

Filed On Behalf Of:

C4 Therapeutics, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

C4 THERAPEUTICS, INC.

Petitioner,

v.

FOGHORN THERAPEUTICS, INC.

Patent Owner.

PGR No.: To Be Assigned

U.S. Patent No. 11,414,416

**PETITION FOR POST GRANT REVIEW OF
U.S. PATENT NO. 11,414,416**

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PETITIONER'S LIST OF EXHIBITS

Exhibit No.	Document
1001	U.S. Patent No. 11,414,416
1002	File History of U.S. Patent No. 11,414,416
1003	U.S.S.N. 62/798,374
1004	U.S.S.N. 62/881,195
1005	PCT/US2020/015746
1006	U.S.S.N. 62/985,774
1007	U.S.S.N. 63/061,659
1008	U.S.S.N. 17/425,153
1009	PCT/US2021/021240
1010	WO2021/178920
1011	U.S.S.N. 17/478,505
1012	U.S.S.N. 17/541,035
1013	US 2022-0098194 A1
1014	Declaration of Stevan W. Djuric, Ph.D.
1015	Brien et al., Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma. Elife. 2018 Nov 15;7:e41305
1016	Hohmann et. al., Sensitivity and Engineered Resistance of Myeloid Leukemia Cells to BRD9 Inhibition, Nature Chemical Biology, 12, 672-679 (2016)
1017	Declaration of Christopher G. Nasveschuk, Ph.D.
1018	Remillard, et al, Degradation of the BAF Complex Factor BRD9 by Heterobifunctional Ligands. Angew. Chem Int Ed Engl. 56(21):5738-5743 (2017)
1019	Martin, et al, Structure-Based Design of an in Vivo Active Selective BRD9 Inhibitor. J. Med. Chem. 59(10):4462-4475 (2016)
1020	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)
1021	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

1022	Sender et al., Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLOS Biology 14(8): e1002533 (2016)
1023	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. INTRODUCTION

C4 Therapeutics, Inc. (“Petitioner”) requests Post Grant Review (“PGR”) of claims 1-15 of United States Patent No. 11,414,416 to Ruppel et al., titled “Compounds and Uses Thereof” (“’416 Patent”) (Ex.1001), owned by Foghorn Therapeutics, Inc. (“Patent Owner” or “PO”). This Petition establishes that it is more likely than not that the claims of U.S. Patent No. 11,414,416 are invalid.

Petitioner supports this Petition with a Declaration from Stevan W. Djuric, Ph.D. (Ex.1014), the President of DCaT Consulting LLC and former Vice President, Discovery Chemistry and Technology, Abbvie Inc.; and a Declaration from Christopher G. Nasveschuk, Ph.D. (Ex.1017), Senior Vice President, Chemistry, C4 Therapeutics, Inc.

Petitioner is a clinical stage 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

¹The term heterobifunctional compound 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).

(CFT8634 to degrade BRD9; and CFT1946 to degrade mutant BRAF). It has a third heterobifunctional protein degrader (CFT8919 to degrade mutant EGFR) for which an Investigational New Drug application is expected to be submitted later this year.

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

The issued claims of the '416 Patent are an undeserved land grab for an exclusionary interest in compounds PO had not invented as of its priority filing dates. As described in detail below, and supported by the Declaration of Stevan W. Djuric, Ph.D., (Ex.1014), the '416 Patent claims genres of heterobifunctional pharmaceutical compounds, without a single claimed compound synthesized, tested, evaluated or even specifically drawn, in the patent (Ex.1014 ¶19). The claims represent an aspirational basket of compounds that the '416 Patent specification 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). Therefore, the '416 Patent claims are not entitled to their first provisional patent priority date of January 29, 2019 (Ex.1003), the second provisional patent priority date of July 31, 2019 (Ex.1004), the PCT priority date of January 29, 2020 (Ex.1005), the PCT continuation priority date of July 22, 2021 (Ex.1008), or even its current filing date of September 17, 2021 (Ex.1011).

Further, as described in detail below, because the '416 Patent claims are not entitled to any priority date earlier than their actual filing date of September 17, 2021 (and not that date either), the claims are also invalid as anticipated under 35 U.S.C. §102 and obvious under 35 U.S.C. §103 over intervening PCT/US2021/021240 (“’240 Application” (Ex.1009)), 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.1006)) and August 5, 2020 (U.S.S.N. 63/061,659 (Ex.1007)), which was filed in the U.S. as U.S.S.N. 17/541,035 on Dec. 2, 2021 (Ex.1012). In fact, the intervening ’920 PCT Publication does something that the ’416 Patent fails to do—it actually draws, makes, and tests over a dozen species encompassed by the ’416 Patent claims, including C4T’s oral BRD9 degrader currently in Phase 1 human clinical trials, CFT8634, thereby clearly anticipating the challenged unsupported ’416 Patent claims.

In addition, as described in detail below, the ’416 Patent claims are invalid as indefinite under 35 U.S.C. §112(b) because the metes and bounds of the claims cannot be determined by a POSA (Ex.1014, ¶19). Each of the ’416 Patent claims includes the term “optionally substituted” (in fact all claims include the term multiple times due to embedded variables), which, as purportedly defined in the ’416 Patent specification, results in compounds that can have absurd structures, and some

with a vast or even infinite number of substituents (*Id.*). The scope and boundaries of these claimed compounds also exemplify the “infinite loop” fatal flaw sometimes seen in patent specification drafting which results in compounds that are not definable because they are open to and include unlimited substitutions and size (*Id.*). None of these compounds were drawn or shown to exist by PO, certainly were not made (nor could they be made), and would not work for the intended purpose (*Id.*). Because a POSA cannot determine the metes and bounds of the claims with reasonable certainty, the claims are indefinite, and thus invalid (*Id.*).

Further, the claims also violate the enablement requirement of 35 U.S.C. §112(a), as the unclear, infinite or boundless compounds were not (and cannot be) taught, drawn, made, or tested in the specification (*Id.*). 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.*).

II. 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))

Petitioner is not aware of any presently pending judicial matters that would affect, or be affected by, a decision in the proceedings. PO’s U.S. Application Nos.

17/425,153 and 17/993,330 which are presently pending before the USPTO claim priority to the same PCT application (PCT/US2020/015746) as the '416 Patent. U.S. Patent No. 11,560,381 is a continuation of the '416 Patent.

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.

III. TIME FOR FILING PETITION (37 C.F.R. §42.202)

The '416 Patent issued on August 16, 2022. (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 (May 16, 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. The written description, indefiniteness, enablement, and prior art arguments raised by Petitioner here were not raised by the Examiner during prosecution, because no rejections at all were given by the Patent Office---these invalid claims were granted with a first action Notice of Allowance. (Ex.1002, 520-527).

A. 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.

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

Petitioner certifies under 37 C.F.R. §42.204(a) that the '416 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 '416 Patent is available for PGR, because the claims have an effective filing date on or after March 16, 2013.

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

Petitioner respectfully requests PGR of claims 1-15 of the '416 Patent and cancellation of claims 1-15 as unpatentable under 35 U.S.C. §112(a), §112(b), §102(a)(1), and §103. It is more likely than not that claims 1-15 are unpatentable in view of the following unpatentability grounds and prior art references.

Ground	Claims	Statutory Basis	Prior Art References
1	1-15	35 U.S.C. §112(a) – Lack of Written Description	
2	1-15	35 U.S.C. §112(b) – Indefinite	
3	1-15	35 U.S.C. §112(a) – Lack of Enablement	
4	1-15	35 U.S.C. §102(a)(1)	'920 PCT Publication (Ex.1010)
5	1-15	35 U.S.C. §103	'920 PCT Publication (Ex.1010)

IV. EXPERT TESTIMONY FROM STEVAN W. DJURIC, PH.D.

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 their 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 held the role as a Distinguished Research Fellow at Abbvie from 2015-2019, which is the highest ladder of scientific achievement at the company. Dr. Djuric was also a member of their 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 degrader compounds that can address diseases of aging (*Id.*, ¶7).

Prior to his role as VP of Discovery Chemistry, Dr. Djuric was the Senior Director of Discovery Chemistry and Technology and Head of the Abbvie Global Medicinal Chemistry leadership team (Ex.1014, ¶9).

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 is also a member of the faculty in the School of Pharmacy at the University of Kansas and has held an adjunct faculty position in the School of Pharmacy at High Point University, N.C. (*Id.*, ¶12).

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).

Dr. Djuric confirms that Petitioner has explained to him the meets and bounds of the legal standards of 35 U.S.C. §112 (a) and (b) as well as 35 U.S.C. §102 and §103 (*Id.*, Sec. IV). Based on his extensive experience, including in particular with heterobifunctional protein degrader compounds, Dr. Djuric concludes that the inventors of the '416 Patent did not invent the compounds currently claimed in the '416 Patent because if they had, certainly some would have been drawn, made, and/or tested as of the relevant priority dates, which they were not (*Id.*, ¶19). Dr. Djuric also concludes that the claims of the '416 Patent are unclear and boundless leading to absurd and impossible compounds (*Id.*). They do not place a POSA on notice whether it would be infringing the claims (*Id.*). In addition, Dr. Djuric concludes that Petitioner's '920 PCT Publication is anticipatory to the '416 Patent, or renders it obvious (*Id.*, ¶19).

V. BACKGROUND

A. Protein Degradation Primer

(i) Basics of Heterobifunctional Compounds for Protein Degradation

Dr. Djuric has provided the following Protein Degradation Primer in Section V of his Declaration (*Id.*, ¶¶ 27-32).

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. (Ex.1014, ¶66).

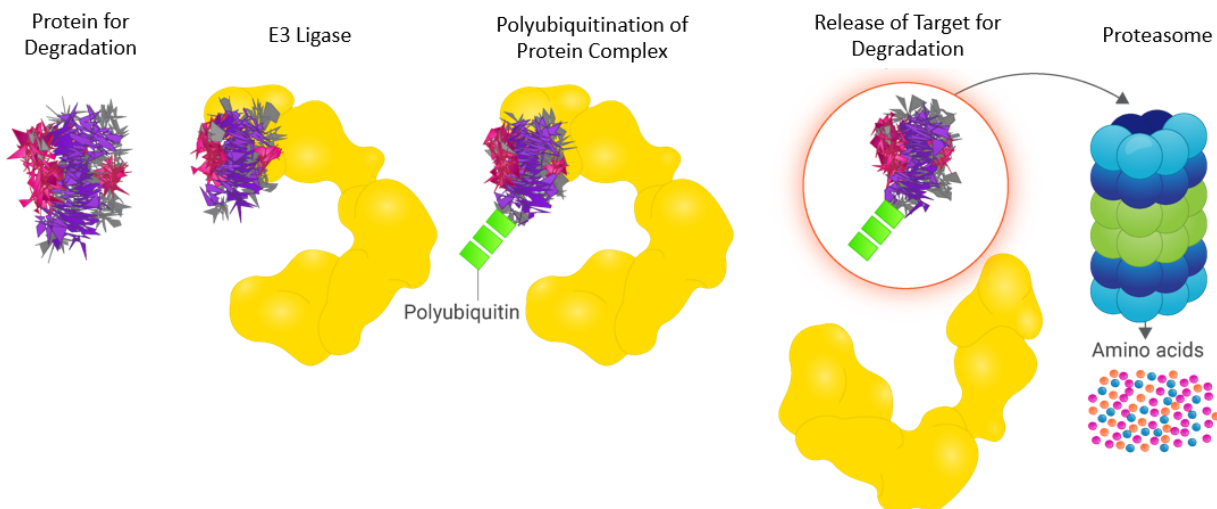


FIG. 1

Cereblon is the enzyme receptor component of the multi-protein complex cullin 4-RING E3 ligase that is relevant to the '416 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.*, ¶67).

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.*, ¶68). 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.*, ¶68)

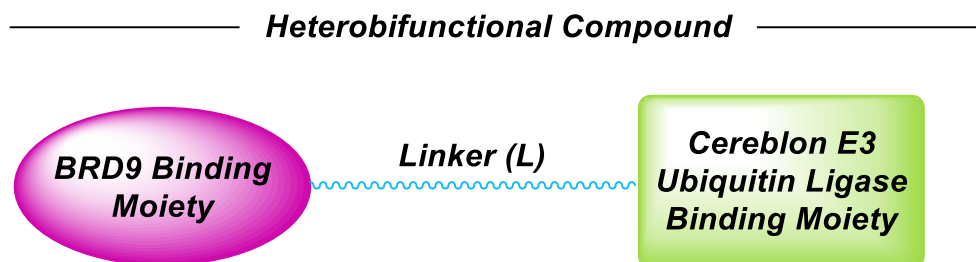


FIG. 2

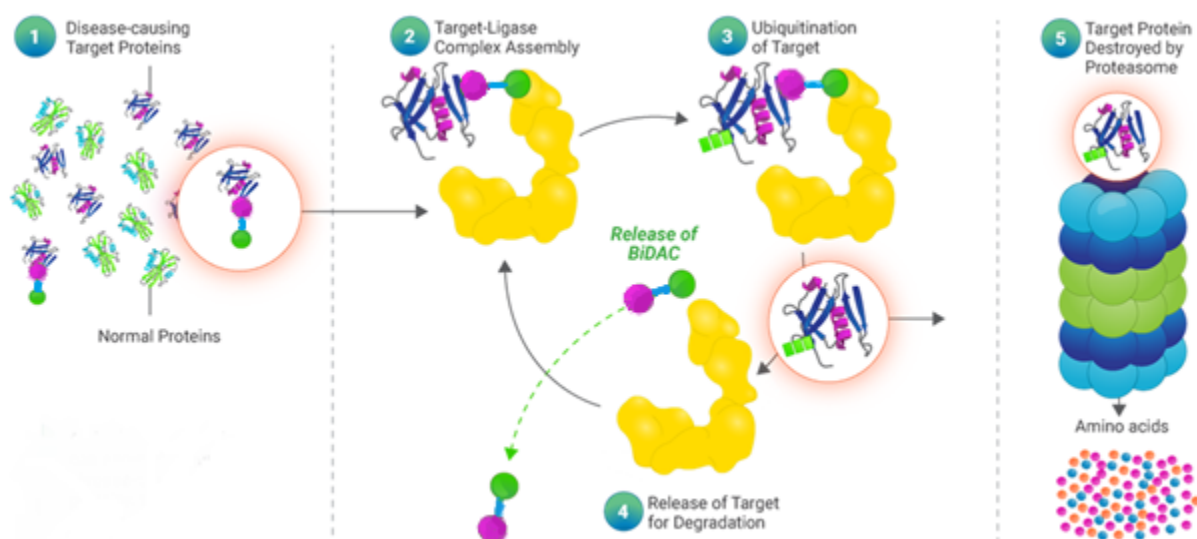


FIG. 3

(ii) 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.*, ¶69)

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.*, ¶70).

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.*, ¶71).

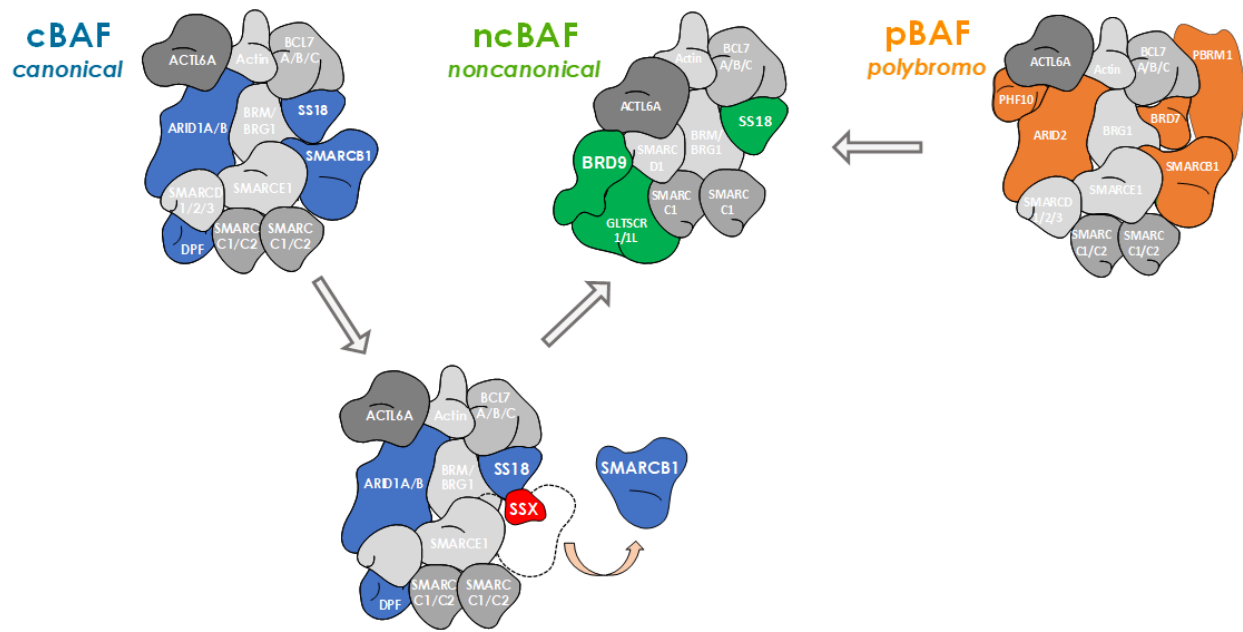


FIG. 4

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.*, ¶72).

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.*, ¶73).

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) (Ex.1015). 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.1016) (Ex.1014, ¶74).

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)

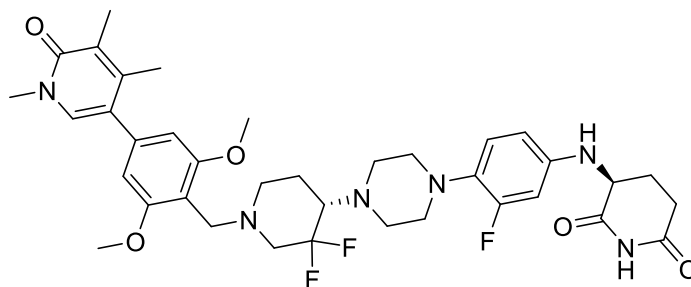
lipophilicity of the compound (potentially leading to increased rates of clearance and metabolism); (v) rate of clearance of free drug which is also affected by metabolism; (vi) polar surface area; (vii) aqueous solubility; (viii) volume of distribution; (ix) off-target degradation; (x) insufficient cell permeability (which can be highly dependent on physicochemical properties), insufficient tissue selectivity, and (xi) toxicity to a non-targeted tissue (e.g., heart or liver) (Ex.1014, ¶75).

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.*, ¶76).

B. BACKGROUND FACTS

PO’s BRD9 clinical protein degrader, FHD-609, is an IV-administered drug for synovial sarcoma in Phase I clinical trials. It has been the subject of at least a partial clinical hold by the U.S. FDA for an adverse side effect. FHD-609 does not fall within the claims of the ’416 Patent (Ex.1017, ¶21)

Petitioner has created new forms of heterobifunctional BRD9 protein degraders that are orally biodegradable, including CFT8634, which is specifically described in the '920 PCT Publication (Ex.1010, 704-705).



CFT8634

On September 10, 2021, Petitioner's '240 Application (Ex.1009) published as the '920 PCT Publication (Ex.1010, 1). All of the Figures in the '920 PCT Publication were based on analyses of Compounds 172 or 176, which have the structure of CFT8634 with varying stereochemistries.

One week later, on September 17, 2021, PO quickly filed a Track One continuation application (U.S.S.N. 17/478,505; "'505 Con") (Ex.1011) of its unexamined '153 Parent application (U.S.S.N. 17/425,153 filed July 22, 2021) (Ex.1008). The '505 Con patent claims brazenly reached out beyond PO's disclosed invention to retroactively grab and obtain an exclusionary right in the superior compounds Petitioner had invented but PO had not, but wanted anyway. These claims were a carefully cobbled together patchwork Markush formula that "created"

a genus of compounds that were not synthesized, tested, evaluated or even drawn in the PO's patent specification. The '416 Patent invalidly claims a subgenus with Petitioner's clinical CFT8634 compound.

PO cherry picked from its patent application to claim a mosaic of substituent groups never called out in the specification as a group and tried to carefully mutate claim terms to awkwardly fit the situation they needed—to capture in hindsight a competitor's invention without PO actually making or having possession of such innovation. This is unacceptable under U.S. patent law. While PO apparently tried to be clever and strategic, it forgot that U.S. patent law requires actual invention as of the filing date.

For the foregoing reasons, and as explained in detail below, Petitioner requests Post Grant Review and cancellation of claims 1-15 of the '416 Patent.

VI. THE '416 PATENT PRIORITY CLAIMS

The '416 Patent priority applications are described in the following table.

Application	Filing Date	Exhibit
U.S.S.N. 62/798,374 (“’374 Provisional”)	Jan 29, 2019	1003
U.S.S.N. 62/881,195 (“’195 Provisional”)	July 31, 2019	1004
PCT/US2020/015746 (“’746 PCT”)	Jan 29, 2020	1005
U.S.S.N. 17/425,153 (“’153 Parent”)	July 22, 2021	1008
U.S.S.N. 17/478,505 (“’505 Con”)	Sep. 17, 2021	1011

VII. THE PROSECUTION HISTORY

A. The Parent '153 Application of the '416 Patent

PO filed U.S.S.N. 17/425,153 on July 22, 2021 (Ex.1008; the '153 Parent). 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.1004), filed July 31, 2019; and U.S. Provisional Application No. 62/798,374 (Ex.1003), filed January 29, 2019.

According to the USPTO Patent Center, the '153 Parent has not been substantively reviewed yet.

B. 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.1011). The file history is provided as Ex.1002. The '505 Con was granted without any substantive prosecution with a first action allowance (Ex.1002, 520-527).

PO's Track One request was granted December 8, 2021. (*Id.*, 504-505). **One week later**, on December 16, 2021, **without any substantive Office Action**, the USPTO issued a Notice of Allowance (*Id.*, 520-527). Thereafter, PO filed an Information Disclosure Statement (*Id.*, 506-519). PO filed an Amendment After Notice of Allowance Under 37 C.F.R. §1.312 on December 17, 2021 to delete the

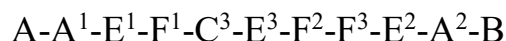
variable “p” (which was already limited to 1), and delete one moiety from E2 in claim 3. (*Id.*, 1325-1333). The claims were maintained in scope (*Id.*).

The USPTO issued a miscellaneous communication accepting the December 17, 2021, IDS (*Id.*, 1335-1340). A Notice to File Corrected Application Papers was issued by the USPTO on December 28, 2021 (*Id.*, 1341-1343). The Notice requested PO provide legible text in the Specification, pages 183-197, and provide missing text on page 112 (*Id.*). PO filed an Amendment After Notice of Allowance Under 37 C.F.R. §1.312 to comply with the Notice to File Corrected Application Papers on December 29, 2021 (*Id.*, 1344-2207). PO paid the issue fee on March 16, 2022 (*Id.*, 2212-2216).

A series of Notices to File Corrected Application Papers were then issued by the USPTO. The Notices requested PO provide legible text regarding the Specification, page 263, Example 22, and to correct FIG 5. of the Drawings (*Id.*, 2217-2219). On July 27, 2022, the USPTO mailed the Issue Notification informing PO the ’505 Con application will issue as U.S. Patent No. 11,414,416 on August 16, 2022 (*Id.*, 2242).

As issued, the ’416 Patent, entitled “Compounds and Uses Thereof” purports to describe compositions and methods for the treatment of BAF-related disorders by degrading the protein BRD9 (Ex.1001, 1:1-35). It provides an extremely broad chemical formula that is defined by letter variables--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. 132 (*Id.*, 1-82). None of the genres presented in the first 131 columns of the ’416 Patent is the genus that is presented in the granted claims of the ’416 Patent (Ex.1014, ¶118). The ’416 Patent then proceeds from col. 132 through col. 443, with no less than 310 columns of examples of compound species (Ex.1001, 82-238). Fatally, not a single one of the compounds in the 310 columns of the patent fall within the issued claims of the ’416 Patent (Ex.1014, ¶118).

The ’416 Patent then proceeds through a list of indications (Ex.1001, 238-241:cols 443-450) and purports to define chemical terminology in cols 450-465 (*Id.*, 241-249), which where relevant will be addressed below.

The ’416 Patent presents 14 Figures, which present data for only two compounds (Compound 1 and 2) (*Id.*, 4-16). However, neither Compound 1 nor Compound 2 fall within the purported invention, much less the claims, of the ’416 Patent. They are both published prior art compounds. Example 2, col. 493, lines 35-

38 (*Id.*, 263), where Compound 1 is defined as a compound first appearing in Remillard, et al, *Angew. Chem Int Ed Engl.* 56(21):5738-5743 (2017) (Ex.1018) and Example 3, which defines Compound 2 as a BRD9 ligand first published in 2016 Martin, et al, *J. Med. Chem.* 59(10):4462-4475 (2016) (Ex.1019) (Ex.1001, 264) (Ex.1014, ¶112).

The Detailed Description starts in col. 466 (Ex.1001, 249). In cols. 466-473, the patent has broad language about pharmaceutical uses and combinations. (*Id.*, 249-253).

The Examples start in col. 473 (*Id.*, 253). Example 1 merely 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 19 columns of space) that are completely irrelevant to the invention, because no RNA sequences are in the described broad general formulas of the '416 Patent, much less the claimed compounds (*Id.*, 253-263; Ex.1014, ¶114).

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, 263-264). 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.*, 264). Examples 4 and 5 also provide data for the inhibition of synovial sarcoma cells with prior art compounds (FIGS. 8-13) (*Id.*, 264). 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, Ex.1015: Gerard Brien et. al., “Targeted Degradation of BRD9 Reverses Oncogenic Gene Expression in Synovial Sarcoma,” eLife, 2018, 7 (e41305)) (Ex.1014, ¶115).

Examples 7-85 (spanning 309 columns) provide syntheses for compounds **that do not fall within the issued claims**. Example 86 assesses the ability of compounds to inhibit BRD9 in a competitive binding assay, **none** of which fall within the scope of the issued claims. Example 87 provides data on the ability of compounds to degrade a tagged-BRD9 fusion protein in a synovial sarcoma cell, **none** of which fall within the scope of the issued claims (which data spans over 7 columns) (Ex.1014, ¶116).

VIII. A PERSON OF ORDINARY SKILL IN THE ART

The '416 Patent claims are directed to complex pharmaceutical heterobifunctional molecules for the treatment of cancers and viruses. (*See, e.g.*, Ex.1001, 17-82; cols. 1-132). According to Dr. Djuric, a POSA in the field of the granted '416 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 for the treatment of cancers (Ex.1014, ¶20-21).

IX. CLAIM CONSTRUCTION OF THE '416 PATENT

The Board gives claims their ordinary and customary meaning, 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 '416 Patent based on the '416 Patent specification and explanation in the declaration of Dr. Djuric: “Optionally Substituted”, “C₆-C₁₂ aryl”, “C₆-C₁₀ arylene” and “B”.

A. “Optionally Substituted”

Petitioner requests that the Board interpret the term “optionally substituted” as used in the '416 Patent as incapable of claim construction because it is meaningless and unbounded as defined and used in the specification and claims (Ex.1001, 241 (col. 450-end and col. 451 lines 1-3) followed by *Id.*, 243 (col. 454, lines 4-60)). In the alternative, Petitioner asks that the Board construe the term “optionally substituted” exactly as defined in the two locations of the '416 Patent, which are inconsistent with each other and are both open-ended (*Id.*, first definition at 241 (col. 450-end and col. 451 lines 1-3) and second definition at 243 (col. 454, lines 4-60)).

The term “optionally substituted” is used in every one of Claims 1-15. 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 or at least have to be considered (Ex.1014, 81). It is only when the term is used as a form of shorthand for a definite bounded list of clearly defined substituents that it can be used by the POSA to understand what the breadth of the claimed compound is (*Id.*).

Thus, it is the position of the Petitioner that the term “optionally substituted” is incapable of claim construction because it is meaningless and unbounded as defined and used in the specification (*Id.*, at 82).

Dr. Djuric notes that the '416 Patent specification has not one but two definitions of the term “optionally substituted” and he has studied both of them (*Id.*, ¶83). He concludes that he has identified a multitude of reasons why, as used by PO, the '416 Patent's claimed compounds are undefined, indefinite and meaningless to a POSA (*Id.* ¶¶81-93). Critically, 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.*, 83)

Specifically, Dr. Djuric points out that not only are both provided definitions of “optionally substituted” boundless, but they are also even inconsistent in the

boundless state. (*Id.*, ¶84). For example, in col. 450, lines 46-end to col. 451-lines 1-3 (Ex.1001, 241-242), the '416 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.

According to Dr. Djuric's reading of the col. 450-451 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 "described herein" (but without saying where "herein" is or how described). (Ex.1014., ¶85). Further, the substituents don't need to be the same because any combination is allowed (*Id.*). The combinations of substituents are only "preferably" stable (*Id.*, ¶86). Stability is not required (*Id.*). Further, Dr. Djuric points out that the resulting compound is only "preferably" chemically feasible (*Id.*). Chemical feasibility is not required (*Id.*). And the stability of the "optionally substituted" compound can be altered, as long as not "substantially altered" (which is also not defined or bounded), when subjected to conditions to allow for their production, detection, recovery, purification or use (*Id.*). This is not capable of definite meaning (*Id.*).

Dr. Djuric compares this first definition to a second definition of "optionally substituted" provided in col. 454, lines 44-60 (Ex.1001, 243) in the '416 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.

According to Dr. Djuric, this second col. 454 definition of “optionally substituted” adds to the confusion a POSA already faces about this term (Ex.1014, ¶88). In this alternative definition, Dr. Djuric points out that 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 in that respect it is not significantly different in scope from the col. 450-451 definition of “optionally substituted” (*Id.*, ¶88). However, Dr. Djuric highlights that this alternative definition has its own set of myriad problems (*Id.*). As a first example, in the col. 454 definition, the specification purportedly teaches that a chemical moiety “when substituted, will generally have 1 to 4 substituents” (Ex.1001, 243). However, nothing in the specification provides a pointer to which chemical moieties are to be substituted, so the “when substituted” term is without context (Ex.1014, ¶88). Second, in the col. 454 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. 454 do not constitute concrete guidance because the lists are not bounded as the definition states, “[s]ubstituents include, for example” (emphasis added) (*Id.*).

Dr. Djuric then explains there is another very serious and in fact fatal problem with the col. 454 definition of “optionally substituted”. (*Id.*, ¶89). The definitions provided by PO create “infinite loops” where chemical definitions refer to other definitions which then loop back to the first definition (*Id.*). This creates the known chemical problem of a purportedly boundless or infinite molecule. As an example “optionally substituted alkyl” may be substituted with another optionally substituted substituent (*Id.*). Examples of substituents in col. 454 include alkyl, which may be substituted (*Id.*). This creates a fatal mistake (*Id.*). 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. (*Id.*) This dilemma can be applied to all of the optional substituents in col. 454 that refer to “e.g., unsubstituted and substituted” (*Id.*). Worse, the optional substituents are boundless so any substituent can be used including unnamed substituents, for example the substitution of an

amino on a hydroxyl that is subsequently substituted with a thiol and then another amino or hydroxyl, etc (*Id.*).

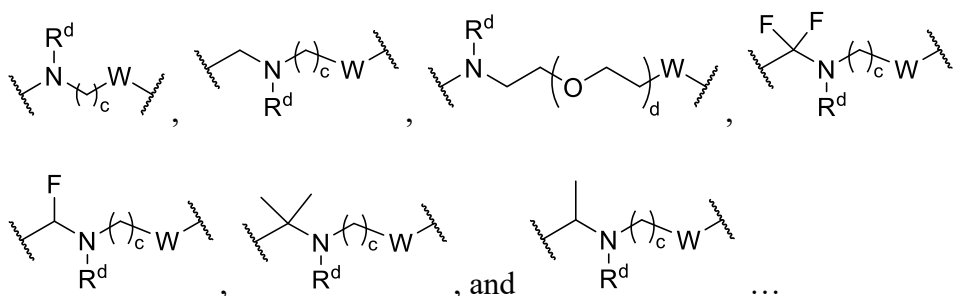
Dr. Djuric then highlights that the potentially infinite serial nature of optional substitutions is exemplified for example by the dependent claim structure in which dependent claim 3 includes chemical moieties for E² which are only properly dependent if you consider the term “optionally substituted C₁-C₁₀ heteroalkylene” to include optional substitutions that are in turn optionally substituted (yellow provided for emphasis) (*Id.*, ¶90).

Claim 1 provides:

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, 515)

Claim 3:

E² includes several groups including:



where

R^d is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl (*Id.*, 515-516).

For claim 3 to be properly dependent, these E^2 groups must have been optionally substituted C_{1-10} heteroalkylene with various substituents including for example R^d (Ex.1014, ¶90). And R^d in turn is defined to include optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl (*Id.*). This claim dependency provides an example of PO's use of the optional substituent infinite loop and demonstrates the boundless scope of the claims (*Id.*). Figure 5 below is provided to help graphically demonstrate this phenomenon (*Id.*).

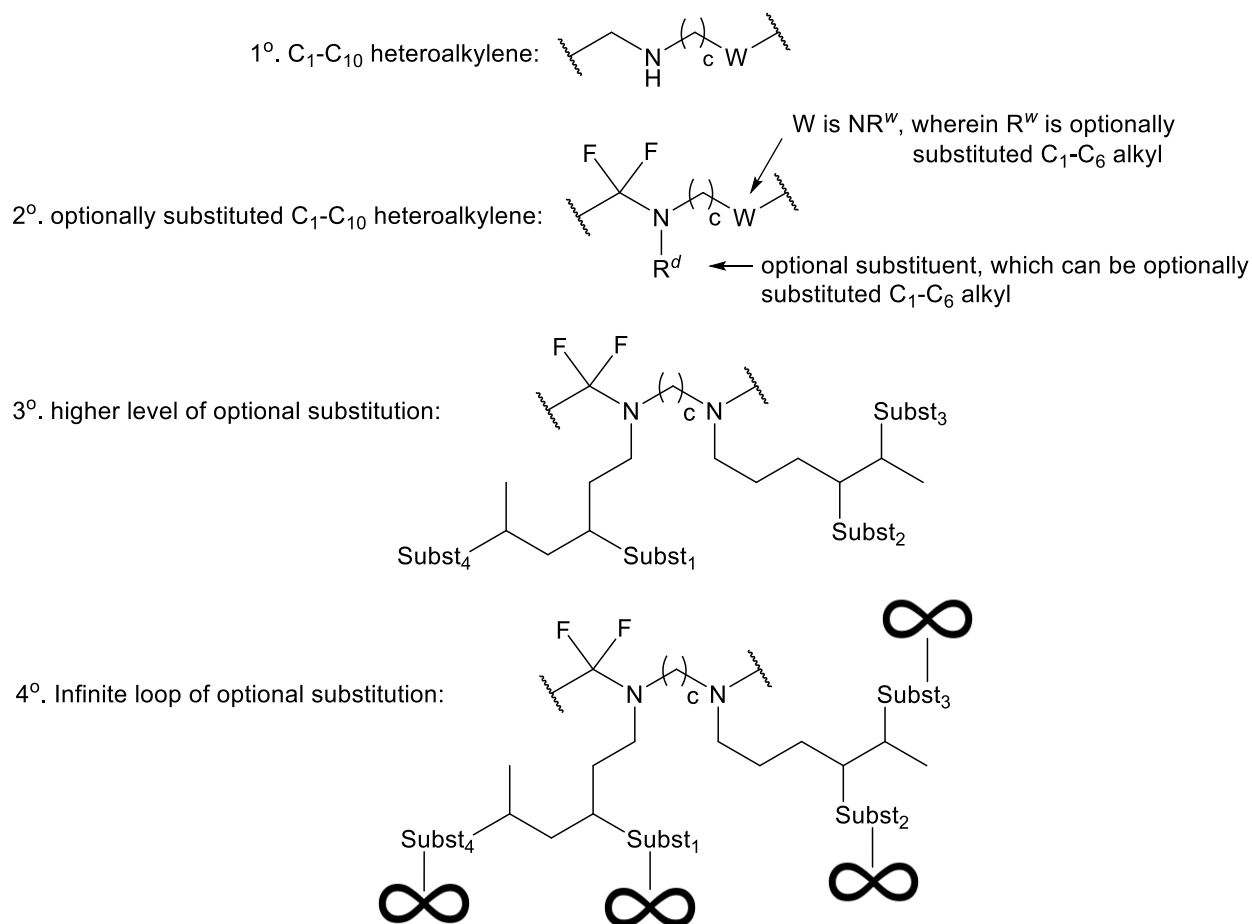


FIG. 5

Because the term “optionally substituted” as used is incapable of construction as vague and indefinite, every term in the challenged claims 1-15 that include this term is boundless, vague, indefinite, and incapable of construction (*Id.*, ¶91). These terms are listed in (i)-(xxv) below.

(i) Optionally substituted C₆-C₁₀ arylene. The term “optionally substituted C₆-C₁₀ arylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 (Ex.1001, 515-518).

(ii) Optionally substituted C₆-C₁₀ aryl. The term “optionally substituted C₆-C₁₀ aryl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*, 515-517).

(iii) Optionally substituted C₁-C₆ alkyl. The term “optionally substituted C₁-C₆ alkyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 (*Id.*, 515-518).

(iv) Optionally substituted C₁-C₆ heteroalkyl. The term “optionally substituted C₁-C₆ heteroalkyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 (*Id.*).

(v) Optionally substituted C₃-C₁₀ carbocyclyl. The term “optionally substituted C₃-C₁₀ carbocyclyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 (*Id.*, 515-517).

(vi) Optionally substituted C₂-C₉ heteroaryl. The term “optionally substituted C₂-C₉ heteroaryl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(vii) Optionally substituted C₂-C₆ alkenyl. The term “optionally substituted C₂-C₆ alkenyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(viii) Optionally substituted C₂-C₆ heteroalkenyl. The term “optionally substituted C₂-C₆ heteroalkenyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(ix) Optionally substituted amino. The term “optionally substituted amino” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(x) Optionally substituted C₁₋₁₀ alkylene. The term “optionally substituted C₁₋₁₀ alkylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(xi) Optionally substituted C₂₋₁₀ alkenylene. The term “optionally substituted C₂₋₁₀ alkenylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(xii) Optionally substituted C₂₋₁₀ alkynylene. The term “optionally substituted C₂₋₁₀ alkynylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(xiii) Optionally substituted C_{2-C10} polyethylene glycol. The term “optionally substituted C_{2-C10} polyethylene glycol” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(xiv) Optionally substituted C₁₋₁₀ heteroalkylene. The term “optionally substituted C₁₋₁₀ heteroalkylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(xv) Optionally substituted C₁₋₄ alkyl. The term “optionally substituted C₁₋₄ alkyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 (*Id.*, 515-518).

(xvi) Optionally substituted C₂₋₄ alkenyl. The term “optionally substituted C₂₋₄ alkenyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 (*Id.*).

(xvii) Optionally substituted C₂₋₄ alkynyl. The term “optionally substituted C₂₋₄ alkynyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 (*Id.*).

(xviii) Optionally substituted C₂₋₆ heterocyclyl. The term “optionally substituted C₂₋₆ heterocyclyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 (*Id.*).

(xix) Optionally substituted C₂₋₉ heterocyclyl. The term “optionally substituted C₂₋₉ heterocyclyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*).

(xx) Optionally substituted C₂₋₁₀ heterocyclylene. The term “optionally substituted C₂₋₁₀ heterocyclylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*, 515-517).

(xxi) Optionally substituted C₆₋₁₂ aryl. The term “optionally substituted C₆₋₁₂ aryl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 (*Id.*, 515-518).

(xxii) Optionally substituted C₁₋₇ heteroalkyl. The term “optionally substituted C₁₋₇ heteroalkyl” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 (*Id.*).

(xxiii) Optionally substituted C₃-C₁₀ carbocyclylene. The term “optionally substituted C₃-C₁₀ carbocyclylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*, 515-517).

(xxiv) Optionally substituted C₂-C₉ heteroarylene. The term “optionally substituted C₂-C₉ heteroarylene” is used in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 (*Id.*, 515-517).

(xxv) Optionally substituted C₃-C₆ carbocyclyl. The term “optionally substituted C₃-C₆ carbocyclyl” is used in claims 3, 4, 5 and 14 (*Id.*, 515-518).

Every claim of the '416 Patent contains the term optionally substituted modifying at least 6 different chemical groups wherein each one of these terms is unbounded because neither of the two attempts to define optional substituent in the specification actually limit the definition or provide a closed set of variables (Ex.1014, ¶92). Most of the claims include many more “optionally substituted” terms (*Id.*).

For example, claim 15, which appears to be the most narrow claim of the '416 Patent, actually embeds a multitude of the phrase “optionally substituted”:

- (i) optionally substituted C₆-C₁₀ arylene; wherein optionally substituted is open ended as defined in either the first definition of “optionally substituted” (col. 450, lines 46-end to col. 451

- lines 1-3) (Ex.1001, 241-242) or the second definition of “optionally substituted” (col. 454, lines 44-60) (*Id.*, 243); and
- (ii) claim 15 is dependent on claim 14, wherein E^2 is $-NR^N$. Regarding the variable R^N , claim 14 refers back to claim 1, wherein R^N is defined as “optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl” (*Id.*, 515-518). (Ex.1014, ¶93).

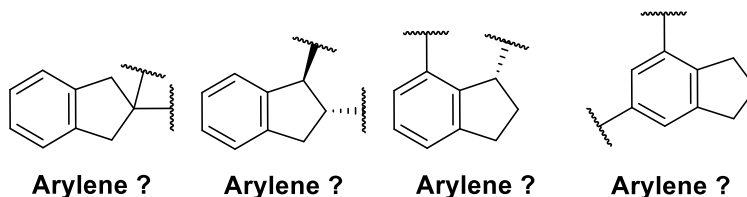
B. “C₆-C₁₂ Aryl”

Aryl is defined in column 452 lines 21-26 as “an aromatic mono- or polycarbocyclic radical of, e.g., 6 to 12, carbon atoms having at least one aromatic ring.” (Ex.1001, 242). PO’s Aryl definition does not teach where the attachment point should be on the Aryl moiety, and there are two possibilities-either attachment through the aromatic ring or the non-aromatic ring. In the absence of a definite teaching or limitation, Petitioner urges that the attachment point should be permitted through either the aromatic ring or the non-aromatic ring. Petitioner therefore requests that the Board construe the term “C₆-C₁₂ Aryl” to be “an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring,

and wherein the attachment point can be either at the aryl group or the non-aromatic group.” (Ex.1014, ¶94)

C. “C₆-C₁₀ Arylene”

The specification does not provide a definition of “arylene” or “C₆-C₁₀ arylene,” which is used in all of claims 1-15 (Ex.1014, ¶95). The specification teaches that when the suffix “ene” is added to the end of the term, that means the moiety is in the divalent state (see for example, col. 451, line 64 “an alkylene is a divalent alkyl group”; and col. 452 “an alkenylene is a divalent alkene group”) (Ex.1001, 242; Ex.1014, ¶95). However, when the term aryl is defined (see col. 452, lines 21-26) (Ex.1001, 242), it refers to an aromatic mono- or polycarboxylic radical, of e.g., 6 to 12 carbon atoms having at least one aromatic ring (Ex.1001, 242; Ex.1014, ¶95). The definition of aryl includes “phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl”, however, the attachment point is not specified (*Id.*). This lack of clarity is further compounded by the divalent nature of arylene (Ex.1014, ¶96). For example, it is not clear which valences of indanyl are included within the term C₆-C₁₀ arylene (*Id.*).

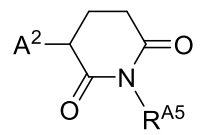


In the absence of a definite teaching or limitation, Petitioner urges that the attachment point should be permitted through either the aromatic ring or the non-aromatic ring of the arylene moiety. Petitioner therefore requests that the Board construe the term “C₆-C₁₀ Arylene” to be “a divalent aromatic mono- or polycarbocyclic radical of 6 to 10 carbon atoms having at least one aromatic ring, and wherein the attachment points can be either at the aryl group or the non-aromatic group.”

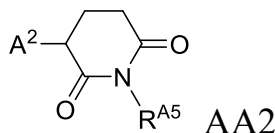
D. “B”

Petitioner requests that the Board construe “B” as used in the '416 Patent

claims to be “a cereblon binding moiety” of structure



Claim 1 defines “B” as “Formula AA2” (Ex.1001, 515).



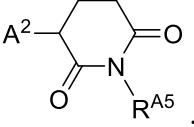
wherein A² is defined as the bond between the degradation moiety and the linker (col. 69, lines 36-37) (*Id.*, 51) and R^{A5} is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl (col. 998, lines 28-29) (*Id.*, 515)².

“B” is defined by PO in column 1, line 41, as a “degradation moiety” (Ex.1001, 17). In col. 69, lines 14-15, the specification states that “In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.” (*Id.*, 51). In col. 69, lines 16-20, the specification states that the ubiquitin ligase binding moiety can be a cereblon ligand (*Id.*).

² According to the specification Formula AA2 is the degradation moiety (see col. 69, lines 21-35 which defines degradation moiety Formula “Y”; col. 71, lines 28-29 wherein Y can be Formula “Z”; col. 71, lines 48-49, wherein Z can be Formula “AA0”; col. 72, lines 49-50 wherein AA0 is Formula “AA”; and then col. 73, wherein AA can be Formula AA2, Ex.1001, 52-53). Formula AA2 is also defined as a “degradation moiety” in the ’746 PCT claims (Ex.1005, 457, claim 128 is dependent on claim 127, which is ultimately dependent on claim 1 defining B to be “a degradation moiety” and claim 95 requiring that “the degradation moiety is a ubiquitin ligase binding moiety”).

Formula AA2 is a glutarimide moiety (Ex.1014, ¶105). Certain glutarimides are used in heterobifunctional compounds to bind to the cereblon component of the E3 ligase (*Id.*). Dr. Djuric states that cereblon is the enzyme receptor component of the multi-protein complex cullin 4-RING E3 ligase that is relevant to the '416 Patent claims (*Id.* ¶105).

Therefore, it is reasonable to construe “B” as used in the '416 Patent claims

to be “a cereblon binding moiety” of structure .

X. GROUND 1: CLAIMS 1-15 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 '416 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. 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.*, No. 2021-2168, 2023 U.S. App. LEXIS 5253, at *6-7 (Fed. Cir. Mar. 6, 2023) (citing *Ariad*, 598 F.3d at 1350-52). 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.”); *see also Regents of the Univ. of Minn.*, No. 2021-2168, 2023 U.S. App. LEXIS 5253, at *10. 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.*, No. 2021-2168, 2023 U.S. App. LEXIS 5253, at *7-8. 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.

Likewise, a “mere wish or plan” for obtaining the claimed invention does not satisfy the written description requirement. *Eli Lilly & Co.*, 119 F.3d at 1566.

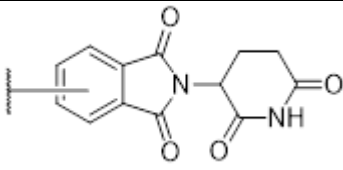
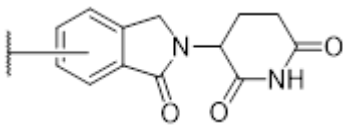
B. Application of Written Description Law to ’416 Patent Specification

Table 2 below shows the number of species drawn, synthesized or tested in the ’416 Patent that fall within the scope of the granted claims. As indicated, every

box is a “0”. Dr. Djuric has reviewed Table 2, compared it to the ’416 Patent specification and confirmed that these depictions are accurate (Ex.1014, ¶112).

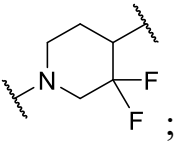
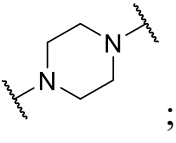
TABLE 2

Claim	Drawn	Made	Data	Note
1	0	0	0	<p>1) The compound of claim 1 contains an $-(F^1)-(F^2)-(F^3)-$ fragment in the linker L, where each of F^1, F^2, and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_{2-10} heterocyclylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_2-C_9 heteroarylene.</p> <p>However, none of the compounds in Tables 1A, 1B, 1C, 1D, and 1E have this fragment, in which all the three cyclic groups are connected by a single bond only.</p> <p>2) E^2-A^2-B in formula of claim 1 cannot be</p>

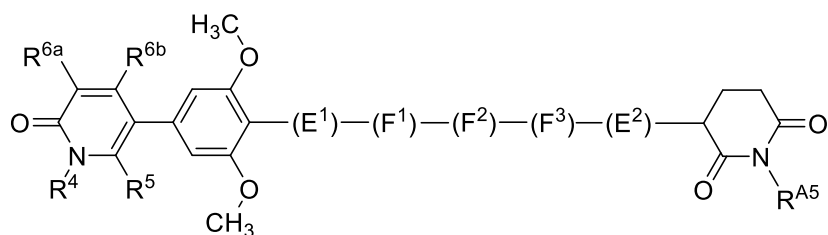
Claim	Drawn	Made	Data	Note
				 <p style="text-align: right;">or</p>  <p>because E², as defined in claim 1, is O, S, NR^N, optionally substituted C₁₋₁₀ alkylene, optionally substituted C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C_{2-C10} polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene.</p>
2	0	0	0	The claim is directed to the compound of claim 1, wherein E ¹ is CH ₂ .
3	0	0	0	The claim is directed to the compound of claim 1, wherein E ² is limited to narrower defined groups.
4	0	0	0	The claim is directed to the compound of claim 3, wherein E ² is limited to NR ^N .

Claim	Drawn	Made	Data	Note
5	0	0	0	The claim is directed to the compound of claim 4, wherein E ² is limited to NH.
6	0	0	0	The claim is directed to the compound of claim 1, wherein F ¹ is limited to a narrower group of cyclic moieties encompassed by the term C ₂₋₁₀ heterocyclylene.
7	0	0	0	The claim is directed to the compound of claim 1, wherein F ² is limited to a narrower group of cyclic moieties encompassed by the term C ₂₋₁₀ heterocyclylene.
8	0	0	0	The claim is directed to the compound of claim 1, wherein F ³ is limited to optionally substituted C ₆ -C ₁₀ arylene.
9	0	0	0	The claim is directed to the compound of claim 1, wherein R ^{A5} is H.
10	0	0	0	The claim is directed to the compound of claim 1, wherein R ⁴ is CH ₃ .
11	0	0	0	The claim is directed to the compound of claim 1, wherein R ⁵ is H or CH ₃ .

Claim	Drawn	Made	Data	Note
12	0	0	0	The claim is directed to the compound of claim 1, wherein R ^{6a} is H, F, cyano, -CH ₃ , -CF ₃ , -CHF ₂ , or -CH ₂ NH-C(=O)-NH-CH ₃ .
13	0	0	0	The claim is directed to the compound of claim 1, wherein R ^{6b} is H, F, cyano, -CH ₃ , -CF ₃ , -CHF ₂ , or -CH ₂ NH-C(=O)-NH-CH ₃ .
14	0	0	0	The claim is directed to the compound of claim 1, wherein E ¹ , E ² , F ¹ , F ² , F ³ in the Linker; R ⁴⁵ in the degradation moiety B; and R ⁴ , R ⁵ , R ^{6a} , R ^{6b} in the BRD9 binding moiety A are further limited to a narrower group.
15	0	0	0	The claim is directed to the compound of claim 14, wherein: E ¹ is CH ₂ ; E ² is NR ^N ; R ^N is H, optionally substituted C ₁₋₄ alkyl, optionally substituted C ₂₋₄ alkenyl, optionally substituted C ₂₋₄ alkynyl, optionally substituted

Claim	Drawn	Made	Data	Note
				<p>C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl;</p> <p>F¹ is  ;</p> <p>F² is  ;</p> <p>F³ is optionally substituted C₆-C₁₀ arylene;</p> <p>R^{A5} is H;</p> <p>R⁴ is CH₃;</p> <p>R⁵ is H;</p> <p>R^{6a} and R^{6b} are CH₃.</p>

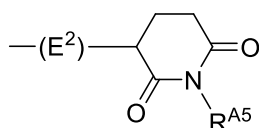
For convenience, Formula I can be drawn as follows:



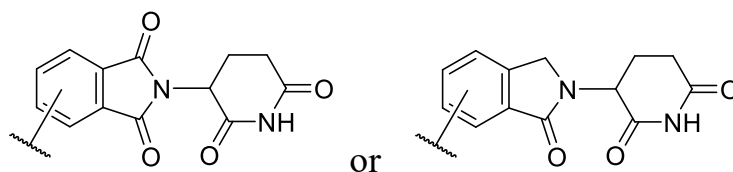
This formula does not cover a single compound drawn, synthesized or tested in the '416 Patent specification, Tables 1A to 1E. Dr. Djuric provides reasons for this observation as follows (Ex.1014, ¶¶113-145).

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, 515).

It follows from this definition that E² cannot be a bond, carbocyclylene, heterocyclylene, arylene, or heteroarylene (Ex.1014, ¶115). Because of this, the structure in claim 1 does not fit any of the drawn structures in the specification of the '416 Patent. For example, fragment (E²)-B of formula:

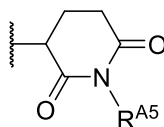


cannot form a thalidomide-type structure:

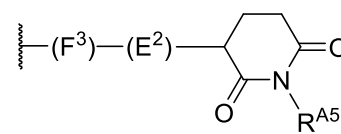


either of which is present in most of the compounds presented in Tables 1A to 1E of the '416 Patent specification (compounds D1-D333, D335-D371, DD2, DD4, DD8, DD10, D372-D381, D384-D387, D396-D431, D433-D470, D474, DD11-DD16) (Ex.1001, 82-238; Ex.1014, ¶115). Additionally, the non-thalidomide '416 drawn compounds D334, DD1, DD3, DD5, DD6, DD7, DD9, D382-D383, D388-D395, D432, and D471-D473 also do not fall within the genus of the claim 1 formula because E² cannot be a heterocycle (as required in D334, D394, D432, DD3, DD5,

DD6, and DD9), E² cannot be a heteroaryl (as required in D393), E² cannot be carbocycle (as required in DD7), and compounds DD1, D382, D383, and D388-

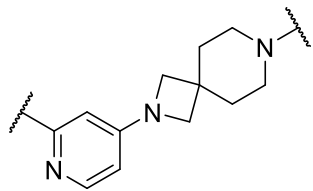
D390 do not even contain the required glutarimide moiety  (Ex.1014, ¶115).

There is not a single compound within the claimed genus drawn in the '416 Patent specification (Ex.1014, ¶116). And all but six of the drawn structures do not even fit the limitations required by the cereblon ligand portion of the molecule

 (Id.). These six structures (acyl containing compounds D391, D392, D395, and D471-D473) are still not species of the claimed genus because the linking portion of the molecule does not meet the claim limitations of F¹, F², and F³ (Id.).

According to the definitions of F¹, F², and F³ given 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, 515). It follows from this definition that the linker L in Formula I, as defined in claim 1, always requires three ring moieties F¹, F², and F³ (carbocyclylene, heterocyclylene, arylene or

heteroarylene) sequentially connected by a single bond $-(F^1)-(F^2)-(F^3)-$ (Ex.1014, ¶117). Therefore, structures like



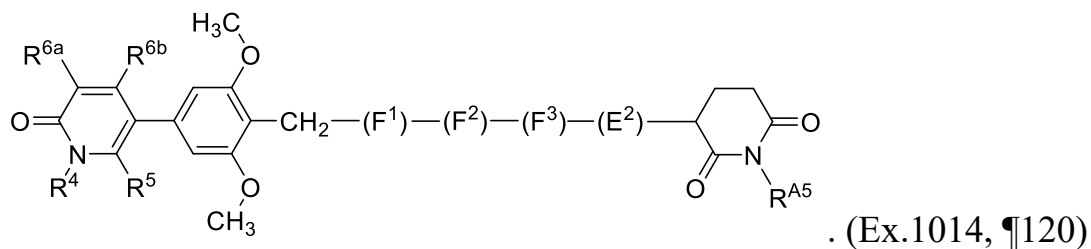
are not covered by the definition of L in claim 1 (*Id.*).

Therefore, Formula I in claim 1 of the '416 Patent does not encompass even a single compound described in the '416 Patent specification (Tables 1A to 1E). (Ex.1014, ¶118).

Claims 2-15 similarly lack support of even a single disclosed structure in the '416 Patent (*Id.*, ¶119).

Claim 2

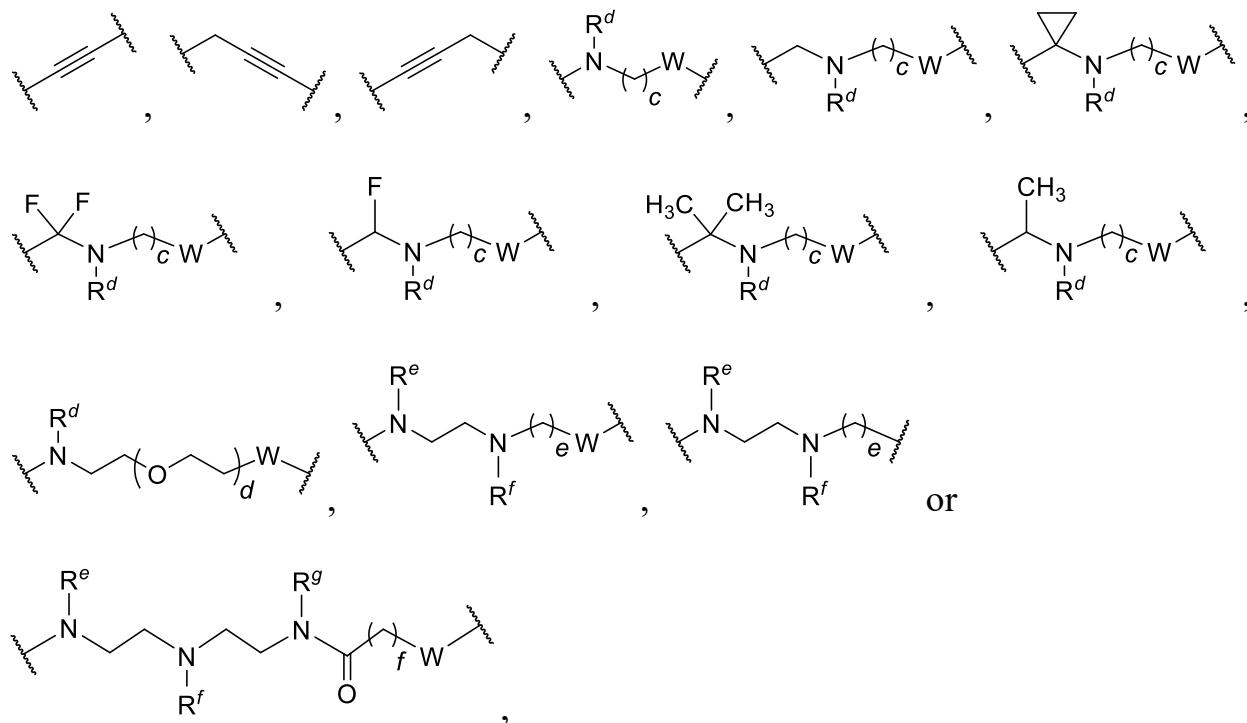
Claim 2 is directed to the compound of Formula I of claim 1 with the only limitation that variable E^1 is CH_2 (Ex.1001, 515). Therefore, with this limitation, Formula I can be represented by the following structure:



For the reasons presented when discussing claim 1 above, this Formula also does not encompass any compounds described in the '416 Patent specification (Tables 1A to 1E) (*Id.*).

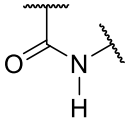
Claim 3

This claim is directed to the compound of Formula I, in which variable E² is limited to a narrower subset of non-cyclic groups. Specifically, E² is O, NR^w,

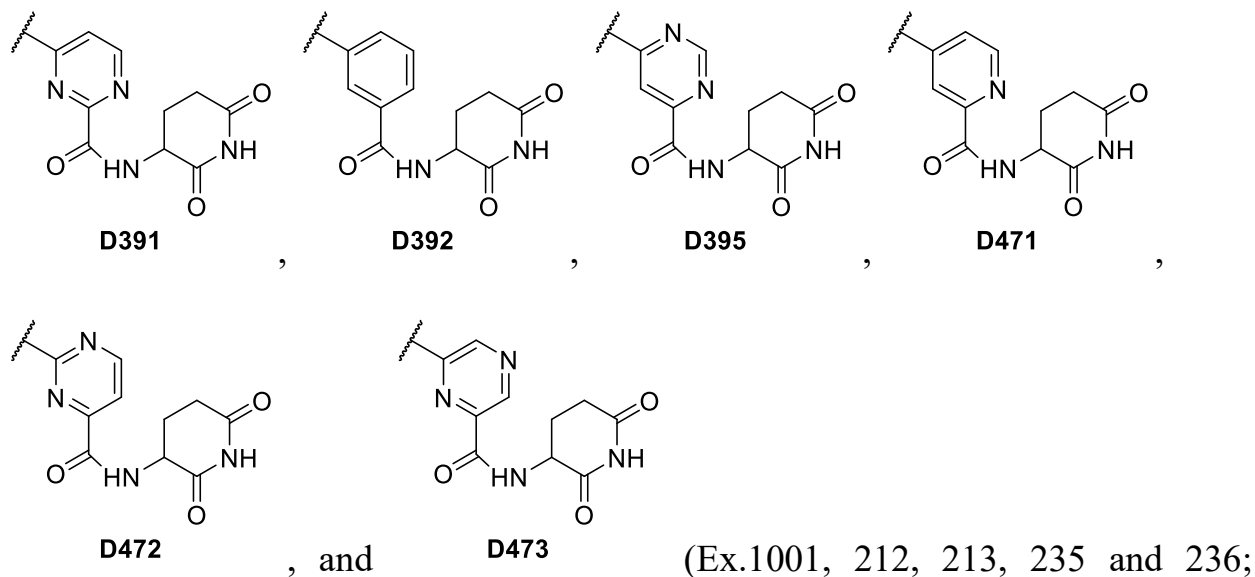


wherein W is O or NR^w, and wherein R^w is H or optionally substituted C₁-C₆ alkyl (Ex.1001, 515-516).

Because claim 3 includes all the limitations of claim 1 regarding the structure of the (F¹)-(F²)-(F³) moiety (three sequential ring fragments connected by single bonds), and E² is neither a cyclic moiety, nor a bond, claim 3 does not cover a single compound described in the '416 Patent specification. (Ex.1014, ¶122). Definitions

of E² in this claim also do not encompass group  connecting a glutarimide

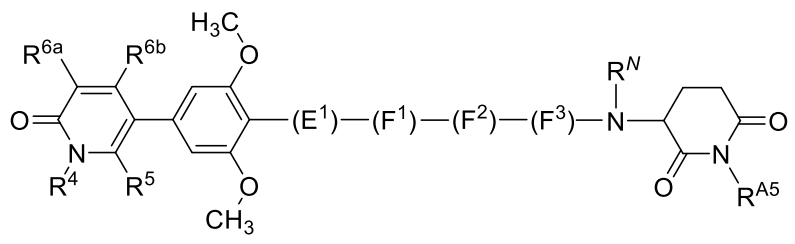
residue with a cyclic group in compounds D391, D392, D395, D471, D472, and D473:



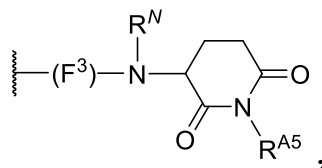
Ex.1014, ¶122).

Claim 4

Claim 4 is directed to the compound of claim 3, in which variable E² is further limited to -NR^N-, and, therefore, Formula I may be represented by the structure:



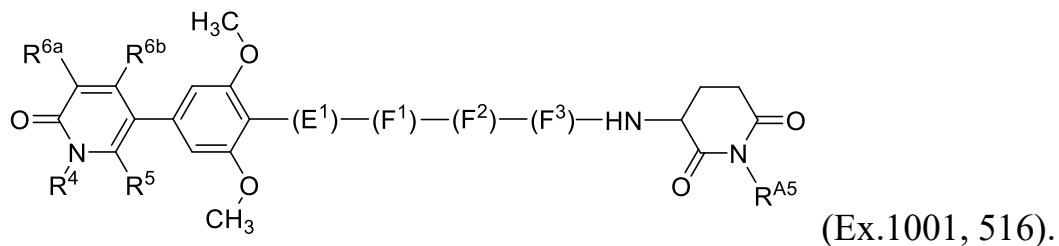
where R^N is H, optionally substituted C₁₋₄ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl. (Ex.1001, 516). None of the compounds of the '416 Patent contain fragment:



in which a cyclic fragment F^3 is linked to the glutarimide through a linking nitrogen (Ex.1014, ¶123). Therefore, Formula I as limited in claim 4 does not encompass even a single compound described in the '416 Patent specification. (*Id.*).

Claim 5

Claim 5 is directed to the compound of claim 4, in which variable E^2 is further limited to $-NH-$, and Formula I may be represented by the structure:



Therefore, Formula I as limited in claim 5 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶124).

Claim 6

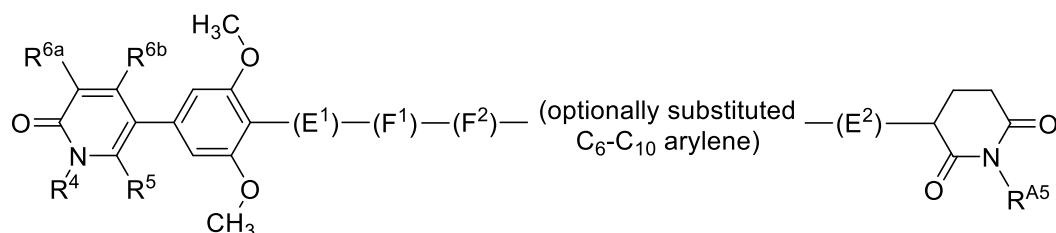
Claim 6 is directed to the compound of claim 1, in which variable F^1 is further limited to a narrower subset of substituted or unsubstituted 4- or 5-membered heterocyclic moieties with one nitrogen heteroatom: azetidiny or piperidinyl (Ex.1001, 516). Formula I as limited in claim 6 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶125).

Claim 7

Claim 7 is directed to the compound of claim 1, in which variable F^2 is further limited to a narrower subset of substituted or unsubstituted 4- or 5-membered heterocyclic moieties with one or two nitrogen heteroatom(s): azetidiny, piperidiny, or piperazinyl (Ex.1001, 516). Formula I as limited in claim 7 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶126).

Claim 8

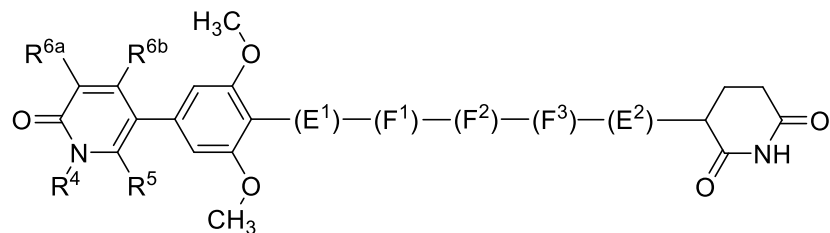
Claim 8 is directed to the compound of claim 1, in which variable F^3 is further limited to a narrower subset of optionally C_6 - C_{10} arylene (Ex.1001, 516), and Formula I may be represented by the structure:



Formula I as limited in claim 8 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶128).

Claim 9

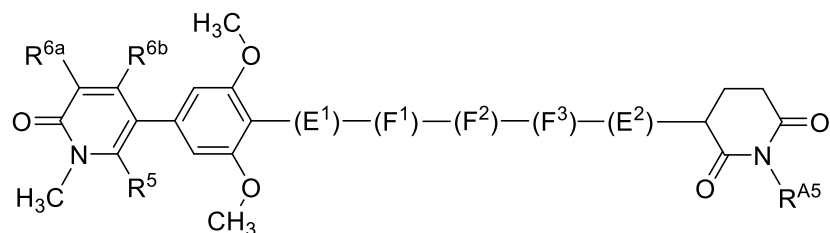
Claim 9 is directed to the compound of claim 1, in which variable R^{A5} is hydrogen (Ex.1001, 516), and Formula I may be represented by the structure:



Formula I as limited in claim 9 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶130).

Claim 10

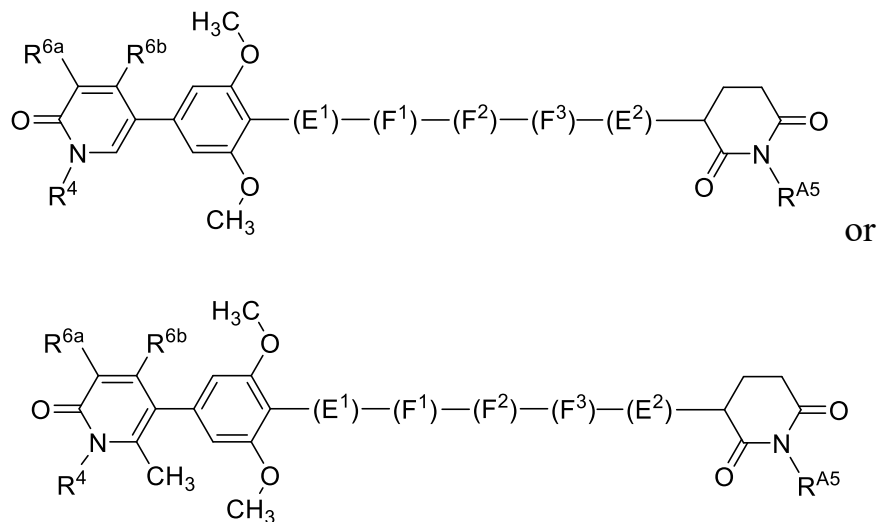
Claim 10 is directed to the compound of claim 1, in which variable R⁴ is methyl (Ex.1001, 516), and Formula I may be represented by the structure:



Formula I as limited in claim 10 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶132).

Claim 11

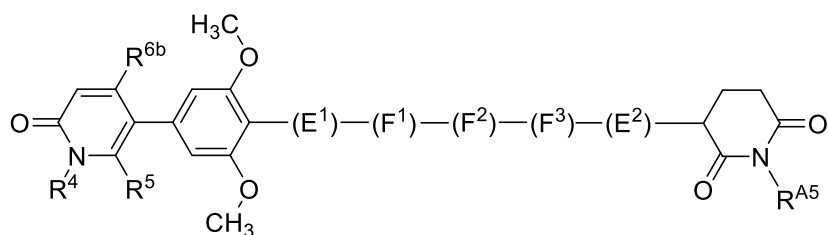
Claim 11 is directed to the compound of claim 1, in which variable R⁵ is hydrogen or methyl (Ex.1001, 517), and Formula I may be represented by the structures:



Formula I as limited in claim 11 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶134).

Claim 12

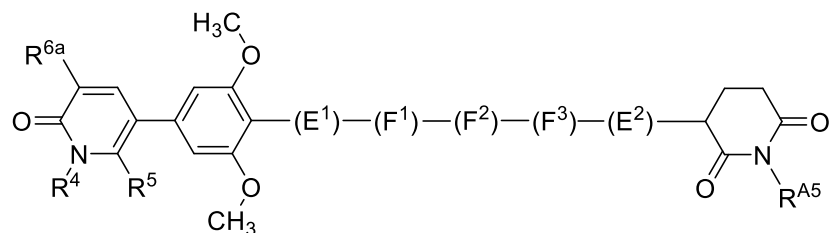
Claim 12 is directed to the compound of claim 1, in which variable R^{6a} is hydrogen, F, cyano, methyl, CF_3 , CHF_2 , or $CH_2NHC(O)NHCH_3$ (Ex.1001, 517). For example:



Formula I as limited in claim 12 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶136).

Claim 13

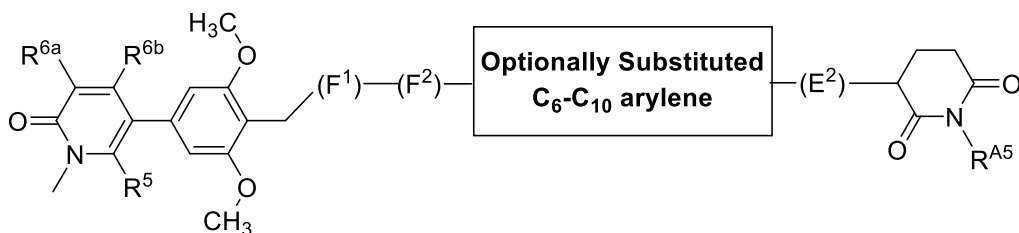
Claim 13 is directed to the compound of claim 1, in which variable R^{6b} is hydrogen, F, cyano, methyl, CF_3 , CHF_2 , or $CH_2NHC(O)NHCH_3$ (Ex.1001, 517). For example:



Formula I as limited in claim 13 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶138).

Claim 14

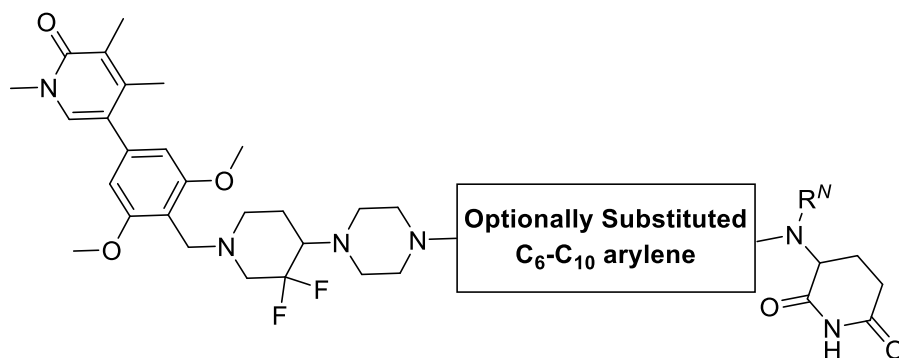
Claim 14 is directed to the compound of claim 1, in which variable E^1 is limited to CH_2 , variable E^2 is "limited" as described in claim 3, variable F^1 is limited to specific heterocycles, variable F^2 is limited to specific heterocycles, F^3 is limited to optionally substituted C_6-C_{10} arylene, R^{A5} is limited to hydrogen, R^4 is limited to $-CH_3$, R^5 is limited to H or $-CH_3$, R^{6a} is limited to the groups in claim 12, and R^{6b} is limited to the groups in claim 13 (Ex.1001, 517).



Formula I as limited in claim 14 does not encompass even a single compound described in the '416 Patent specification (Ex.1014, ¶140).

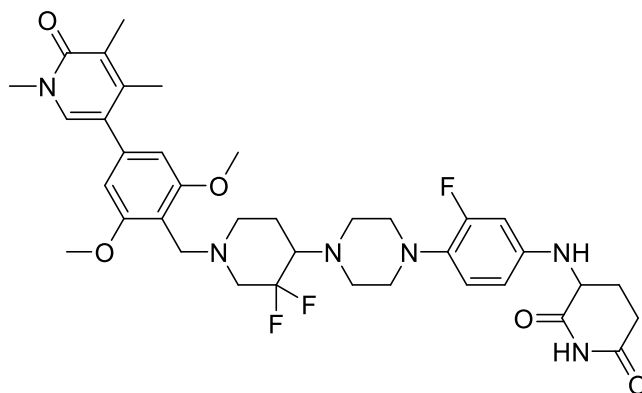
Claim 15

The patchwork nature of the claims becomes even more absurd as the dependent claims become narrower (Ex.1014, ¶141). For example, claim 15 combines 11 selections from 8 lists each of which contains at least two optionally substituted chemical moieties to claim a compound of Formula:



Claim 15 (Ex.1001, 517) (Ex.1014, ¶141)

Formula I as limited in claim 15 does not encompass even a single compound described in the '416 Patent specification. (Ex.1014, ¶142). Furthermore, there is no disclosure in the specification combining these specific chemical moieties or any guidance or blaze marks to a POSA to the many selections and combinations in this claim (*Id.*). Moreover, the resulting formula is more similar to compounds, such as Compound 176, in the Petitioner's '920 PCT Publication than any compound in the '416 Patent (*Id.*).



Compound 176 of '920 PCT Publication

Indeed, it is not a stretch to conclude that PO started with Compound 176, which is Petitioner's valuable compound that was disclosed after PO's priority date, and worked backwards to craft the claimed genres that are outside of the scope of PO's written description. (Ex.1014, ¶143). As the Federal Circuit has noted, close scrutiny is "particularly important when, as here, claims are added later during prosecution in response to development by others." *FWP IP ApS v. Biogen MA, Inc.*, 749 Fed. Appx. 969, 974 (Fed. Cir. 2018); *see also Quake v. Lo*, 928 F.3d 1365, 1373 (Fed. Cir. 2019) (noting "[t]he purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not, and the requirement is particularly important when, as here, claims are added later during prosecution in response to development by others"). This is exactly the scenario presented in this PGR, where PO submitted a Track One continuation one week after apparently seeing a competitor's (i.e., Petitioner's) PCT publication to

claim a genus that it didn't have a single representative species of in PO's specification.

It is also concerning to note that the USPTO allowed PO's claims without a single Office Action one week after grant of the Track One status.

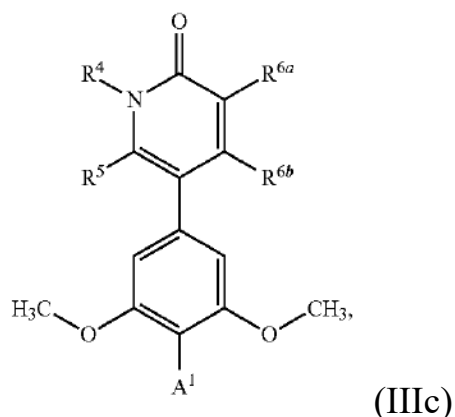
C. Application of Written Description Law to '746 PCT and '153 Parent Patent Application

The defects in the written description identified in Section A and Section B above are not rectified by any priority applications including the '746 PCT Application and '153 Parent patent application. These two applications share similar specification sections with the '416 Patent but differ in the presented claims (Ex.1001; Ex.1005; and Ex.1008). The '153 Parent Patent Application was filed with the '746 PCT claims and thus the analysis below applies to both applications (Ex.1005, 427-500; Ex.1008, 440-513).

Despite including over 10,000 claims through multiple dependencies the '746 PCT Application claims do not describe a single combination that includes the "A" "L" or "B" moieties as defined in the '416 patent claims either separately or in combination.

“A” Moiety

The “A” Moiety recited in claim 1 of the '416 patent is a compound of Formula IIIc



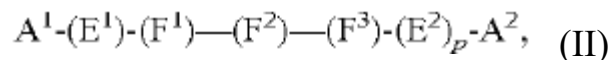
wherein:

R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. (Ex.1001, 515).

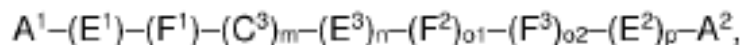
In the '746 PCT Application claims Formula IIIc is recited in claim 218 which requires that R⁴ is hydrogen. None of the claims in the '416 patent limit R⁴ to hydrogen and every claim of the '416 patent recites additional groups for R⁴ (Ex.1001, 515-518). Thus, there is not a single '416 patent claim which corresponds to the scope of the “A” Moiety described in the '746 PCT Application.

“L” Moiety

The “L” Moiety recited in claim 1 of the '416 patent is a compound of Formula II



Formula II as recited in the '746 PCT Application and the '746 PCT claims is a compound of Formula:

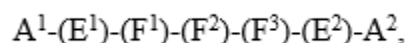


Formula II

(Ex.1005, 427).

Moieties and variables C^3 , E^3 , m , n , $o1$, and $o2$ which are recited in Formula II of the '746 PCT Application and claims are missing from Formula II as recited in the '416 claims. Additionally, variable "p" was removed from Formula II during prosecution of the '416 patent and thus this variable (7 in total) is also missing from Formula II in the '416 patent claims (Ex.1002, 1325-1333).

The closest Linker formula in the '746 PCT Application is the combination of claims 78 (m is 0), 79 (p is 1), 81 ($o1$ is 1), 83 ($o2$ is 1), and 86 (n is 0) to arrive at a compound of Formula:



It would not be straight forward to choose this specific combination of six claims (claims 1, 78, 79, 81, 83, and 86) to arrive at this linker out of over 10,000 possible combinations. And even if it were, there is no claim or embodiment that describes these combinations with the "A" and "B" moieties of the '416 Patent.

The lack of congruity between the specification and '416 claim Linker formula becomes even more pronounced when looking at the dependent claims

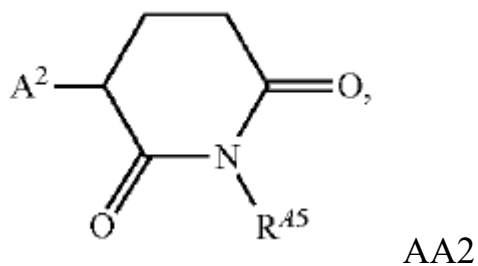
which limit the Linker moiety (“L”). In claim 6, F¹ is limited to a list of 11 specific heterocycle groups (Ex.1001, 516), however, when F¹ is limited to these specific heterocycles in the ’746 PCT Application, claims F² and F³ are also limited to C₂-C₆ heterocyclylene (Ex.1005, 437: claim 52 which depends on any one of claims 41 to 51 which ultimately depend on claim 40 which depends on claim 39 and recites “the compound of any one of claims 1 to 30, wherein each of F¹, F², or F³ is, independently, optionally substituted C₂-C₆ heterocyclylene.”). Similarly, claims 7, 14, and 15 have the same defect where F¹, F², and F³ are not all required to be heterocycle (Ex.1001, 516-518).

In claim 8, F³ is optionally substituted C₆-C₁₀ arylene, (*Id.*, 516) however, when F³ is limited to C₆-C₁₀ arylene in the ’746 PCT Application, claims F¹ and F² are also limited to C₆-C₁₀ arylene (claim 69 which depends on any one of claims 1 to 30 “wherein each of F¹, F², or F³ is independently, optionally substituted C₆-C₁₀ arylene.”) (Ex.1005, 441).

Thus, there is not a single ’416 patent claim which corresponds to the scope of the “L” moiety (Linker) described in the ’746 PCT Application.

B Moiety

The “B” moiety recited in claim 1 of the ’416 patent is a compound of Formula AA2



wherein:

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

R^{A5} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl (Ex.1001, 515).

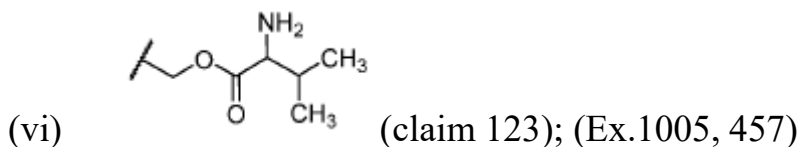
Claim 128 recites a compound of Formula AA2 wherein:

A^2 is a bond between the degradation moiety and linker (claim 97)

R^{A5} is either:

- (i) H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl (claim 97);
- (ii) H or optionally substituted C_1 - C_6 alkyl (claim 119);
- (iii) H (claim 120);
- (iv) methyl (claim 121);

(v) optionally substituted C₁-C₆ heteroalkyl (claim 122); or



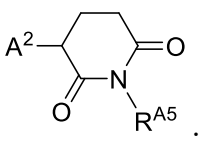
And the degradation moiety (Formula AA2) is a **ubiquitin ligase binding moiety** (claim 95) (Ex.1005, 452).

None of the claims of the '416 patent recite the limitation that the "B" moiety is a ubiquitin ligase binding moiety. Thus, there is not a single '416 patent claim which corresponds to the scope of the "B" moiety described in the '746 PCT Application.

In conclusion, none of the recited "A", "L", and "B" moieties of the '416 patent claims are described independently or in combination in the '746 PCT Application. A POSA would not be led to the subject matter of the '416 patent claims from the '746 PCT Application. In the analogy of picking a tree out of a forest the correct tree isn't even in the forest. And even if there were a congruent claim of the '746 PCT Application that was coterminous with a '416 claim, which there is not, the '416 claim would still violate the written description requirement for lack of a single representative species.

D. The “B” Moiety of Claim 1 does Not Serve its Defined Function

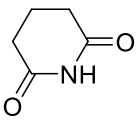
Petitioner has requested the Board to construe “B” as used in the ’416 Patent

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

“B” is defined by PO in column 1, line 41, 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.1017, ¶¶15-16).

Table 1

Structure	CRBN Binding -FP assay K _d (μM)
	230

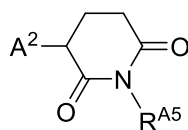
Dr. Nasveschuk states that it would be very difficult to administer enough heterobifunctional drug to a human to reach a concentration of 230 micromolar of the moiety AA2 in the target human cells (Ex.1017, ¶17). Dr. Djuric agrees (Ex.1014, ¶150) In fact, Dr. Nasveschuk calculates that one would have 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.1017, ¶18-19)

A POSA would thus not consider the structure of Formula AA2 alone to be an effective cereblon binder and thus not a “degradation moiety” (Ex.1014, 151). It is only when AA2 is bound to a second chemical moiety that it becomes a cereblon binder that might work to form an effective ternary structure in a human (*Id.*). However, that is not how it is defined in the ’416 Patent. A² is the bond between B and linker, and linker is not defined in the ’416 Patent as contributing to the degradation of the protein (*Id.*).

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

Indeed, Dr. Nasveschuk states that Petitioner uses heterobifunctional molecules 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.1017, ¶20).



It is Petitioner’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. (Ex.1014, ¶153; Ex.1017 ¶20).

XI. GROUND 2: CLAIMS 1-15 ARE INVALID UNDER 35 U.S.C. §112(B) FOR INDEFINITENESS

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.” Accordingly, 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 35 U.S.C. §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, however, 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 35 U.S.C. §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) (*Id.*). 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.”).

But a claim is indefinite when the boundaries of the protected subject matter are not clearly delineated and the scope is unclear. MPEP §2173.04. For example, a genus claim that covers multiple species is broad, but is not indefinite because of its breadth, which is otherwise clear (*Id.*). But, a genus claim that could be interpreted in such a way that it is not clear which species are covered would be indefinite (e.g., because there is more than one reasonable interpretation of what species are included in the claim) (*Id.*).

A. The term “optionally substituted” is indefinite

Petitioner urges that the pervasive use of the term “optionally substituted” in each of the claims of the '416 Patent renders each claim indefinite for the reasons extensively discussed in the Claim Construction Section IX. For efficiency of space, those arguments will not be repeated here but are considered to support a conclusion of indefiniteness and violation of 35 U.S.C. §112(b) of each claim.

B. 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 35 U.S.C. §112(b) for the reasons extensively discussed in the Claim Construction Section IX if they are not construed by the Board to allow attachment of a substituent group on either the aromatic or non-aromatic moiety. Dr. Djuric confirms that without this proper 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 ¶155). The POSA would not then have

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

XII. GROUND 3: CLAIMS 1-15 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) (“Once the precise scope of the claimed invention is defined, the question is whether undue experimentation is required to make and use the full scope of embodiments of the invention claimed.”); *Trs. Of Boston Univ. V. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018) (“Our precedents make clear that the specification must enable the full scope of the claimed invention.”). “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) (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 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 '416 Patent that the Claimed Compounds have Utility under 35 U.S.C. §101 as BRD9 Degrading Compounds.

Dr. Djuric explains that a POSA would interpret the '416 Patent as establishing a threshold for utility for a BRD9 degrader as having an IC₅₀ activity of less than 1 micromolar (“μM”) in at least one of the only two biological examples in the specification, Example 86 and Example 87. (Ex.1014 ¶156).

Example 86 measured the ability of a test compound to biochemically inhibit BRD9 bromodomain in a competition binding assay (Ex.1001, 419; col. 805, lines

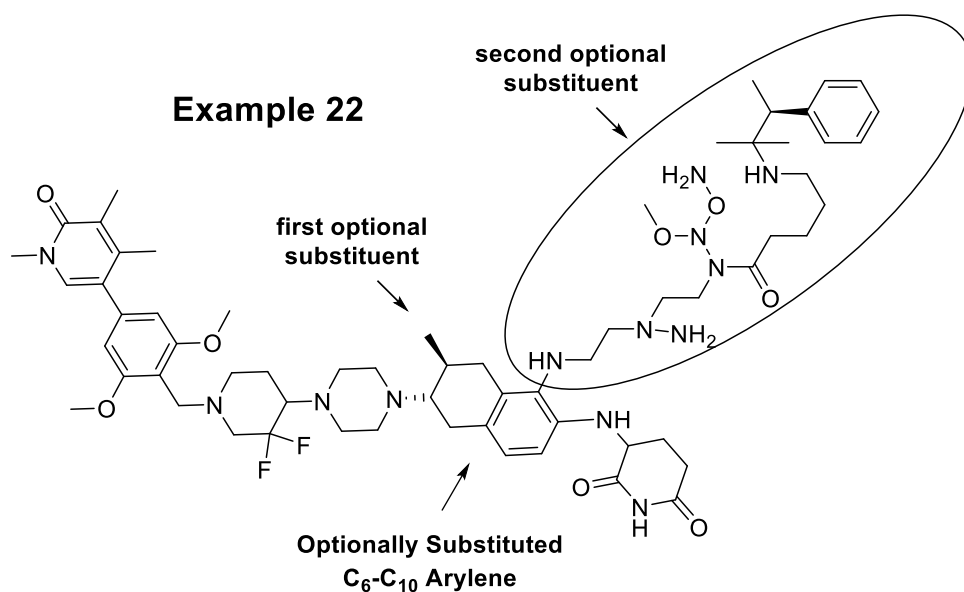
46-48) (Ex.1014, ¶157). In col. 806, lines 49-52, PO stated that “as shown by the results in Table 4, a number of compounds of the present disclosure exhibit an IC₅₀ value of <1 µM for BRD9 binding, indicating their affinity for targeting BRD9.” (Ex.1001, 419). According to Dr. Djuric, this teaches the reader two things: (i) not all of the compounds in the ’416 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 (Ex.1014, ¶157).

Likewise, Dr. Djuric refers to PO’s ’416 Patent Example 87 where it states that the example demonstrates the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay (Ex.1014, ¶158). In col. 809, lines 61-67, 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, 421). Dr. Djuric concludes that this teaches a POSA that (i) not all of the compounds in the ’416 Patent 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 ¶158). Thus, the claims lack enablement under 35 U.S.C. §102 and utility under 35 U.S.C. §101.

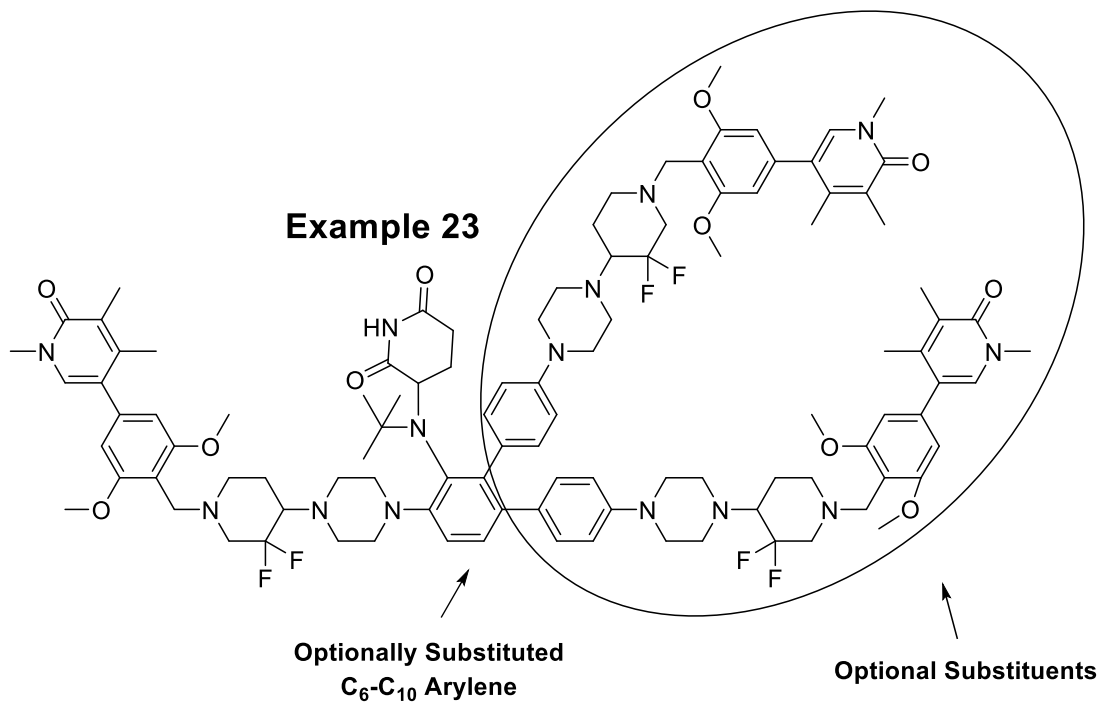
Together, Examples 86 and 87 confirm that PO was aware at the filing date that not all of the described compounds would work for the intended function—treating a BRD9 mediated medical disorder, and that the threshold for expectation of activity is $< 1 \mu\text{M}$ in these assays (Ex.1014, ¶159).

In addition, because **no** compounds that fall within the '416 Patent's issued claims were described, made, or tested, according to Dr. Djuric, there can be no reasonable expectation whether they would work for the intended function or not. (Ex.1014, ¶160). And even if some of them would, there was no way to know which would and which would not (*Id.*). Therefore, the '416 Patent specification is not enabling to a POSA for the claimed compounds (*Id.*).

Moreover, the uncertainty regarding the use of the claimed compounds increases drastically when the multitude of included optional substitutions is considered. All the '416 Patent claims include at least one chemical moiety that can be optionally substituted and even the narrowest claim (claim 15) includes at least 6 references to the vague and unbounded term. Just two examples are Examples 22 and 23 below which are listed in Dr. Djuric's Declaration in Attachment 2:



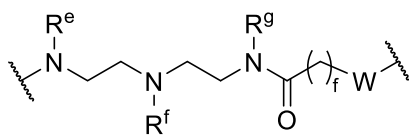
and



(Ex.1014, ¶98).

The optional substituent of Example 22 drawn above does not even require the use of the infinite loop as described in Section IX above to fit within the genus

of claim 15. (Ex.1014, ¶99). In fact PO's own claim dependency requires that the second optional substituent fits within the definition of "optionally substituted C₁₋₁₀ heteroalkylene" because this moiety fits within the definition of E² provided in claim 3 which is only properly dependent on claim 1 when optionally substituted C₁₋₁₀

heteroalkylene includes moiety  (Ex.1001, 515-516; Ex.1014, ¶99).

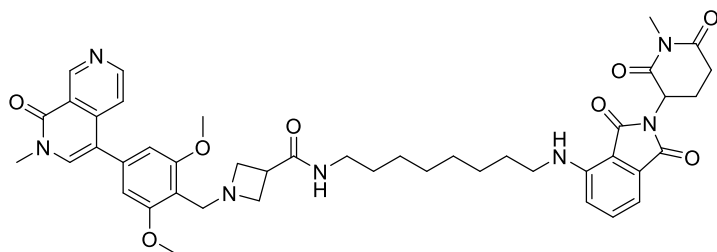
When the infinite loop is applied to the claimed compound, Example 23 can be drawn within the genus. As discussed by Dr. Djuric (Ex.1014, ¶100) it is impossible to know based on the teachings of the specification if Example 22 which includes three BRD9 Targeting moieties could be used as a BRD9 degrader without synthesis and testing.

Dr. Djuric was asked to draw additional compounds which fall within the claims of the '416 Patent. These are provided in Attachment 2 of the Djuric Declaration (Ex.1014, Attachment 2). These exemplary compounds can have vast ranges of sizes (Ex.1014, Attachment 2). According to Dr. Djuric, determining where to draw the line on which of these compounds could or could not be used as BRD9 degraders is impossible without synthesizing and testing them (Ex.1014, ¶101). Thus, undue experimentation is required to use the full scope of embodiments

of the invention claimed. *Trs. Of Boston Univ. V. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018).

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 moiety such as alkyl are typically inactive (Ex.1017, ¶20).

The only compound that PO tested with R^{A5} as 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. 810).



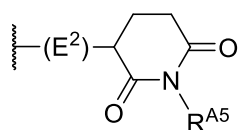
D8 (Ex.1001, 84).

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

The '416 Patent specification does not provide sufficient detail to teach a POSA how to make the claimed compounds across the scope of the claims. In fact, as discussed extensively in Sections IX, XI, and in the Djuric Declaration, the scope of the claimed invention has no set boundaries and includes an infinite number of compounds. A skilled artisan would require infinite experimentation to make and use compounds across an infinite scope. (Ex.1014, ¶162). Thus, the specification

does not enable the synthesis of the claimed compounds across the scope of the claims (*Id.*).

A detailed synthetic procedure is provided for fewer than a fourth of the drawn molecules (D1 to D74) (Ex.1014, ¶163). And, even when synthetic methods are provided, the synthesis is for compounds that aren't covered by the '416 Patent claims and often these compounds differ in several structural motifs from the limitations required by the '416 Patent claims (*Id.*). For example focusing on the

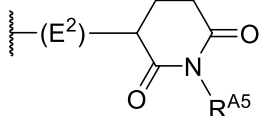
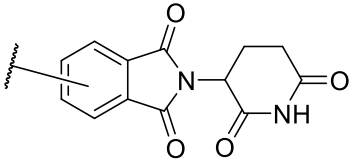
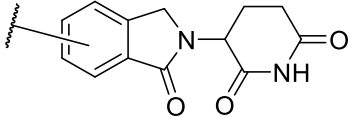


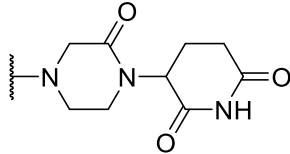
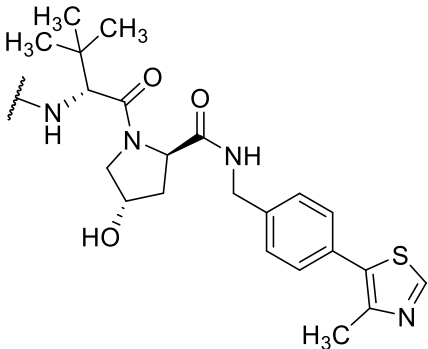
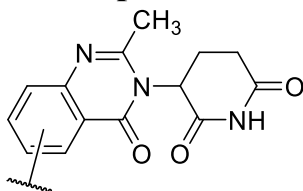
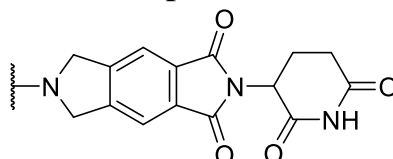
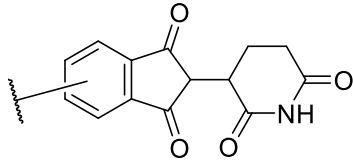
and Linker moieties below every molecule with a detailed synthesis differs in both moieties (*Id.*).

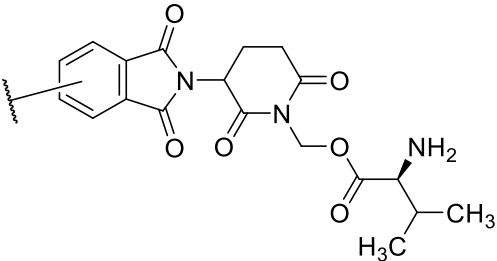
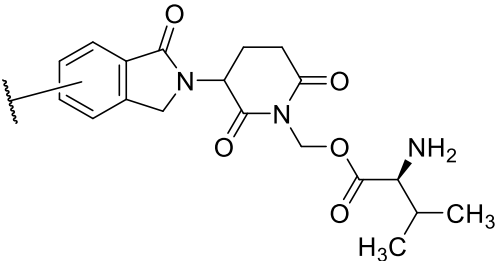
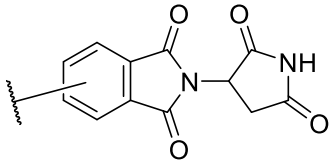
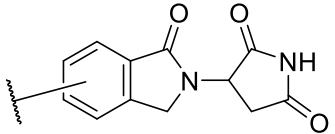
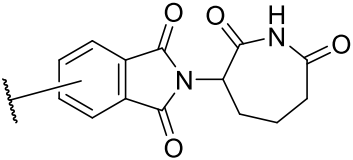
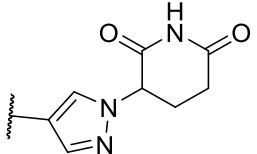
Moiety		
Cpd. ID		$-(F^1)-(F^2)-(F^3)-$
D1 to D74	<p>Not covered by the claims of the '416 Patent due to the presence of</p> <p>in the compounds</p>	<p>Not covered by the claims of the '416 Patent because the $-(F^1)-(F^2)-(F^3)-$ motif requires 3 cyclic moieties directly and sequentially connected to each other in the compounds</p>

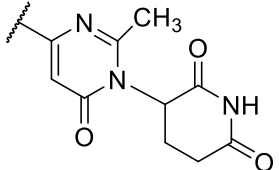
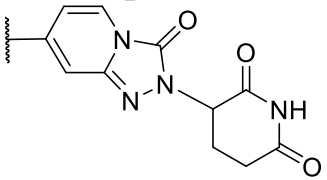
The synthesis of compounds D75-D476 and DD1-DD16 is not described and instead the specification states that they were prepared in analogy to the described

syntheses of D1 to D74 using appropriate starting materials (Ex.1014, ¶165). These compounds are also not covered by claims of the '416 Patent (*Id.*).

	Moiety	
Cpd. ID		$-(F^1)-(F^2)-(F^3)-$
D75 to D326, D328 to D333, D335 to D355, D359, DD2, DD6, DD8, DD10, D372 to D373, D376, D385 to D386, D398, D406, D413, D415, D418, D420, D430, D436, D439, D445 to D446, DD11	<p>Not covered by the claims of the '416 Patent due to the presence of</p>  <p>in the compounds</p>	<p>Not covered</p>
D356 to D358, D360 to D371, DD4, D374 to D375, D377 to D380, D387, D389 to D431, D433 to D390, D396 to D397, D399 to D405, D407 to D412, D414, D416 to D417, D419, D421 to D429, D431, D433 to D435, D437 to	<p>Not covered by the claims of the '416 Patent due to the presence of</p>  <p>in the compounds</p>	<p>Not covered</p>

D438, D440 to D444, D447 to D470, D474, DD12-DD16		
D334	<p>Not covered by the claims due to the presence of</p> 	Not covered
DD1	<p>Not covered by the claims due to the presence of</p> 	Not covered
DD3, DD5	<p>Not covered by the claims due to the presence of</p> 	Not covered
DD6, DD9	<p>Not covered by the claims due to the presence of</p> 	Not covered
DD7	<p>Not covered by the claims due to the presence of</p> 	Not covered

D381	<p>Not covered by the claims due to the presence of</p> 	Not covered
D384	<p>Not covered by the claims due to the presence of</p> 	Not covered
D383	<p>Not covered by the claims due to the presence of</p> 	Not covered
D382	<p>Not covered by the claims due to the presence of</p> 	Not covered
D388	<p>Not covered by the claims due to the presence of</p> 	Not covered
D393	<p>Not covered by the claims due to the presence of</p> 	Not covered

D394	<p>Not covered by the claims due to the presence of</p> 	Not covered
D432	<p>Not covered by the claims due to the presence of</p> 	Not covered

Only six drawn compounds (D391, D392, D395, D471, D472, and D473) include a NH moiety in position E2 and even these compounds do not have an explicit synthesis and still do not fall within the claim because of the presence of a carbonyl at position F³. (Ex.1014, ¶166).

Application of the *In re Wands* factors demonstrates the lack of enablement, as described below, when the pervasively used vague and open-ended term “optionally substituted” is included in the claim analysis.

(1) The quantity of experimentation necessary.

The claims cover a vast and unbounded number of molecules. The quantity of experimentation necessary to enable a POSA to make compounds across an infinite scope is an infinite amount of undue experimentation. (Ex.1014, ¶167).

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

The necessary experimentation in this instance is beyond routine experimentation for medicinal chemistry because the compounds in the '416 Patent claims are not sufficiently defined. For example, as noted by Dr. Djuric, Example 22 includes moieties that are likely unstable and for which a known synthetic route does not exist (*Id.*). As noted in the Claim Construction Section IX the '416 Patent claims do not even exclude compounds which are unstable or chemically infeasible (*Id.*).

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

The '416 Patent doesn't describe a single compound within claims 1-15, much less a working example for the synthesis of a claimed compound (*Id.*).

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

The guidance of the '416 Patent specification is focused on the synthesis and use of thalidomide containing BRD9 degraders that are not covered by the claims. There is not a single drawn, synthesized, or tested compound in the '416 Patent that is covered by the claims (*Id.*).

(5) The nature and predictability of the field.

The field of BRD9 degraders is unpredictable. As discussed in Dr. Djuric's declaration, small changes in degraders can create profound differences in activity. Dr. Djuric notes that several of the compounds he drew that fall within the scope of

the claims would be very difficult to synthesize and that the '416 Patent specification does not provide useful synthetic methods to prepare these exemplary compounds (*Id.*).

(6) The level of ordinary skill.

As discussed in Section VIII, a POSA would have either a Ph.D. in chemistry, medicinal chemistry, biochemistry, or a closely related discipline in the pharmaceutical area, or a Master's degree and relevant industry experience. However, as noted by Dr. Djuric there is no level of training that would enable a POSA to make and use an infinite list of compounds (*Id.*). The claims cover compounds that can be infinitely large. Thus, the level of ordinary skill in the art does not extend to synthesizing and using compounds that can be infinitely large (*Id.*).

(7) The scope of the claimed invention.

As discussed in Section IX the scope of the invention is infinite because of the infinite loop created by various substituent definitions and includes at least the exemplary compounds drawn in Ex.1014 Attachment 2 (*Id.*).

Thus, all seven of the recited *In re Wands* factors weigh in favor of finding the claims invalid for lack of enablement over the full scope of the granted claims.

XIII. NONE OF THE CLAIMS ARE ENTITLED TO A PRIORITY DATE EARLIER THAN SEPTEMBER 17, 2021

As discussed in detail in Section IX and X above, the priority applications, PCT Application, and even the parent application of the '416 Patent fail to disclose the presently claimed combination of substituents. Thus, the claims are not entitled to a priority date earlier than September 17, 2021, which is when PO filed the claims with the USPTO.

XIV. GROUND 4: THE INTERVENING '920 PCT PUBLICATION IS A NOVELTY DESTROYING REFERENCE TO CLAIMS 1-15 OF THE '416 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).

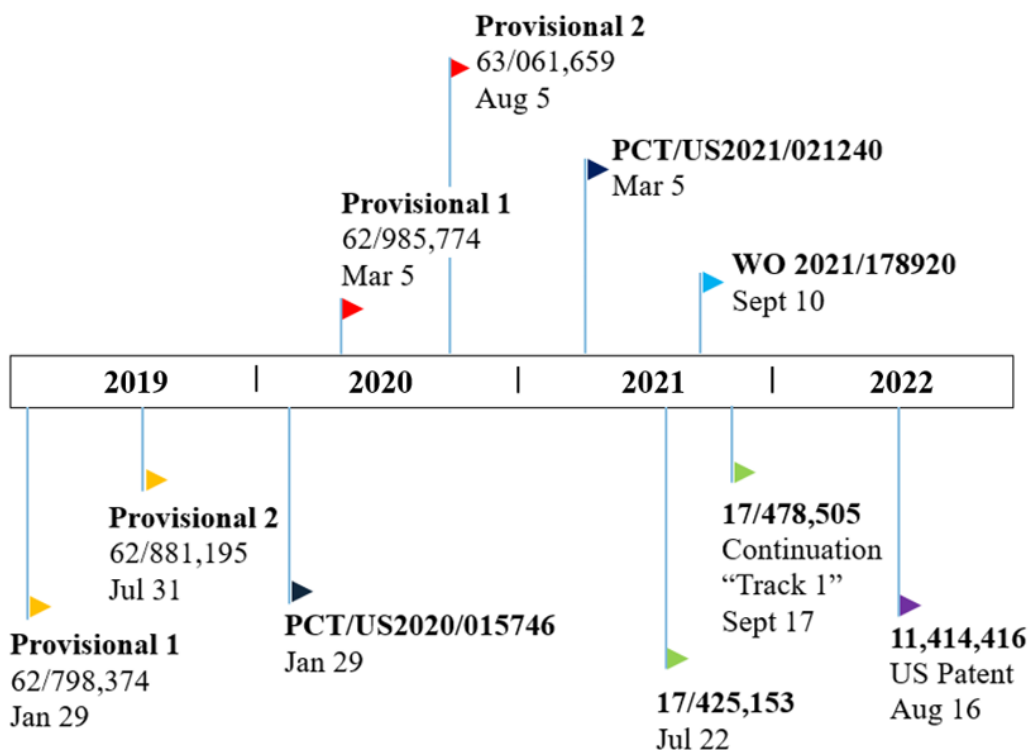
Table 3 below provides a timeline of the patent filings of Petitioner and PO. Since PO is not entitled to any of its priority dates, Petitioner’s '920 PCT Publication becomes an anticipatory reference.

TABLE 3

Application	Assignee	Filing Date	Exhibit
U.S.S.N. 62/798,374 (“’374 Provisional”)	FOGHORN THERAPEUTICS, INC.	Jan. 29, 2019	1003
U.S.S.N. 62/881,195 (“’195 Provisional”)	FOGHORN THERAPEUTICS, INC.	Jul. 31, 2019	1004
PCT/US2020/015746 (“PCT ’746”)	FOGHORN THERAPEUTICS, INC.	Jan. 29, 2020	1005
U.S.S.N. 62/985,774 (“’774 Provisional”)	C4 THERAPEUTICS, INC.	Mar. 5, 2020	1006
U.S.S.N. 63/061,659 (“’659 Provisional”)	C4 THERAPEUTICS, INC.	Aug. 05, 2020	1007
U.S.S.N. 17/425,153 (“’153 Parent ”)	FOGHORN THERAPEUTICS, INC.	Jul. 22, 2021	1008
PCT/US2021/021240 (’240 Application”)	C4 THERAPEUTICS, INC.	Mar. 05, 2021	1009
Publication of ’240 Application WO2021/178920 (“’920 PCT Publication”)	C4 THERAPEUTICS, INC.	Sep. 10, 2021	1010
U.S.S.N. 17/478,505 (“’505 Con”) Issues as 11,414,416	FOGHORN THERAPEUTICS, INC.	Sep.17, 2021	1011
U.S.S.N. 17/541,035 (“C4T ’035 Application”)	C4 THERAPEUTICS, INC.	Dec. 02, 2021	1012
Publication of C4T ’035 Application (“’194 Publication”)	C4 THERAPEUTICS, INC.	Dec. 02, 2021	1013

The timeline is also provided in diagram form.

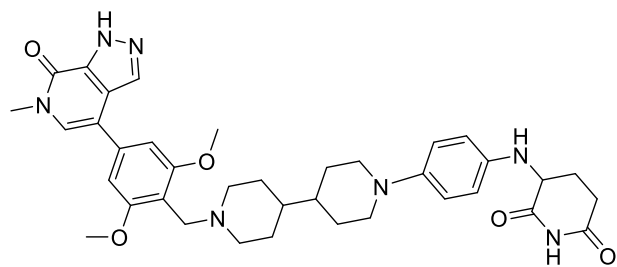
Petitioner (C4 Therapeutics) Timeline



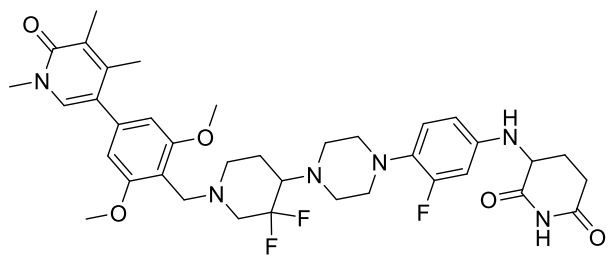
Patent Owner (Foghorn Therapeutics) Timeline

Specifically, claims 1-15 of the '416 Patent are anticipated by the '920 PCT Publication which describes over a dozen compounds that are within the scope of at least one claim of the '416 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 4 below) (Ex.1014, ¶173). Dr. Nasveschuk confirms that these compounds were synthesized and tested according to the procedures provided in the '920 PCT Publication (Ex.1017, ¶¶9-14). Each of the described compounds exhibited a DC_{50} of less than 100 nM. (Ex.1014, ¶173).

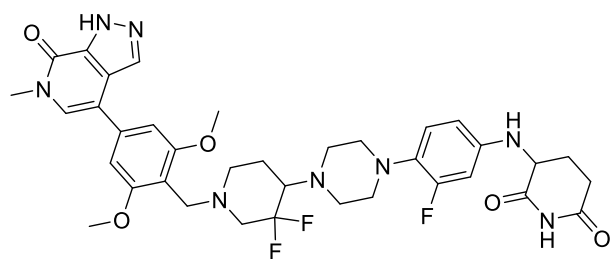
Table 4



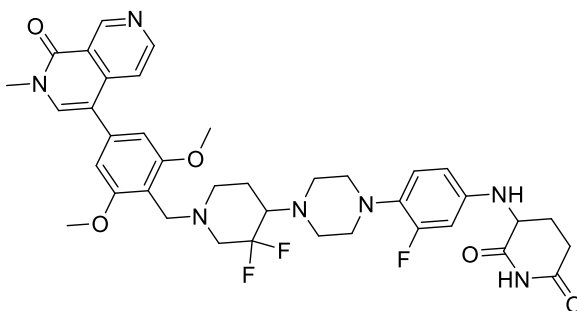
C4T Compound 70 Ex. 1010 at 679



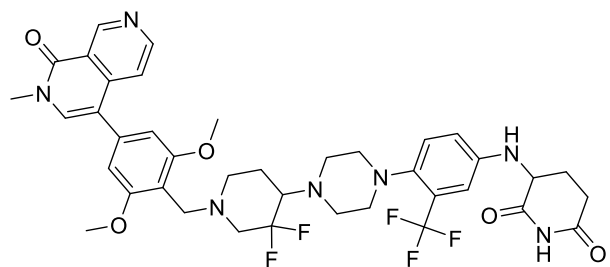
C4T Compounds 172-176 Ex. 1010 at 704-705



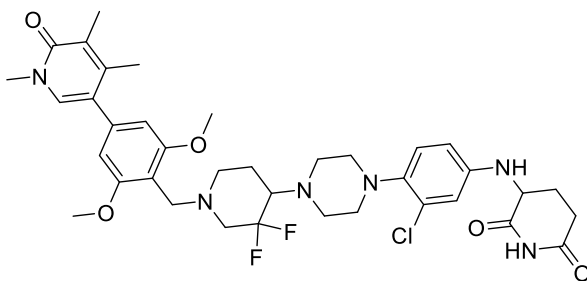
C4T Compound 182 Ex. 1010 at 707



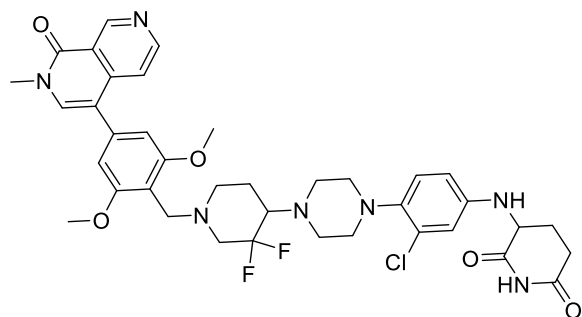
C4T Compound 184 Ex. 1010 at 707



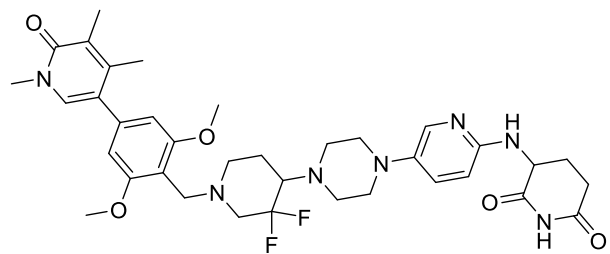
C4T Compound 185 Ex. 1010 at 707



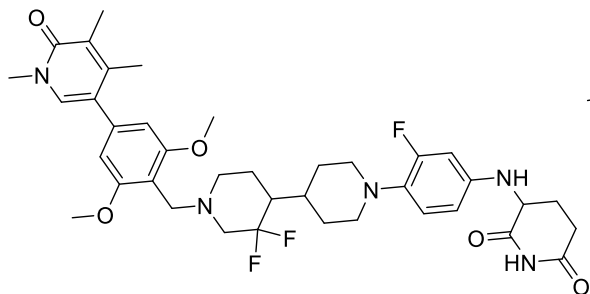
C4T Compound 187 Ex. 1010 at 708



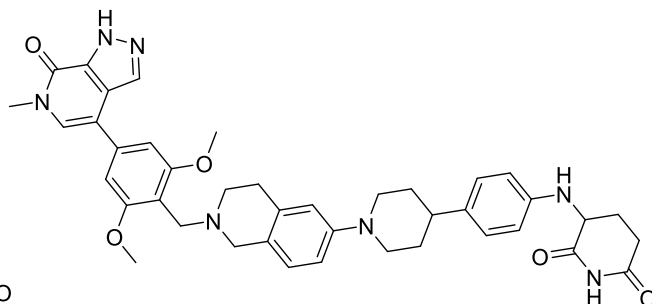
C4T Compound 188 Ex. 1010 at 708



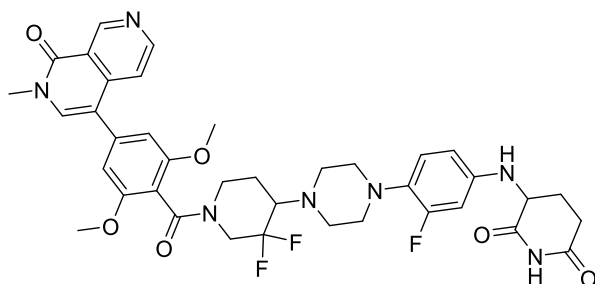
C4T Compound 195 Ex. 1010 at 710



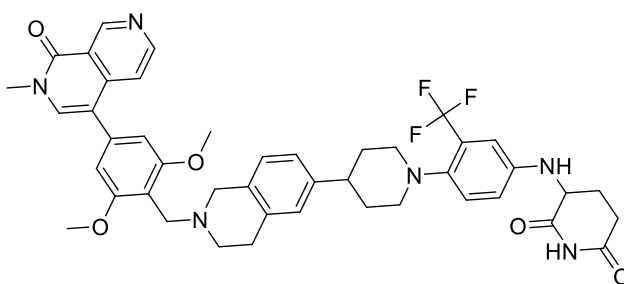
C4T Compound 198 Ex. 1010 at 711



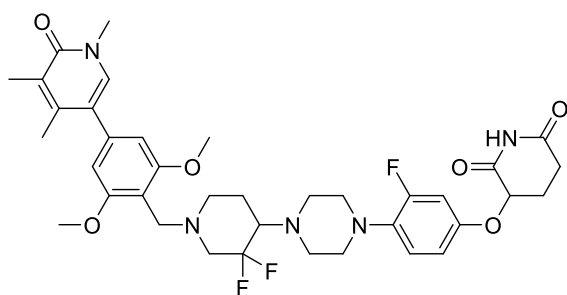
C4T Compound 206 Ex. 1010 at 713



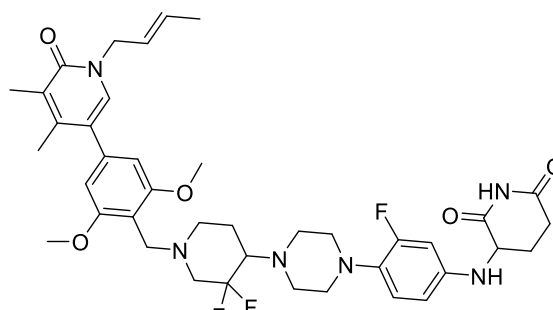
C4T Compound 225 Ex. 1010 at 717



C4T Compound 231 Ex. 1010 at 719



C4T Compound 251 Ex. 1010 at 724



C4T Compound 265 Ex. 1010 at 728

The '920 PCT Publication provides NMR characterization, mass spectra characterization, and BRD9 protein degradation data for each of the compounds described above. (See Ex.1010, 411-412, 528-531, 533-536, 539, 556, 568-570, 579, 596-600, 620-624, 649-650, 678-704, 707, 708, 710, 711, 713, 717, 719, 724, and 728). In fact, the '920 PCT Publication provides the synthesis and data for over a dozen compounds that fall within the claims of the '416 Patent. (Ex.1014, ¶174)

This is in sharp contrast to the specification of the '416 Patent which does not provide synthesis or data on a single compound in its issued claims (*Id.*).

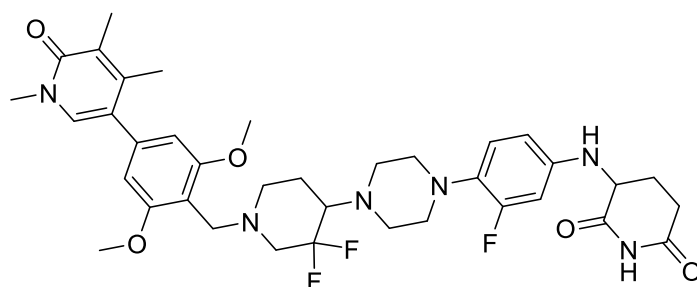
The following Table 5 matches the identified compounds in Table 4 to the claims which they anticipate in the '416 Patent.

Table 5

US Patent No. 11,414,416 Claim	Compound from '920 PCT Publication
1	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, and 265. (Ex.1014, ¶175).
2	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 231, 251, and 265. (<i>Id.</i>)
3	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, and 265. (<i>Id.</i>)
4	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, and 265. (<i>Id.</i>)
5	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, and 265. (<i>Id.</i>)
6	Compounds 172-176, 182, 184-185, 187-188, 195, 198, 225, 251, and 265. (<i>Id.</i>)
7	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, and 265. (<i>Id.</i>)
8	Compounds 70, 172-176, 182, 184-185, 187-188, 198, 206, 225, 231, 251, and 265. (<i>Id.</i>)
9	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, and 265. (<i>Id.</i>)

10	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, and 251. (<i>Id.</i>)
11	Compounds 70, 172-176, 182, 184-185, 187-188, 195, 198, 206, 225, 231, 251, and 265. (<i>Id.</i>)
12	Compounds 172-176, 187, 195, 198, 251, and 265. (<i>Id.</i>)
13	Compounds 172-176, 187, 195, 198, 251, and 265. (<i>Id.</i>)
14	Compounds 172-176, 187, 198, and 251. (<i>Id.</i>)
15	Compounds 172-176 and 187. (<i>Id.</i>)

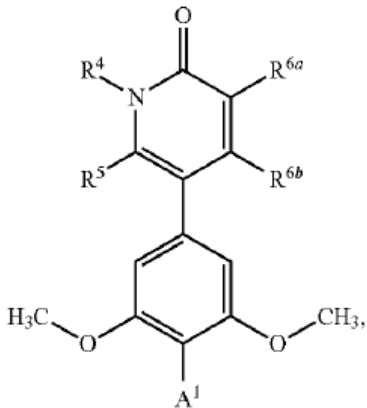
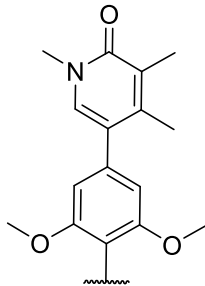
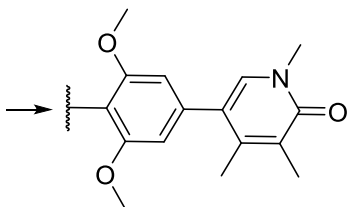
Of the compounds described in the '920 PCT Publication at least C4T Compound 172 reads on every claim of the '416 Patent.

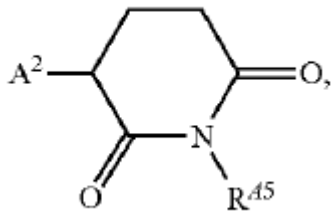
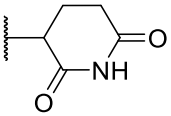


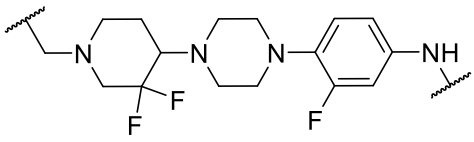
C4T Compound 172 - Exh. 1010 at 704 (Ex.1014, ¶176)

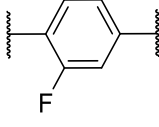
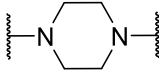
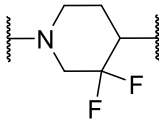
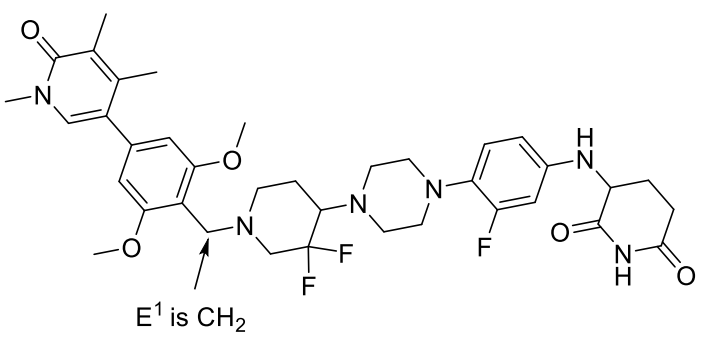
In Table 6 below the selection of variables for each substituent in the '416 Patent claim is provided which when selected and combined cover C4T Compound 172 (Ex.1014, ¶177). In the table below yellow is provided for emphasis.

Table 6

Claim 1	
A compound having the structure of Formula I: A-L-B	
'416 Patent	Cmp 172 ('920 PCT)
<p>A is</p> 	<p>Reads on the corresponding moiety</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> 
<p>R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;</p>	<p>Methyl is subset of optionally substituted C₁-C₆ alkyl</p>
<p>R⁵ is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl,</p>	<p>H is hydrogen</p>

optionally substituted C ₃ -C ₁₀ carbocyclyl, or optionally substituted C ₆ -C ₁₀ aryl;	
R ^{6a} is H, halogen, cyano, optionally substituted C ₁ -C ₆ alkyl, optionally substituted C ₁ -C ₆ heteroalkyl, optionally substituted C ₃ -C ₁₀ carbocyclyl, optionally substituted C ₂ -C ₉ heterocyclyl, optionally substituted C ₆ -C ₁₀ aryl, optionally substituted C ₂ -C ₉ heteroaryl, optionally substituted C ₂ -C ₆ alkenyl, optionally substituted C ₂ -C ₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino	Methyl is subset of optionally substituted C ₁ -C ₆ alkyl
R ^{6b} is H, halogen, cyano, optionally substituted C ₁ -C ₆ alkyl, optionally substituted C ₁ -C ₆ heteroalkyl, optionally substituted C ₃ -C ₁₀ carbocyclyl, optionally substituted C ₂ -C ₉ heterocyclyl, optionally substituted C ₆ -C ₁₀ aryl, 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;	Methyl is subset of optionally substituted C ₁ -C ₆ alkyl
<p>B is</p> 	<p>Reads on the corresponding moiety</p>  <p>of C4T Compound 172 as follows</p>

A^2 is a bond between B and L	The A^2 bond is in the same location
R^{A5} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;	H is hydrogen
L is $A^1-(E^1)-(F^1)-(F^2)-(F^3)-(E^2)_p-A^2$,	<p>Reads on the corresponding moiety</p>  <p>of C4T Compound 172 as follows</p>
p is not defined but was amended to be 1 during the prosecution of the '416 Patent	p is 1
<p>E^2 is, independently, O, S, NR^N, optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkenylene, optionally substituted C_{2-10} alkynylene, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkylene;</p> <p>NR^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;</p>	 <p>is a NR^N</p>

<p>F³ is, independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene,</p>	 <p>is an optionally substituted C₆-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>	 <p>is an optionally substituted C₂-C₁₀ heterocyclylene</p>
<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>	 <p>is an optionally substituted C₂-C₁₀ heterocyclylene</p>
<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>	 <p>is an optionally substituted C₁₋₁₀ alkylene</p>
<p style="text-align: center;">Claim 2</p> <p>The compound of claim 1, wherein E¹ is -CH₂-.</p> <div style="text-align: center;">  <p style="text-align: center;">C4T Compound 172</p> </div>	
<p style="text-align: center;">Claim 3</p>	

C4T Compound 172

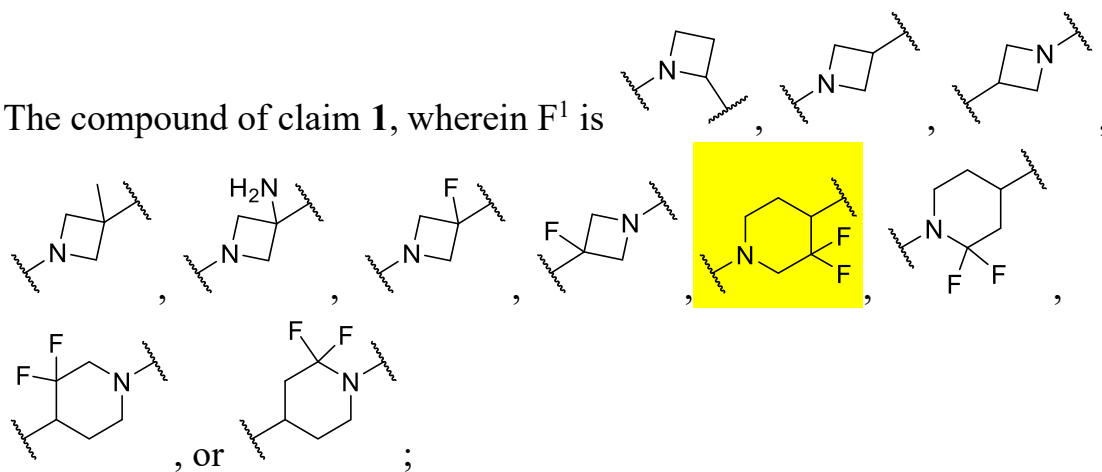
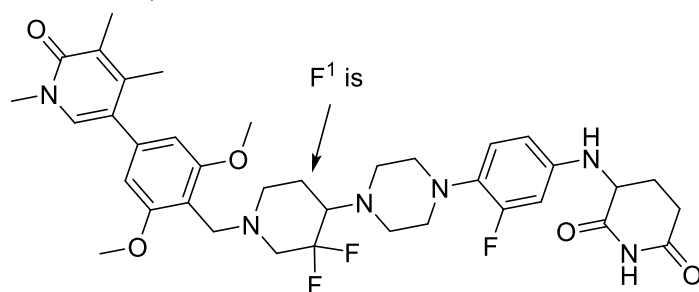
The compound of claim 3, wherein E² is -NR^N-.

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



Claim 6

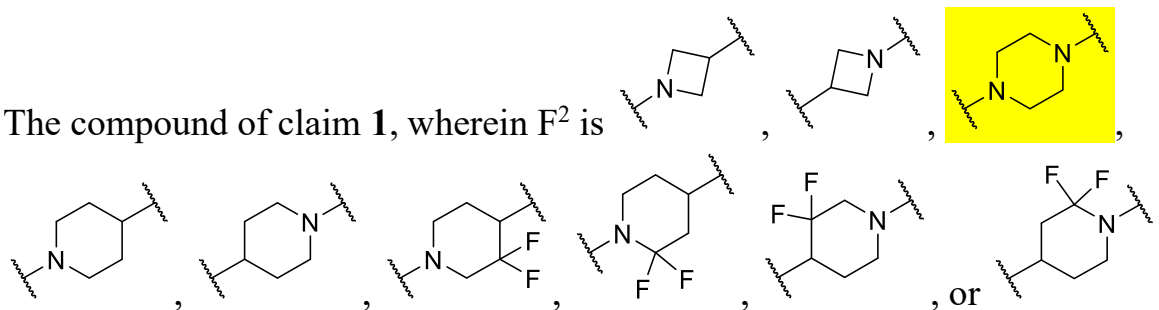
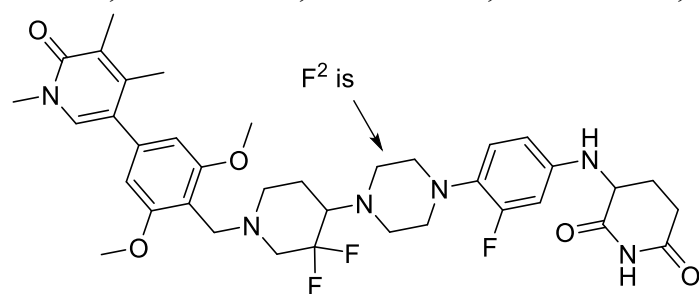
The compound of claim 1, wherein F¹ is



C4T Compound 172

Claim 7

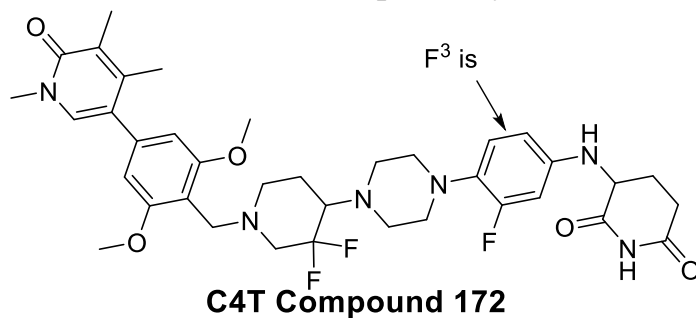
The compound of claim 1, wherein F² is



C4T Compound 172

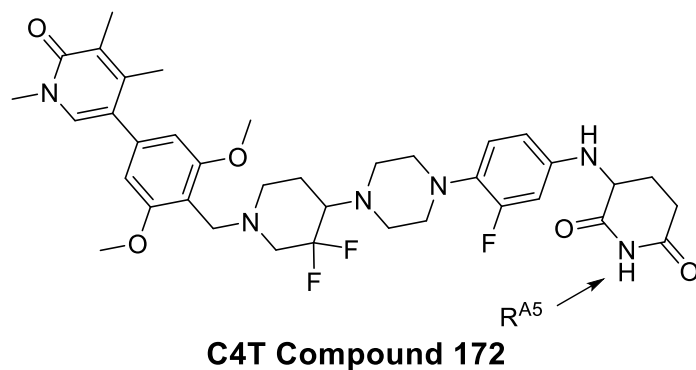
Claim 8

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



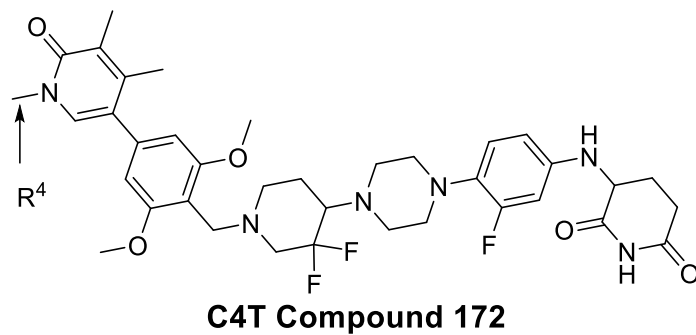
Claim 9

The compound of claim 1, wherein R^{A5} is H.



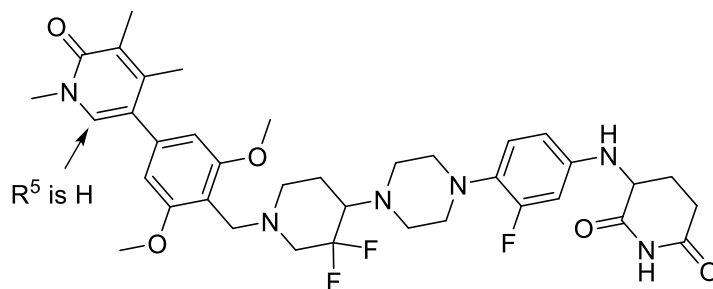
Claim 10

The compound of claim 1, wherein R^4 is $-CH_3$.



Claim 11

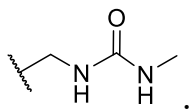
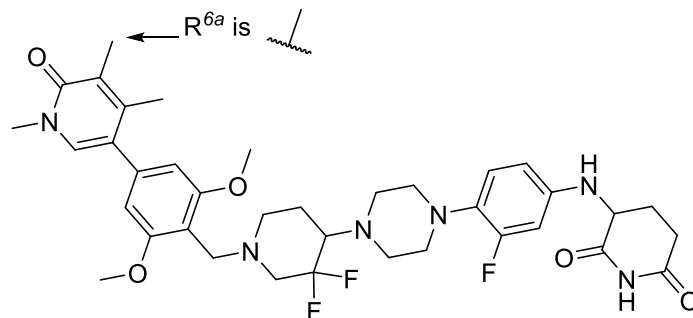
The compound of claim 1, wherein R⁵ is H or -CH₃.



C4T Compound 172

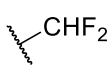
Claim 12

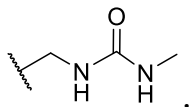
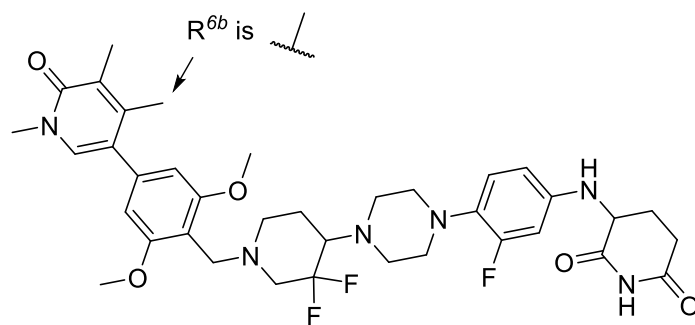
The compound of claim 1, wherein R^{6a} is H, F, cyano, , , , or



C4T Compound 172

Claim 13

The compound of claim 1, wherein R^{6b} is H, F, cyano, , , , or



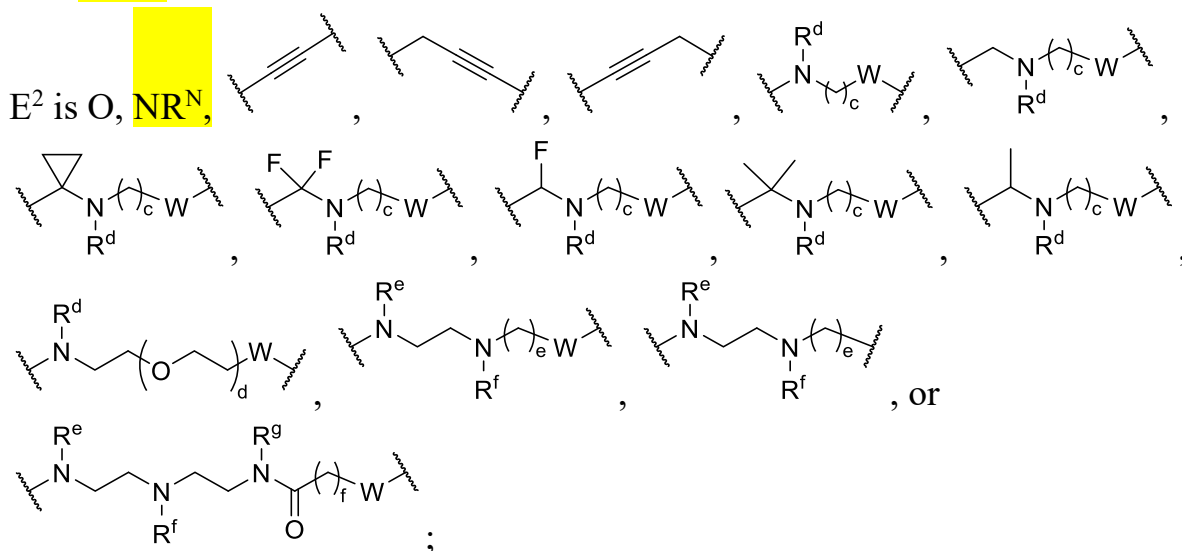
C4T Compound 172

Claim 14

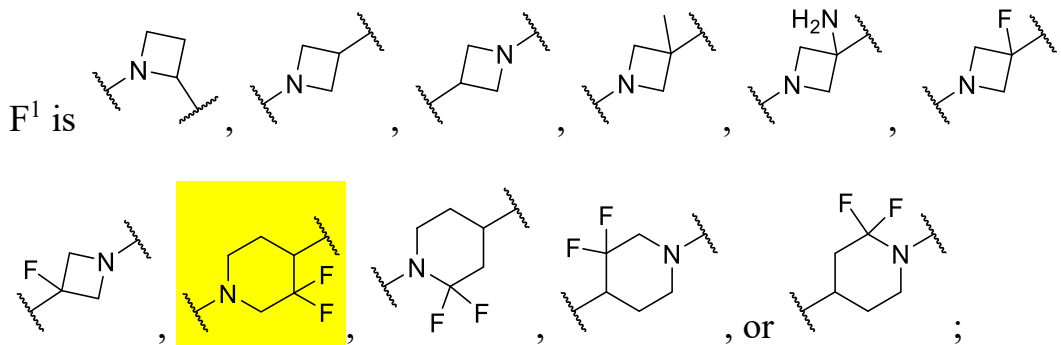
The compound of claim 1, wherein

E¹ is -CH₂-;

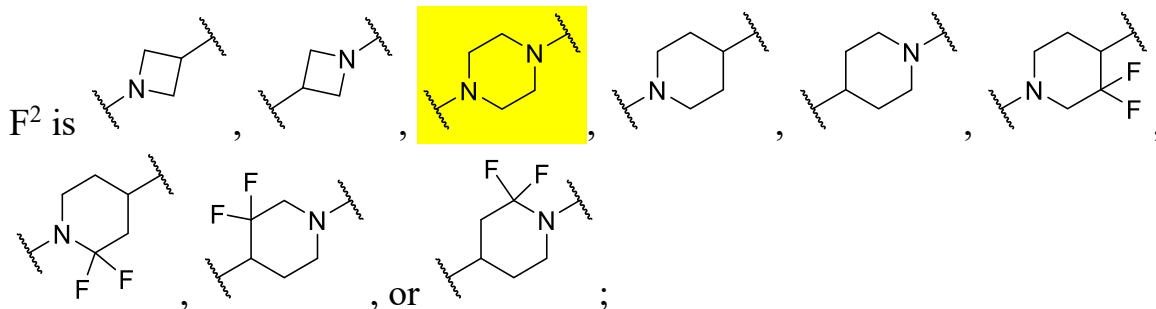
E² is O, NR^N,



F¹ is



F² is



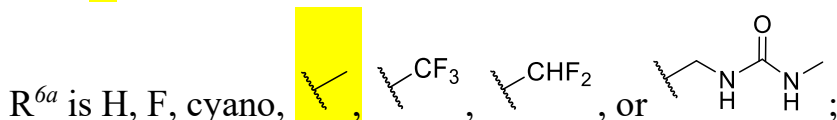
F³ is optionally substituted C₆-C₁₀ arylene;

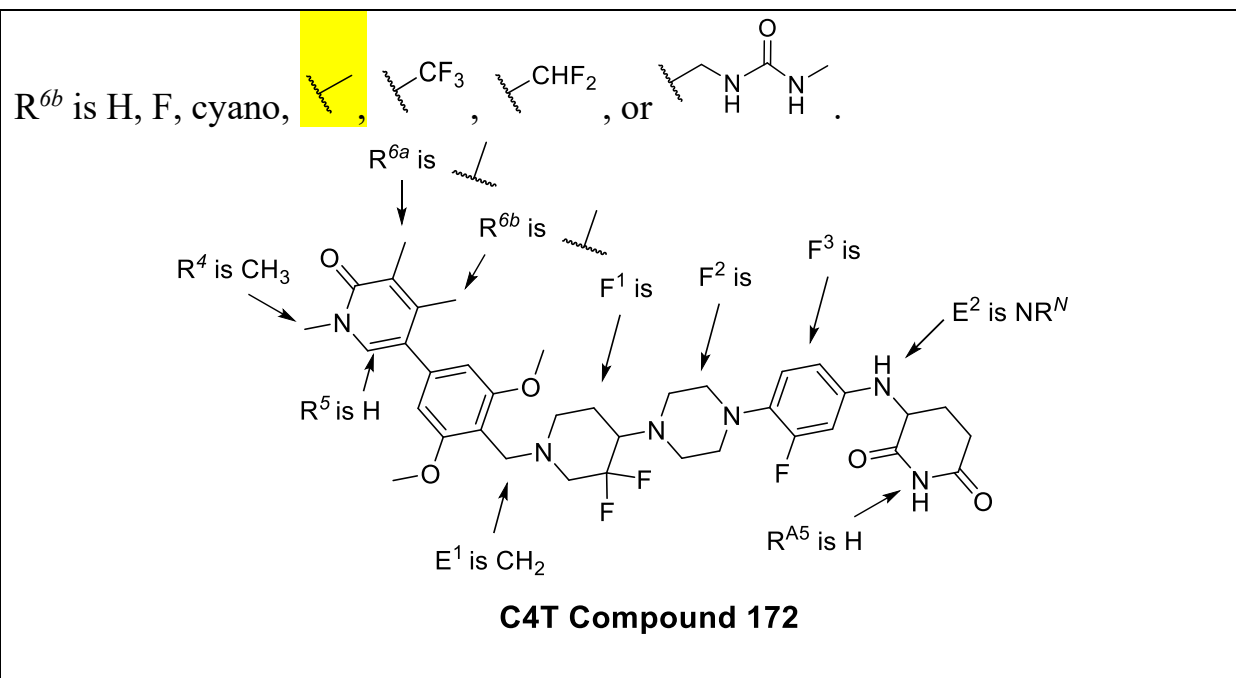
R^{A5} is H;

R⁴ is -CH₃;

R⁵ is H or -CH₃;

R^{6a} is H, F, cyano,

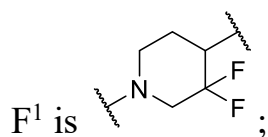
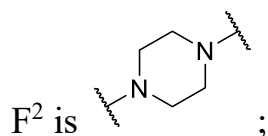




Claim 15

The compound of claim 14, wherein

E^2 is NR^N ;

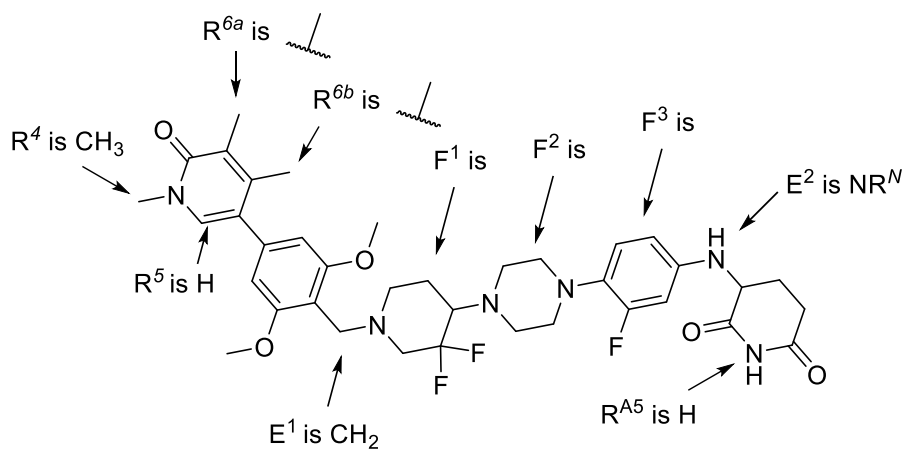


F^3 is optionally substituted C_6-C_{10} arylene;

R^5 is H;

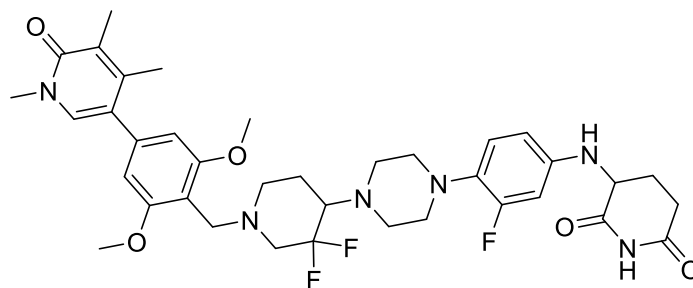
R^{6a} is CH_3 ;

R^{6b} is CH_3 ;



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 (Figures 1-24)).



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 (*Id.*, 3 (lines 27-29); 758 (FIG. 1)).

Figure 2 and Figure 3 demonstrate that C4T Compound 172 selectively degrade BRD9 with respect to BRD7 and BRD4 (*Id.*, 14 (lines 1-6); 758 (FIG. 2); 759 (FIG. 3)).

Figure 4 is a confluence graph that demonstrates the dose response effect (inhibition) on the growth of Yamato synovial sarcoma cells by C4T Compound 172 (*Id.*, 14 (lines 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 (lines 10-13); 760 (FIG. 5)).

Figure 6 provides PK data for C4T Compound 172 in another *in vivo* mouse synovial sarcoma xenograft model (*Id.*, 14 (lines 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 (*Id.*, 14 (lines 17-23); 761 (FIG. 7 & FIG. 8)).

Figure 9 demonstrates the tolerability of C4T Compound 172 in an *in vivo* mouse synovial sarcoma PDX-model (*Id.*, 14 (lines 26-28; 762 (FIG. 9))). Figures 10A and 10B provide dose prediction models for human *in vivo* dosing of C4T Compound 172 (*Id.*, 14 (lines 27-31); 763-764 (FIG. 10A & FIG. 10B))).

Figure 11 demonstrates that C4T Compound 176 selectively degrades BRD9 with respect to BRD7 and BRD4 (*Id.*, 15 (lines 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 (lines 6-13); 765-766 (FIG. 12 & FIG. 13))).

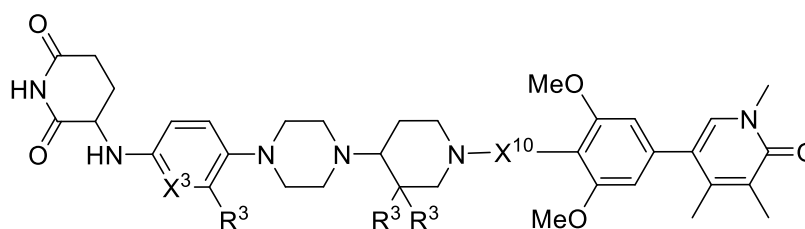
Figure 14 provides the protein level of BRD9 in synovial sarcoma tumors at different time points after administration of a single dose of C4T Compound 172 (*Id.*, 15 (lines 14-16); 766 (FIG. 14))). Figure 15 provides protein degradation data for C4T Compound 176 in four different cancer cell lines including a human rhabdoid tumor cell line, a soft tissue sarcoma cell line, and two synovial sarcoma cell lines (*Id.*, 15 (lines 17-21); 767 (FIG. 15))).

Figure 16 is a confluence graph that demonstrates the dose response effect (inhibition) on the growth of Yamato synovial sarcoma cells by C4T Compound 176 (*Id.*, 15 (lines 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 (*Id.*, 15 (lines 26-28); 769 (FIG. 17))).

Figure 18 provides pharmacokinetic (PK) data for C4T Compound 176 in an *in vivo* mouse synovial sarcoma xenograft model (*Id.*, 15 (lines 29-31)l 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 (lines 1-7); 770-771 (FIG. 19 & FIG. 20)).

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 (*Id.*, 16 (lines 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 (lines14-19); 774-775 (FIG. 23 & FIG. 24)).

The '920 PCT Publication also includes several genus formulas that anticipate the claims of the '416 Patent. For example, on pages 62 and 63 of the '920 PCT Publication there are five formulas that read on the '416 Patent claims (Ex.1014, ¶189). For example, the following formula from the '920 PCT Publication reads on each and every limitation of claims 1, 3-5, and 9-13 of the '416 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 '416 Patent. (Ex.1014, ¶190).

**XV GROUND 5: THE INTERVENING '920 PCT PUBLICATION
RENDERS CLAIMS 1-15 OF THE '416 PATENT OBVIOUS**

A claim of a patent is invalid as obvious under 35 U.S.C. §103 “if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Specifically, there are four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as long-felt but unsolved need, failure of others, praise by others in the industry, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). To establish obviousness, Petitioner must demonstrate both “that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016).

As described in Section XIV the '416 claims are anticipated and therefore invalid in view of over a dozen compounds and at least five subgenuses described in the '920 PCT Publication (Ex.1014, ¶192). The '920 PCT Publication also provides ample data on these compounds including multiple cancer screens, *in vitro* experiments with oral dosing in mice, selectivity data, and degradation data (*Id.*) As discussed by Dr. Djuric these data provided in the '920 PCT Publication provide a compelling rationale for advancing Compound 176 into human clinical trials (Ex.1014, ¶113). A POSA would be motivated by the ample data provided in the '920 PCT Publication for Compound 172, Compound 176, and other related compounds to synthesize and make these compounds and close analogues thereof for use in treating BRD9 mediated disorders (*Id.*).

A POSA would also have a reasonable expectation that the compounds described above from the '920 PCT Application successfully degrade BRD9 because the '920 PCT Publication provides *in vitro* and *in vivo* data showing that they in fact do degrade BRD9 (*Id.*). Thus, the '416 Patent claims are also invalid as obvious in view of the '920 PCT Publication.

XVI. 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 '416 Patent is invalid under one or more grounds of 35 U.S.C. §112(a), §112(b), §102 and/or §103, and order the PGR to proceed. Petitioner also requests a final determination that all claims 1-15 of the U.S. Patent No. 11,414,416 be cancelled as unpatentable.

Respectfully submitted,



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Reg. No. 33,052
Lead Counsel

Date: May 1, 2023

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Reg. No. 75,252
Brent R. Bellows, Ph.D.
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678-941-0187

APPENDIX: CLAIMS OF THE '416 PATENT

The '416 Patent claims are provided below.

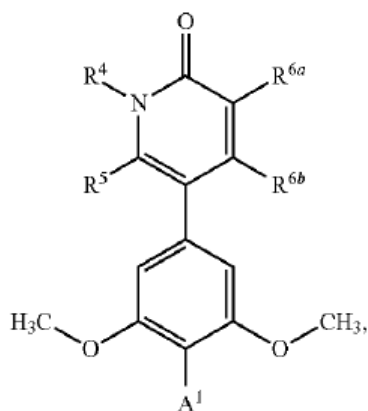
Claim 1

A compound having the structure of Formula I:

A-L-B

wherein

A is:



Formula IIIc

wherein

A¹ is a bond between A and L;

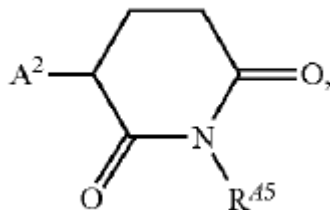
R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

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 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, 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;

B is

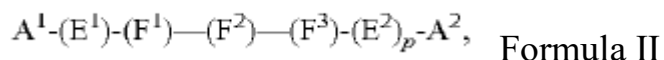


Formula AA2;

A² is a bond between B and L;

R⁴⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

L is



wherein

A¹ is a bond between the linker and A;

A² is a bond between B and the linker;

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;

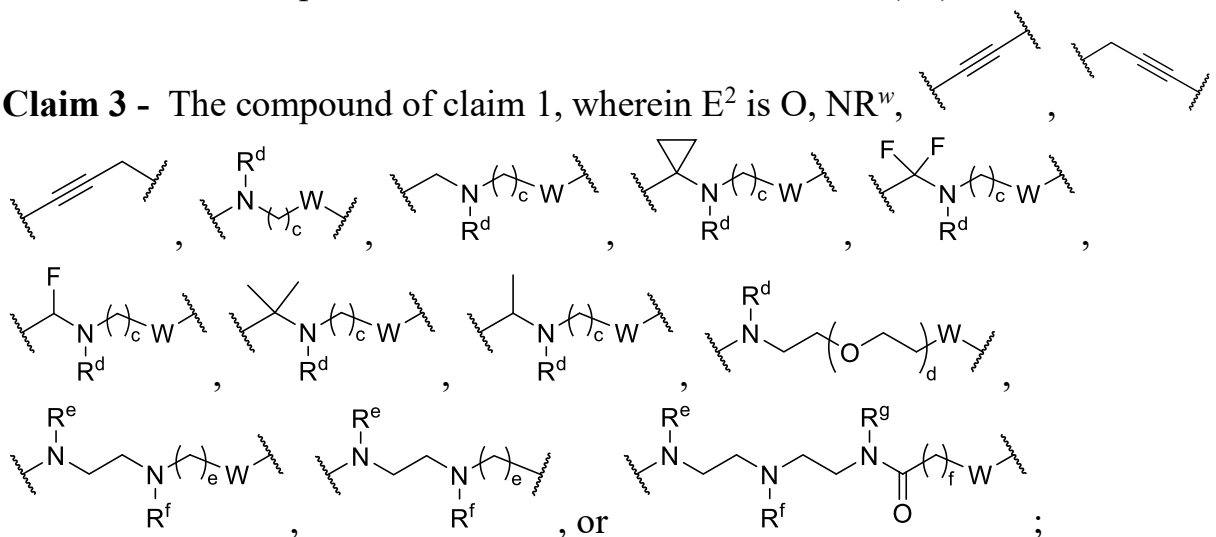
each R^N is, independently, H, optionally substituted C₁₋₄ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl; and

each of F¹, F², and F³ is, independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene;

or a pharmaceutically acceptable salt thereof (Ex.1001, 515³).

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

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;

³ Citation is to Exhibit page number.

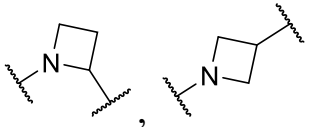
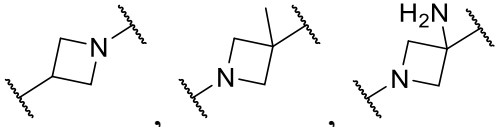
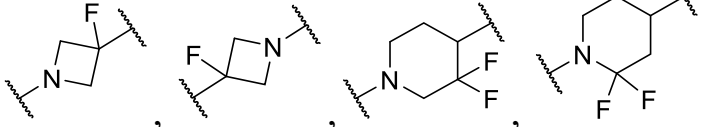
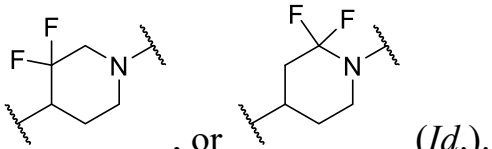
R^f is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

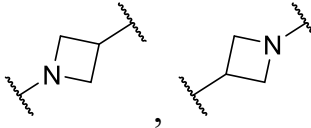
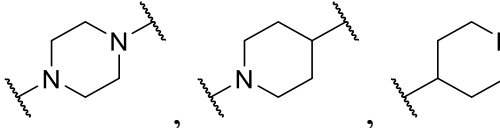
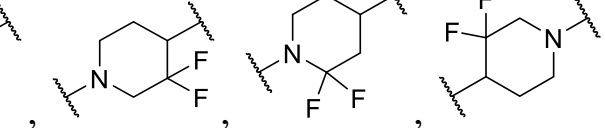
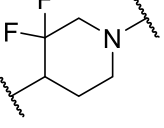
R^g is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl; and

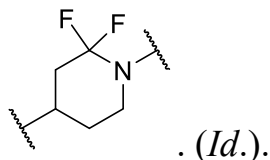
W is O or NR^w , wherein R^w is H or optionally substituted C_1 - C_6 alkyl (Ex.1001, 515-516).

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

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

Claim 6 - The compound of claim 1, wherein F^1 is , , ,  (*Id.*).

Claim 7 - The compound of claim 1, wherein F^2 is , , , or .

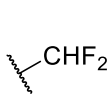
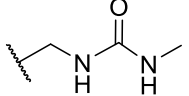


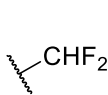
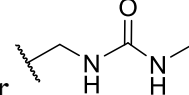
Claim 8 - The compound of claim 1, wherein F³ is optionally substituted C₆-C₁₀ arylene (*Id.*).

Claim 9 - The compound of claim 1, wherein R^{A5} is H (*Id.*).

Claim 10 - The compound of claim 1, wherein R⁴ is -CH₃ (*Id.*).

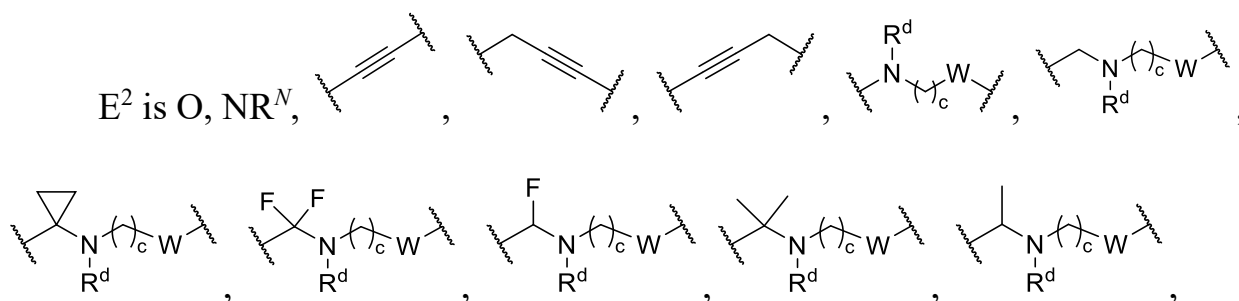
Claim 11 - The compound of claim 1, wherein R⁵ is H or -CH₃ (*Id.*, 517).

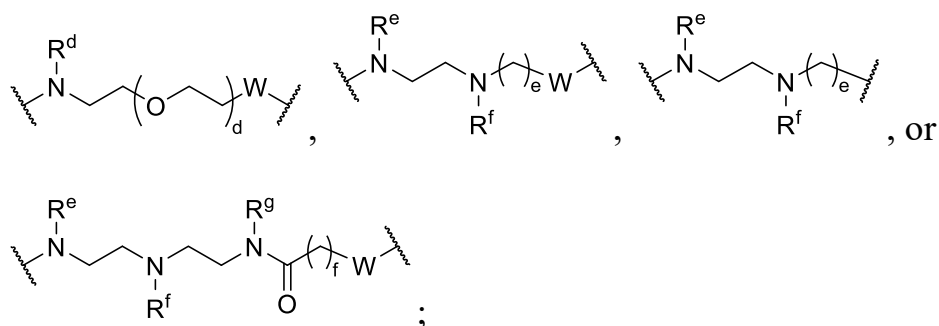
Claim 12 - The compound of claim 1, wherein R^{6a} is H, F, cyano, , , , or  (*Id.*).

Claim 13 - The compound of claim 1, wherein R^{6b} is H, F, cyano, , , , or  (*Id.*).

Claim 14 - 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;

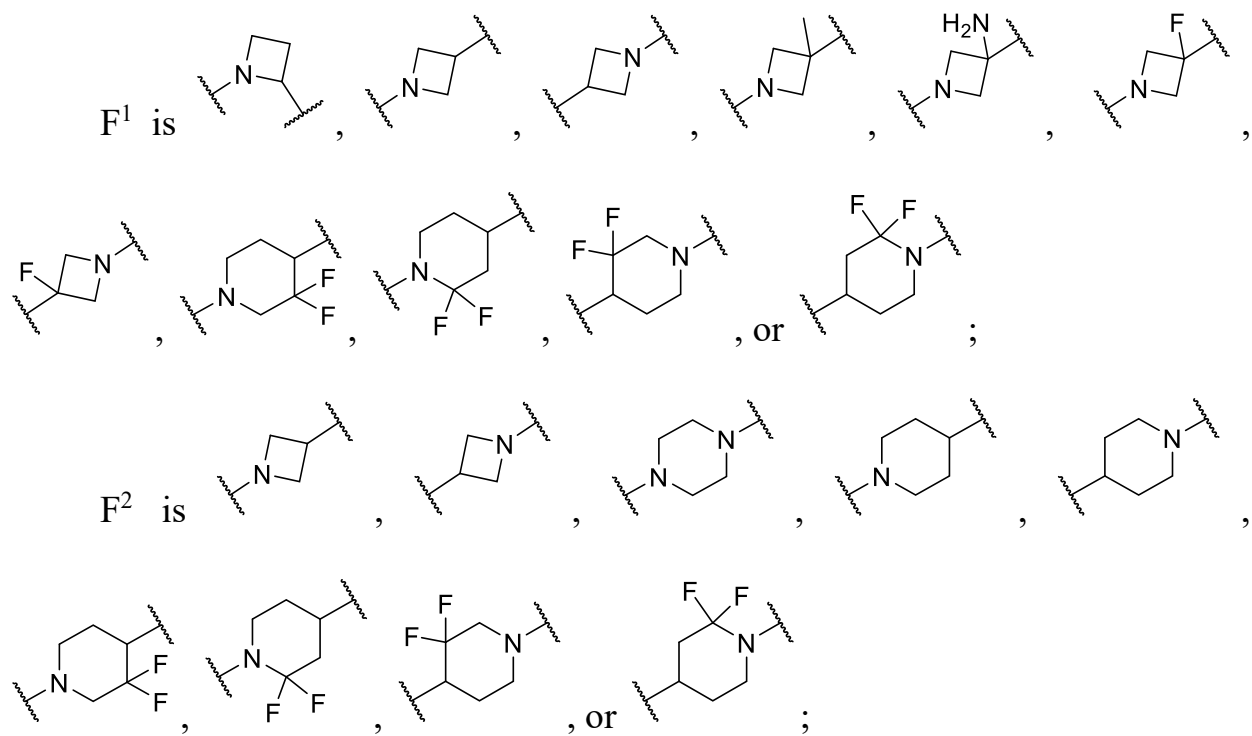
R^d is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

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

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

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

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



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

R^{A5} is H;

R^4 is $-CH_3$;

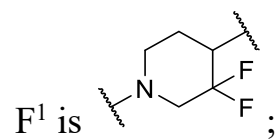
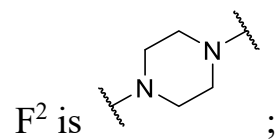
R^5 is H or $-CH_3$;

R^{6a} is H, F, cyano, , , , or , or ; and

R^{6b} is H, F, cyano, , , , or , or  (*Id.*, 517-518).

Claim 15 - The compound of claim 14, wherein:

E^2 is $-NR^N$ -;



F³ is optionally substituted C₆-C₁₀ arylene (from claim 14);

R⁵ is H;

R^{6a} is -CH₃; and

R^{6b} is -CH₃ (*Id.*, 518).

**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 18,293. 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.

Dated: May 1, 2023

Respectfully submitted,
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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. 11,414,416, including all Exhibits, was served on May 1, 2023, via Express Mail delivery directed to the following correspondence address of record for the patent:

172056 – 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. 11,414,416, including all Exhibits, was served on May 1, 2023, via Express Mail delivery directed to the following:

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Date: May 1, 2023

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