures, which present data for only two compounds (Compound 1 and 2). (*Id.*,4-15). However, neither Compound 1 nor Compound 2 fall within the purported invention, much less the claims, of the '381 Patent. They are both published prior art compounds (Example 2, col.473,1.7-10 (*id.*,253)), where Compound 1 is defined as a compound first appearing in Remillard, et al., (Ex.1019) and Example 3, which defines Compound 2 as a BRD9 ligand first published in 2016 Martin, et al, (Ex.1021). (Ex.1001,253; Ex.1014,¶117).

The Detailed Description starts in col. 454 (Ex.1001,243). The Examples start in col. 462 (*id.*,247). Example 1 provides data that sgRNA (single guide RNA) against human BRD9 in synovial sarcoma cells can inhibit cell growth (*id.*). It provides data for fully 470 RNA sequences (filling over 10 columns of space) that are completely irrelevant to the invention, because no RNA sequences are claimed in the '381 Patent. (Ex.1001,247-252; Ex.1014,¶119).

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) (Ex.1001,253). 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). Examples 4 and 5 also provide data for the inhibition of synovial sarcoma cells with prior art compounds (FIGS. 8-13) (*id.*,254). 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 (Brien et al., Ex.1016) (Ex.1014,¶120).

Examples 7-85 (spanning 301 columns) provide syntheses for compounds **that do not fall within the issued claims**. (Ex.1014,¶121). Example 86 assesses the ability of compounds, **none** of which fall within the issued claims, to inhibit BRD9 in a competitive binding assay. (*Id.*). Example 87 provides data on the ability of compounds, **none** of which fall within the issued claims, to degrade a tagged-

BRD9 fusion protein in a synovial sarcoma cell (which data spans over 9 columns) (*Id.*, ¶121).

VI. A PERSON OF ORDINARY SKILL IN THE ART

The '381 Patent claims are directed to complex pharmaceutical heterobifunctional compounds for the treatment of cancers and viruses. (*See, e.g.*, Ex.1001,17-81; cols.1-130). According to Dr. Djuric, a POSA in the field of the granted '381 Patent claims would have (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 two years of practical experience in the field of drug discovery in the area of pharmaceutical compounds (Ex.1014, ¶59).

VII. CLAIM CONSTRUCTION

The Board gives claims their ordinary and customary meaning in light of the specification and file history which is the meaning that the term would have to a POSA at the time of the filing date. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-1313 (Fed. Cir. 2005) (*en banc*); 37 C.F.R. §42.100(b).

Petitioner urges the Board to construe the following claim terms of the '381 Patent based on the '381 Patent and explanation in the Declaration of Dr. Djuric: “Optionally Substituted”; “C₆-C₁₂ aryl”; “C₆-C₁₀ arylene”; and “B” and “AA2”.

A. “Optionally Substituted”

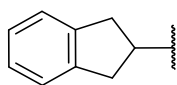
Petitioner requests that the Board interpret the term “optionally substituted” as used in the '381 Patent as incapable of claim construction because it is meaningless and unbounded as defined and used in the specification and claims (Ex.1001,235 (col.438,1.48, and col.439,1.1-5) followed by 237 (col.442,1.48-64)). In the alternative, Petitioner asks that the Board construe the term “optionally substituted” exactly as defined in the two locations of the '381 Patent, which are inconsistent with each other and are both open-ended (*id.*, first definition at 235 (col.438,1.48, and col.439,1.1-5) and second definition at 237 (col.442,1.48-64)).

The term “optionally substituted” is used many times in every one of Claims 1-12. According to Dr. Djuric, the term does not provide any limitations and it does not adequately inform a POSA what the compound actually is, because an infinite number of possibilities would be allowable (Ex.1014,¶¶104-105). A detailed analysis of the term “optionally substituted” is provided in Sections VIII-G and VIII-H below.

Thus, it is Petitioner's position that the term "optionally substituted" is incapable of claim construction because it is meaningless and unbounded as defined and used in the specification (*see id.*, ¶106).

B. "C₆-C₁₂ Aryl"

Aryl is defined in col. 440, lines 24-29 of the '381 Patent 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, Dr. Djuric opines that one aspect of uncertainty is where the attachment point on polycyclic aryl groups can be. (Ex.1014, ¶45). For example, does an indanyl attached through the non-aromatic ring fall within the claim term "aryl"? (*Id.*).

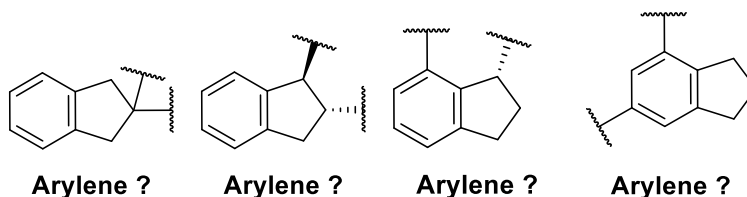


Aryl ?

Because the attachment points on "aryl" are capable of two different interpretations the term is indefinite. (*Id.*). However, to facilitate analysis of the claims Dr. Djuric applied the broader interpretation and considers that the attachment point can be through any ring in the multi-ring systems, given that the definition is not otherwise limited. (*Id.*).

C. “C₆-C₁₀ Arylene”

The specification does not provide a definition of “arylene” or “C₆-C₁₀ arylene.” (*Id.*,46). Dr. Djuric notes that 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*, e.g., Ex.1001,236, col.439,1.67: “an alkylene is a divalent alkyl group”; col.440,1.5-6: “an alkenylene is a divalent alkene group”). (Ex.1014,¶46). However, when the term aryl is defined (*see* Ex.1001,236 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. (Ex.1014,¶46). 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.*). In Dr. Djuric’s opinion this lack of clarity is further compounded by the divalent nature of arylene. (*Id.*). For example, it is not clear which attachment points of indanyl are included within the term C₆-C₁₀ arylene. (*Id.*).

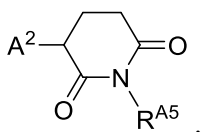


Because the attachment points on “arylene” are capable of several different interpretations the term is indefinite. (*Id.*). However, to facilitate analysis of the claims Dr. Djuric applied the broader interpretation and considers that the

attachment point can be through any ring in the multi-ring systems, given that the definition is not otherwise limited. (*Id.*).

D. “B” and “AA2”

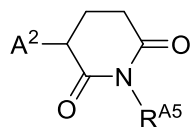
Petitioner requests that the Board construe “B” as used in the ’381 Patent claims to be “a cereblon binding moiety” of Formula AA2



Dr. Djuric carefully considered how a POSA would interpret “B” as used in the ’381 Patent claims. (*Id.*, ¶47-52). He notes that “B” is defined by PO in column 1, line 46 (Ex.1001,17), as a “degradation moiety.” (Ex.1014, ¶47). The specification states that “In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.” (Ex.1001,50; Ex.1014, ¶47). In col 68, lines 52-53, the specification states that the ubiquitin ligase binding moiety can be a cereblon ligand. (Ex.1001,50; Ex.1014, ¶47). 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. In one example, the moiety binds to a protease or a ubiquitin ligase that promotes the degradation of the protein, e.g., BRD9.” (Ex.1001,240; Ex.1014, ¶47).

Claim 1 specifically defines “B” as “Formula AA2.” (Ex.1001,503). According to the specification, Formula AA2 is the degradation moiety which is the

cereblon binding moiety.³ AA2 has the structure below, wherein A² is defined as the bond between the degradation moiety and the modular Linker (*id.*,51; col.69,1.12-13) and R^{A5} is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl (*id.*,503; col.973,1.16-17).

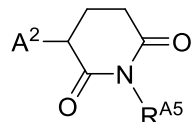


Formula AA2

Dr. Djuric notes that in col. 68, lines 65-66 of the '381 Patent it indicates that the degradation moiety “includes” the structure of Formula Y (Ex.1001,50; Ex.1014,¶49). In Dr. Djuric’s opinion the term “includes” is in itself ambiguous because it doesn’t indicate what is missing or where it would be placed. (Ex.1014,¶49). 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. (*Id.*).

³ See col 68, lines 65-66 which defines degradation moiety Formula “Y” (Ex.1001,50); 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).

Thus, the Board should construe the term “B” to mean “a cereblon binding moiety” of Formula AA2



because this limitation is consistently applied to “B” and subformulas thereof throughout the specification. This is important because Formula AA2’s ability to bind cereblon is so meager that it would take 230 micromolar concentration and at a minimum, 22 grams of compound (see Declaration of Dr. Nasveschuk (Ex.1018,¶19)), and thus is not capable of adequately performing the specified function, i.e., binding to cereblon in a human cell at a concentration that is therapeutically useful. (Ex.1014,¶51).

VIII. GROUND 1: CLAIMS 1-12 ARE INVALID UNDER 35 U.S.C. §112(A) FOR LACK OF WRITTEN DESCRIPTION

A. Law

It is bedrock law that the purpose of the written description requirement of 35 U.S.C. §112(a) is to establish that the inventor(s) had possession of the claimed subject matter as of the filing date. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

The written description requirement as applied to the '381 Patent specifically concerns the application of §112(a) to chemical genus claims that are presented by PO for the first time well after all of its priority dates. This scenario raises the highest level of concern because it is among the most likely to violate the written description requirement, which it does in this case.

The written description requirement for a claimed genus is satisfied through a sufficient description of a representative number of species by actual reduction to practice established in the specification or by a disclosure of relevant, identifying characteristics, i.e., structure or other physical and chemical properties sufficient to show actual mental possession of the later claimed subject matter. *Eli Lilly*, 119 F.3d at 1568. A representative number of species means that the species that are adequately described are representative of the entire genus. *Abbvie Deutschland GmbH & CoKG v. Janssen Biotech, Inc.* 759 F. 3d. 1285, 1300 (Fed. Cir. 2014). This requires that (i) there are species in the specification that fall within the claims and that those species are adequately described and (ii) the species are representative of the entire genus (*id.*). Neither of these two requirements are met in this case.

With regard to (i) above, the Federal Circuit recently reaffirmed this written description requirement as applied to chemical genus claims, reiterating that written description of a broad genus requires description not only of the outer limits of the genus but also either a representative number of members of the genus or structural

features common to the members of the genus, in either case with enough precision that a relevant artisan can visualize or recognize the members of the genus. *Regents of the Univ. of Minn. v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023). A broad outline of a genus's perimeter is insufficient (*id.*)

With regard to (ii) above, the Federal Circuit has confirmed that picking and choosing from a “laundry list” disclosure does not constitute an *ipsis verbis* disclosure of every subgenus. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) (“[J]ust because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a “laundry list” disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not “reasonably lead” those skilled in the art to any particular species.”); *Regents of the Univ. of Minn.*, 61 F.4th 1350 at 1357-58. As here where *ipsis verbis* disclosure does not exist, written description support for a claimed subgenus, in description of a broader genus, must be established through “blaze marks that single out particular trees in a forest.” *In re Ruschig*, 379 F.2d 990, 994–95 (CCPA 1967); *see also Regents of the Univ. of Minn.*, 61 F.4th at 1358. These blaze marks must be clear because “it is easy to bypass a tree in the forest, even one that lies close to the trail.” *Fujikawa*, 93 F.3d at 1571. To provide adequate written description support for a single subgenus,

“reasonably specific supporting disclosure,” or, as the *Ruschig* court put it, “something more than the disclosure of a class of 1000, or 100, or even 48, [subgenera] is required.” 379 F.2d at 994; *see also* *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1341-42 (Fed. Cir. 2013) (noting that simply disclosing all of the individual limitations is not sufficient to establish blaze marks to the claimed species). What is required is a “guide indicating or directing that this particular [subgenus] selection should be made rather than the many others which could also be made.” *In re Ruschig*, 379 F.2d at 995.

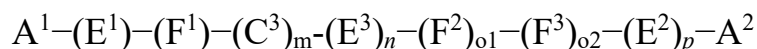
Finally, to claim “the benefit of the filing date of an earlier application under 35 U.S.C. §120, each application in the chain leading back to the earlier application must comply with the written description requirement of 35 U.S.C. §112.” *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997); *see also* *Novozymes*, 723 F.3d at 1344 (“[C]laims added during prosecution must find support sufficient to satisfy §112 in the written description of the original priority application.”). Where PO’s priority applications do not satisfy this requirement, intervening references can novelty destroy or render obvious the granted claims, as is the situation here.

Petitioner below addresses the three modular components of the claimed ’381 compounds (Linker, Degradation Moiety, and BRD9 Binder) to explain why, as claimed, they lack adequate written description in the specification as filed.

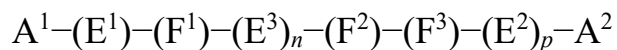
B. Interpretation of the Modular “Linker” Structure in the ’381 Patent Claims

In the opinion of Dr. Djuric, there is a lack of written description support for the claimed Linker structure in the ’381 Patent. (Ex.1014,¶¶62-79). After a careful review, he does not see the ’381 claimed Linker definition listed anywhere in the specification. (*Id.*). Dr. Djuric concludes it was first presented in Claim 1 in U.S.S.N. 17/696,656, filed March 16, 2022 (Ex.1002,558). (Ex.1014,¶¶62). After reviewing the priority PCT application and claims (Ex.1005), Dr. Djuric also does not see this specific modular form of Linker as presented in Claim 1 of the ’381 Patent. (Ex.1014,¶¶62). 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. (*Id.*).

Formula II in the specification:



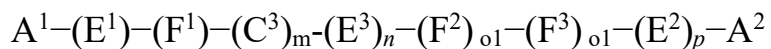
Formula II in the claims:



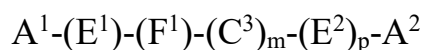
As highlighted by Dr. Djuric, the claimed Linker structure requires the presence of at least E¹, F¹, F², and F³. (*Id.*,¶¶63). The ’381 Patent, in col. 1-2 (Ex.1001,17) provides a genus (Formula II) and numerous subgenuses (Formulas

Ila-g) defining the Linker and none of these subgenres require all of the F¹, F², and F³ moieties. (Ex.1014,¶63).

(a.) Formula II in the specification is a broad genus that encompasses a very large number of variations:⁴



(b.) Formula Ila is a subgenus:



⁴ According to Dr. Djuric, Formula II actually covers an infinite number of variations because of the inclusion of the term “optionally substituted” (*see* Section VIII-G) which includes an infinite loop (*see* Section VIII-H). (Ex.1014,¶63). However, even if he ignores “optionally substituted” the Formula II subgenus still contains over 633,600 possible subgenres from which 1 subgenus was selected in Claim 1. (*Id.*). Dr. Djuric comes to this number by multiplying the number of classes of substituents that each variable covers. (*Id.*). 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. (*Id.*).

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

(c.) Formula IIb is a subgenus:

$$A^1-(E^1)-(F^1)-(E^2)_p-A^2$$

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

(d.) Formula IIc is a subgenus:

$$A^1-(E^1)-(F^1)-A^2$$

Formula IIc does not include F^2 or F^3 and also omits E^3 and E^2 . (*Id.*).

(e.) Formula IId is a subgenus:

$$A^1-E^1-(F^1)-(C^3)_m-(F^2)_{o1}-A^2$$

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 . (*Id.*).

(f.) Formula IIe is a subgenus:

$$A^1-(E^1)-(F^1)-(E^3)_n-(F^2)_{o1}-(E^2)_p-A^2$$

Formula IIe does not have F^3 and F^2 is optional. (*Id.*).

(g.) Formula IIg is a subgenus:

$$A^1-(E^1)-(F^1)-(C^3)_m-(E^3)_n-(F^2)_{o1}-(E^2)_p-A^2$$

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

(h.) Formula IIh is a subgenus:

$$A^1-(E^1)-(F^1)-(E^3)_n-(F^2)_{o1}-A^2$$

Formula IIg does not have F³, F² is optional, and does not have E². (*Id.*).

Therefore, according to Dr. Djuric, none of the subgenuses described in the '381 Patent specification include F² and F³ as required components as set forth in the claimed Linker. (Ex.1014,¶64). 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-E). (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 as filed. (Ex.1014,¶64). 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).

Dr. Djuric notes that he is baffled by the inconsistency between the asserted Formula II in Claim 1 and a very different Formula II in the specification, and that it appears to be an after-the-fact manufactured Formula without support. (Ex.1014,¶65).

Dr. Djuric has also reviewed the priority PCT application (PCT/US2020/015746, Ex.1005), filed on January 29, 2020, and does not see the actual Linker presented in Claim 1 of the '381 Patent. (Ex.1014,¶66). 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 F² and F³. (*Id.*).

Thus, according to Dr. Djuric, 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. (*Id.*, ¶67).

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). Dr. Djuric states that a POSA would study this section to try to learn how to create a Linker according to the claimed invention. (Ex.1014, ¶68).

For the purposes of Dr. Djuric's analysis, he focuses on F¹, F² and F³. (*Id.*, ¶69). Claim 1 specifies that "each of F¹, F² and F³ is, independently, optionally substituted (which as Dr. Djuric explains, is open-ended and impossible to interpret; see Section VIII-G) 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; Ex.1014, ¶69). These terms have to be interpreted in light of the teaching of and use in the specification, not in a vacuum. (Ex.1014, ¶69).

The explanations of F¹, F² and F³ in the '381 Patent begin at col. 13, line 65 and go through col. 43, line 48. (Ex.1001,23-38; Ex.1014, ¶70). Thus the '381 Patent

provides fully 30 columns of text and structures to explain how to interpret and use F¹, F² and F³. (Ex.1014,¶70).

The description starts out by stating “In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₃-C₁₀ carbocyclylene” (Ex.1001,23; col.13,1.66-67). It then provides embodiments and examples of carbocyclylene structures (*id.*; col.14, 1.1-59). (Ex.1014, ¶71).

Thereafter, the '381 Patent states “In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heterocyclylene” (Ex.1001,23; col.14,1.1-59). The '381 Patent continues by providing examples of C₂-C₉ heterocyclylenes (*id.*,23-28; col.14,1.63-col.23,1.29). (Ex.1014,¶72). Every example of a heterocyclylene provided in these 9 columns is a monocyclic, polycyclic (Ex.1001,23; col.14,1.65) or a bridged heterocyclic compound. (Ex.1014,¶72).⁵

⁵ Despite the definition of “heterocyclyl” in col. 441, lines 47-58 (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. (Ex.1014,¶72,fn.8). Dr. Djuric also notes that there are no examples in the definition of heterocyclyl in col. 441 (Ex.1001,237) that is a phthalimide or an analog thereof, nor in the col. 14-23 text (*id.*,23-28). (Ex.1014,¶72,fn.8).

The '381 Patent then provides individual examples of embodiments of F¹, F² and F³ from col. 23, line 32 to col. 26, line 46 (Ex.1001,28-29), all of which are monocyclic heterocyclic moieties. (Ex.1014,¶73). The '381 Patent then continues at col. 26, line 52 through col. 42, lines 19 (Ex.1001,29-37) with examples of bicyclic and fused saturated heterocyclic compounds. (Ex.1014,¶73).

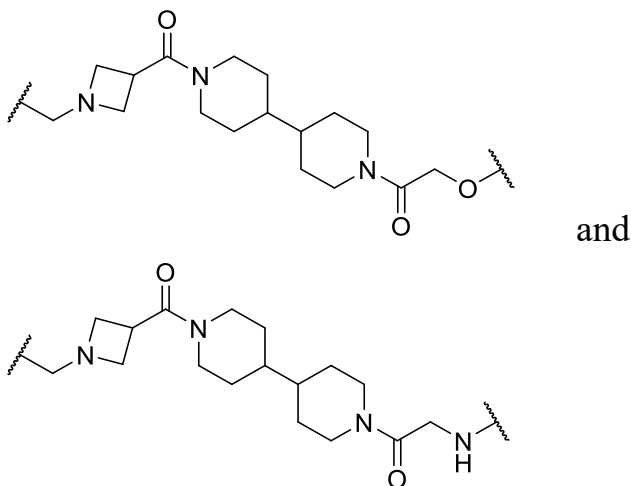
The '381 Patent then indicates that “In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heteroarylene” (Ex.1001,37-38; col.42,1.37-col.43,1.30). All of the examples are five-membered rings. There is no example of a phenyl or a fused aryl. (Ex.1014,¶74).

The '381 Patent follows with examples of fully drawn Linker structures, which run from col. 44, line 1 through col. 68, line 49 (Ex.1001,38-50). (Ex.1014,¶75). Therefore, the '381 Patent provides fully 24 columns of fully drawn exemplary divalent Linker structures. (*Id.*). Of all of these structures, Dr. Djuric notes that none has a phthalimide or an analog thereof (i.e., the phthalimide in Formula A or A1-A10, which for clarity is provided in the attached Appendix 2) in the Linker, despite the fact that 467 of the 489 examples of fully drawn Degradation compounds have a phthalimide or an analog thereof linked directly to the glutarimide. (*Id.*). 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. (*Id.*).

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). (Ex.1014, ¶76). In Dr. Djuric's opinion, the specification teaches a POSA through exemplification that the phthalimide or analogs (*see* Appendix 2) exclusively falls within the definition of "B", not Linker. (Ex.1014, ¶77). He concludes this has to be the case based on the teaching in the specification. (*Id.*).

Dr. Djuric identifies 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 (Ex.1001,40-41)). (Ex.1014, ¶78).



In Dr. Djuric's 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. (*Id.*).

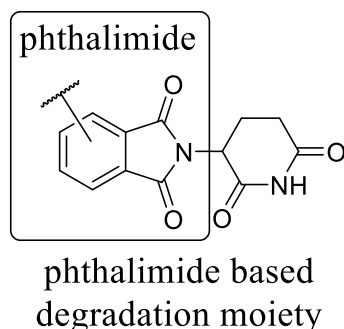
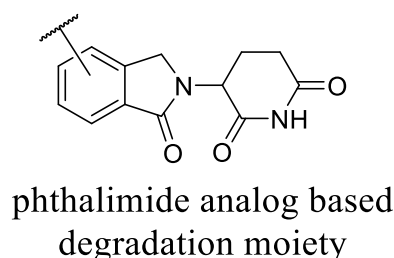
In addition, using the same analysis, based on Dr. Djuric's review, none of the 489 drawn degrader structures in the entire '381 Patent fall under the scope of Claim 1, due to the restrictions in the Linker structure, and the fact that the modular moiety "B" is limited to Formula AA2. (*Id.*, ¶79). Again,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

C. Interpretation of the Modular "B" Degradation Moiety in the '381 Patent Claims

Dr. Djuric highlights that the '381 Patent 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). (Ex.1014, ¶80). Of these over three dozen different degradation moiety formulas, the claims of the '381 Patent are limited to Formula AA2. (*Id.*) 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. (*Id.*).

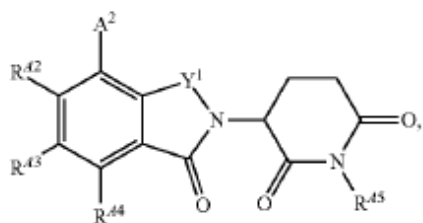
The vast majority of drawn, synthesized, and tested molecules in the '381 Patent have a phthalimide based degradation moiety or an analog thereof. (*Id.*, ¶ 81).



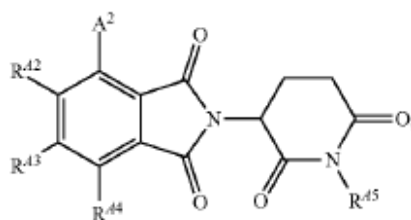
For example starting at column 130, compounds D1-D333, D335-D355, D359, D372-D373, D376, D385-D386, D398, D406, D413, D415, D418, D436, D445-D446, DD2, DD8, and DD11 all contain phthalimide based degradation moieties and compounds D356-D358, D360-D371, D374-D375, D377-D380, D387, D396-D397, D399-D405, 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). (Ex.1014, ¶81).

Formulas A, A1, A2, A3, A4, A5, A6, A7, A8, A9, A10 (reproduced below), and the more than a dozen subgenuses thereof described in columns 77-81 (Ex.1001,55-57) are related to the phthalimide containing compounds described in the '381 Patent and analogs thereof. (Ex.1014, ¶82). A POSA would be led to these formulas instead of Claimed Formula AA2 based on the teachings of the '381 Patent

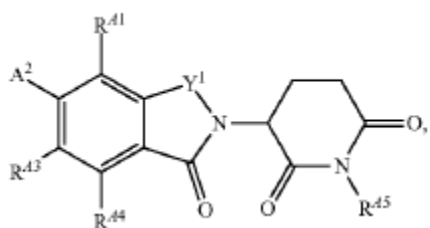
because these formulas correspond to drawn structures in the application. (*Id.*). Dr. Djuric notes that it is abundantly clear, and it would be to a POSA, from the '381 Patent that the inclusion of a phthalimide or analog structure comes from the modular “B” degradation moiety, not the Linker structure. (*Id.*).



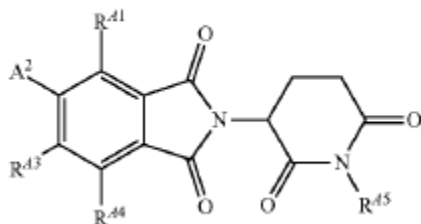
Formula A1



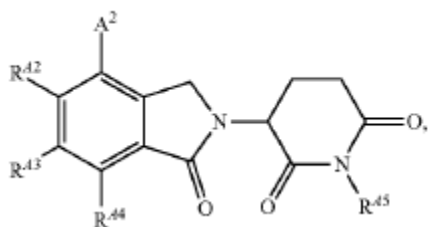
Formula A2



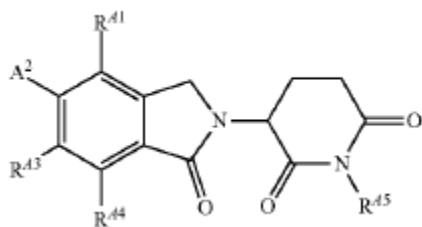
Formula A3



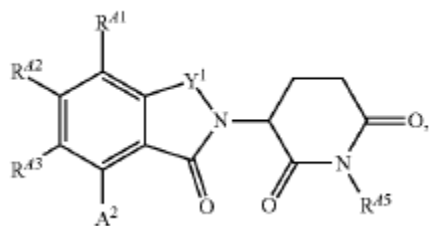
Formula A4



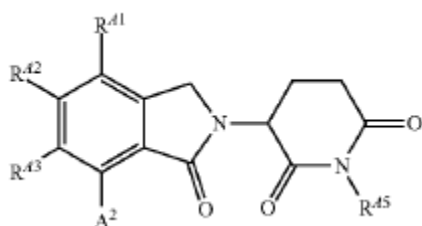
Formula A5



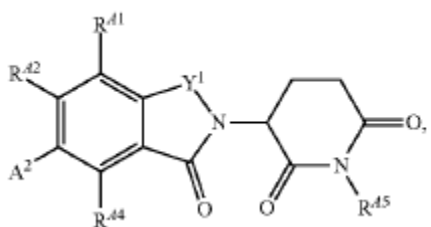
Formula A6



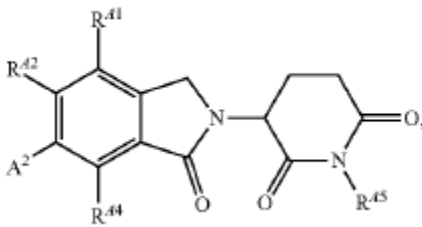
Formula A7



Formula A8



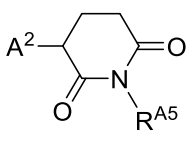
Formula A9



Formula A10

D. The Claimed “B” Moiety Does Not Accomplish its Defined Function

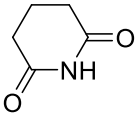
Petitioner has requested the Board to construe “B” as used in the ’381 Patent

claims to be “a cereblon binding moiety” of structure .

“B” is defined by PO in column 1, line 46, as a “degradation moiety” (Ex.1001,17).

Dr. Nasveschuk has provided testimony that the binding K_d of Formula AA2 in its most active form (R^{A5} is hydrogen) is only 230 μM. (Ex.1018,¶¶16-17).

Table 2

Structure	CRBN Binding -FP assay K_d (μM)
	230

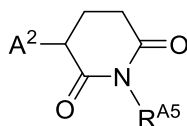
Dr. Nasveschuk states that it would be very difficult to administer enough heterobifunctional drug to a human to reach a concentration of 230 micromolar of the moiety AA2 in the target human cells (Ex.1018,¶17). Dr. Djuric agrees (Ex.1014,¶51). In fact, Dr. Nasveschuk calculated that one would have to administer approximately about 22 grams of a heterobifunctional compound to achieve a

concentration of 230 micromolar of the Formula AA2 moiety in the cell. (Ex.1018,¶18-19).

According to Dr. Djuric, a POSA would not consider the structure of Formula AA2 alone to be an effective cereblon binder and thus not a “degradation moiety,” and linker is not defined in the ’381 Patent as contributing to the degradation of the protein (Ex.1014,¶51).

Therefore, Petitioner urges that PO was not in possession of Formula AA2 as a cereblon binding agent that by itself defined as “B” would perform as a “degradation moiety”.

Indeed, Dr. Nasveschuk states that Petitioner uses heterobifunctional compounds wherein R^{A5} is stable on the nitrogen *in vivo*, for example alkyl such as methyl, as a “null”, or non-active control comparator (Ex.1018,¶20).



It is Dr. Nasveschuk’s experience that any substituent other than hydrogen at R^{A5}, or a moiety that cleaves to hydrogen *in vivo*, negates the degradation activity of the heterobifunctional molecule by significantly reducing or blocking binding to the E3 ligase cereblon (*id.*). Therefore, stable R^{A5} substituents such as methyl on Formula AA2 render the heterobifunctional compound non-operational and not useful. (*Id.*). Dr. Djuric agrees with Dr. Nasveschuk on this point. (Ex.1014,¶52).

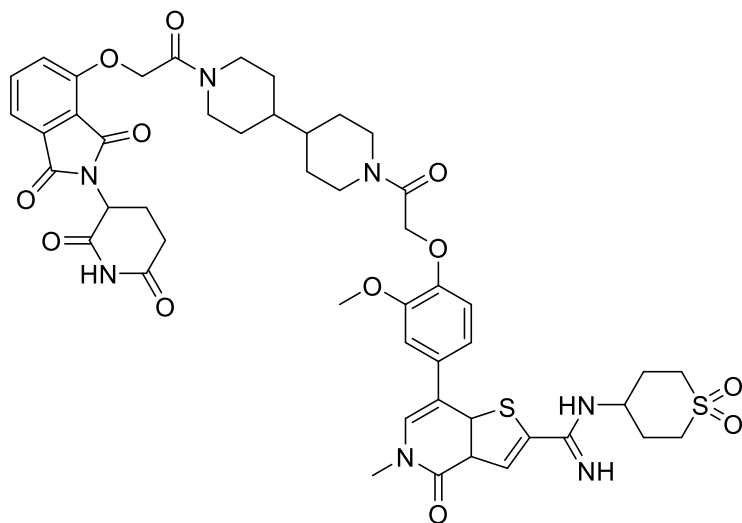
E. Misleading Statements to the USPTO during Prosecution Regarding Scope of Linker

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 §102 as anticipated by Remillard et al. (Ex.1019) and Rao et.al. (Ex.1020).

Dr. Djuric opines that, in responding to the rejection, PO presented arguments that were inconsistent with the written description of the claimed subject matter in the specification. (Ex.1014,¶84). Under U.S. law, a patent applicant should not present an argument to the USPTO that is inconsistent with its own written description in the specification.⁶

⁶ Under 37 CFR §11.18(b)(2)(ii) and (iii), the signature of an applicant on a submission to the USPTO is a certification that the legal contentions are warranted by law and the factual contentions have evidentiary support.

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



(Ex.1002;53-54).

Referring to the Remillard structure, PO stated:

Quite simply, this linker [i.e., the claimed Linker] 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 directly 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).⁷

⁷ The same analysis was applied to Rao.

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 misrepresented to the USPTO that phthalimide is F³, a component of the modular Linker, in the chemical formula without referring to any stated or inherent written description support in the specification for this assertion (Ex.1014,¶87-90). Based on Dr. Djuric’s review, this position is wholly unsupported by the specification (*id.*,¶87-91).

On the contrary, phthalimide is part of the degradation moiety “B” in the ’381 Patent, which is Formula A (*see generally* Formulas A1-A10). (Ex.1014,¶88).

There are no examples of phthalimide in the Linker in the entire ’381 Patent (*see* Section VIII-B). (*Id.*,¶89). Claim 1 requires Formula AA2 to be the degradation moiety, not Formula A. (*Id.*). The difference between Formula AA2 and Formula A is that Formula AA2 does not include phthalimide or an analog thereof and Formula A does. (*Id.*).

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-B) and was never previously drawn. (Ex.1014¶90; Ex.1002). Petitioner considers this an unacceptable lack of candor to the USPTO.

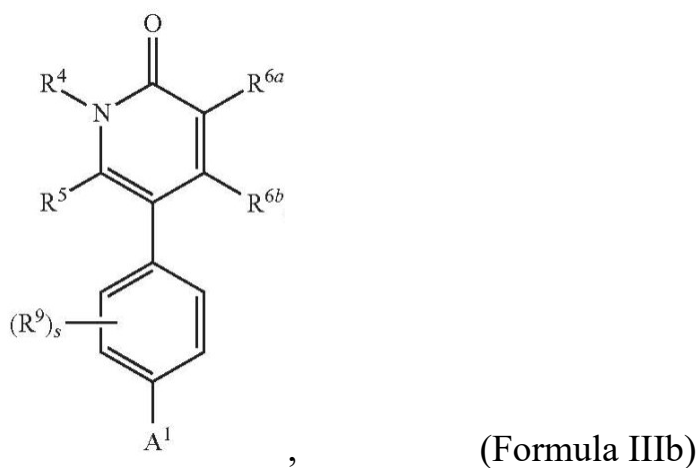
The misrepresentation of the interpretation of the modular segments of the claimed compounds is not trivial or inconsequential. In fact, it is critical. It

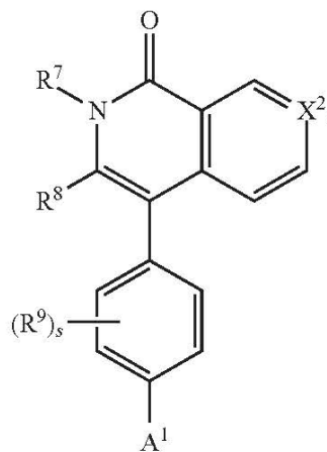
determines whether there is written description and enablement support for the issued claims (there is not) and which compounds fall under the scope of Claim 1 for infringement purposes. (*Id.*, ¶92).

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

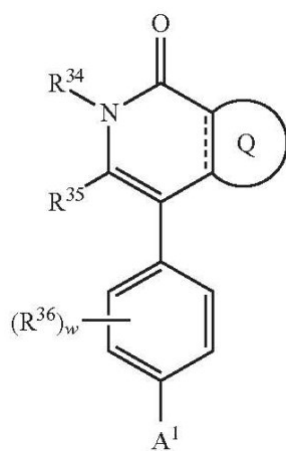
Claim 1 of the ’381 Patent provides three structures for “A” of Formula I which is the moiety that binds to BRD9.

A is:





(Formula IVa), or

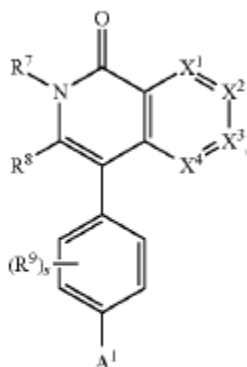


(Formula IX)

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) (Ex.1014, ¶94):

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

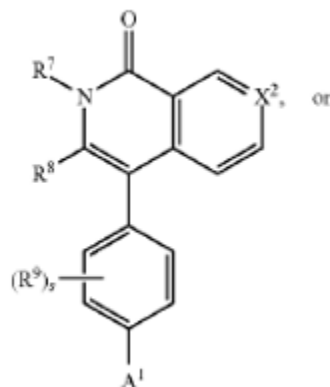
Formula IVa



or a pharmaceutically acceptable salt thereof.

Each of X^1 , X^3 , and X^4 can be N or CR^{10a} , CR^{10c} , or CR^{10d} respectively. As Dr. Djuric notes (Ex.1014, ¶95), this structure covers dramatically more compounds than Formula IVa of Claim 1, shown below.

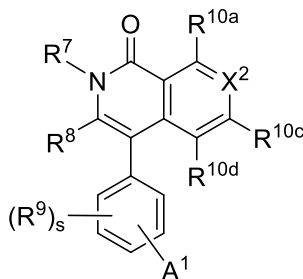
Formula IVa :



Despite searching the entire '381 Patent, Dr. Djuric did not find any representation of the revised Formula IVa as found in Claim 1. (*Id.*, ¶96). As with

the inconsistency in referencing Formula II as the Linker in Claim 1, Petitioner considers this another unacceptable lack of candor to the USPTO.⁸

Looking to the asserted PCT priority document, the multiply dependent PCT claims 226-231 (Ex.1005,481-482) describe a subgenus of the formula:



However, under 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. The Federal Circuit recently held that multiply dependent claims cannot be cherry picked to support a later filed subgeneric claim even if a combination of the multiply dependent claims would otherwise be an *ipsis verbis* disclosure of the claimed subgenus. *Regents of the Univ. of Minn.*, 61 F.4th at 1358 (holding that claim 47 of the priority document when combined with other relevant multiply dependent claims did not provide written description support because “following this maze-like path, each step providing multiple alternative paths, is not a written description of what

⁸ See footnote 6 above.

might have been described if each of the optional steps had been set forth as the only option.”)

Even if, *arguendo*, the PCT claims supported a subgenus of compounds as shown above, which in Dr. Djuric’s opinion they do not, claims 246-255 (Ex.1005,483-484) do not properly define R^{10a}, R^{10c}, and R^{10d} as hydrogen as recited in Claim 1 of the ’381 Patent. (Ex.1014,¶99). PCT claims 247-255 (*id.*), each of which recites hydrogen as one of several possible options depends from claim 246, which does not recite hydrogen as a possible selection. (Ex.1014,¶99).

Based on this, Dr. Djuric concludes that there is insufficient written description support for Formula IVa as presented in Claim 1. (Ex.1014,¶100).

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

In addition to the numerous written description issues discussed above, in Dr. Djuric’s opinion 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. (Ex.1014,¶101).

According to Dr. Djuric’s count, PO used “optionally substituted” at least 119 times in Claim 1 (see Table 3 below), and in Claim 3, the term was used even more

times (at least 121). (*id.*, ¶102). Dr. Djuric concludes that a chemical compound with that many variations would be literally impossible for a POSA to visualize and that the term “optionally substituted” as defined in the specification is open-ended and thus non-sensical and incapable of any meaning. (*Id.*).

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; 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
2	Depends on Claim 1. E^1 is defined as CH_2 Total: at least 108 times
3	Depends on Claim 1. E^2 is separately defined. 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
4	Depends on claim 3. E^2 is defined as NR^N Total: at least 116 times
5	Depends on claim 4. E^2 is defined as NH Total: at least 110 times
6	Depends on Claim 1. E^3 is separately defined. Total: at least 111 times
7	Depends on Claim 1. F^1 is separately defined. Total: at least 115 times
8	Depends on Claim 1. F^2 is separately defined. Total: at least 115 times
9	Depends on Claim 1. F^3 is optionally substituted C_6 - C_{10} arylene. Total: at least 116 times

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
11	Depends on Claim 1. Wherein p is 1. Total: at least 119 times
12	Depends on Claim 10. Wherein p is 1. Total: at least 91 times

In Dr. Djuric’s opinion, the term “optionally substituted” as used in the ’381 Patent does not provide adequate notice to a POSA of potential infringement because the term does not specifically describe what the substituents can be or where they are to be linked to the base molecule. (*Id.*, ¶104). It opens the molecule to unbounded speculation and possibilities. (*Id.*). In general, when a molecule is “optionally substituted” in the ’381 Patent 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. (*Id.*).

As shown in Table 3 above, the term “optionally substituted” is used many times in every claim of the ’381 Patent. This term as used in the ’381 Patent does not provide any limitations and in Dr. Djuric’s 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. (*Id.*, ¶105).

Thus, in Dr. Djuric's opinion, the term "optionally substituted" as used in the '381 Patent is incapable of claim construction because it is meaningless and unbounded as defined and used in the specification. (*Id.*, ¶106).

Dr. Djuric notes that the '381 Patent has not one but two definitions of the term "optionally substituted" (Ex.1001,235-237), and he studied both of them. (*Id.*, ¶107). In his 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. (*Id.*). Dr. Djuric concludes that 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. (*Id.*).

Not only are both provided definitions of "optionally substituted" boundless, but they are also even inconsistent in the boundless state. For example, in col. 438, lines 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. (Ex.1014,¶108).

According to Dr. Djuric’s 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, e.g., a substituent “described herein” (but without saying where “herein” is or how it is described). (Ex.1014,¶109). Further, the substituents don’t need to be the same because any combination is allowed. (*Id.*).

In addition, the combinations of substituents are only “preferably” stable. (*Id.*,¶110). Stability is not required. (*Id.*). Also, the resulting compound is only

“preferably” chemically feasible. (*Id.*). It is surprising to Dr. Djuric that neither stability nor chemical feasibility is required. (*Id.*). 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. (*Id.*). Dr. Djuric does not see any interpretation of this paragraph that would make sense to a POSA. (*Id.*). This is not capable of definite meaning. (*Id.*).

Dr. Djuric next compared the first definition of optionally substituted at col. 438, lines 48 to col. 439, lines 1-5 (Ex.1001,235-236) to a second definition that he found in the '381 Patent 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. (Ex.1014,¶111).

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. (*Id.*,¶112). In this alternative definition, it names all of the functional groups that are defined in the Markush Claim 1 other than amino (and wherein polyethylene glycol referred to in Claim 1 is a heteroalkyl group), so Dr. Djuric notes that in that respect it is not significantly different in scope from the col. 438-439 definition of “optionally substituted.” (*Id.*). However, this alternative definition has its own set of myriad problems. (*Id.*). Dr. Djuric gives several examples of the 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.” (Ex.1001,237). (Ex.1014,¶112). Again, this is open ended because the term “generally” doesn’t mean “absolutely.” (*Id.*). Further, nothing in the specification provides a pointer to which chemical moieties are to be substituted, so the “when substituted” term is without context. (*Id.*). Second, in the col. 442 definition, the specification teaches that when substituted, there will generally be 1 to 4 substituents, but doesn’t say where on the chemical moieties these substituents will

or should be located. (*Id.*). Third, all of the purported substituents listed in col. 442 do not constitute concrete guidance because the lists are not bounded (“[s]ubstituents include, for example”) (Ex.1001,237) (emphasis added). (Ex.1014,¶112).

H. Incorporation of Infinite Loops in the '381 Patent Claims

Dr. Djuric identified 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. (*Id.*,¶113-116). 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 (Ex.1001,237). Examples of substituents in col. 442 include alkyl, which may be substituted (*Id.*,237). This creates a fatal mistake. (Ex.1014,¶113). 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. Dr. Djuric points out that this dilemma can be applied to all of the optional substituents in col. 442 that refer to “e.g., unsubstituted and substituted”(see Ex.1001,237). (Ex.1014,¶113). Worse, the optional substituents are boundless so any substituent

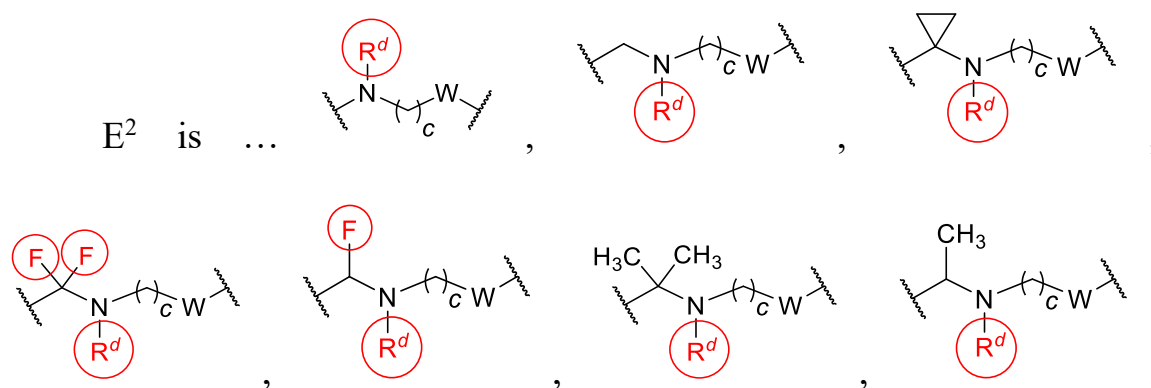
can be used including unnamed substituents. (*Id.*). For example, the substitution of an amino on a hydroxyl that is subsequently substituted with a thiol and then another amino or hydroxyl, etc. (*Id.*).

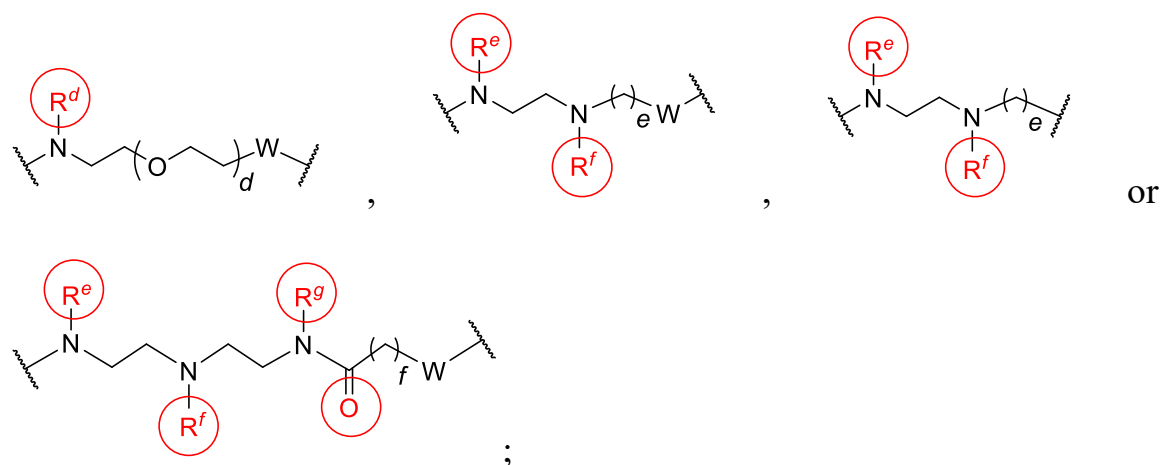
This infinite loop is not just “optional”, it is actually necessary for dependent claims 3 and 10 to be properly dependent on Claim 1. Dr. Djuric identified that the definitions of E² in claims 3 and 10 are only properly dependent on Claim 1 if you consider the term “optionally substituted C₁-C₁₀ heteroalkylene” to include optional substitutions that are in turn optionally substituted. (Ex.1001,503; Ex.1014,¶115). Here is the explanation provided by Dr. Djuric (Ex.1014,¶115) (with yellow and red 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-C₁₀ polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene (Ex.1001,503);

Claim 3 and Claim 10:





wherein

R^d , R^e , R^f , and R^g are each independently H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl (*id.*).

For claim 3 and Claim 10 to be properly dependent, these E^2 groups must be optionally substituted C_{1-10} 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 E^2 groups are identified.

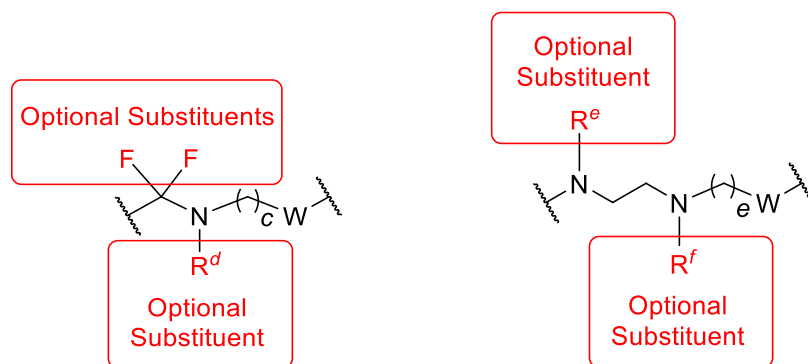


FIG. 5

And the optional substituents R^d , R^e , and R^f in turn are defined to include optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, and optionally substituted C_3 - C_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.

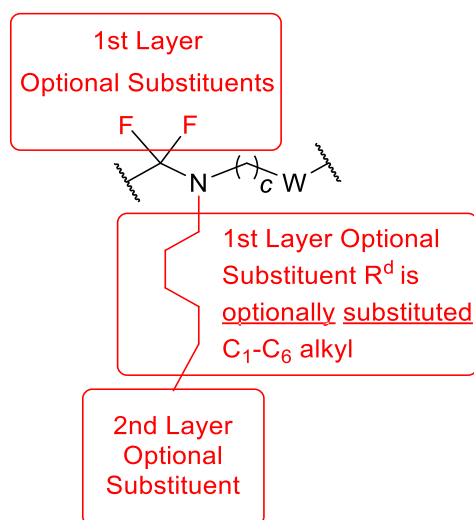


FIG. 6

Dr. Djuric concludes 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. (Ex.1014, ¶116). In addition, every term in the challenged claims 1-12 that includes this term is likewise boundless, vague, indefinite, and incapable of construction. (*Id.*).

I. The Content and Data Provided in the '381 Patent is Inadequate to Support the Breadth of the Claims

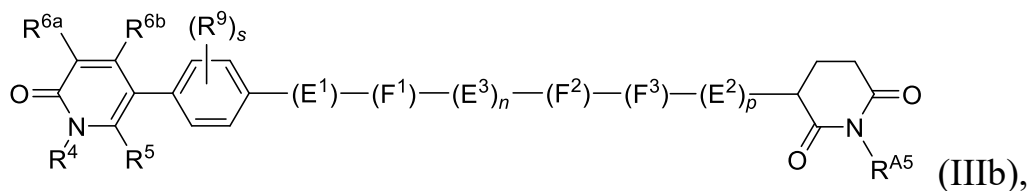
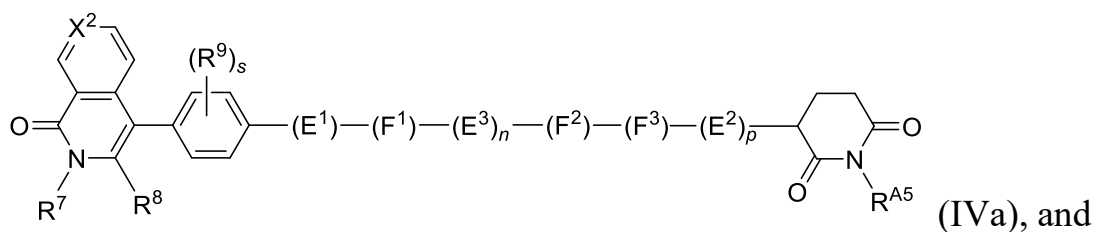
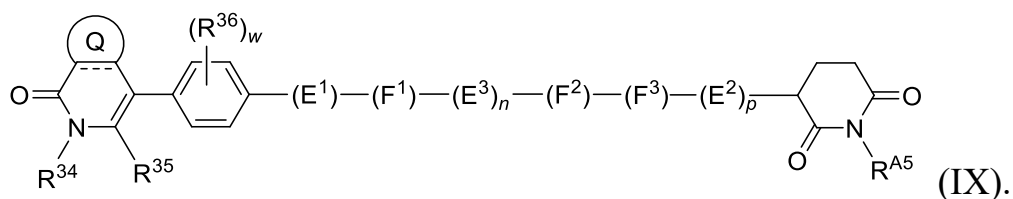
Examples 7-85 (spanning over 300 columns) provide syntheses of compounds. (Ex.1001,254-404). Dr. Djuric reviewed these compounds and concluded that **none** of them fall within the issued claims. (Ex.1014,¶121). Example 86 assesses the ability of compounds to inhibit BRD9 in a competitive binding assay. (Ex.1001,404-406). Dr. Djuric reviewed these compounds and concluded that **none** of them fall within the scope of the issued claims (Ex.1014,¶121). Example 87 provides data on the ability of compounds to degrade a tagged-BRD9 fusion protein in a synovial sarcoma cell. (Ex.1001,406-410). Dr. Djuric reviewed these compounds and concluded that **none** of them fall within the scope of the issued claims. (Ex.1014,¶121). Petitioner provided Dr. Djuric 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. (*Id.*). As indicated, every box is a “0.” Dr. Djuric reviewed Table 4, compared it to the '381 Patent, added notes, and confirmed that these representations are accurate. (*Id.*).

Table 4

Claim	Drawn	Made	Data
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0

Claim	Drawn	Made	Data
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0

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

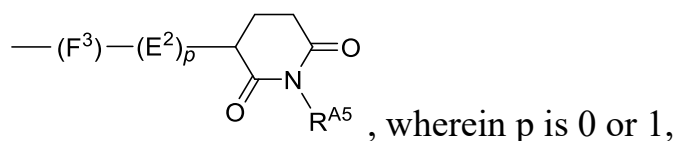


As noted in Table 4 above, these formulas do not cover a single compound drawn in the '381 Patent, Tables 1A to 1E. (*Id.*, ¶123). The reasons for Dr. Djuric's observations are as follows.

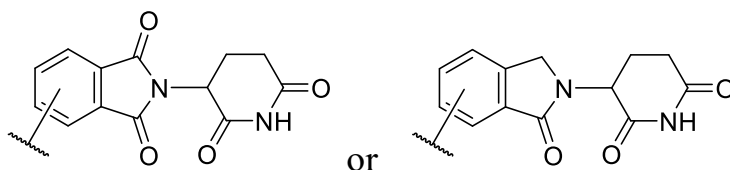
As defined in Claim 1, each of E¹ and E², independently, is -O-, -S-, -NR^N-, optionally substituted C₁-C₁₀ alkylene, optionally substituted C₂-C₁₀ alkenylene, optionally substituted C₂-C₁₀ alkynylene, optionally substituted C₂-C₁₀ polyethylene glycol, or optionally substituted C₁-C₁₀ heteroalkylene (Ex.1001,503). (Ex.1014,¶124).

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 (Ex.1001,503). (Ex.1014,¶125).

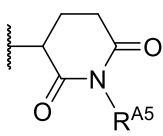
In Dr. Djuric's opinion (Ex.1014, ¶126), it follows from the definitions of F³ and E² that the structures in Claim 1 do not fit the drawn structures of compounds D1-D333, D335-D371, DD2, DD4, DD8, DD10, D372-D381, D384-D387, D396-D429, D431, D433-D468, D470, D474, DD11-DD16 in the specification of the '381 Patent (Ex.1001,81-232). For example, fragment -(F³)-(E²)_p-B of formula:



cannot form a phthalimide-type 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 (compounds D1-D333, D335-D371, DD2, DD4, DD8, DD10, D372-D381, D384-D387, D396-D429, D431, D433-D468, D470, D474, DD11-DD16) (Ex.1001,81-232). (Ex.1014,¶126). Additionally, the non-phthalimide '381 drawn compounds DD1, D382, D383, and D388-D390 do not contain the required

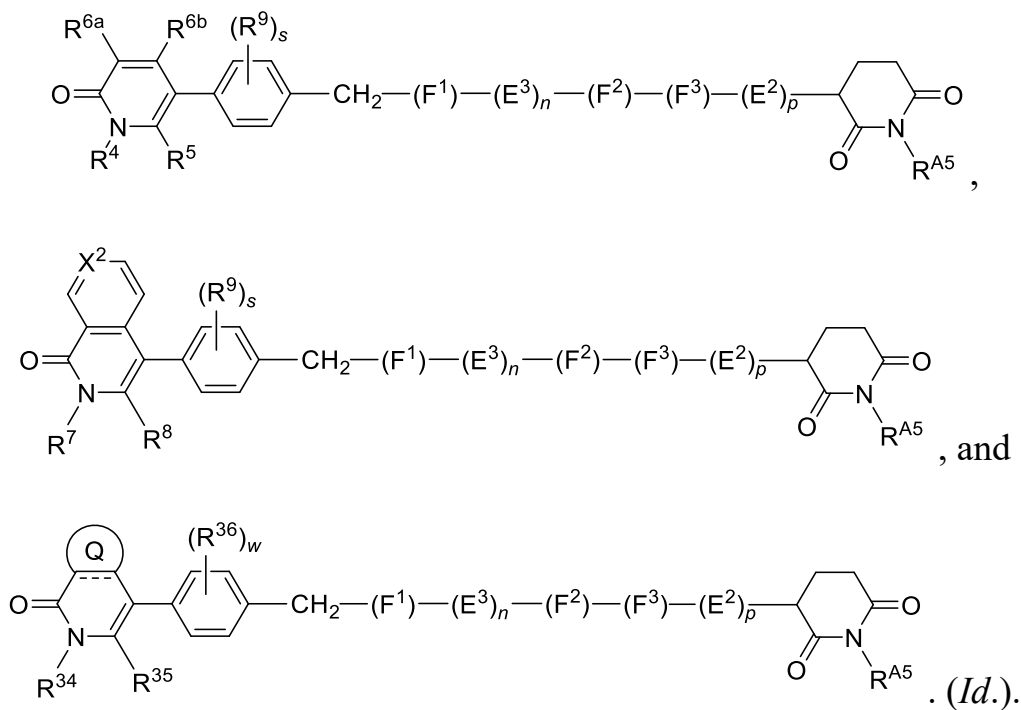
glutarimide moiety . Compounds D334, DD1, DD3, DD5, DD6, DD7, DD9, D382-D383, D391-D395, D430, D432, and D471-D473 also do not fall within the genus of the Claim 1 formula because they do not contain the linker as claimed in Claim 1 ($-A^1-(E^1)-(F^1)-(E^3)_n-(F^2)-(F^3)-(E^2)_p-A^2-$). (*Id.*).

Dr. Djuric concludes that there is not a single compound within the claimed genus described in the '381 Patent. (*Id.*,¶127). Therefore, Formula I in Claim 1 of the '381 Patent does not cover a single compound described in the '381 Patent. (Ex.1014, ¶127).

Claims 2-12 similarly do not cover a single disclosed structure in the '381 Patent.

Claim 2

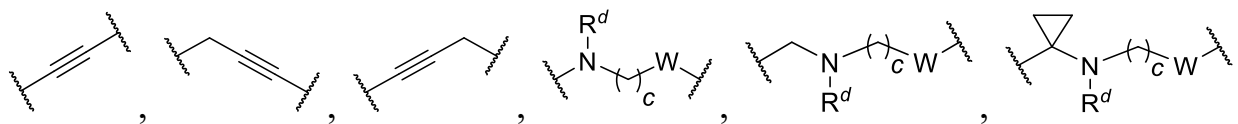
Claim 2 is directed to the compound of Formula I of Claim 1 with the only limitation that variable E^1 is CH_2 . (*Id.*,¶128). Therefore, with this limitation, compounds of Claim 2 can be represented by the following structures:

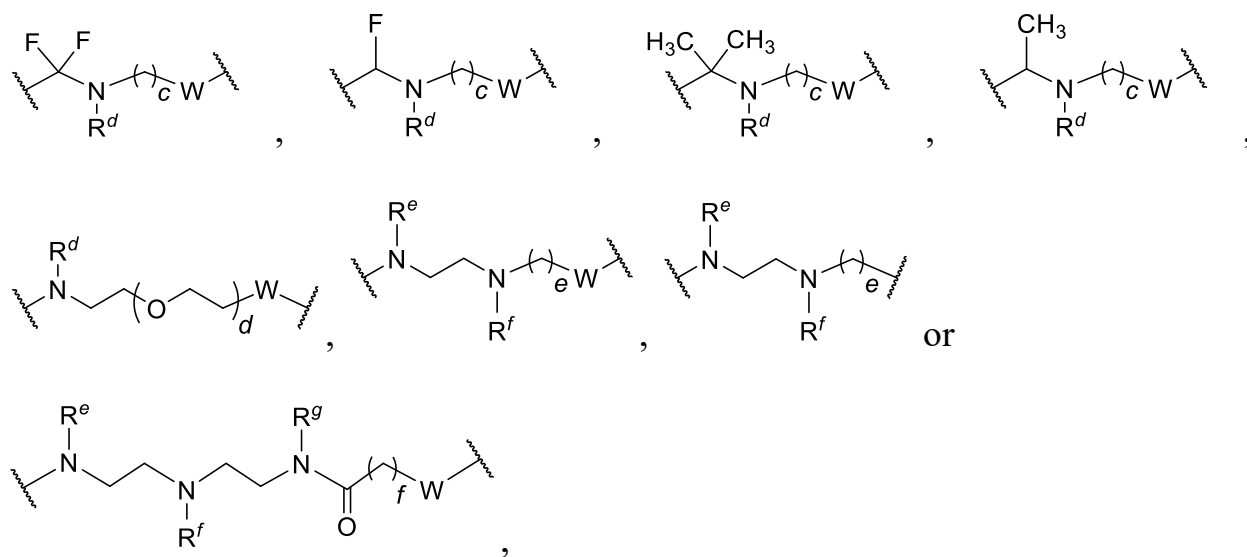


For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent (Tables 1A to 1E). (*Id.*, ¶129).

Claim 3

Claim 3 is directed to the compound of Formula I, where variable E² is limited to a narrower subset of non-cyclic groups. (*Id.*, ¶130). Specifically, E² is O, NR^w,





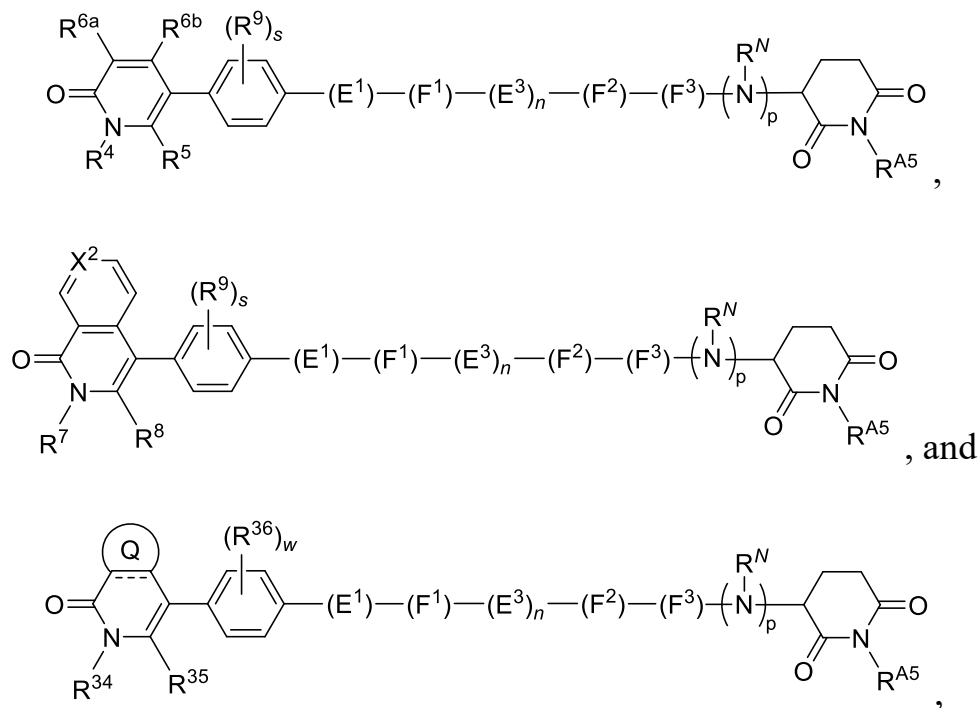
wherein W is O or NR^w, and wherein R^w is H or optionally substituted C₁-C₆ alkyl (Ex.1001,503).

Dr. Djuric points out that Claim 3 demonstrates PO's use of optional substituents on optional substituents and the open-ended nature of this term. (Ex.1014,¶131). For example, the last structure of E² is a heteroalkylene with five optional substituents (R^e, R^f, R^g, oxo, and NR^w). (*Id.*). And these substituents (except oxo) in turn are each optionally substituted. (*Id.*).

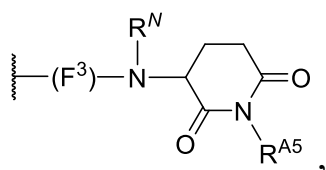
For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent (Tables 1A to 1E). (*Id.*,¶132).

Claim 4

Claim 4 is directed to the compound of claim 3, where variable E² is further limited to -NR^N-, and, therefore, compound of Claim 4 may be represented by the structures:



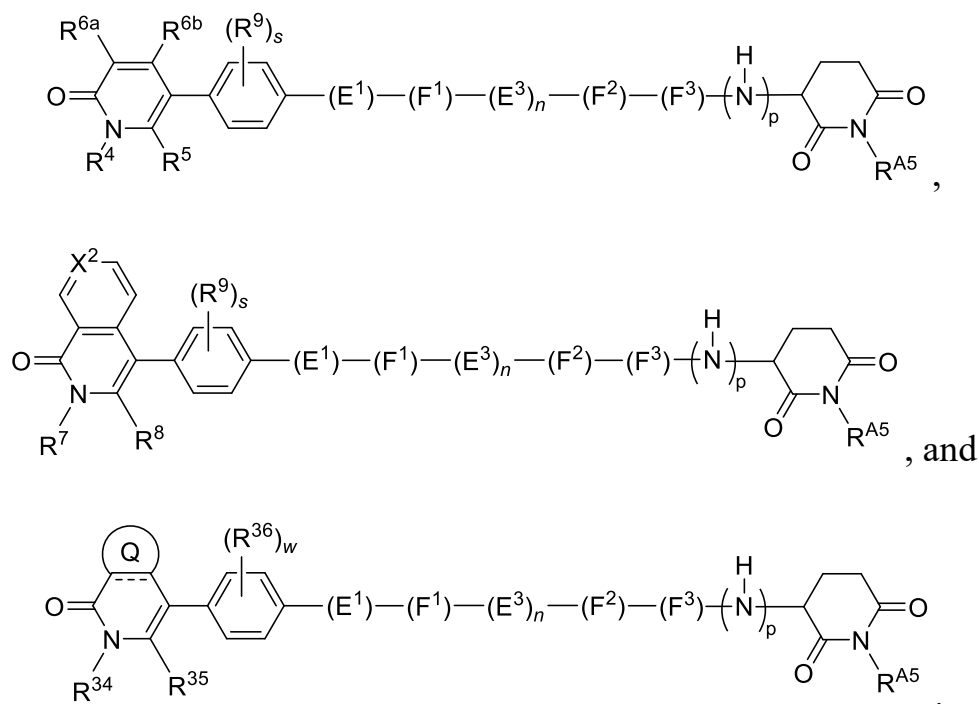
where R^N is H, optionally substituted C₁₋₄ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl (Ex.1001,503). Dr. Djuric opines that none of the compounds of the '381 Patent contain fragment



where a cyclic fragment F³ is linked to the glutarimide through a linking nitrogen.
(Ex.1014,¶133).

Claim 5

Claim 5 is directed to the compound of claim 4, where variable E² is further limited to –NH– (Ex.1001,503), and Formula I may be represented by the structures:

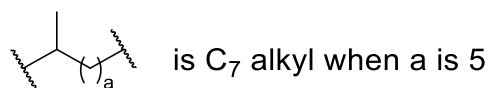
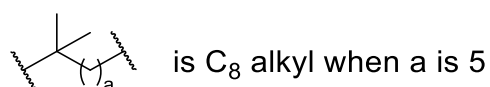


Therefore, Dr. Djuric concludes that Formula I as limited in Claim 5 does not cover a single compound described in the '381 Patent. (Ex.1014,¶135).

Claim 6

Claim 6 is directed to the compound of Claim 1, where variable n is 1 and variable E³ is further limited to a narrower subset of substituted or unsubstituted C₁-C₆ alkylene (Ex.1001,503-504). Dr. Djuric points to the “narrower” C₁-C₆ alkylene

moieties of Claim 6 with more than six carbons demonstrating PO's use of an alkyl substituent on an optionally substituted alkylene and making their recitations of length nearly meaningless. (Ex.1014, ¶136).



For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent. (*Id.*, ¶137).

Claim 7

Claim 7 is directed to the compound of Claim 1, where variable F¹ is further limited to a narrower subset of substituted or unsubstituted 4- or 5-membered heterocyclic moieties with one nitrogen heteroatom: azetidinyI or piperidinyl (Ex.1001,504). For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent. (Ex.1014, ¶138).

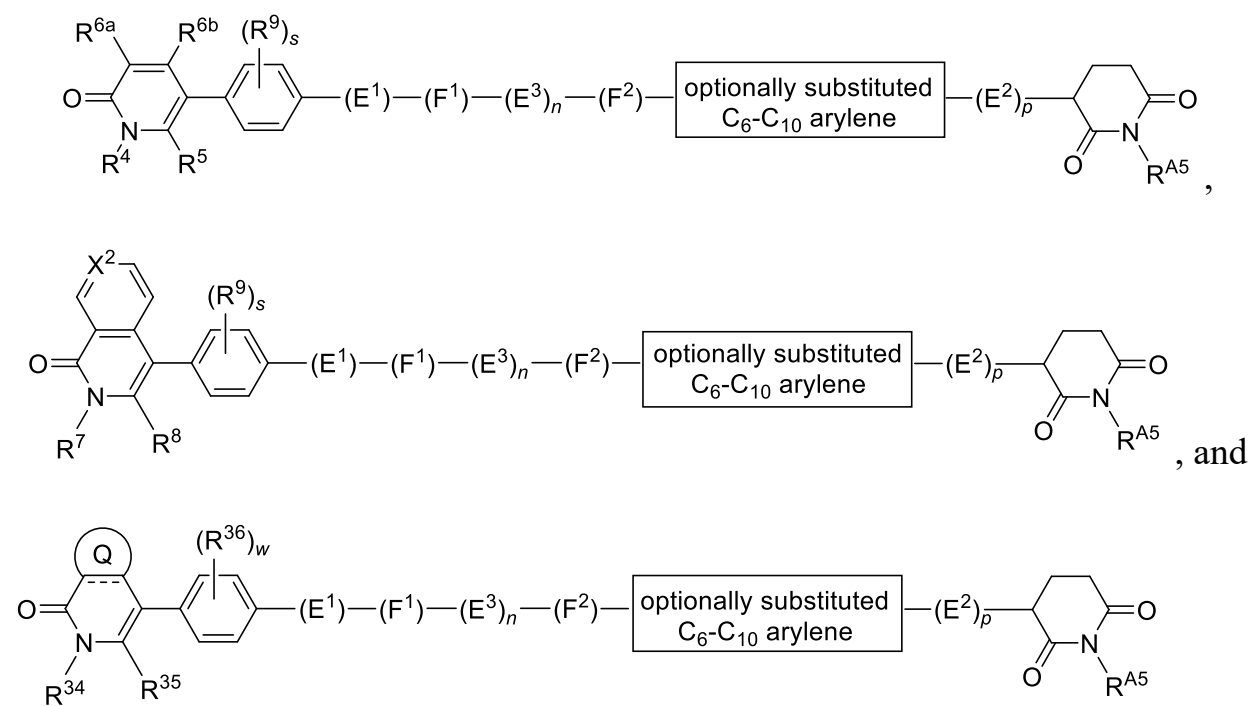
Claim 8

Claim 8 is directed to the compound of Claim 1, where variable F² is further limited to a narrower subset of substituted or unsubstituted 4- or 5-membered heterocyclic moieties with one or two nitrogen heteroatom(s): azetidinyI, piperidinyl, or piperazinyl (Ex.1001,504). For the reasons presented by Dr. Djuric

when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent. (Ex.1014,¶139).

Claim 9

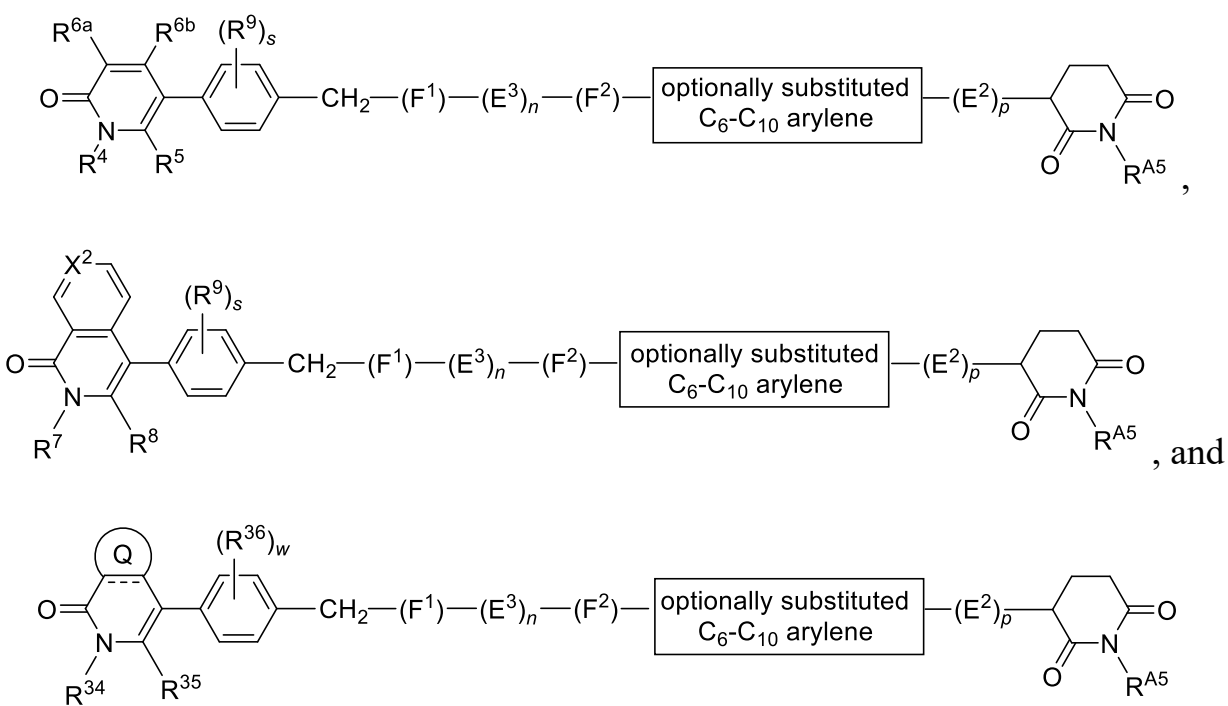
Claim 9 is directed to the compound of Claim 1, where variable F^3 is further limited to optionally substituted C_6 - C_{10} arylene (Ex.1001,504), and Formula I may be represented by the structures:



For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent. (Ex.1014,¶141).

Claim 10

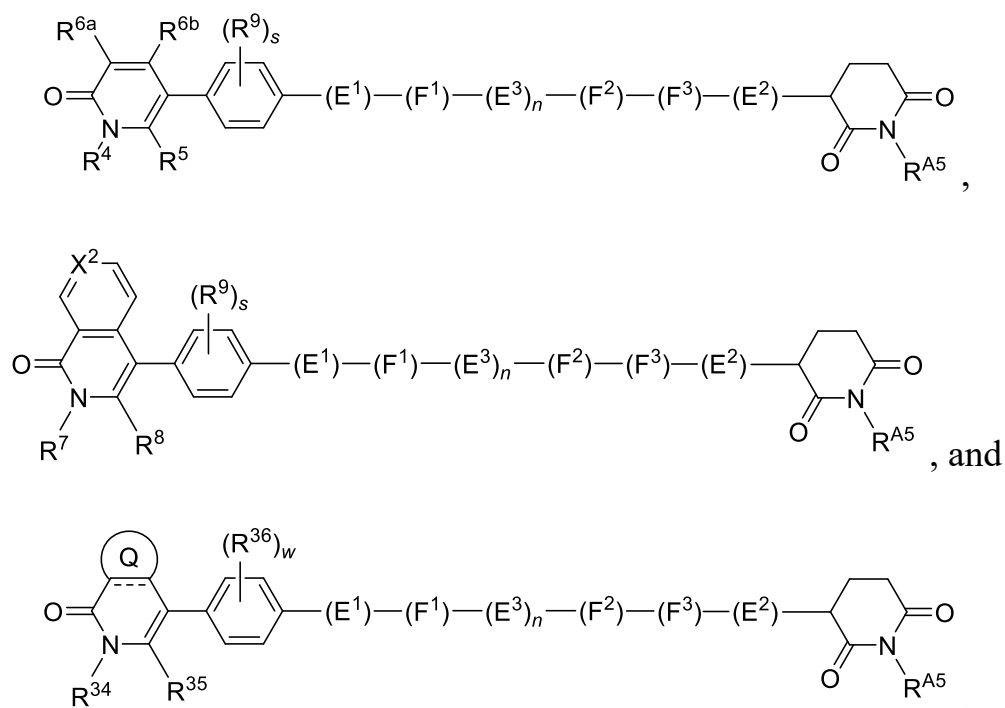
Claim 10 is directed to the compound of Claim 1, where variable E^1 is limited to CH_2 , variable E^2 is “limited” as described in Claim 3, variable E^3 is limited as described in claim 6, variable F^1 is limited to specific heterocycles as described in claim 7, variable F^2 is limited to specific heterocycles as described in Claim 8, and variable F^3 is limited to optionally substituted C_6-C_{10} arylene, (Ex.1001,504-505):



For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent. (Ex.1014,¶143).

Claim 11

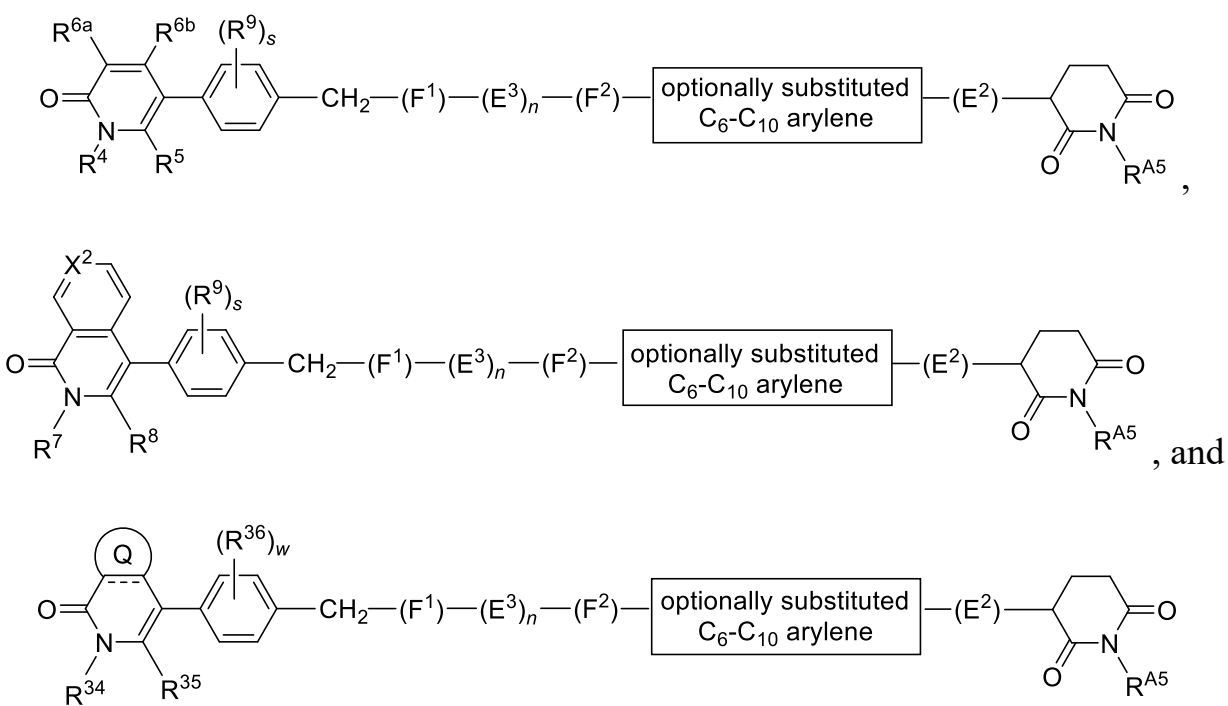
Claim 11 is directed to the compound of Claim 1, where variable p is 1. (Ex.1001,505)



For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent. (Ex.1014,¶145).

Claim 12

Claim 12 is directed to the compound of Claim 10, where variable p is 1. (Ex.1001,505).



For the reasons presented by Dr. Djuric when discussing Claim 1 above, this Formula also does not cover any compounds described in the '381 Patent. Furthermore, Dr. Djuric reviewed the specification and concluded that 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. (Ex.1014,¶147).

On the basis that the '381 Patent does not include a single compound that is drawn, made, or tested that falls within the scope of the issued claims, nor does the specification combine the elements of the subgenus of Claim 1 into one formula in the specification, Dr. Djuric concludes that the '381 Patent does not provide an adequate written description for the POSA of the claimed subject matter. (*Id.*,¶148).

Dr. Djuric's opinion on the lack of written description for the claims of the '381 Patent is bolstered by every claims reference to the multitude of nebulous "optionally substituted" which lack meaningful metes and bounds. (*Id.*,¶144).

IX. GROUND 2: CLAIMS 1-12 ARE INVALID UNDER 35 U.S.C. §112(B) FOR INDEFINITENESS

A. Law

Under 35 U.S.C. §112(b), a patent must "particularly point[] out" and "distinctly claim[]" "the subject matter which the applicant regards as his invention." A patent must be precise enough to afford clear notice of what is claimed, thereby "appris[ing] the public of what is still open to them." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 909 (2014) (citations omitted). Claims are in compliance with §112(b), "if viewed in light of the specification and prosecution

history, inform those skilled in the art about the scope of the invention with reasonable certainty.” (*Id.* at 910.)

In certain circumstances, a Markush group may be so expansive that persons skilled in the art cannot determine the metes and bounds of the claimed invention. MPEP §2173.05(h); *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1357 n.2 (Fed. Cir. 2016) (“Under the PTO’s guidelines for patent examination, “[a]lternative expressions are permitted” so long as the claim “recites a list of alternatively useable species” with no “uncertainty or ambiguity with respect to the question of scope or clarity of the claims.”).

For example, if a claim defines a chemical compound using one or more Markush groups, and that claim encompasses a massive number of distinct alternative members, the claim is indefinite under §112(b) if one skilled in the art cannot determine its metes and bounds due to an inability to envision all of the compounds defined by the Markush group(s). MPEP §2173.05(h); *see also In re Wiggins*, 488 F.2d 538, 541 (C.C.P.A. 1973) (“The terminology [“a saturated heterocyclic group of ... from one to two nitrogen atoms, and up to one oxygen atom”] employed is so loose as to be indefinite and to be entirely speculative as to the inclusion of groups forming final products having the therapeutic activity herein required... If the scope of the invention sought to be patented is unclear from the language of the claim, a second paragraph rejection will properly lie.”).

B. The Term “Optionally Substituted” is Indefinite

Petitioner urges that the pervasive use of the term “optionally substituted” in each of the '381 Patent claims renders each claim indefinite for the reasons extensively discussed in Sections VIII-G and VIII-H. For efficiency of space, those arguments will not be repeated here but are considered to support a conclusion of indefiniteness and violation of §112(b) for each claim.

C. The Terms “C₆-C₁₂ Aryl” and “C₆-C₁₀ Arylene” Are Indefinite

Petitioner urges that the terms “C₆-C₁₂ Aryl” and “C₆-C₁₀ Arylene” are indefinite under §112(b) for the reasons extensively discussed in the Claim Construction Section VII unless the Board finds that the definitions unambiguously allow attachment of a substituent group on either the aromatic or non-aromatic moiety in which case the terms violate the written description requirement. Dr. Djuric confirms that without this construction, a POSA would not have enough information from the specification to know where the substituent groups can be attached on the “C₆-C₁₂ Aryl” and “C₆-C₁₀ Arylene” moieties, leaving the terms vague, unclear and indefinite (Ex.1014, ¶¶45-46,151). The POSA would not then

have enough information to know whether a compound of interest infringes the claims due to structural uncertainty.

X. GROUND 3: CLAIMS 1-12 ARE INVALID UNDER 35 U.S.C. §112(A) FOR LACK OF ENABLEMENT

A. Law

Enablement under §112(a) requires that the “the specification teach those in the art to make and use the invention without undue experimentation.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A claim is not enabled when, “at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.” *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013); *see also In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983) (An enabling disclosure must “be commensurate in scope with the claim.”); *McRO, Inc. v. Bandai Namco Games Am., Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020) “It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997)

In analyzing undue experimentation, the factors first enumerated in *In re Wands* are considered, which include: (1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the

amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention. *In re Wands*, 858 F.3d at 737.

Although a specification does not need to “describe how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range.” *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1085 (Fed. Cir. 2021) (internal citations omitted). A specification that requires a POSA to “engage in an iterative, trial-and-error process to practice the claimed invention” does not provide an enabling disclosure.” *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010)). *See also Wyeth and Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013) (finding of nonenablement as a matter of law notwithstanding the fact that screening an individual compound for effectiveness was considered “routine” because there were “at least tens of thousands of candidate compounds” and “it would be necessary to first synthesize and then screen each candidate compound” to practice the full scope of the claims); *McRO*, 959 F.3d at 1100, n.1 (“In cases involving claims that state certain structural requirements and also require performance of some function (e.g., efficacy for a certain purpose), we have explained that undue experimentation can include undue experimentation in identifying, from among the many concretely identified

compounds that meet the structural requirements, the compounds that satisfy the functional requirement.”).

The '381 Patent claims violate the enablement requirement of §112(a), as the unclear, infinite, or boundless compounds encompassed by the claims were not (and cannot be) taught, drawn, made or tested in the specification. The specification does not and cannot teach how to make and use the full scope of the “optionally substituted” compounds that fall within the claims.

B. There is No Evidence in the '381 Patent that the Claimed Compounds have Utility under 35 U.S.C. §101 as BRD9 Degrading Compounds.

Dr. Djuric studied the '381 Patent claims and concluded that they are not enabled across their full scope for several reasons, including that there are no syntheses or biological data for any of the claimed compounds. (Ex.1014, ¶¶152-159). Dr. Djuric found that it is impossible to know how to make or use compounds covered by claims that are inadequately defined and have boundless terms. (*Id.*).

Dr. Djuric studied Examples 86 and 87 of the '381 Patent (Ex.1001,404-410). In his 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.*). (Ex.1014, ¶153).

Example 86 measured the ability of a test compound to biochemically inhibit BRD9 bromodomain in a competition binding assay (Ex.1001,404; col.775,1.57-59). In col. 777, lines 9-12, PO stated that “[a]s 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.*). According to Dr. Djuric, 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. (Ex.1014,¶154).

Likewise, Dr. Djuric refers to PO’s Example 87 to identify the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay (Ex.1001,406-410). (Ex.1014,¶155). 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 IC₅₀ value of <1 μM 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” (Ex.1001,406). Dr. Djuric concludes 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 IC₅₀ value of <1 μM in that degradation assay.

(Ex.1014,¶155). Thus, the claims lack enablement under §112 and utility under 35 U.S.C. §101.

Dr. Djuric found that 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 $< 1 \mu\text{M}$ in these assays. (*Id.*,¶156).

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

Dr. Djuric found that the problem is further compounded because the claimed compounds can have any number of unspecified “optional substituents.” (*Id.*,¶158). Dr. Djuric concludes that it is simply impossible for a POSA to determine whether any of the claimed compounds would act as intended to degrade BRD9 in a human. (*Id.*).

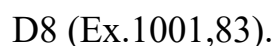
The uncertainty regarding the activity of claimed compounds is even further exacerbated by the inclusion of an infinite loop in the definition of “optionally substituted.”

Dr. Sprott has drawn over 70 compounds covered by the issued claims and identified why each drawn structure would require undue experimentation to make or use them as a BRD9 degrader, if possible at all (Ex.1015, ¶¶20-21). Several of his drawn structures required an infinite loop and he noted the uncertainty in biological activity for compounds that depart so dramatically from known structure activity relationships (“SAR”). (*Id.*, ¶¶15, 19-23). Attached Appendix 3 provides non-limiting examples of structures from Dr. Sprott that would require undue experimentation to make and use.

As Dr. Sprott notes there are limits to how much structural bulk a target protein will accept at each position and that limit cannot be determined without trial and error. (*Id.*, ¶23). Thus, a POSA would have to make and test compounds that sample the entire scope of the claimed invention to determine these SAR and use the claimed compounds as BRD9 degraders. (*Id.*) It would take an infinite amount of experimentation to test compounds across an infinite claim scope. (*Id.*)

Even without considering the infinite loop issue, the claims cover compounds that are known or at least predicted to be unable to degrade BRD9. As discussed above and in Dr. Nasveschuk’s Declaration, compounds wherein R^{A5} is a moiety such as alkyl are typically inactive. (*Id.*, ¶20).

The only compound that PO tested with R^{A5} as an alkyl (methyl) is consistent with this observation. Compound D8 has an activity of >10,000 nM according to PO's Table 5A (Ex.1001,421; col.780).



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

Dr. Djuric and Dr. Sprott agree that the specification does not provide sufficient detail to teach a POSA how to make the claimed compounds across the scope of the claims. (*See* Ex.1014,¶159; Ex.1018,¶15). In fact, as discussed extensively above in Sections VIII-G and VIII-H, 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. According to both experts a skilled artisan would require infinite experimentation to make and use compounds across an infinite scope. (Ex.1014,¶159; Ex.1018,¶23). Thus, the specification does not enable the synthesis of the claimed compounds across the scope of the claims.

Dr. Djuric notes that a detailed synthetic procedure is provided for fewer than a fourth of the drawn molecules (D1 to D74) (Ex.1001,254-382). (Ex.1014,¶160). 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. (*Id.*). For example,

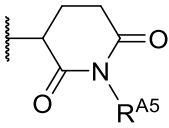
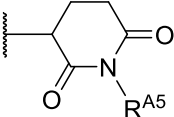
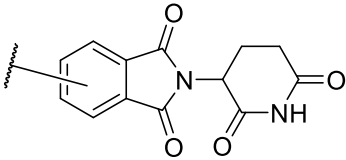
focusing on the  and Linker moieties Dr. Djuric found that every molecule except D6 with a detailed synthesis differs in both moieties, and D6 does not have the claimed degradation moiety. (*Id.*).

Table 5

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

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* Ex.1001,382, 385,

393, 394, 404). Dr. Djuric notes that these compounds are also not covered by the '381 Patent claims. (Ex.1014,¶162).

Even if a POSA concludes that it would have been routine to make compounds falling within the claims where there are no optional substituents, Dr. Djuric finds it impossible for a POSA to conclude that it would be routine to make a virtually infinite number of compounds with an unspecified variety of substituents. (*Id.*,¶156).

Dr. Sprott identified dozens of other compounds which are covered by the claims which would be extremely difficult or impossible to make and isolate. (Ex.1018,¶20).

D. Application of the Wand's Factors Demonstrates a Lack of Enablement

Dr. Djuric analyzed the claims by considering relevant factors and found a lack of enablement as described below when the continuously used vague and open-ended term “optionally substituted” is used in the claim analysis (Ex.1014,¶163):

- (i) The quantity of experimentation necessary.

According to Dr. Djuric, the claims cover a vast and unbounded number of molecules. (*Id.*). He concludes that the quantity of experimentation necessary to enable a POSA to make and use compounds across an infinite scope is an infinite amount of experimentation. (*Id.*).

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

The necessary experimentation is beyond routine experimentation for medicinal chemistry because in Dr. Djuric's opinion the compounds in the claims are not sufficiently defined. (*Id.*). As noted in the Section VII, the claims do not even exclude compounds which are unstable. (*Id.*). And it would take infinite experimentation to test the utility of an infinite number of compounds as fall within the claims when the scope of "optionally substituted" is considered. (*Id.*).

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

Dr. Djuric found that 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. (*Id.*).

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

In Dr. Djuric's opinion the guidance of the specification is primarily focused on the synthesis and use of BRD9 degraders with phthalimide-like cereblon binders which are not covered by the claims. (*Id.*). There is not a single drawn, synthesized, or tested compound in the patent which is covered by the claims. (*Id.*).

(v) The nature and predictability of the field.

As noted by Dr. Djuric the field of BRD9 degraders is complex and unpredictable. Small changes can create profound differences in activity. (*Id.*). The claims are packed with optional substituents and there are an unbounded number of

compounds covered which would require synthesis and testing to determine if their optional substituents were appropriate. (*Id.*).

(vi) The level of ordinary skill.

As discussed in Section VI Dr. Djuric's definition of a POSA requires 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. (*Id.*). Likewise, it would be impossible to predict whether they would work for the intended function. (*Id.*). The claims cover compounds of potentially infinite size, which exceeds the level of ordinary skill. (*Id.*).

(vii) The scope of the claimed invention.

As discussed in Dr. Djuric's Declaration and in Sections VIII-G and VIII-H the scope of the invention is unbounded because of the multiple uses of "optionally substituted" in the claims. (*Id.*). And the scope can be considered infinite because of the infinite loop problem. (*Id.*).

Dr. Djuric concludes that all seven of these factors weigh in favor of finding the claims invalid for lack of enablement over the full scope of the granted claims (Ex.1014, ¶159).

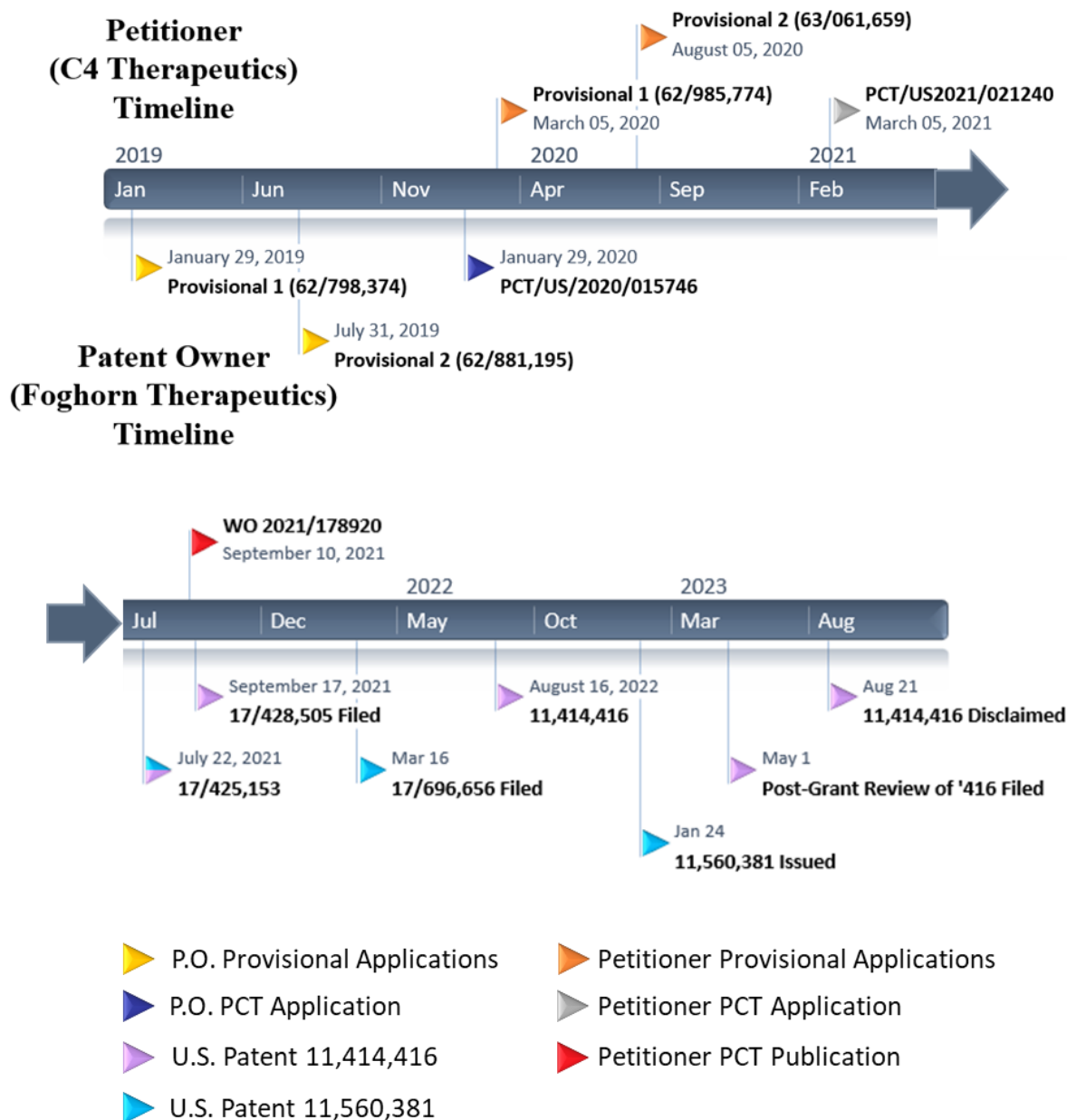
XI. NONE OF THE CLAIMS ARE ENTITLED TO A PRIORITY DATE EARLIER THAN MARCH 16, 2022

As discussed in Sections VIII-X above, the priority applications, PCT Application, and even the parent application of the '381 Patent fail to disclose the presently claimed combination of substituents. (Ex.1014,¶165). Thus, the claims are not entitled to a priority date earlier than March 16, 2022, which is when PO filed the claims with the USPTO (*see* Ex.1002,137-563), and not that date either.

XII. GROUND 4: THE INTERVENING '920 PCT PUBLICATION IS A NOVELTY DESTROYING REFERENCE TO CLAIMS 1-12 OF THE '381 PATENT

A claim is invalid for anticipation if “a single prior art reference discloses each and every limitation of the claimed invention.” *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (citation omitted). “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.” *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) (citation omitted).

The timeline below provides in diagram form the filing dates of the '381 Patent and the intervening '920 PCT publication (Ex.1010).

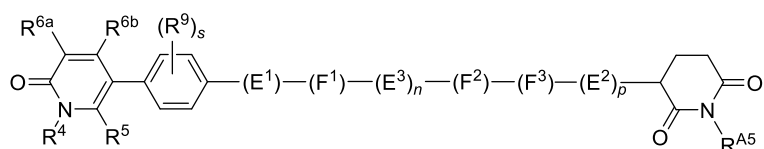
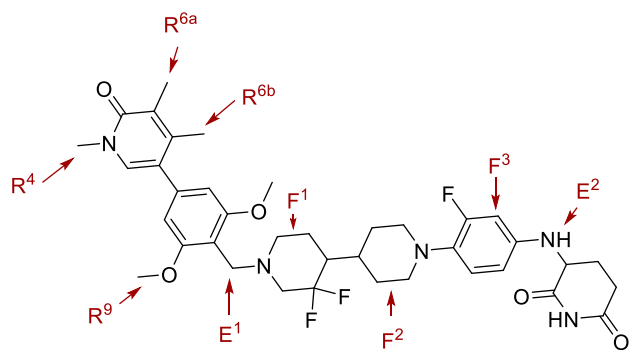


Dr. Djuric determined that claims 1-12 of the '381 Patent are anticipated under 35 U.S.C. §102 by the '920 PCT Publication, which describes over a dozen compounds that are within the scope of at least one claim of the '381 Patent including, for example, Compounds 70, 172, 182, 184, 185, 187, 188, 195, 198, 206, 225, 231, 251, and 265 of the '920 PCT Publication (see structures and citations in

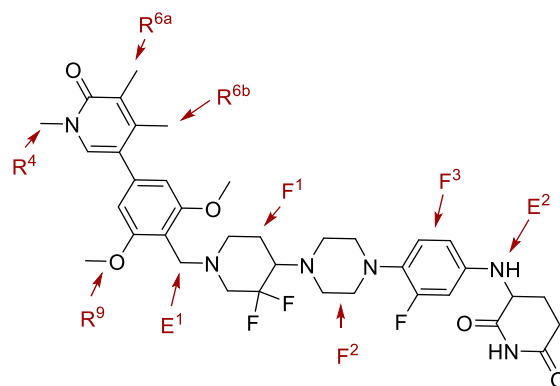
Table 5 below) (Ex.1014,¶¶174-188). Dr. Nasveschuk confirms that these compounds were synthesized and tested according to the procedures provided in the '920 PCT Publication (Ex.1018,¶¶9-14). Each of the described compounds exhibited a DC_{50} of less than 100 nM. (Ex.1014,¶171).

Table 5

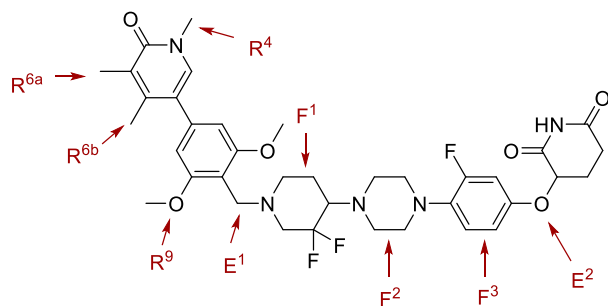
For Formula I where A is Formula IIIb:



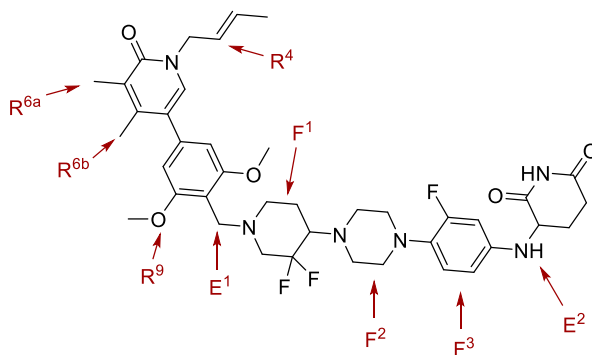
C4T Compound 198 Ex. 1010 at 711



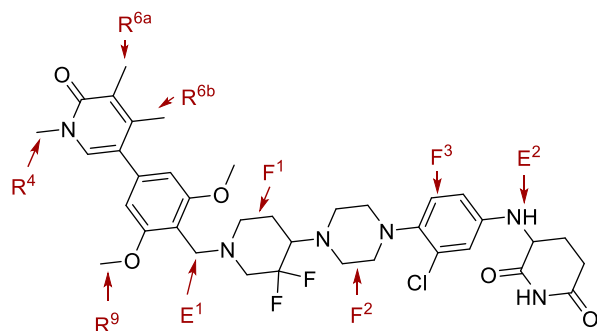
C4T Compounds 172-176 Ex. 1010 at 704-705



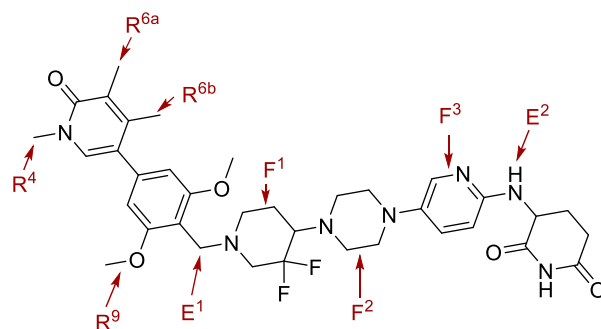
C4T Compound 251 Ex. 1010 at 724



C4T Compound 265 Ex. 1010 at 728

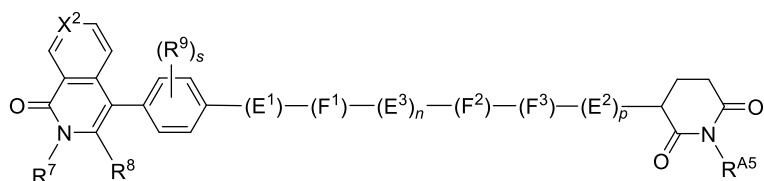
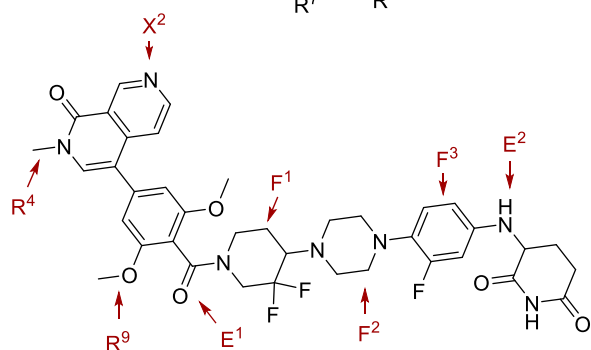


C4T Compound 187 Ex. 1010 at 708

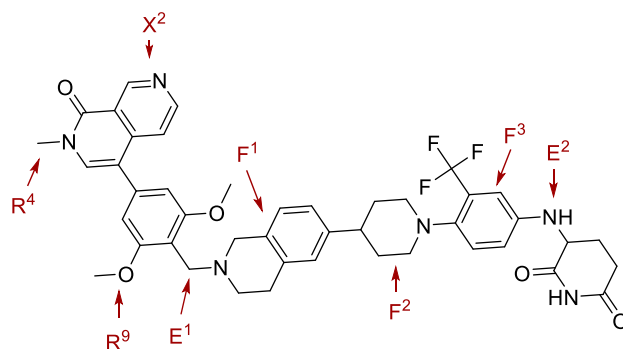


C4T Compound 195 Ex. 1010 at 710

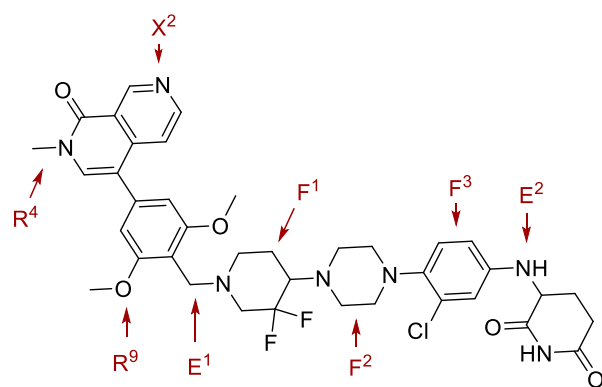
For Formula I where A is Formula IVa:



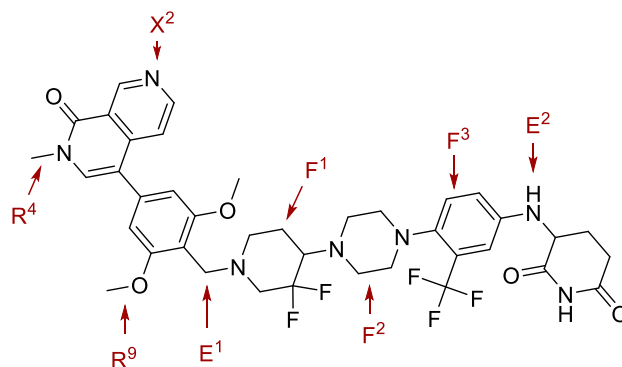
C4T Compound 225 Ex. 1010 at 717



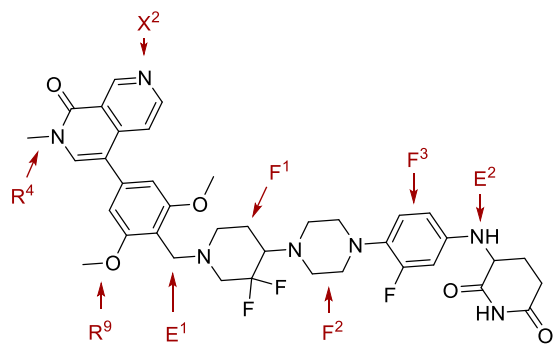
C4T Compound 231 Ex. 1010 at 719



C4T Compound 188 Ex. 1010 at 708

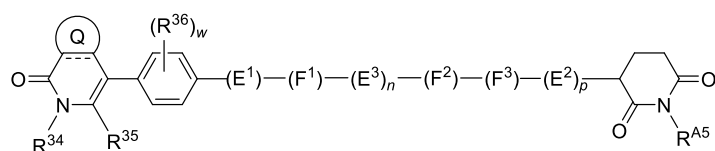
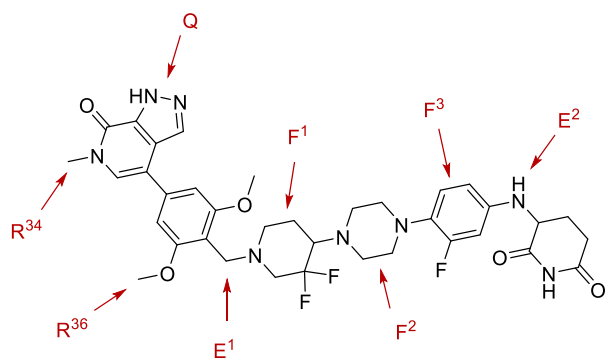


C4T Compound 185 Ex. 1010 at 707

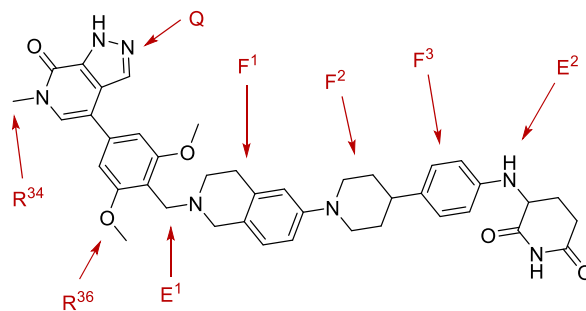


C4T Compound 184 Ex. 1010 at 707

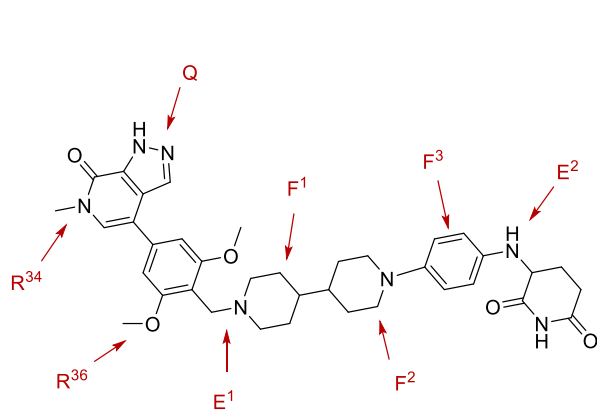
For Formula I where A is Formula IX:



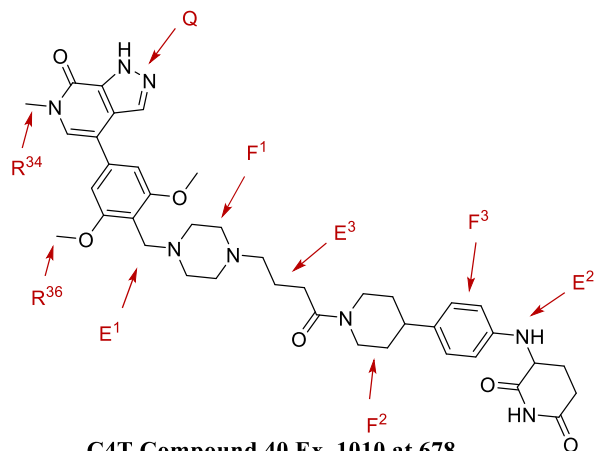
C4T Compound 182 Ex. 1010 at 707



C4T Compound 206 Ex. 1010 at 713



C4T Compound 70 Ex. 1010 at 679



C4T Compound 40 Ex. 1010 at 678

C4T's '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, as Dr. Djuric notes the '920 PCT Publication provides the synthesis and data for over a dozen compounds that fall within the claims of the '381 Patent. (Ex.1014,¶172). This is in sharp contrast to the '381 Patent which does not provide synthesis or data for a single compound in its issued claims. (*Id.*).

The following Table matches representative compounds of the '920 PCT Publication (Ex.1010) to claims that they anticipate in the '381 Patent. Dr. Djuric confirms the accuracy of this table (Ex.1014,¶173).

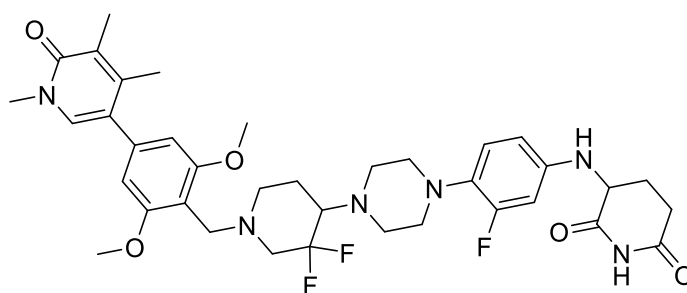
Table 6

US Patent No. 11,560,381 Claim	Compound from C4T '920 PCT Publication
1	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, 265. (<i>See</i> Ex.1010, 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).

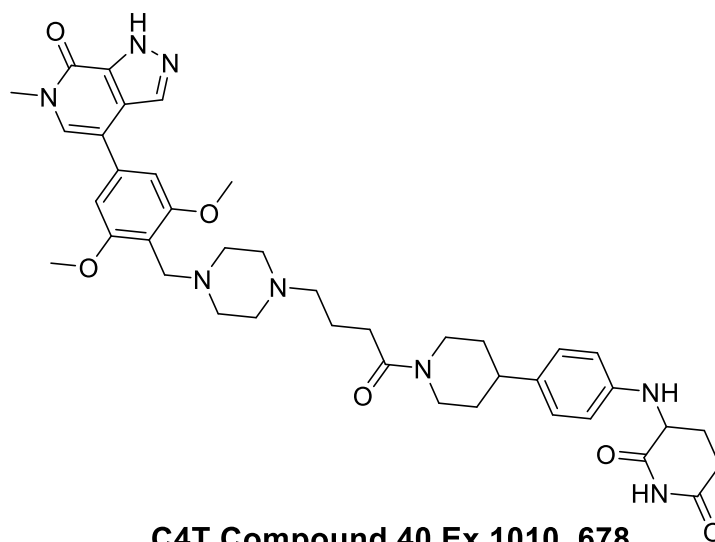
3	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708, 710-711, 713, 707, 719, 724, 728).
4	C4T Compounds 40, 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 265. (<i>See id.</i> , 671, 679, 704-705, 707-708,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

C4T Compound 172 reads on every claim of the '381 Patent except claim 6. (Ex.1014, ¶174). Claim 6 is anticipated by C4T Compound 40. (*Id.*).



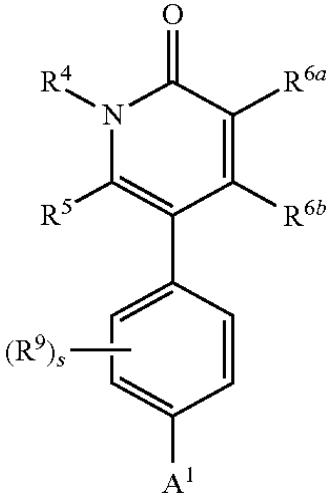
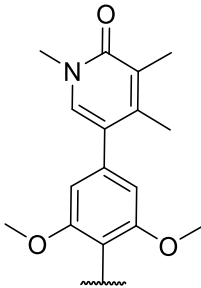
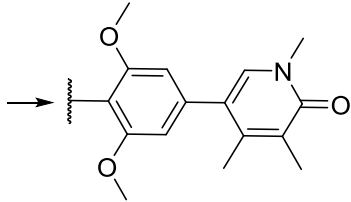
C4T Compound 172 - Exh. 1010 at 704



C4T Compound 40 Ex.1010, 678

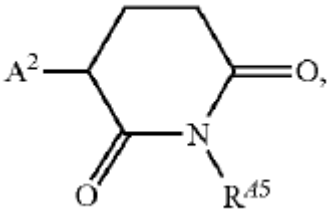
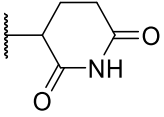
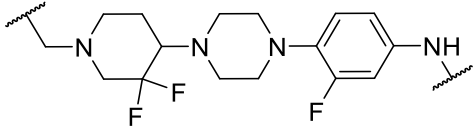
In the Table below, Dr. Djuric provides the selection of variables for each substituent in the '381 Patent claims which when combined cover C4T Compound 172. (Ex.1014,¶175).

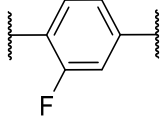
Table 7

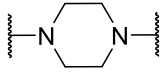
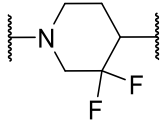
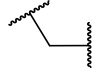
Claim 1	
A compound having the structure of Formula I: A-L-B	
'381 Patent	Cmp 172 ('920 PCT)
<p>Reads on the corresponding moiety</p>  <p>A is</p>	<p>of C4T Compound 172 as follows</p> 
<p>A¹ is bond between A and L</p>	<p>The A¹ bond is in the same location</p> 

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;	Methyl is a subset of optionally substituted C ₁ -C ₆ alkyl
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 a 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	Methyl is a subset of optionally substituted C ₁ -C ₆ alkyl

<p>carbocyclyl, optionally substituted C₂-C₉</p> <p>heterocyclyl, optionally substituted C₆-C₁₀ aryl,</p> <p>optionally substituted C₂-C₉ heteroaryl,</p> <p>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;</p>	
<p>each R⁹ is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀</p> <p>carbocyclyl, optionally substituted C₂-C₉</p> <p>heterocyclyl, optionally substituted C₆-C₁₀ aryl,</p> <p>optionally substituted C₂-C₉ heteroaryl,</p> <p>optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino</p>	<p>Methoxy is a subset of optionally substituted C₁-C₆ heteroalkyl</p>
<p>s is 0, 1, 2, 3 or 4</p>	<p>s is 2</p>

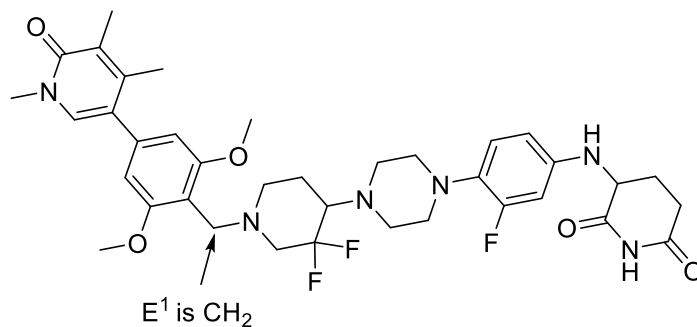
<p>B is</p> 	<p>Reads on the corresponding moiety</p>  <p>of C4T Compound 172 as follows</p>
<p>A^2 is a bond between B and L</p>	<p>The A^2 bond is in the same location</p>
<p>R^{45} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;</p>	<p>H is hydrogen</p>
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

<p>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;</p> <p>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;</p>	<p> is a NR^N wherein R^N is hydrogen</p>
<p>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,</p>	<p> is an optionally substituted C_{6-C10} arylene</p>

<p>F² is, independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene,</p>	 is an optionally substituted C ₂ -C ₁₀ heterocyclylene
<p>F¹ is, independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene,</p>	 is an optionally substituted C ₂ -C ₁₀ heterocyclylene
<p>E¹ is, independently, O, S, NR^N, optionally substituted C₁₋₁₀ alkylene, optionally substituted C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C₂-C₁₀ polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene;</p>	 is an optionally substituted C ₁₋₁₀ alkylene

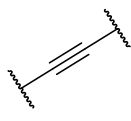
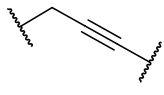
Claim 2

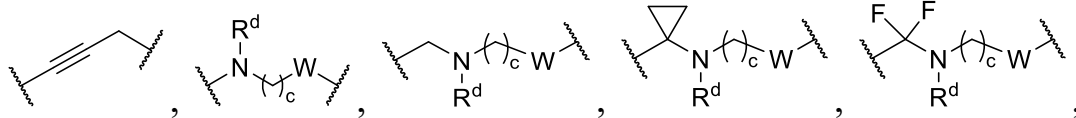
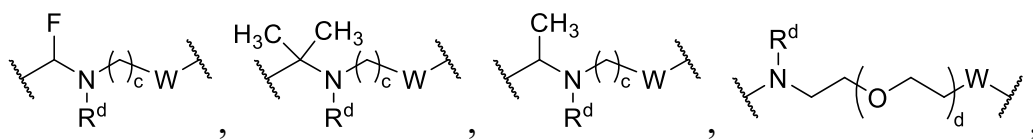
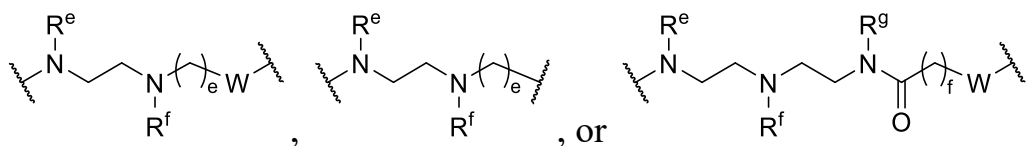
The compound of Claim 1, wherein E¹ is -CH₂-.

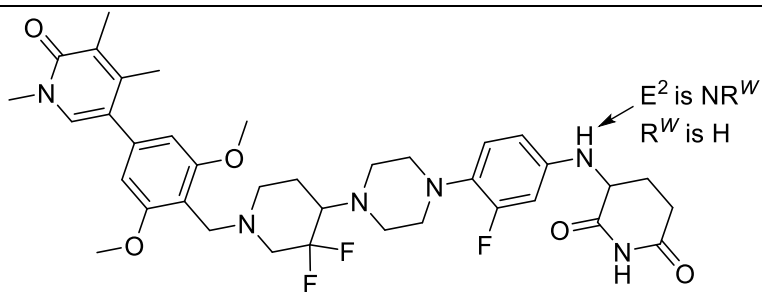


C4T Compound 172

Claim 3

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





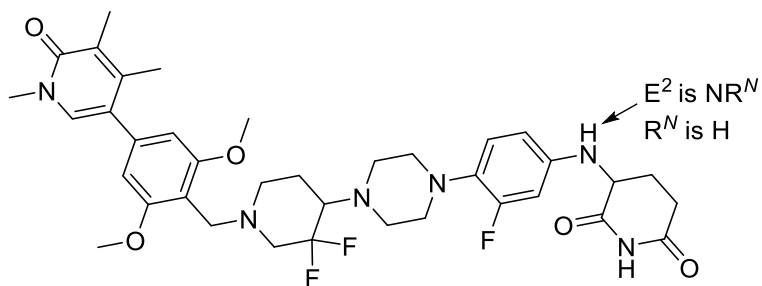
C4T Compound 172

Claim 4

The compound of claim 3, wherein E^2 is $-NR^N-$.

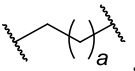
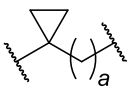
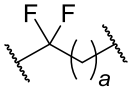
Claim 5

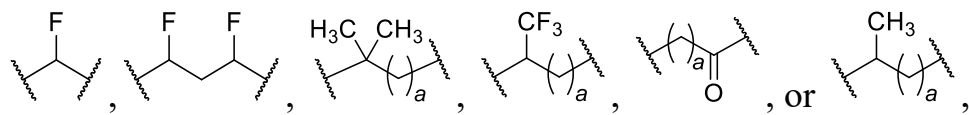
The compound of claim 4, wherein E^2 is $-NH-$.



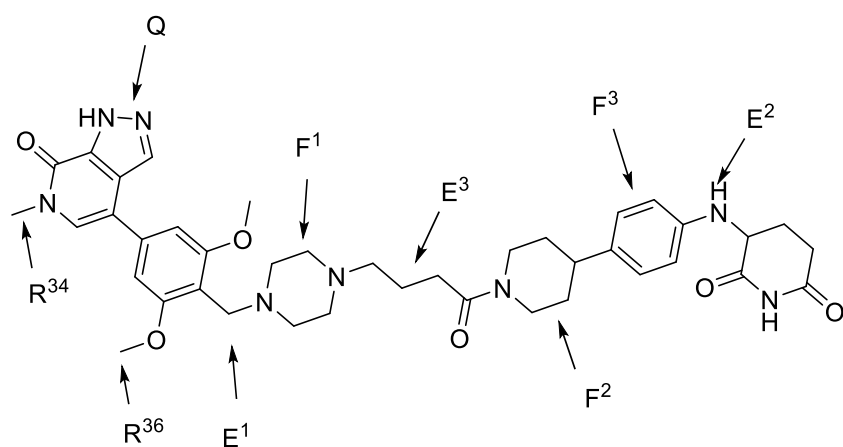
C4T Compound 172

Claim 6

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



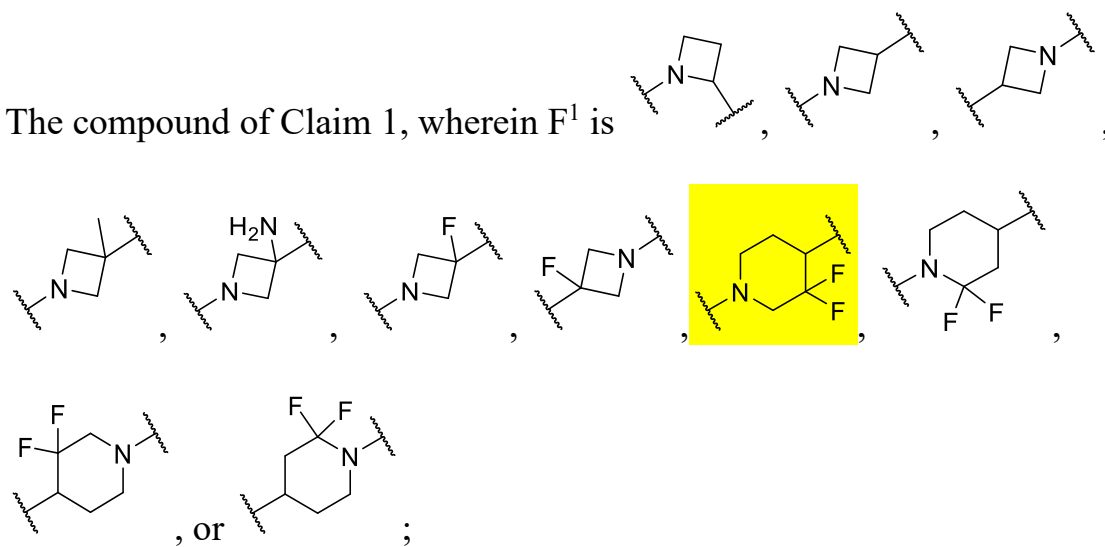
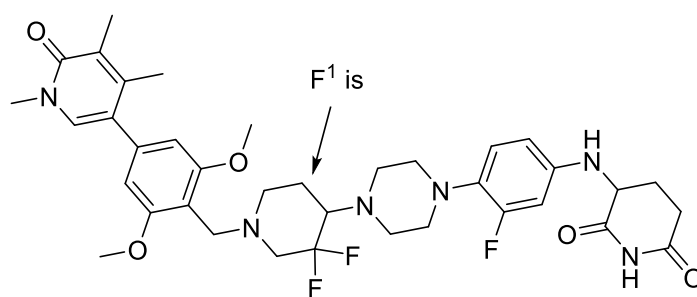
where a is 0, 1, 2, 3, 4, or 5.



C4T Compound 40

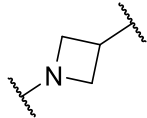
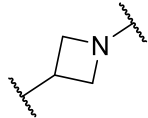
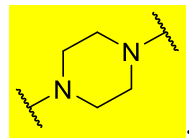
Claim 7

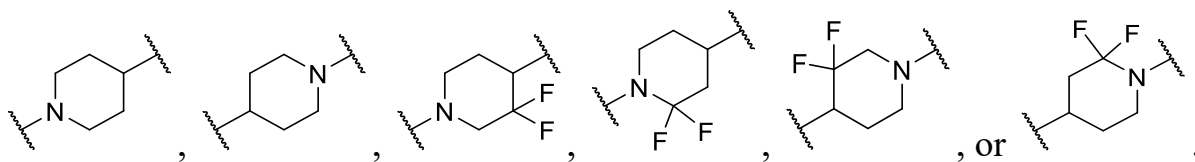
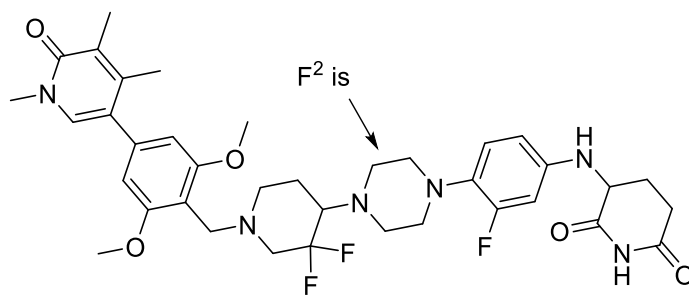
The compound of Claim 1, wherein F¹ is



C4T Compound 172

Claim 8

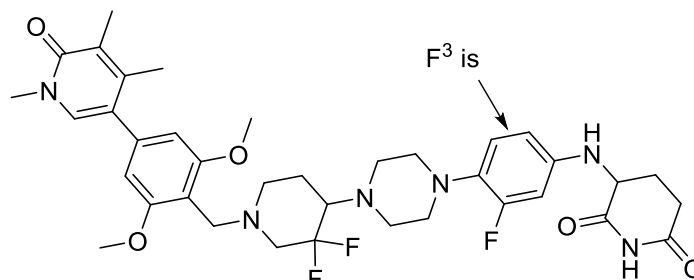
The compound of Claim 1, wherein F^2 is , , , or



C4T Compound 172

Claim 9

The compound of Claim 1, wherein F^3 is optionally substituted C_6 - C_{10} arylene.

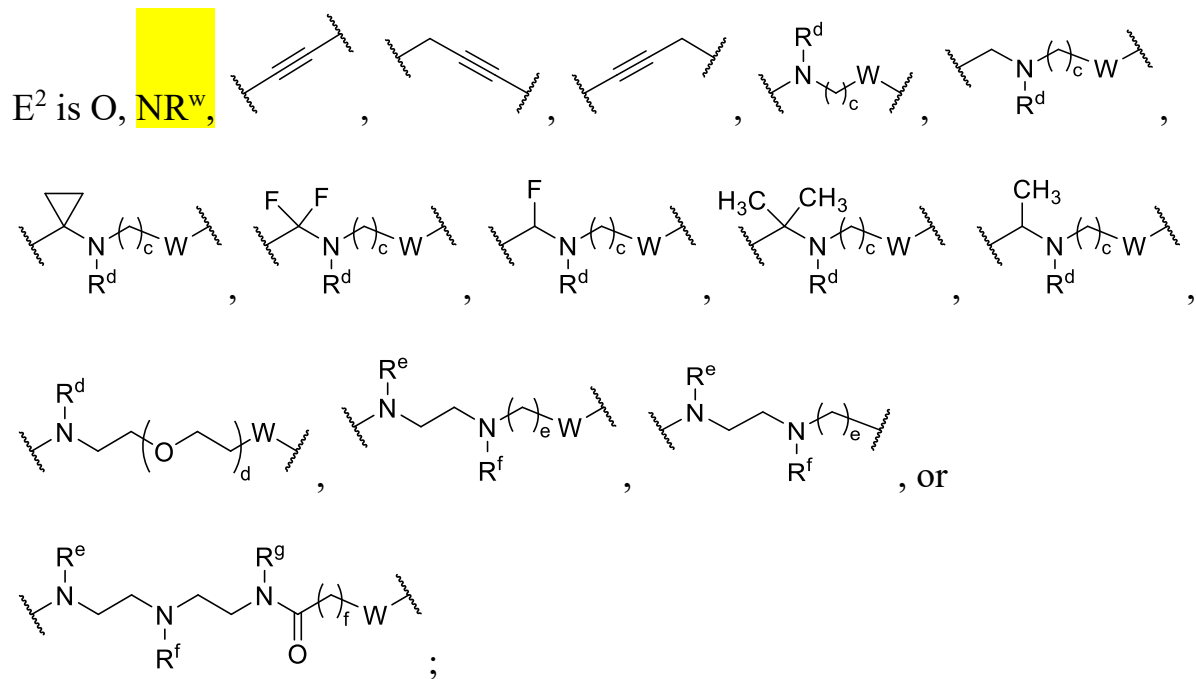


C4T Compound 172

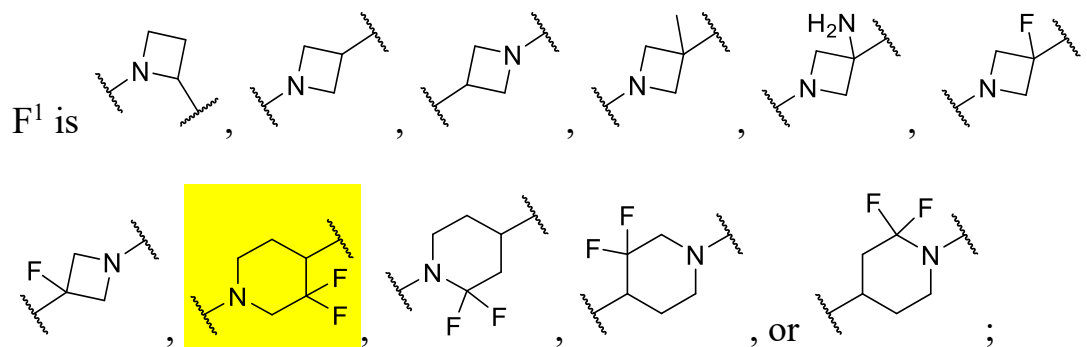
Claim 10

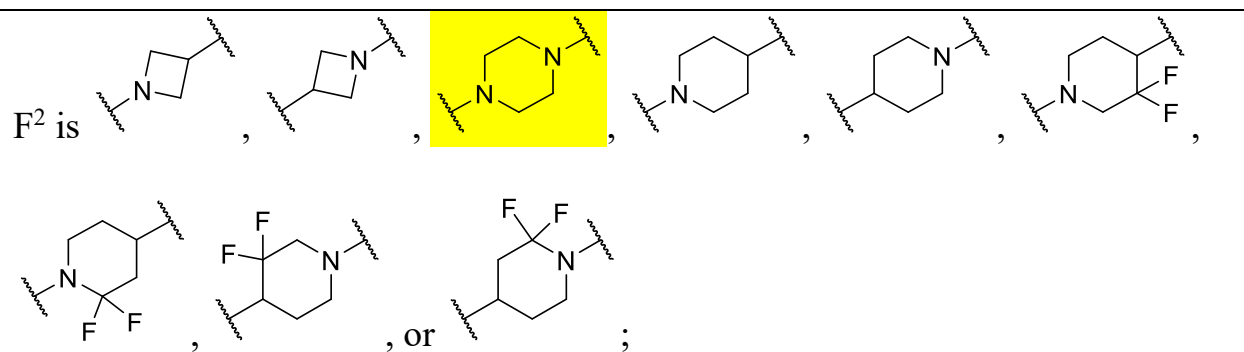
The compound of Claim 1, wherein

E¹ is -CH₂-;

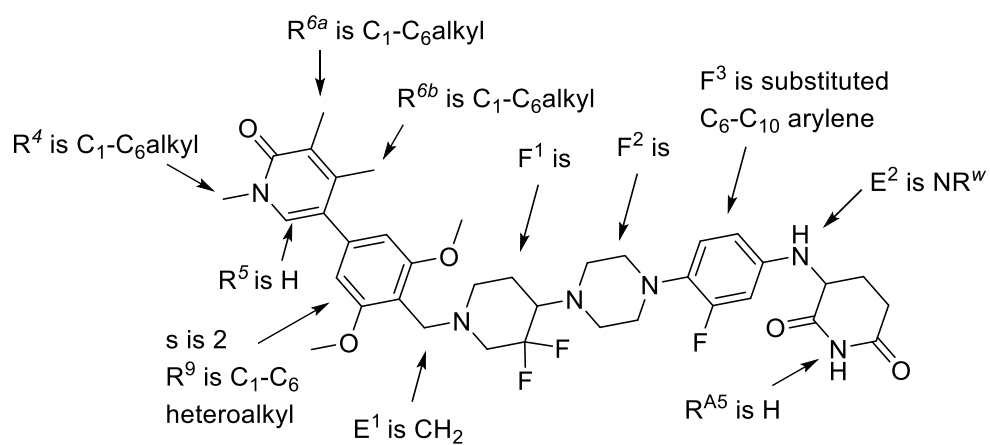


n is 0 or 1;





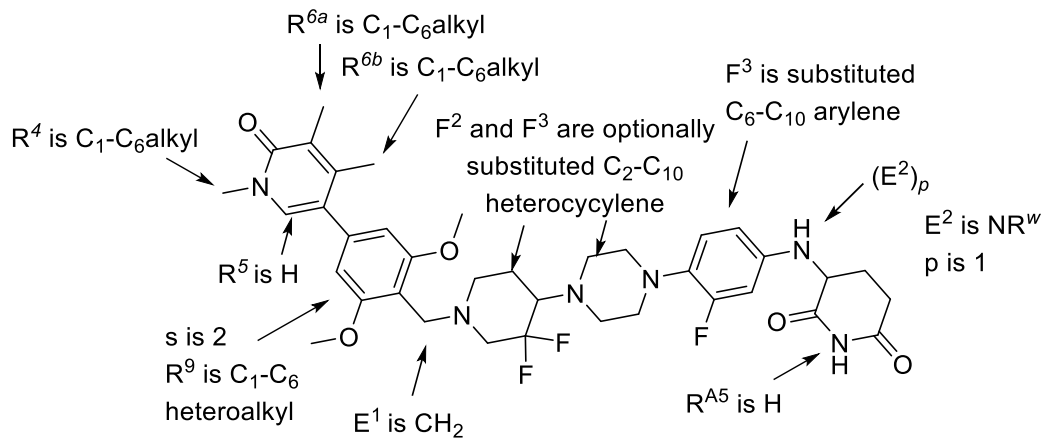
F^3 is optionally substituted C_6-C_{10} arylene;



C4T Compound 172

Claim 11

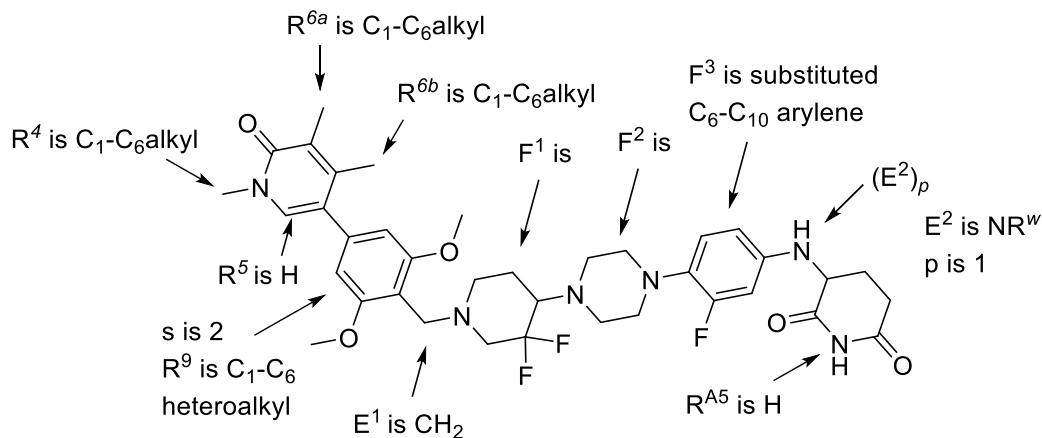
The compound of Claim 1, wherein p is 1.



C4T Compound 172

Claim 12

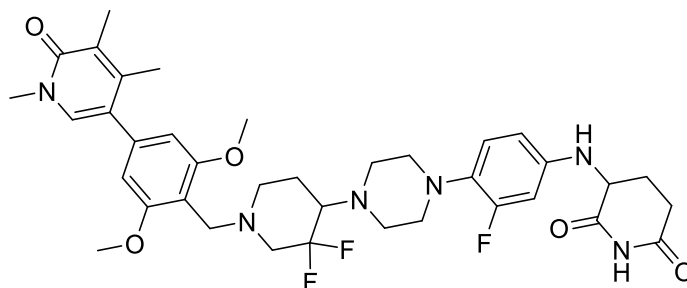
The compound of Claim 10, wherein p is 1.



C4T Compound 172

C4T Compound 172 and its isolated diastereomer (C4T Compound 176) were tested in over a dozen additional assays and experiments beyond the DC_{50}

determination (Ex.1010,13-16 and 758-775 (FIGS.1-24)). (Ex.1014,¶176). Dr. Djuric reviewed the figures and data and came to the following conclusions (*Id.*,¶¶177-188).



C4T Compound 172 - Exh. 1010 at 704

Figure 1 demonstrates that C4T Compound 172 has a strong effect on tumor volume in an *in vivo* mouse synovial sarcoma xenograft model (Ex.1010,13; 1.27-29; 758 (FIG.1)). (Ex.1014,¶177).

Figure 2 and Figure 3 demonstrate that C4T Compound 172 selectively degrades BRD9 over BRD7 and BRD4 (Ex.1010,14 (1.1-6); 758 (FIG.2); 759 (FIG.3)). (Ex.1014,¶178).

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 (Ex.1010,14 (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)). (Ex.1014,¶179).

Figure 6 provides PK data for C4T Compound 172 in another *in vivo* mouse synovial sarcoma xenograft model (Ex.1010,14 (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)). (Ex.1014,¶180).

Figure 9 demonstrates the tolerability of C4T Compound 172 in an *in vivo* mouse synovial sarcoma PDX-model (Ex.1010,14 (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)). (Ex.1014,¶181).

Figure 11 demonstrates that C4T Compound 176 selectively degrades BRD9 over BRD7 and BRD4 (Ex.1010,15 (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))). (Ex.1014,¶182).

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 (Ex.1010,15 (1.14-16); 766 (FIG.14))). (Ex.1014,¶183).

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 (Ex.1010,15 (1.17-21); 767 (FIG.15))). (Ex.1014,¶183).

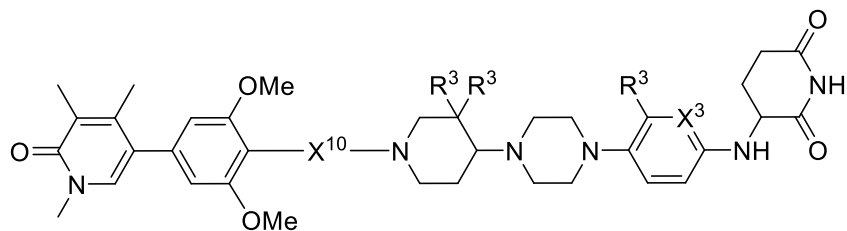
Figure 16 is a confluence graph that demonstrates the dose response effect (inhibition) on the growth of Yamato synovial sarcoma cells by C4T Compound 176 (Ex.1010,15 (1.22-25); 768 (FIG.16)). Figure 17 demonstrates the lack of BAF wildtype growth inhibition in the presence of C4T Compound 176 in a SW982 cell line (*see id.*,15 (1.26-28); 769 (FIG.17)). (Ex.1014,¶184).

Figure 18 provides pharmacokinetic (PK) data for C4T Compound 176 in an *in vivo* mouse synovial sarcoma xenograft model (Ex.1010,15 (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)). (Ex.1014,¶185).

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* Ex.1010,16 (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)). (Ex.1014,¶186).

Dr. Djuric also found that the C4T '920 PCT Publication also includes several genus formulas that anticipate the '381 Patent claims. For example, on pages 62 and 63 of the '920 PCT Publication there are at least five formulas that read on the claims of the '381 Patent (Ex.1010,64-65). (Ex.1014,¶187). 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 (*Id.*).



Ex. 1010 at 64

In total there are over a dozen compounds and at least five formulas described in the '920 PCT Publication that anticipate at least one claim of the '381 Patent. (Ex.1014,¶188).

XIII. CONCLUSION

For reasons described herein, Petitioner urges the Board to determine that it is more likely than not that at least one claim of the '381 Patent is invalid under one or more grounds of 35 U.S.C. §112(a), §112(b), and/or §102 and order the PGR to proceed. Petitioner also requests a final determination that all of claims 1-12 of U.S. Patent No. 11,560,381 be cancelled as unpatentable.

Respectfully submitted,

Date: October 23, 2023



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**CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION
OF 37 C.F.R. §42.24**

Pursuant to Rule 37 C.F.R. §42.24(d), the undersigned certifies that, based on the word count of the word-processing system used to prepare this paper, the number of words in this Petition is 18,655. This word count does not include the items that may be excluded from the count under 37 C.F.R. §42.24(a), including the table of contents, table of authorities, mandatory notices, list of exhibits, certificate of service and certificate of word count.

Date: October 23, 2023

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing petition for Post Grant Review of U.S. Patent No. 11,560,381, including all Exhibits, was served on October 23, 2023, via Express Mail delivery directed to the following correspondence address of record for the patent:

Clark+Elbing LLP/Foghorn Therapeutics,
101 Federal Street
Boston, MA 02110

A courtesy copy of the foregoing petition for Post Grant Review of U.S. Patent No. 11,560,381, including all Exhibits, was served on October 23, 2023, via Express Mail delivery directed to the following:

Michael LaCascia
Chief Legal Officer
500 Technology Square
Suite 700
Cambridge, MA 02139

Date: October 23, 2023

/Brent R. Bellows/

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APPENDIX 1: CLAIMS OF THE '381 PATENT

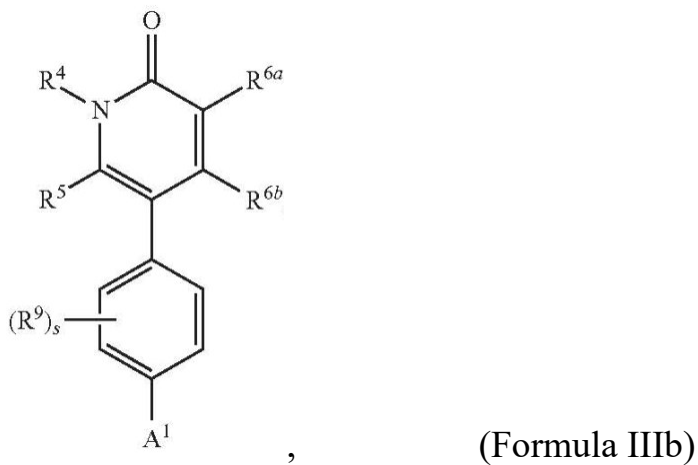
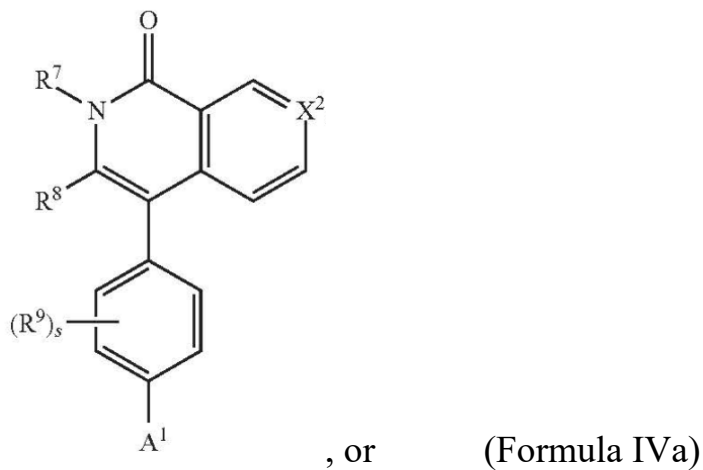
The '381 Patent claims are provided below.

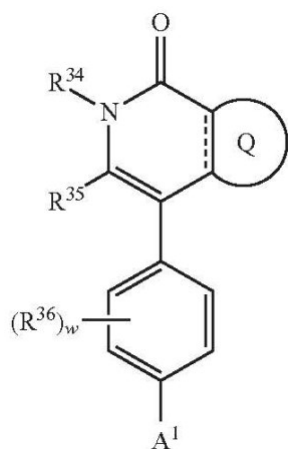
Claim 1 - A compound having the structure of Formula I:



wherein

A is:





(Formula IX)

wherein

A¹ is a bond between A and L;

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

R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl,

R⁵ is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl;

R^{6a} is H, halogen, cyano, 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^{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;

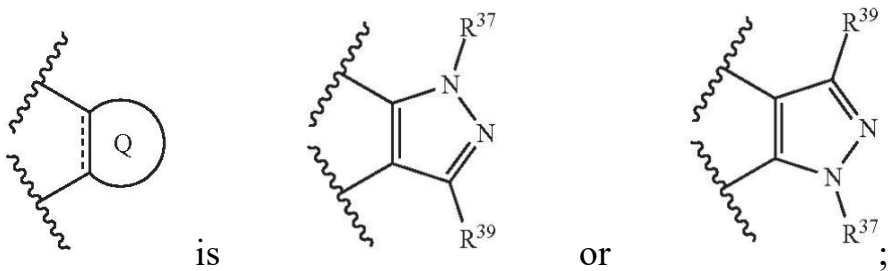
X^2 is N or CR^{10b} ;

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;

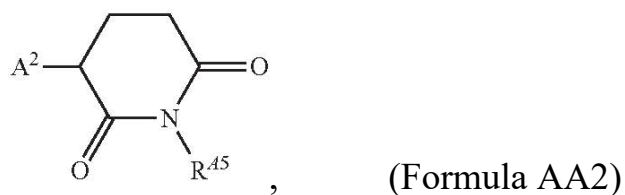
each R³⁶ is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted 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:

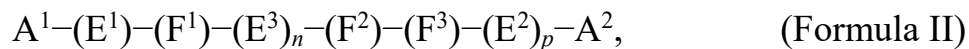


wherein

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;

A^2 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

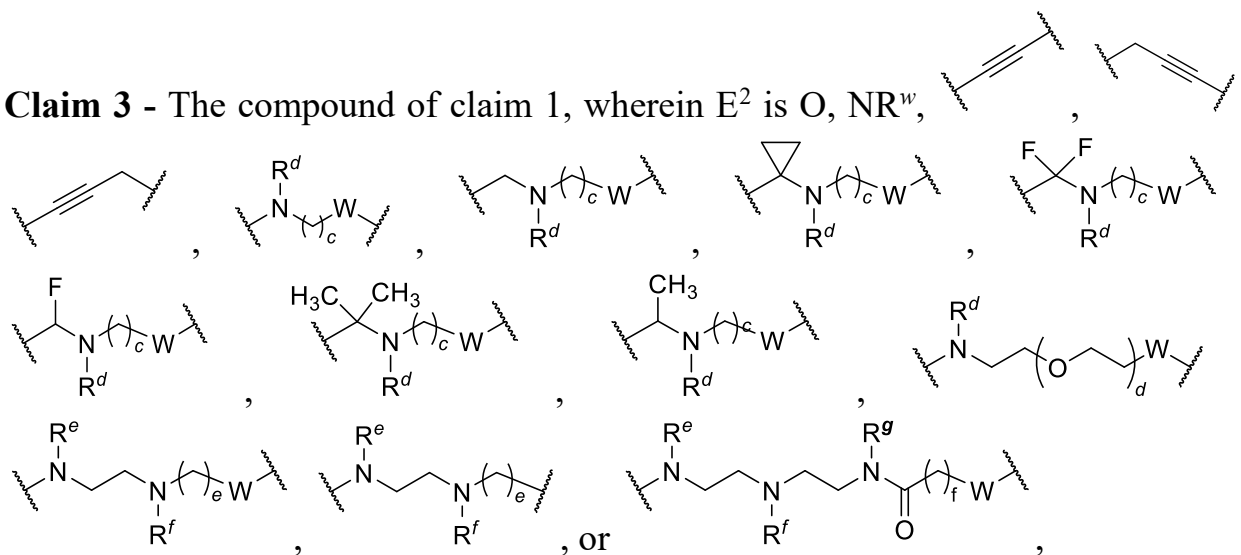
each of F¹, F², and F³ is, independently, optionally substituted C_{3-C10} carbocyclylene, optionally substituted C_{2-C10} heterocyclylene, optionally substituted C_{6-C10} arylene, or optionally substituted C_{2-C9} heteroarylene,

or a pharmaceutically acceptable salt thereof. (Ex.1001,502-503⁹).

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

⁹ 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;

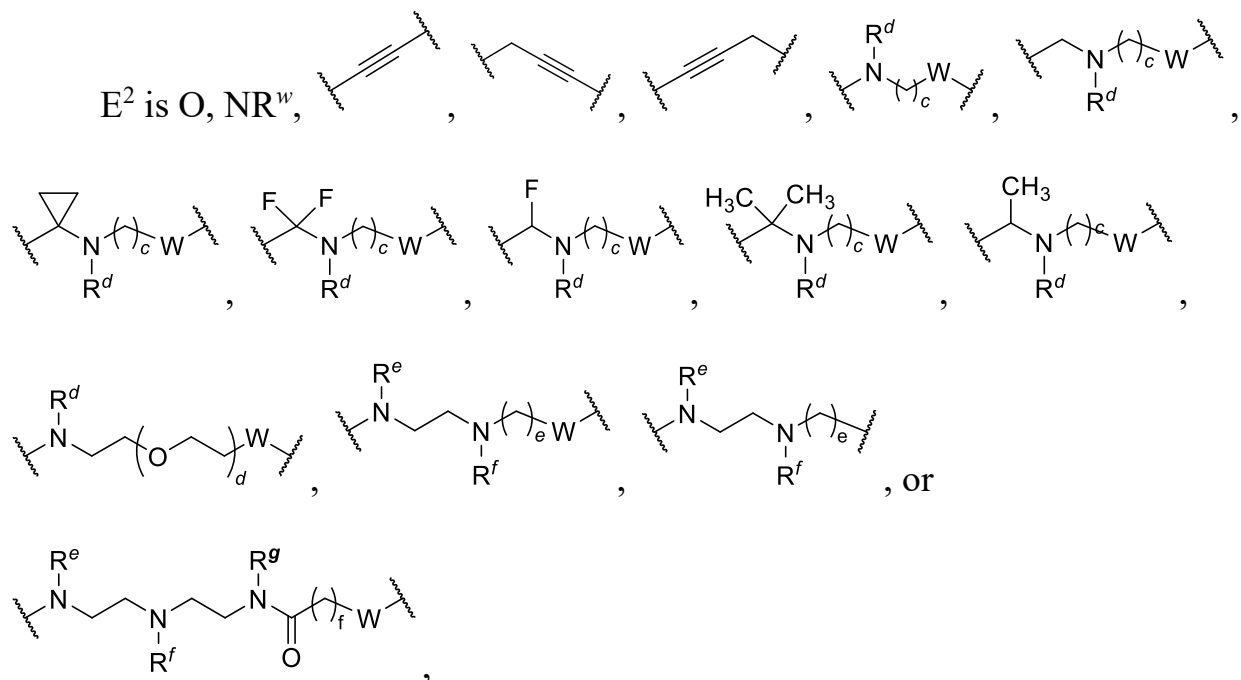
R^f is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

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

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-;



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 C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

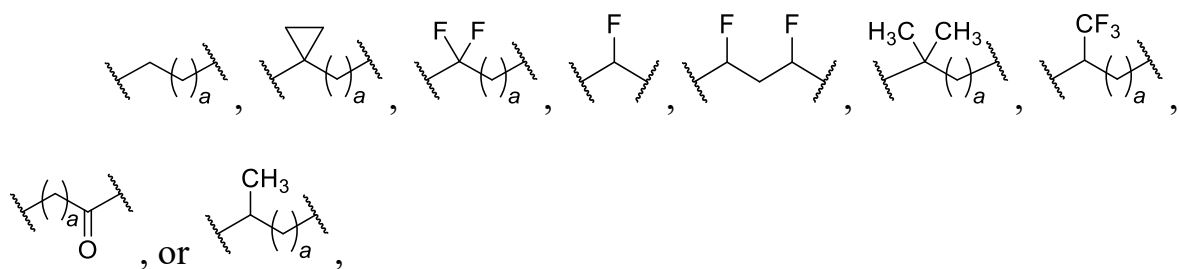
R^f is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

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;

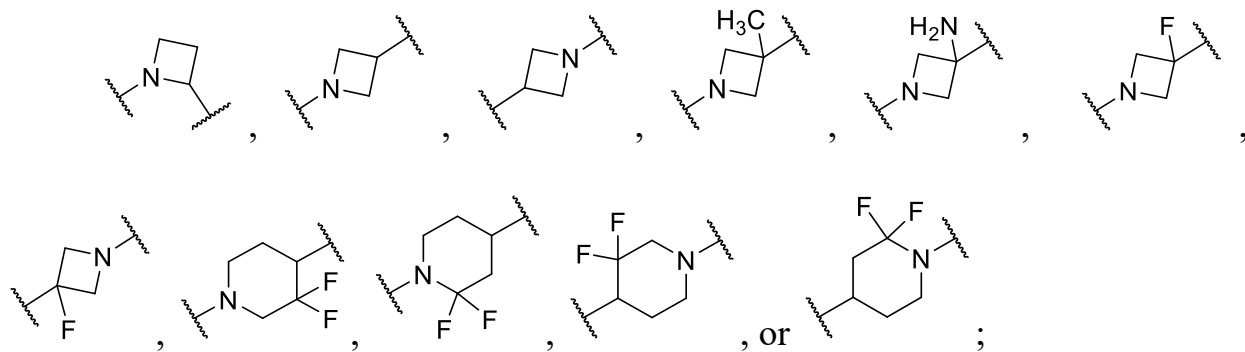
n is 0 or 1;

E^3 is

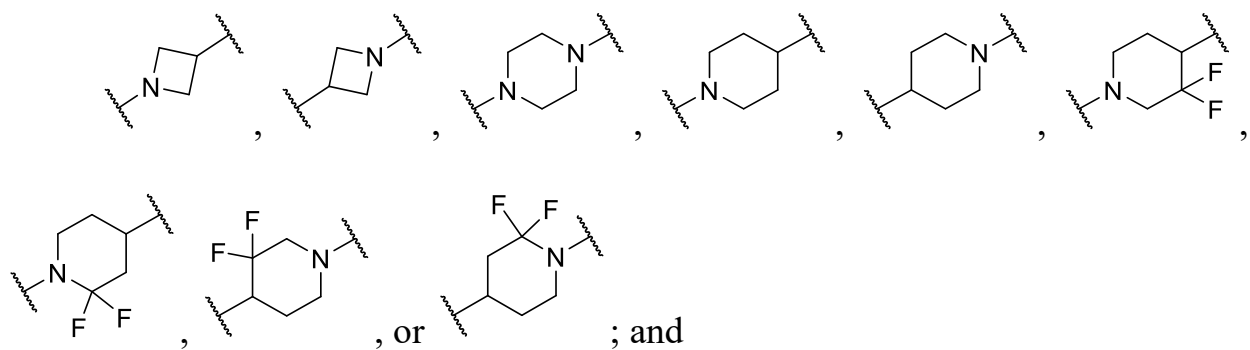


where a is 0, 1, 2, 3, 4, or 5; and

F^1 is



F^2 is



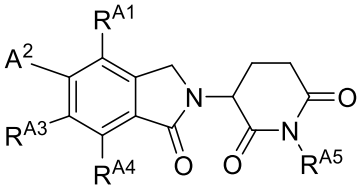
F^3 is optionally substituted C_6-C_{10} arylene. (*Id.*, at 504-505).

Claim 11 - The compound of claim 1, wherein p is 1. (*Id.*, at 505)

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

APPENDIX 2

Pthalimide or Analog Thereof Formulas			
Formula	Structure	Formula	Structure
Formula A		Formula A7	
Formula A1		Formula A8	
Formula A2		Formula A9	
Formula A3		Formula A10	
Formula A4		Formula in col. 81, lines 55-65	
Formula A5		Formula in col. 82, lines 1-10	

<p>Formula</p> <p>A6</p>			
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APPENDIX 3

EXEMPLARY COMPOUNDS OF THE '381 PATENT CLAIMS WHICH REQUIRE UNDUE EXPERIMENTATION TO MAKE AND/OR USE

