UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CONJUPRO BIOTHERAPEUTICS, INC.,

Petitioner,

v.

Ascletis Pharma China Co Ltd,

Patent Owner.

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Case No. PGR2025-00057

Patent No. 12,234,236

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**EXPERT DECLARATION OF**

**MICHAEL C. PIRRUNG, Ph.D.**

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I, Michael C. Pirrung, Ph.D., declare as follows:

1. I have been retained by counsel for Conjupro Biotherapeutics, Inc., ("Petitioner"). I understand that Petitioner is submitting a petition for post grant review ("PGR") of U.S. Patent No. 12,234,236 ("the '236 patent," attached as EX1001), which is assigned to Ascletis Pharma China Co Ltd. ("Patent Owner"). It is my understanding that Petitioner is requesting that the United States Patent and Trademark Office ("USPTO") cancel claims 1-9, 12-17, and 21-25 of the '236 patent as unpatentable. I submit this expert declaration in support of Petitioner's PGR petition for the '236 patent. I make the following statements based on personal knowledge and, if called to testify to them, could and would do so.

## I. QUALIFICATIONS

2. I am Distinguished Professor of Chemistry at the University of California, Riverside. I also hold an appointment as Professor of Pharmaceutical Sciences at the University of California, Irvine. I have over four decades of experience in the field of organic chemistry, with expertise spanning medicinal chemistry, chemical biology, bioorganic chemistry, and pharmaceutical sciences.

3. I received my B.A. in Chemistry with Highest Honors from the University of Texas at Austin in 1975, and a Ph.D. in Organic Chemistry from the University of California, Berkeley in 1980. I completed postdoctoral research in organic chemistry at Columbia University as an NSF Postdoctoral Fellow.

4. My academic appointments have included faculty positions at Stanford University, Duke University, and the University of California, Riverside. I have also served as Director of the Duke University Program in Biological Chemistry and have held various visiting professorships at leading institutions including the University of Oxford and Caltech.

5. I have conducted research and published extensively in the fields of synthetic and medicinal chemistry. I am an author or co-author of over 170 peer-reviewed papers that include technical subject matter relating to the fields of organic and bioorganic chemistry, combinatorial chemistry, and drug discovery. I have received a number of honors and awards in my fields of study, including the Chemical Pioneer Award from the American Institute of Chemists. I have been elected a Fellow of the American Association for the Advancement of Science (AAAS) and the National Academy of Inventors. Along with several co-authors, I received the Newcomb Cleveland Prize from the AAAS for the best paper published in the journal *Science* in 1991. This group also received a Distinguished Inventor Award from Intellectual Property Owners and the European Inventor of the Year Award for small- and medium-sized enterprises from the European Patent Office.

6. I have served on editorial boards of major scientific journals such as *Cell Chemical Biology* and *Journal of Combinatorial Chemistry*, have reviewed

thousands of scientific manuscripts, and have submitted many nominations for major career awards such as the Nobel Prize and the MacArthur Fellowship.

7. I have also served in advisory and consultancy roles for numerous pharmaceutical and biotechnology companies, including Abbott Laboratories, Wyeth Pharmaceuticals, and Affymax Research Institute.

8. My current research interests include organic synthesis, molecular diversity, peptide and nucleic acid chemistry, and the development of novel pharmaceutical compounds. I have trained over 100 graduate students and postdoctoral fellows in these subjects, many of whom now hold prominent positions in academia and industry.

9. Additional information regarding my education, experience, publications, awards and honors, patents, publications, and presentations is detailed in a true and correct copy of my curriculum vitae as of April 1, 2025 (**Appendix A)**.

10. A list of the materials relied upon, in addition to my experience, education, and training, to provide the opinions contained in this declaration is listed below in Section III.

11. I am being compensated for my time in connection with this PGR at my standard consulting rate, which is $450 per hour. My compensation is not dependent in any way upon the outcome of this matter.

12. I have reviewed the ’236 patent (EX1001) and relevant portions of its prosecution history at the USPTO (EX1003). Specifically, I have reviewed the ’236 patent and its prosecution history in relation to the asserted prior art and arguments at issue in the present PGR.

13. Based on my experience described above and contained in my CV, I have an established understanding of the relevant field in the relevant timeframe and the knowledge that would have been known by a person of ordinary skill in the art, as defined above and during the relevant time frame (on or before September 14, 2023 – the claimed priority date of the ’236 patent.

## II. SUMMARY OF OPINIONS

14. I have been asked to consider whether claims 1-9, 12-17, and 21-25 (the “Challenged Claims”) of the ’236 patent are obvious in view of the references discussed in Section VIII. The Challenged Claims are directed to one or more of seven GLP-1R modulating compounds (i.e., Compounds 1, 13, 18, 19, 20, 21, and 65) or a pharmaceutically acceptable salt thereof.

15. In my opinion, claims 1-4, 6, 12-14, 24, and 25 would have been obvious at least with respect to Compound 19 in view of the state of the art and general knowledge of a person of ordinary skill in the art (“POSA”) before the effective filing date of the ’236 patent, in particular, Su (EX1005), Yoshino (EX1008), and Kawai (EX1004) in view of Talele (EX1009).

16. In my opinion, claims 1-9, 12-17, 24, and 25 would have been obvious, at least with respect to Compounds 1, 19, or 20, based on the state of the art and the general knowledge of a POSA before the effective filing date of the '236 patent, in particular, in view of Yoshino and Kawai combined with Talele.

17. In my opinion, claims 1-4 and 21-25 would have been obvious, at least with respect to Compound 65, based on the state of the art and the general knowledge of a POSA before the effective filing date of the '236 patent, in particular, in view of Su, Yoshino, Kawai, Talele, Meng (EX1028) combined with Patel (EX1026) and Ren (EX1030).

18. In my opinion, claims 4 and 9 would have been obvious at least with respect to ½ calcium salt of Compound 1 in view of the state of the art and the general knowledge of a POSA before the effective filing date of the '236 patent, in particular, Su and Bethel (EX1032).

19. Finally, there are no apparent secondary considerations supporting non-obviousness of the claims. I reserve the right to address any secondary considerations put forth by Patent Owner (e.g., unexpected results) in any later response to this declaration or the petition it accompanies.

## III. MATERIALS RELIED UPON

20. I have reviewed the Petition and supporting evidence. I have also reviewed all Challenged Claims of the '236 patent, as well as the specification of the

’236 patent and relevant parts of its file history. I have examined the prior art references asserted against the ’236 patent in the Petition. My opinions are based on my own knowledge, experience, and education and with further reference to the exhibits cited herein. I will use the exhibit numbers listed on the “Table of Exhibits” on pages vii-viii of the Petition (Paper 1), which I have included for ease of reference below:

**LIST OF EXHIBITS**

| Exhibit | Description |
|---|---|
| EX1001 | U.S. Patent No. 12,234,236 (“the ’236 patent”) |
| EX1003 | Excerpts of File History of U.S. Patent No. 12,234,236 |
| EX1004 | Kawai, et al., Proc Natl Acad Sci U S A., 117(47):29959-29967 (2020) (“Kawai”) |
| EX1005 | International Publication No. WO 2025/026270A1 (“Su”) |
| EX1006 | Chinese Patent Application No. 202311372605.9 (“Su II”), which is a priority document of Su |
| EX1007 | Certified English Translation of Chinese Patent Application No. 202311372605.9 (“Su II”) |
| EX1008 | U.S. Patent No. 10,858,356 (“Yoshino”) |
| EX1009 | Talele, Journal of Medicinal Chemistry, 59(19):8712–8756 (2016) (“Talele”) |
| EX1010 | Liu, et al., Expert Opinion on Therapeutic Patents, 30(10):781-794 (2020) |
| EX1011 | Pratt, et al., Diabetes Obes Metab., 25(9):2642-2649 (2023) |
| EX1012 | Frias, et al., Lancet, 402(10400):472–483 (2023) |
| EX1013 | Chinese Patent Application No. 202311371725 (“the ’725 Provisional”) |
| EX1014 | Certified English Translation of Chinese Patent Application No. 202311371725 |

| Exhibit | Description |
|---|---|
| EX1015 | Chinese Patent Application No. 202311189557 (“the ’557 Provisional”) |
| EX1016 | Certified English Translation of Chinese Patent Application No. 202311189557 |
| EX1017 | U.S. Patent Provisional Application No. US 63/538,892 (“the ’892 Provisional”) |
| EX1018 | Chinese Patent Application No. 202410142451 (“the ’451 Provisional”) |
| EX1019 | Certified English Translation of Chinese Patent Application No. 202410142451 (“the ’451 Provisional”) |
| EX1020 | Chinese Patent Application No. 202311582240 (“the ’240 Provisional”) |
| EX1021 | Certified English Translation of Chinese Patent Application No. 202311582240 |
| EX1022 | Chinese Patent Application No. 202311686034 (“the ’034 Provisional”) |
| EX1023 | Certified English Translation of Chinese Patent Application No. 202311686034 |
| EX1024 | U.S. Patent Provisional Application No. 63/545,615 (“the ’615 Provisional”) |
| EX1025 | U.S. Patent Provisional Application No. 63/603,854 (“the ’854 Provisional”) |
| EX1026 | Patel SC, Burns NZ. Conversion of Aryl Azides to Aminopyridines. J Am Chem Soc. 2022 Oct 5;144(39):17797-17802 (“Patel”) |
| EX1027 | Pennington LD, Moustakas DT. J Med Chem. 2017 May 11;60(9):3552-3579 |
| EX1028 | Chinese Patent Publication No. CN117069743A (“Meng”) |
| EX1029 | Certified English Translation of Chinese Patent Publication No. CN117069743A |
| EX1030 | U.S. Patent No. 12,037,339 (“Ren”) |
| EX1031 | Certified English Translation of International Publication No. WO 2025/026270 (“Su”) |
| EX1032 | International Publication No. WO 2024/129676A1 (“Bethel”) |

## IV. THE UNDERSTANDING APPLIED TO MY ANALYSIS

21. In preparing and forming my opinions set forth in this declaration, I have been informed by counsel of relevant legal principles. I applied my understanding of those principles in forming my opinions. My understanding of those principles is summarized below. In performing my analysis and reaching my opinions and conclusions, I have been informed of and have been advised to apply various legal principles relating to unpatentability, which I set forth herein. In setting forth these legal standards, it is not my intention to testify about the law. I only provide my understanding of the law, as explained to me by counsel, as a context for the opinions and conclusions I am providing.

22. I understand that my opinions regarding unpatentability are presented from the viewpoint of a POSA in the field of technology of the patent as of the patent's priority date. In this declaration, my opinions are premised on the perspective of a POSA at the time of the earliest claimed priority date for the '236 patent, which I have been informed for this proceeding is September 14, 2023. (EX1001 at 1.) To the extent Patent Owner asserts that the claims of the '236 patent are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

23. I understand that in a PGR proceeding, claims should be construed as having their ordinary and customary meaning as understood by a POSA at the time

of the invention. I understand that claims should be read in the context of the claim language of which they are a part. I further understand that the specification and file history can also inform the scope of the claims. If, after a review of this evidence, the construction is not apparent, I understand that extrinsic evidence, such as dictionary definitions, treatises, and trade journals, may be consulted to discern the meaning of a term. For terms where no construction is necessary, I have simply read the terms according to their ordinary and customary meaning. My understandings herein are made in light of how a POSA in or around 2023 would view the ordinary and customary meaning of the claim terms. I reserve the right to supplement my Declaration should any claim terms be given different constructions.

24. I understand that a claim is anticipated if a single prior art reference discloses each and every limitation of the claimed invention. I understand that a limitation can be expressly disclosed by the reference or be inherent. I further understand that for a feature to be inherently disclosed, a POSA would understand the inherent feature would necessarily and inevitably be present when the teaching of the reference is practiced. That is, I understand that if a feature is not necessarily and inevitably present, it is not inherently disclosed.

25. I understand that a patent claim may be unpatentable for obviousness if the difference between the claimed subject matter and the prior art is such that the subject matter as a whole would have been obvious to a POSA at the time the

invention was made. I understand that a finding of obviousness requires a determination of: (1) the scope and content of the prior art; (2) the difference(s) between the claimed invention and the prior art; and (3) the level of skill of the ordinary artisan in the pertinent art. I understand this analysis looks at whether the differences are such that the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

26. It is my understanding from counsel that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. It is my understanding that any need or problem known in the field of endeavor at the time of invention or addressed by the patent can provide a reason for combining prior art elements to arrive at the claimed subject matter. I understand that only a reasonable expectation of success is necessary to show obviousness.

27. My understanding is that the obviousness inquiry is not limited to just the prior art references being applied, but includes the knowledge and understanding of one of ordinary skill in the art. However, I understand that merely demonstrating that each element, independently, was known in the prior art is, by itself, insufficient to establish a claim was obvious. My understanding is that the test for obviousness

is not whether the features of one reference can be incorporated into the structure of another reference, but rather what the combined teachings would have suggested to those of ordinary skill in the art. I further understand that a party seeking to invalidate a patent must show a person of ordinary skill in the art would have been motivated to combine the teachings of the prior art references to achieve the claimed invention.

28. I understand that a combination of old, familiar, or known elements used according to known methods is likely to be obvious when it does no more than yield predictable results. Predictable variations of a work from one field are likely to be obvious, even if the variation is in another field. For example, where a technique has been used to improve a device, use of the same technique to improve similar devices is a predictable variation and likely obvious. Likewise, if the use of prior art for improvements is simply done according to the prior art's established functions, a POSA has simply implemented a predictable variation. If there existed at the time of invention a known problem for which there was an obvious solution, a patent claim encompassing that solution is not patentable.

29. I further understand that any obviousness analysis must consider objective evidence of non-obviousness, where such evidence is present. I understand that objective evidence of non-obviousness includes (1) copying, (2) long-felt but unsolved need, (3) failure of others, (4) commercial success of the invention, (5) unexpected results created by the claimed invention, (6) unexpected properties of

the claimed invention, (7) licenses showing industry respect for the invention, (8) skepticism of skilled artisans before the invention, (9) recognition of the invention's advancement, and (10) contemporaneous invention by others or absence thereof. In general, there must be a connection between any of the factors and the claimed invention. For instance, the "commercial success" of a product practicing the claimed invention is relevant to the obviousness analysis only if the commercial success is attributable to advantages from the use of the invention that were not available to the purchasing public before the invention was made.

30. I understand that a claim in a granted patent must be sufficiently supported by the original disclosure of the granted patent, read in the context of what one of ordinary skill in the art would have known at the time of the claimed invention. I understand that the basic inquiry for written description is whether the specification provides sufficient information for a skilled artisan to recognize that the named inventors possessed the full scope of the claimed invention. To satisfy the written description requirement for such claims, I understand that the specification must disclose either a representative number of species falling within the scope of the claimed genus or structural features common to the members of the genus such that one skilled in the art can "visualize or recognize" the members of the claimed genus. I understand that a disclosure of a species may be insufficient to demonstrate

possession of a larger claimed genus. However, I understand the same disclosure in a prior art reference may be sufficient to render a claim to that genus obvious.

31. I also understand that claims must be enabled by the original disclosure of the patent. For the claims to be enabled, the information contained in the disclosure must be sufficient to inform those skilled in the relevant art how to make and use the claimed invention without undue experimentation. I understand that the enablement requirement is separate and distinct from the written description requirement.

32. I understand that to establish priority to a previously filed patent application, the earlier application must describe the later-claimed invention in sufficient detail so that a POSA can clearly conclude that the inventor invented and had possession of each element of the claimed invention as of the earlier filing date being sought. I understand that this requires that the earlier disclosure must describe and enable every limitation of the later-claimed invention. I understand that a showing of possession of a single species may be insufficient to demonstrate that the inventor had possession of the larger genus. I understand that to establish possession of the larger genus may require a showing that, as of the earlier desired filing date, the inventor disclosed use of multiple species of the genus and/or that the inventor understood that each species of the genus would create the same result, i.e., could be substituted without modification.

33. Although the following analysis cites to particular pages, lines, paragraphs, or figures of many of the references discussed, these citations are intended to assist in understanding the various bases of my conclusions, and prior art teachings used to reach them. These citations are not intended to be an exhaustive recitation of every page, line number, or paragraph in which these teachings may be found. Similar teachings or disclosures may be found at other pages, lines, figures, or paragraphs, as well as in other references, and it is to be understood that my opinions and statements are made in view of all of the references and teachings I have reviewed.

## V. LEVEL OF ORDINARY SKILL IN THE ART

34. In my opinion, the following definition of a POSA applies to the claims of the ’236 patent.

35. A POSA would have had least a Bachelor’s, Master’s, or Doctoral degree in chemistry, medicinal chemistry, organic chemistry, biochemistry, or a closely related discipline, along with a minimum of two to five years of experience in small-molecule drug discovery or development. Such experience would include the design, chemical synthesis, and structure–activity relationship (SAR) analysis of therapeutic compounds.

## VI. CLAIM CONSTRUCTION

36. I understand that claims of a patent subject to PGR should be construed in accordance with the plain and ordinary meaning of such claim as understood by a POSA in view of the specification of the patent and the prosecution history pertaining to the patent.

## VII. BACKGROUND AND STATE OF THE ART

37. The ’236 patent relates to glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) modulating compounds. In this Section, I present a brief overview of certain aspects of GLP-1R and GLP-1R modulating compounds, that will assist in better understanding the ’236 patent.

38. GLP-1 is an endogenous incretin hormone secreted primarily by enteroendocrine L cells in the distal intestine in response to nutrient ingestion. (See, e.g., EX1010 at 1.) Pharmacological GLP-1R agonists mimic the actions of native GLP-1 by enhancing glucose-dependent insulin secretion, suppressing glucagon release, promoting satiety, delaying gastric emptying, and ultimately reducing caloric intake and energy balance dysregulation. (See id.)

39. Globally, over 10% of the adult population is affected by obesity, a multifactorial metabolic disorder primarily driven by chronic caloric surplus, especially from high-fat and high-carbohydrate diets. (Id.) In addition to dietary contributors, psychosocial stress, disordered eating behaviors, sedentary lifestyle,

and psychological factors such as low self-esteem also play critical roles. (Id.) Obesity is strongly associated with a spectrum of metabolic and systemic pathologies, including type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), cardiovascular diseases, and certain forms of cancer. (Id.)

40. GLP-1R agonists have emerged as a breakthrough therapeutic class for the treatment of obesity and overweight, offering clinically meaningful benefits that extend beyond their initial indications in type 2 diabetes. (Id. at 1, 2.) These agents facilitate sustained weight loss through multiple mechanisms while simultaneously improving metabolic parameters. (Id.)

41. Significant research efforts are currently directed toward the development of next-generation anti-obesity pharmacotherapies that address the limitations of earlier agents. (Id.) Among these, GLP-1R agonists have demonstrated robust efficacy in reducing body weight in both diabetic and non-diabetic populations. (Id.) Clinical data suggest that the weight-reducing effects are primarily attributable to central appetite suppression and reduction in overall energy intake. (Id.)

42. Mechanistic studies indicate that GLP-1R agonists exert pleiotropic physiological effects, with the anorexigenic and insulinotropic actions being most relevant for obesity pharmacotherapy. (Id. at 1.) The anorexigenic effects are mediated through both central nervous system pathways—via activation of

hypothalamic and brainstem GLP-1Rs—and peripheral pathways involving vagal afferents and gastrointestinal signaling, leading to enhanced satiety and reduced food intake. (Id.)

43. Structural optimization of GLP-1R agonists has followed two principal strategies. (Id. at 2.) The first aims to improve resistance to enzymatic degradation by dipeptidyl peptidase-IV, commonly achieved through substitution or modification at the N-terminal region and chemical stabilization of the C-terminal, including cyclization, glycosylation, or amino acid extension. (Id.) The second strategy involves prolonging the plasma half-life by reducing renal clearance through PEGylation, lipidation (e.g., fatty acid conjugation), incorporation of coumarin groups, formation of dimers, or fusion to albumin or Fc-containing proteins. (Id.) In parallel, medicinal chemistry efforts have led to the identification of non-peptidic small-molecule GLP-1R agonists that demonstrate potent in vivo activity, potentially offering an orally bioavailable alternative to injectable peptide therapeutics. (Id.)

### A. Small-Molecule GLP-1 Receptor Agonists

44. Although the clinical weight-loss efficacy of small-molecule GLP-1R agonists is still under investigation, several candidates have shown GLP-1 receptor agonist activity in vitro and in vivo comparable to, or exceeding, that of peptide-based analogs. (Id. at 4.) For example, Pfizer has disclosed a series of benzimidazole-

based compounds bearing 6-carboxylic acid functional groups and various aza-substitutions (e.g., 4-aza-, 5-aza-, and 7-aza-benzimidazoles) as GLP-1R agonists in patent publications CA3045644 and CA2988721. (Id.) Among these, DIAST-X2 has demonstrated potent GLP-1R agonistic activity, with an $EC_{50}$ of 0.99 nM and an $E_{max}$ of 99% relative to 1 μM GLP-1, indicating near-maximal receptor activation. (Id.)

45. In G protein-coupled receptors (GPCRs), the binding site for the endogenous ligand is referred to as the orthosteric site, and ligands that competitively bind at this site are termed orthosteric ligands. (Id.) The orthosteric binding pocket is typically conserved and is located within the transmembrane domain, often near the extracellular region of the seventh transmembrane helix. (Id.) In contrast, an allosteric site is a spatially distinct binding region, structurally different from the orthosteric site. (Id.)

46. Allosteric ligands, which bind to these non-conserved regions, modulate receptor function without directly competing with the endogenous ligand. (Id.) Based on their modulatory effects, these ligands are classified as positive allosteric modulators or negative allosteric modulators. (Id.) The sequence and structural diversity of allosteric sites within a single GPCR subfamily provides an opportunity for the development of selective and safer modulators. Allosteric modulators offer enhanced receptor specificity, reduced off-target activity, and improved therapeutic indices, representing a promising strategy in drug discovery.

(Id.)

47. Several patents disclose small-molecule GLP-1R modulators with allosteric mechanisms of action. WO2016094729 and WO2018200833 describe compounds functioning as GLP-1R modulators or potentiators, either alone or in combination with incretin peptides such as GLP-1(7–36), GLP-1(9–36), or peptide-based therapeutics including exenatide and liraglutide. (Id.) WO2017117556 reports a series of positive allosteric modulators exhibiting GLP-1R agonist activity, with a representative compound displaying an $EC_{50}$ of 4.2 μM and an $EC_{max}$ of 56% relative to endogenous GLP-1. (Id.)

**B. Next-Generation Oral GLP-1 Receptor Agonists**

48. Orforglipron (also known as LY3502970 and previously designated OWL-833 (originally discovered by Chugai Pharmaceutical), is a novel, orally bioavailable, non-peptidic small-molecule agonist of the glucagon-like peptide-1 receptor (GLP-1R) currently under development by Eli Lilly & Co. (Id.)

49. Orforglipron demonstrates full agonist efficacy, promoting cAMP accumulation comparable to native GLP-1. It exhibits an $EC_{50}$ of 1.1 nM for both human and cynomolgus monkey GLP-1 receptors. (Id.) Unlike conventional peptide-based GLP-1R agonists, orforglipron is structurally optimized for once-daily oral administration, addressing adherence barriers associated with injectable formulations in the treatment of type 2 diabetes and obesity. (EX1011 at 1-2.)

50. Pharmacological studies have shown that orforglipron activates the GLP-1R via a non-classical binding mechanism, engaging an allosteric site. (EX1010 at 4.) This signaling profile may contribute to enhanced receptor selectivity and lower toxicity typically observed with full peptide agonists. (Id.)

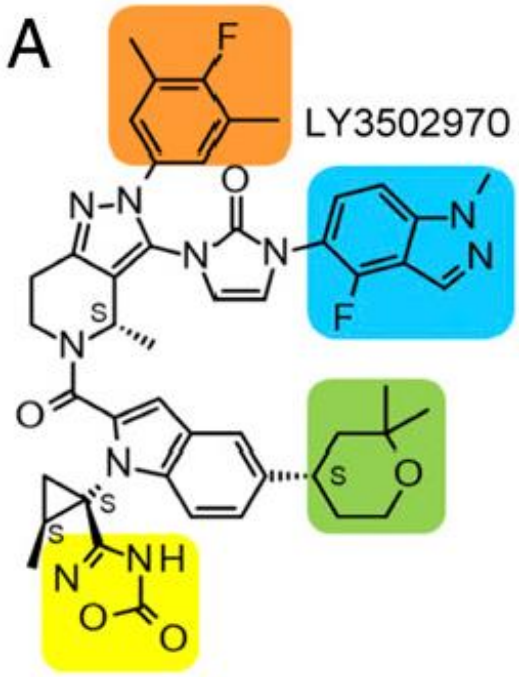
51. Clinical investigations have confirmed that orforglipron induces significant improvements in glycemic control and body weight. (EX1010 at 4.) In a Phase 2 randomized controlled trial, orforglipron significantly reduced HbA1c and body weight compared to placebo, while maintaining a favorable safety profile, thus supporting its continued development as an oral alternative to injectable GLP-1R therapies (EX1012 at 1). Currently in Phase 3 clinical development, orforglipron represents a promising candidate within the expanding class of orally bioavailable GLP-1R agonists, with the potential to transform treatment paradigms for patients with type 2 diabetes and obesity. (Id. at 11)

## VIII. OVERVIEW OF PRIOR ART AND STATE OF THE ART REFERENCES

### A. Kawai (EX1004)

52. Kawai et al., entitled "Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist," was published in the Proc Natl Acad Sci USA on November 11, 2020 (EX1004). I understand that Kawai is prior art at least because it was a printed publication before the earliest possible filing date of the '236 patent.

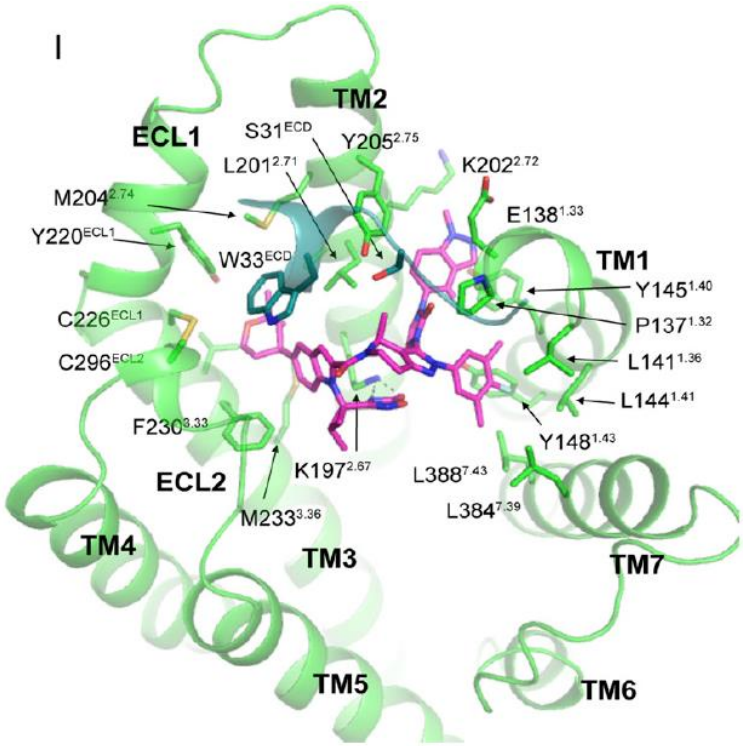
53. Kawai discloses the structural basis for GLP-1 receptor activation by orforglipron. In particular, Kawai presents a high-resolution cryo-electron microscopy (cryo-EM) structure of orforglipron in complex with the N-terminal extracellular domain (ECD) of the GLP-1 receptor. (Id. at 1.) The chemical structure of orforglipron is shown below, with the 2,2-dimethyl-tetrahydropyran moiety highlighted in green shading, the 4-fluoro-1-methyl-indazole moiety highlighted in blue shading, the 3,5-dimethyl-4-fluoro-phenyl ring highlighted in orange shading, and the 4H-1,2,4-oxadiazol-5-one highlighted in yellow shading.




54. Orforglipron is described as a highly potent and selective compound against other class B GPCRs, with a pharmacokinetic profile favorable for oral administration. (Id.) Kawai further states that "[i]n efficacy studies, oral administration of orforglipron resulted in glucose lowering in humanized GLP-1R

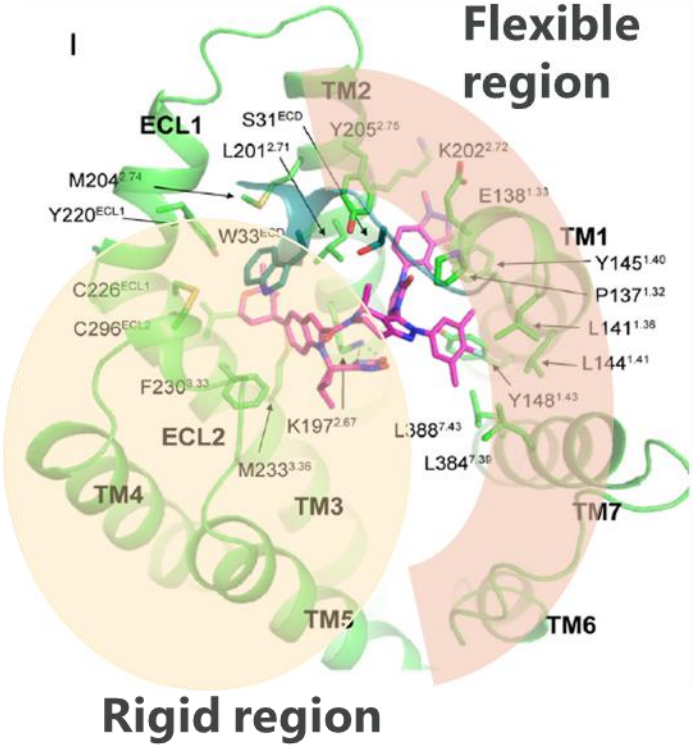
transgenic mice and insulinotropic and hypophagic effects in nonhuman primates," and that "[t]ogether, this work determined the molecular basis for the activity of an oral agent being developed for the treatment of type 2 diabetes mellitus, offering insights into the activation of class B GPCRs by nonpeptide ligands." (Id.)

55. Moreover, Kawai presents a high resolution cryo-EM structure of orforglipron bound to the N-terminal extracellular domain (ECD) of the GLP-1 receptor, revealing the ligand-binding pocket surrounding the compound and providing a detailed three-dimensional protein-ligand interaction model (deposited in the PDB under PDB ID code 6XOX and the Electron Microscopy Data Bank (EMDB) entry ID EMD-22283), as shown below:




(Id. at FIG. 1I, 8)

56. Kawai further teaches that the region of the ligand-binding pocket formed by transmembrane helices TM1, TM2, TM6, and TM7 is in close proximity to the 4-fluoro-1-methyl-indazole moiety, and that this region exhibits conformational flexibility, as illustrated in annotated FIG. 1I above. (Id. at 4.) In contrast, the region formed by transmembrane helices TM3, TM4, and TM5 is described as being relatively rigid. (Id.)




(Id. at FIG. 1I, 1-9(emphases added to indicate the flexible and rigid regions).)

57. The conformational flexibility of the region of the ligand-binding pocket formed by transmembrane helices TM1, TM2, TM6, and TM7 suggests modifications to the 4-fluoro-1-methyl-indazole would not be expected to cause

significant structural disruption to the ligand-binding pocket and, therefore, would likely preserve binding potency.

58. In addition, the binding pocket adjacent to the methyl group of the indazole moiety is shown as being surrounded by a spacious hydrophobic environment formed by the side chain of tyrosine at position 205 (Y205) and the carbon atoms of the lysine at position 202 (K202) and glutamate at position 318 (E318) residues, as shown in the three-dimensional structural model, suggesting that the pocket could reasonably accommodate a compound bearing a bulkier substituent in place of the methyl group. (Id. at FIG. 1I.)

59. The detailed three-dimensional protein–ligand interaction model disclosed by Kawai provides a valuable framework for structure-based drug design, particularly with respect to potential modifications of orforglipron. For example, based on this model, a POSA would have understood which regions of the ligand-binding pocket exhibit conformational flexibility and could accommodate bulkier substituents without significantly disrupting the overall structure or integrity of the binding pocket.

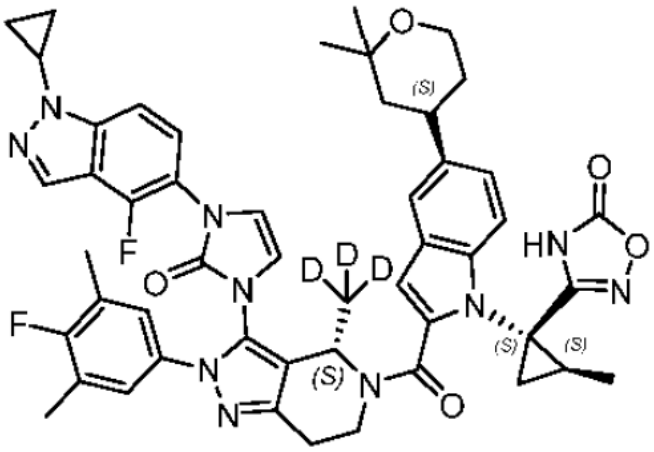
**B. Su (EX1005)**

60. International Patent Application No. PCT/CN2024/108192 to Su Yidong et al., entitled "Benzo Nitrogen-Containing Heterocyclic Derivative Regulator, Preparation Method Therefor And Use Thereof," was filed on July 29,

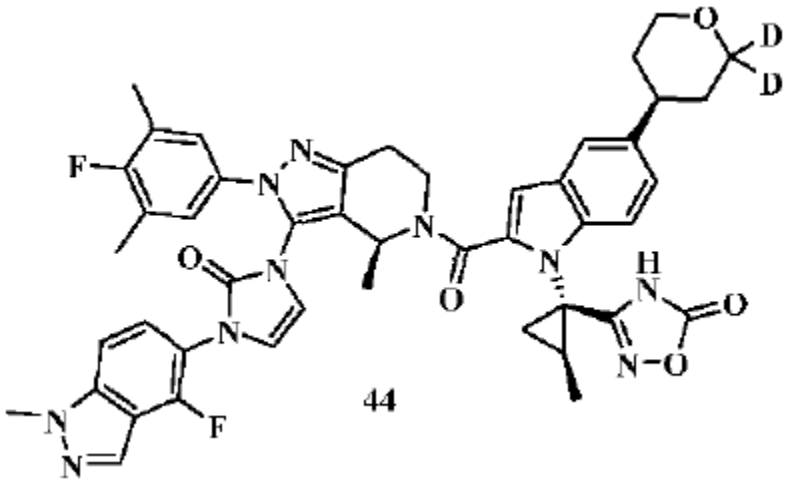
2024 by Hansoh Biomedical Co., Ltd. and was published on February 6, 2025 as WO2025026270A1 ("Su") (EX1005; EX1031). PCT/CN2024/108192 claims priority to the following Chinese priority documents: CN202310946477.8, filed on July 28, 2023; CN202311087184.5, filed on August 25, 2023; CN202311110642.2, filed on August 30, 2023; CN202311269491.5, filed on September 27, 2023; CN202311372605.9, filed on October 20, 2023; CN202311546779.2, filed on November 17, 2023; CN202311690443.3, filed on December 8, 2023; CN202311866263.6, filed on December 29, 2023; CN202410140555.X, filed on January 31, 2024; CN202410241733.8, filed on March 1, 2024; CN202410385768.9, filed on March 29, 2024; CN202410587643.4, filed on May 11, 2024; and CN202410882329.9, filed on July 2, 2024. (Id. at 1.) I was informed that Su is prior art at least because it has an effective filing date earlier than the filing date of the '236 patent at least with respect to claimed Compounds 18, 19, 20, 21, and 65.

61. For purposes of my analysis, I refer to certain disclosures in Su that are contained in Chinese Patent Application No. CN 202311372605.9, filed on October 20, 2023 ("Su II") (EX1006), including, for example, the description of Compounds 44, 175, and 176 discussed below. For ease of reference, any relevant disclosure in Su that is entitled to an effective filing date of October 20, 2023, will be discussed herein with reference to Su II. In Su II, Su discloses 218 working examples but

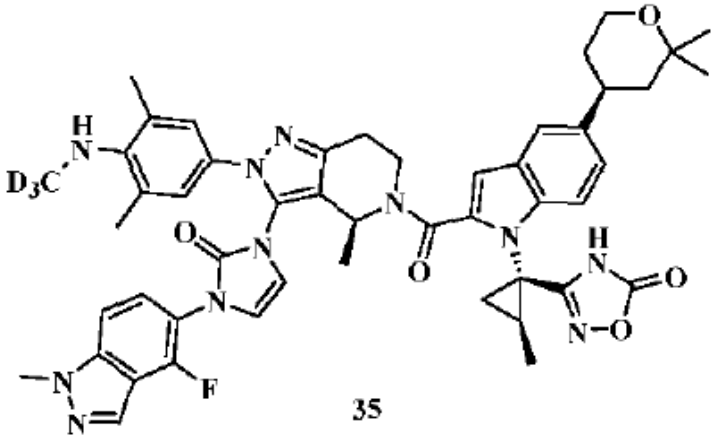
describes only seven deuterated stereoisomerically pure compounds—Compounds 176, 44, 35, 123, 139, 188, and 212, the chemical structures of which are shown below. (EX1007 at Examples 176, 44, 35, 123, 139, 188, and 212).



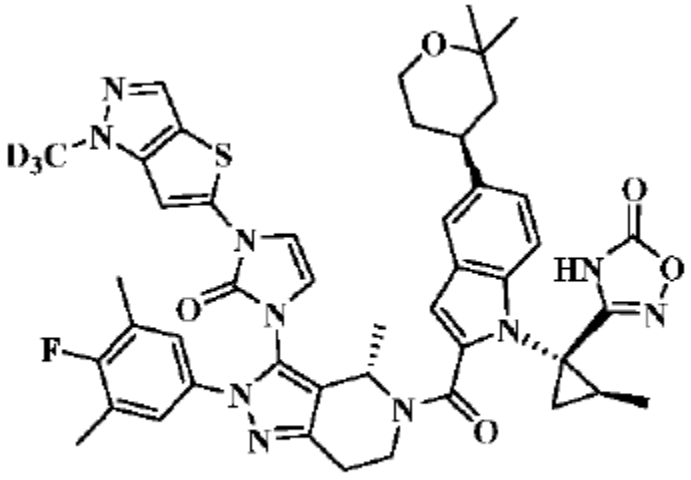
176



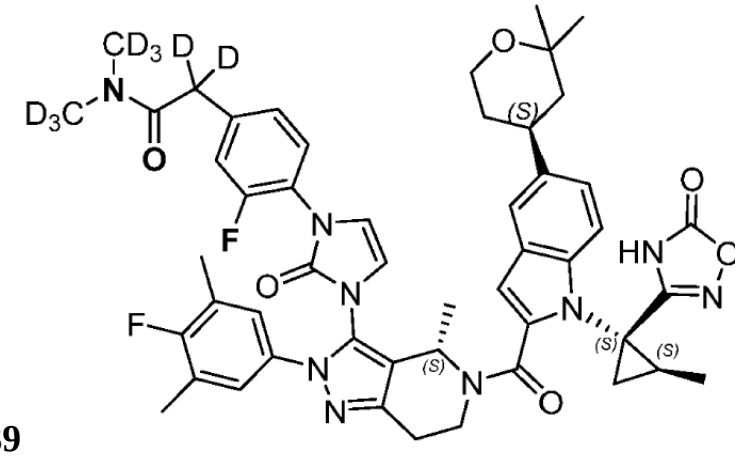
44



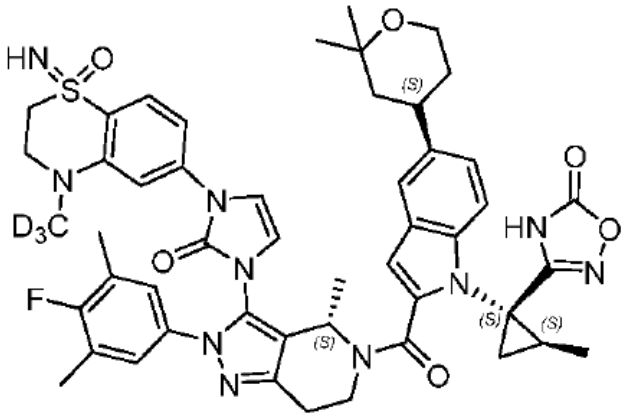
35



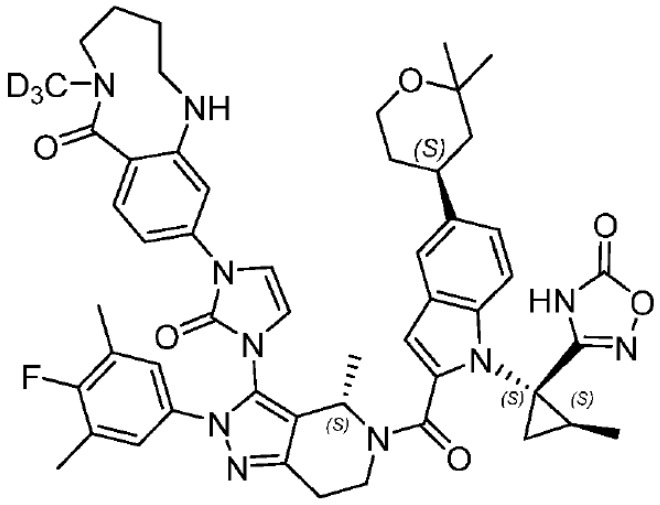
123



139



188



**212**

62. Given that laborious synthetic procedures are required for deuteration (see, e.g., id. at Example 176)—particularly in view of many other stereoisomerically pure compounds among the 200+ disclosed—it is reasonable to infer that the compounds selected for deuteration were viewed as strong candidates

for further development. Deuteration is often examined to enhance metabolic traits of drug candidates. In other words, a POSA would interpret the act of deuteration as indicative of lead compound status.

63. Furthermore, among the seven deuterated stereoisomerically pure compounds, Compounds 176, 44, and 35 share a common scaffold ring structure.

64. Notably, the well-known Lilly compound orforglipron also features this same scaffold ring structure with the original non-deuterated parent compounds, underscoring the scaffold's critical role and supporting the lead status of these parent compounds. In contrast, the other deuterated stereoisomerically pure compounds disclosed in Su each involve modifications to the scaffold ring and differ significantly from one another.

65. Compound 175, as the non-deuterated parent of Compound 176, is thus one of the compounds of priority interest. In addition, the non-stereoisomerically pure counterpart (with an identical structural formula except for the lack of stereochemical purity) of Compound 175 is also synthesized and deuterated. The fact that four compounds (Compound 175, Compound 176, and their respective non-stereoisomerically pure counterparts) share the same scaffold and incorporate the same N-cyclopropyl group underscores the perceived interest in the cyclopropyl group.

66. The deuterated Compound 44 differs from orforglipron in terms of the absence of two methyl groups in the tetrahydropyran ring. A POSA would have immediately recognized that the closest non-deuterated structure of Compound 44 has hydrogens in place of the two deuterium atoms in the tetrahydropyran ring. Such a structure clearly offers the advantage of removal of a chiral center and making the tetrahydropyran ring symmetrical, which enables a significantly simplified synthesis.

67. Although sharing the same scaffold ring structure, deuterated Compound 35 replaces an electron-withdrawing fluorine atom present in orforglipron with an electron-donating amino group. This modification constitutes a more pronounced, yet less favorable, change in electronic character compared to the incorporation of a cyclopropyl group in Compound 175 or the removal of dimethyl groups in Compound 44.

68. The teaching derived from the selective compound deuteration is clear and specific, including (1) incorporation of a cyclopropyl group as demonstrated in stereoisomerically pure Compound 175, its deuterated analog Compound 176, and their respective non-stereoisomerically pure counterparts in comparison with orforglipron; and (2) exclusion of methyl groups from the tetrahydropyran ring as shown in deuterated Compound 44, with its closest non-deuterated structure having the benefit of a symmetrical tetrahydropyran ring.

69. These structural features provide clear guidance for specific modifications. Starting from Compound 175 as a lead, incorporating insights from Compound 44 and its non-deuterated counterpart on removal of methyl groups would result in Compound 19. Similarly, using Compound 44 or its non-deuterated counterpart as a lead, and applying the cyclopropyl modification found in Compound 175 and its parent would also yield Compound 19.

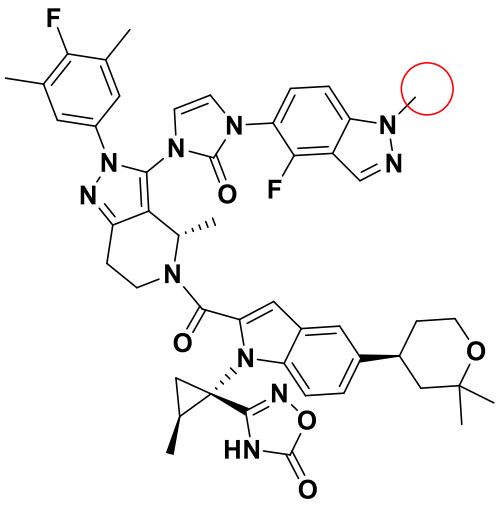
70. Regarding pharmaceutically acceptable salts of the disclosed compounds, Su also discloses GLP-1 receptor agonists and pharmaceutically acceptable salts thereof. (Id. at 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.)

**C. Yoshino (EX1008)**

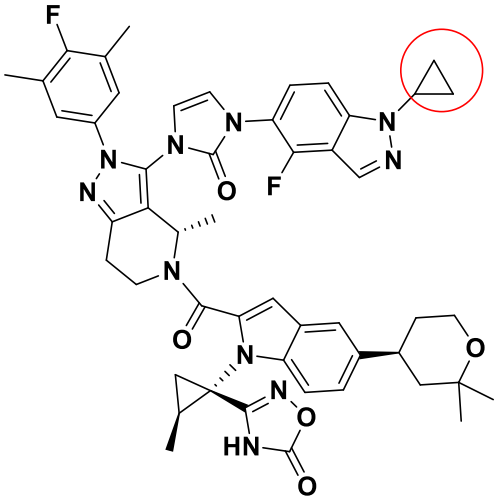
71. U.S. Patent Application No. 15/759,872 to Hitoshi Yoshino et al., entitled "Pyrazolopyridine derivative having GLP-1 receptor agonist effect," was filed on September 26, 2017, published on July 25, 2019 as US20190225604A1, and issued as U.S. Patent No. 10,858,356 ("Yoshino"), assigned to Chugai, on December 8, 2020. (EX1008 at 1.). I understand that Yoshino is prior art at least because it was published before the earliest possible claimed priority date of the '236 patent.

72. Yoshino discloses and claims Compound 67 in claim 13 (non-stereoisomerically pure form) and claim 14 (stereochemically defined in two but not all respects). (Id. at 166, claims 13, 14.) It is also referred to as orforglipron, is identical to the compound studied in Kawai and is the only compound advanced to

pharmacokinetic studies in Yoshino. (Id. at 312:30-313:35.) As such, it can be identified as a lead compound due to its demonstrated potential for further development. The structural difference between Compound 67 (orforglipron) and claimed Compound 1 in the '236 patent is highlighted in the red circle, as shown below.

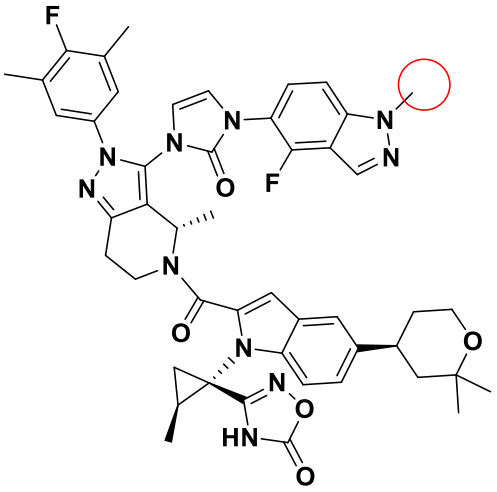



Compound 67 (orforglipron)



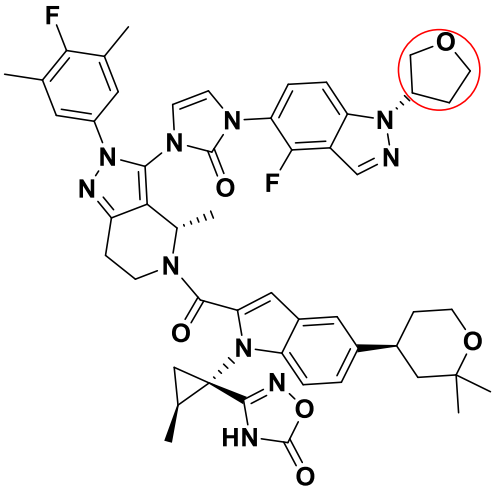

Compound 1

73. In modifying the lead compound 67, Yoshino discloses that the methyl group may be replaced with a tetrahydrofuran ring while maintaining comparable biological activity. For example, replacement of the methyl group in Compound 67 with a tetrahydrofuran ring yielded Compound 40, which exhibited a similar level of activity. (Id. at 50, 99, Table 3.)



Compound 67

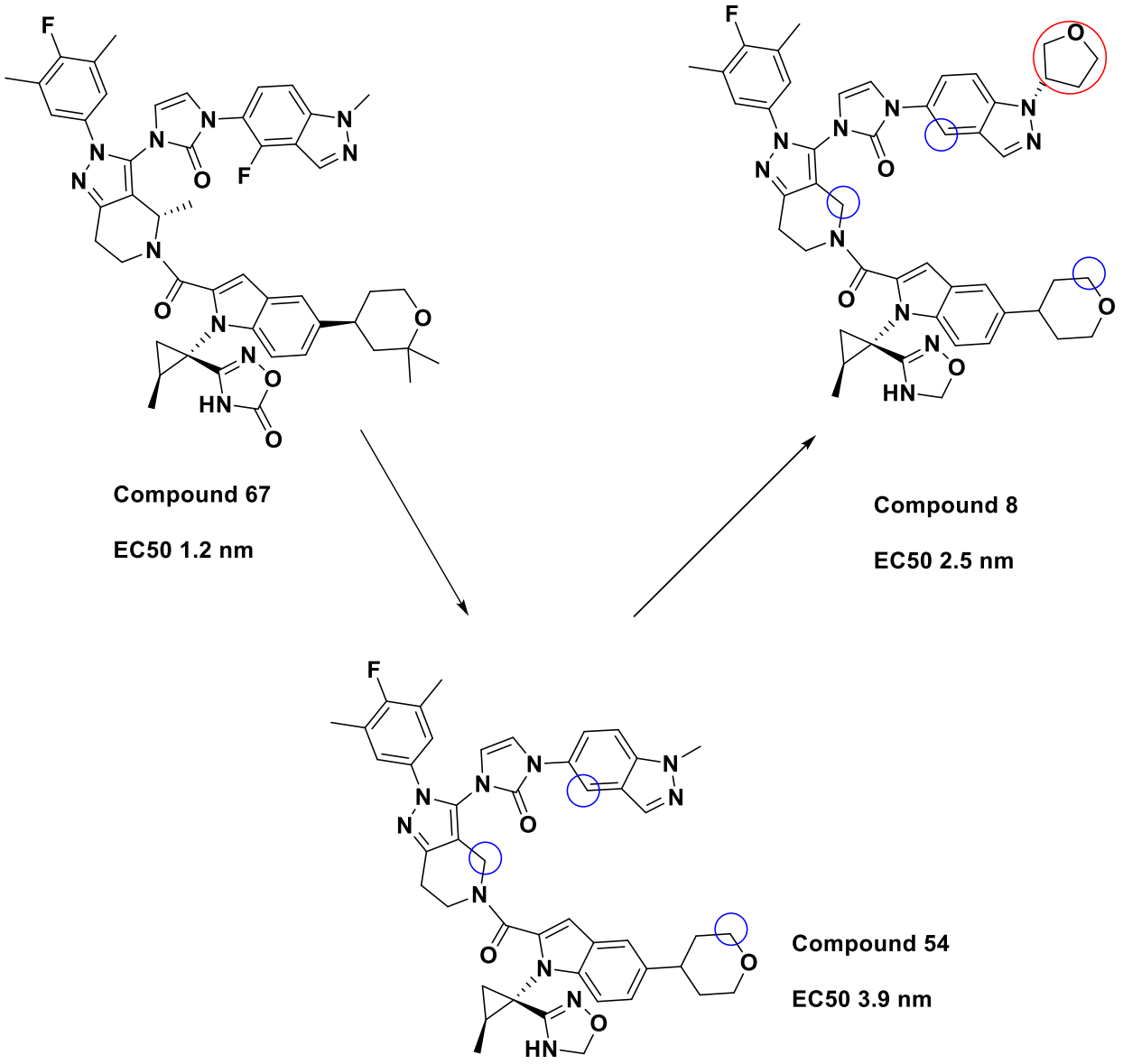
EC50 1.2 nm



Compound 40

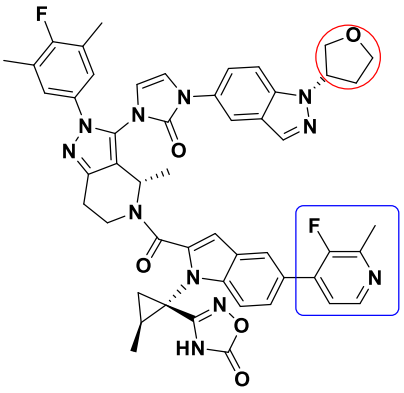
EC50 2.2 nm

74. In addition, although the removal of multiple substituents, as exemplified by Compound 54, resulted in reduced activity of the lead compound, substitution of the methyl group with a tetrahydrofuran moiety mitigated this loss of activity, as shown below:



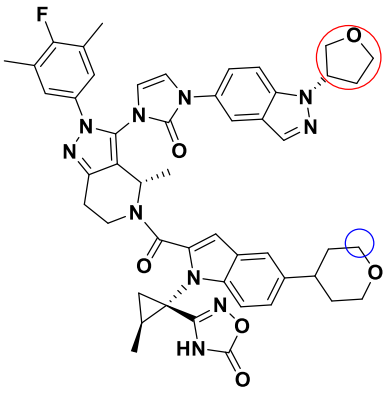

(Id. at 34, 92, 99, Table 3.)

75. Consistent with these observations, several additional analogs disclosed in Yoshino, each containing a tetrahydrofuran ring, also retained activity levels comparable to that of the lead compound. (Id. at 37, 41, 97, Table 3.)



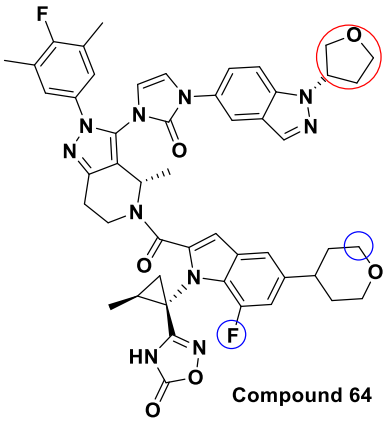
Compound 14

EC50 2.3 nm



Compound 22

EC50 2.3 nm

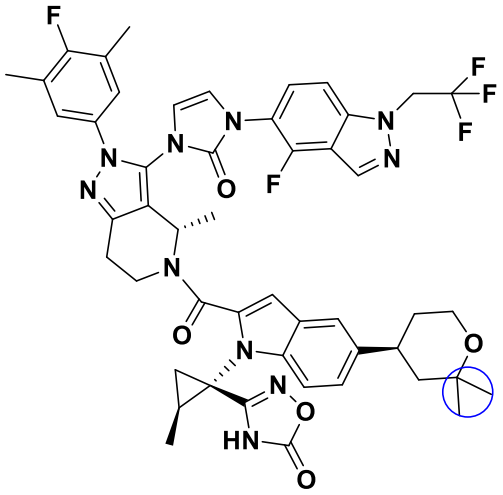


Compound 64

EC50 2.0 nm

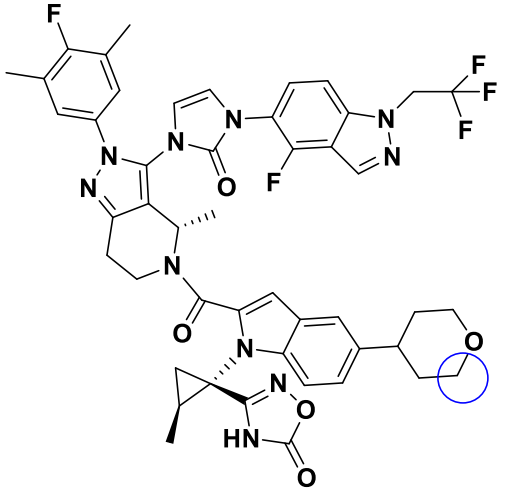
76. Accordingly, Yoshino, when considered as a whole, suggests that replacement of the methyl group with a ring structure can preserve the biological activity of the lead compound.

77. Yoshino further teaches that modifications involving the removal of methyl groups from the tetrahydro-2H-pyran moiety generally preserve the biological activity of the compounds. As illustrated in the comparison below, removal of the dimethyl groups from Compound 35 yielded Compound 28, which shows comparable activity. (Id. at 44, 48, Table 3.) Similarly, Compound 30, which lacks dimethyl groups on the tetrahydropyran ring, exhibited the same level of activity as Compound 38. (Id. at 45, 49, Table 3.)



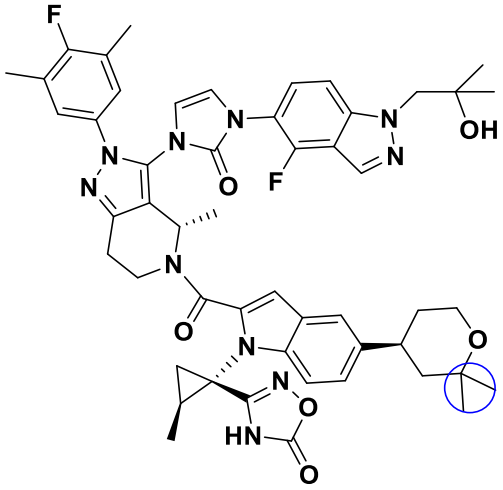
Compound 35

EC50 3.2 nm



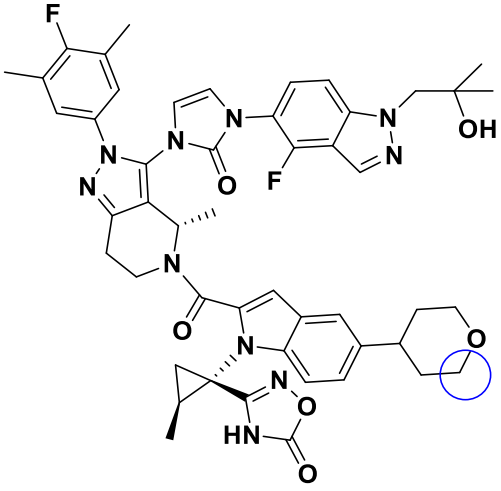
Compound 28

EC50 1.9 nm



Compound 38

EC50 1.7 nm



Compound 30

EC50 1.4 nm

78. It is noteworthy that removal of the methyl groups from the tetrahydropyran renders the ring achiral. This structural change facilitates a more streamlined synthesis and eliminates the possibility of undesirable isomer formation, which would render a compound unmarketable as a pharmaceutical.

79. With regard to "a pharmaceutically acceptable salt thereof" recited in claim 1, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including "a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt." (Id. at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.)

**D. Talele (EX1009)**

80. Talele, entitled "The 'Cyclopropyl Fragment' is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules," (*J. Med. Chem*. 2016, *59*(19), 8712-8756) is a review article published in the Journal of Medicinal Chemistry on June 14, 2016 (EX1009). Talele qualifies as prior art at least because it was a printed publication available before the earliest possible filing date of the '236 patent.

81. Thus, Talele teaches that substitution with a cyclopropyl ring is a well-established strategy in medicinal chemistry for enhancing metabolic stability, improving pharmacokinetic properties, or modulating the biological activity of a drug molecule.

82. In particular, Talele states that "the cyclopropyl fragment is a versatile player," and that "from the 1960s to the present, the cyclopropyl ring has appeared

frequently in U.S. FDA-approved drugs and is likely to continue to play a significant role in the development of new drugs to meet specific therapeutic goals." (Id. at 1.) Talele further observes that "it is striking to find that eight of the 200 best-selling drugs approved by the U.S. FDA contain a cyclopropyl ring," and that "at present, there are about 65 unique cyclopropane-containing compounds in various stages of clinical trials and about 55 in preclinical stages." (Id. at 2.) Talele also discloses that, "The frequent appearance of the cyclopropyl ring system in drug molecules has led to advances in elegant synthetic methods for the preparation of highly strained cyclopropane building blocks." (Id. at 1.) As a result, the medicinal chemistry community has been able to incorporate this ring system into small, pharmacologically active drug molecules." (Id.)

83. Talele provides an extensive review of the influence of the cyclopropane ring on pharmaceutical activity, highlighting its contributions to numerous desirable drug properties. (Id. at 1-37.) These include increased potency, receptor subtype selectivity, bioavailability, half-life, microsomal stability, brain permeability, adaptation to mutable binding sites of target proteins, aqueous solubility, and entropically favorable binding. (Id. at 2.) Additionally, the cyclopropane ring is associated with reductions in lipophilicity, metabolic liability, off-target pharmacology, and entropic penalties upon binding—factors that

collectively enhance the likelihood that a drug molecule will be therapeutically useful. (Id.) Additionally, Talele states:

> Collectively, it is clearly evident that **the cyclopropane ring system has a positive impact** on the biological actions of drugs approved by the FDA for a wide range of human diseases. Consequently, the number of cyclopropyl-containing drugs will continue to rise. **These facts point toward the firm establishment of the sp3-hybridized three carbon ring system in modern drug discovery research**.
>
> Consequently, the cyclopropyl ring addresses multiple roadblocks that can occur during drug discovery such as (a) enhancing potency, (b) reducing off-target effects, (c) **increasing metabolic stability**, (d) increasing brain permeability, (e) **decreasing plasma clearance**, (f) contributing to an entropically more favorable binding to the receptor, (g) conformational restriction of peptides/peptidomimetics to prevent proteolytic hydrolysis, and (h) altering drug pKa to reduce its P-glycoprotein efflux ratio.
>
> (Id. at 1, 2 (emphases added).)

84. In particular, with regard to the replacement of a methyl with a cyclopropyl, Talele discloses that:

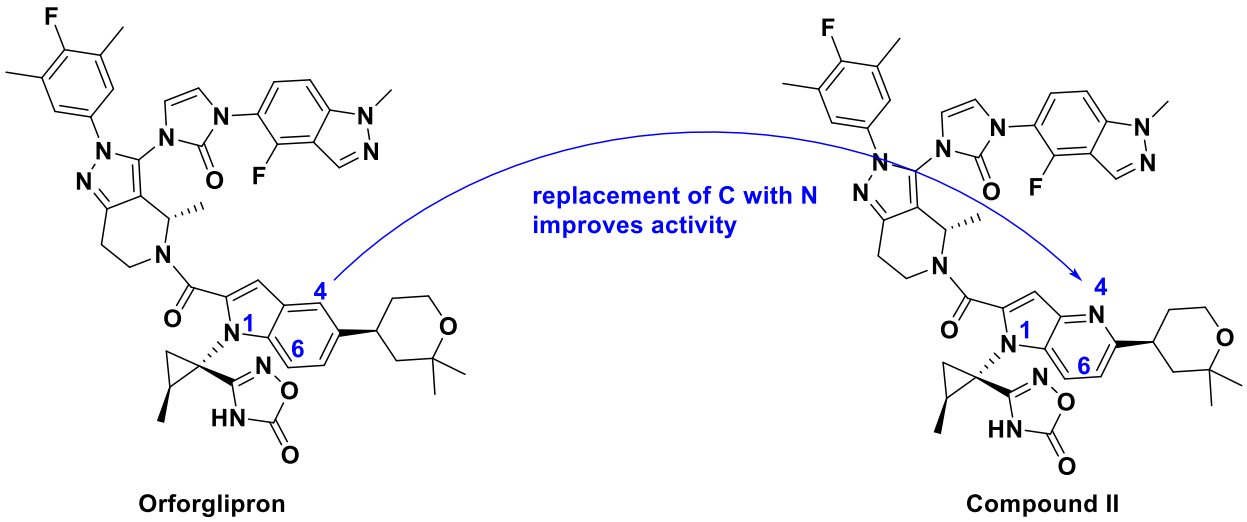
> The cyclopropane ring is exceptional among various carbocycles in both its properties and reactivity because of its uncommon bonding and characteristic ring strain (27.5 kcal/mol).
>
> The C−H bonds in the cyclopropane ring are shorter and stronger (106 kcal/mol) compared to the C−H bonds in ethane (101 kcal/mol). On the basis of this observation, **one can expect to achieve a metabolically stable derivative upon replacement of the methyl group with a cyclopropane ring**. This latter property occurs as proton

> abstraction from a cyclopropane ring would be more difficult than from a methyl group, which is required for oxidative metabolism to proceed.
>
> The cyclopropane scaffold may also contribute toward sp3 disruption of overall planarity due to increased character and three-dimensionality favoring noncoplanarity, less crystal packing, low melting point, and higher aqueous solubility.
>
> (Id. (emphasis added))

**E. Meng (EX1028)**

85. Chinese Patent Application No. 202210505406.X to Kun Meng et al., entitled "GLP-1 receptor agonist," was filed on May 10, 2022, published on November 17, 2023 as CN117069743A ("Meng"), assigned to Beijing Shengnuoji Pharmaceutical Technology Co Ltd. (EX1029 at 1.) I understand that Meng is prior art at least because it was published before the priority date to which Compound 65 in the '236 patent may be entitled.

86. Meng discloses and claims Compound (II) which incorporates an additional nitrogen atom into the core scaffold relative to orforglipron. (See EX1029 at 2–3, claim 5; ¶¶ [0020]–[0025]; Examples 1–3.) From a structural standpoint, Compound (II) is nearly indistinguishable from orforglipron, with the sole variation being the presence and positioning of an additional nitrogen atom within the aromatic ring. (Id.) The structural similarity between orforglipron and Compound (II) is illustrated below.




(Id.)

87. Notably, Compound (II) one of the only two compounds in Meng that are structurally and functionally characterized. (Id. at ¶¶[0027]–[0192]; Examples 1–3.) Meng further reports a comparative study evaluating Compound (II) relative to a reference compound, identified as Compound 67 of TW201827426. (Id. at ¶¶[0186]-[0192].) I understand that TW201827426 is the Taiwanese counterpart of Yoshino, and that Compound 67 disclosed therein is the same as Compound 67 of Yoshino—chemically identical to orforglipron.

88. The data from the comparative study reported in Meng demonstrate that the introduction of a nitrogen atom into the aromatic core of orforglipron analogs can significantly enhance GLP-1 receptor potency. (Id.) Specifically, Compounds (II) is 1.6--fold more potent than orforglipron, as evidenced by its lower $EC_{50}$ value

(reflecting the concentration required to achieve half-maximal activation of the GLP-1 receptor). (Id.)

**F. Patel (EX1026)**

89. Patel, entitled "Conversion of Aryl Azides to Aminopyridines," (*J Am Chem Soc.* 2022 Oct 5;144(39):17797-17802) is a review article published in the Journal of the American Chemical Society on September 22, 2022 (EX1026). Patel qualifies as prior art at least because it was a printed publication available before the earliest possible filing date of the '236 patent.

90. Patel discloses the medicinal chemistry strategy of converting a benzene ring into a pyridine ring is well-precedented. For example, Patel reports a study describing a concise synthetic method for the direct conversion of aromatic C–H bonds into nitrogen-containing heterocycles. (EX1026 at 1-6.) In particular, Patel states:

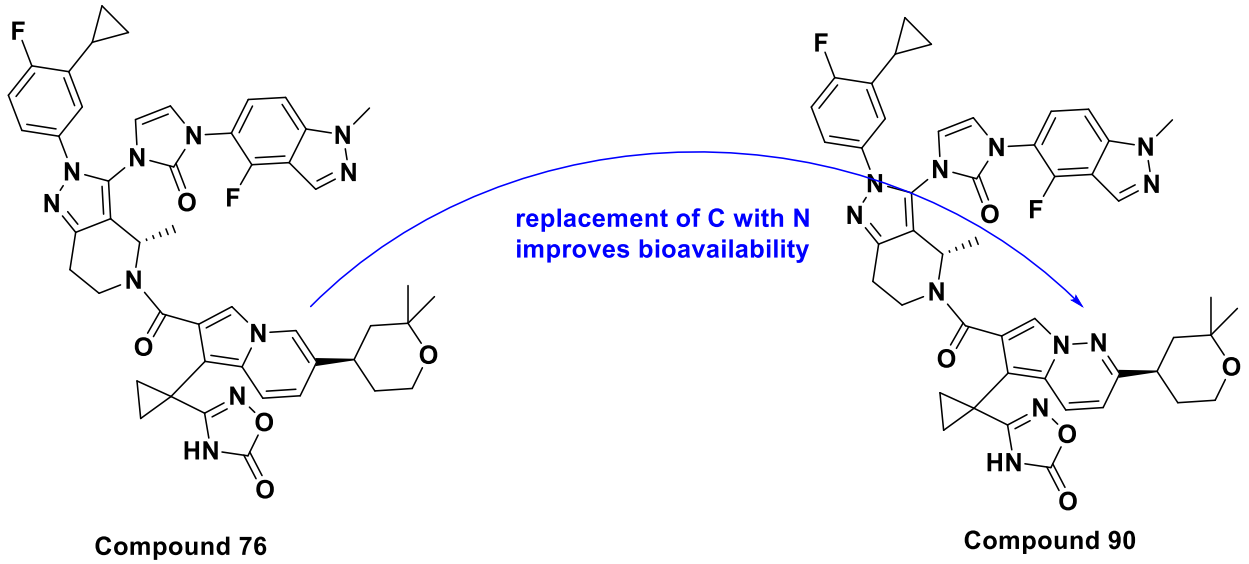
> **Pyridine is the most common aromatic heterocycle and the second most common heterocycle found in FDA-approved drugs in the United States.[1] It is known as an important benzene isostere and used to modulate lipophilicity and improve aqueous solubility, metabolic stability, and hydrogen-bond capability, while still maintaining benzene-like characteristics such as planarity and π-stacking, attributes which saturated carbocyclic isosteres dramatically disrupt.**[2-5] Indeed, drug discovery programs routinely undergo systematic nitrogen atom scans (N-scans), **wherein a CH unit in a lead compound is replaced with a nitrogen atom in an effort to improve molecular and physicochemical properties.** [2,3] This so-called "necessary nitrogen atom"

> effect has been shown to improve a variety of key pharmacological parameters including potency anywhere from 10- to 1000-fold.
>
> (Id. at 1 (emphases added).)

**G. Ren (EX1030)**

91. U.S. Patent Application No. 17/380,084 to Zaifang Ren et al., entitled "Substituted imidazoles as GLP-1 receptor agonists," was filed on July 20, 2021, published on February 16, 2023 as US20230051320A1, and subsequently issued as U.S. Patent No. 12,037,339 ("Ren"), assigned to Eccogene Inc. (EX1030 at 1.) I understand that Ren is prior art at least because it was published before the earliest priority date of the '236 patent.

92. Ren discloses Compounds 76 and 90, as shown below. (EX1030 at 393:1-67, 445:1-67.) These compounds differ solely in that Compound 90 incorporates an additional nitrogen atom at the aromatic ring, as shown below. (Id.)




Compound 76 Compound 90

93. Ren provides pharmacokinetic data in Table 30 below for only four disclosed compounds including Compound 90 and 76, demonstrating that Compound 90, which contains the additional nitrogen atom, exhibits substantially improved oral bioavailability compared to Compound 76. (Id. at 459:46–460:30, Example 81.) Specifically, the bioavailability (F%) of Compound 90 is reported as 59%, compared to only 30% for Compound 76—a nearly two-fold improvement attributed to the nitrogen substitution. (Id.)

TABLE 30-continued

| | PO parameters | | | |
|---|---|---|---|---|
| Cmpd No. | Dose (mg/kg) | $C_{max}$ (ng/mL) | AUC (ng hr/mL) | F (%) |
| 73 | 5 | 1700 | 10193 | 90 |
| 76 | 5 | 962 | 5321 | 30 |
| 90 | 5 | 1370 | 3338 | 59 |
| 91 | 5 | 738 | 2661 | 22 |

94. These data would have reinforced to a POSA the practical benefit of incorporating a nitrogen at of the core aromatic ring of orforglipron —at a position consistent with Compound 90 of Ren—would have been viewed as a rational strategy to enhance bioavailability and overall pharmacological profile.

**H. Bethel (EX1032)**

95. International Patent Application No. PCT/US2023/083545 to Mary Angelyn Bethel et al., entitled "Dosage regime of orforglipron for treating a subject with type 2 diabetes (t2d), obesity, or overweight with at least one weight related

comorbidity," was filed on December 12, 2023 by Eli Lilly And Company and was published on June 20, 2024 as WO2024129676A1 ("Bethel") (EX1032). PCT/US2023/083545 claims priority to the following priority documents: U.S. Provisional Application No. 63/432,197, filed on December 13, 2022, and U.S. Provisional Application No. 63/499,328, filed on May 1, 2023. (EX1032 at 1.) I was informed that Bethel is prior art at least because it has an effective filing date earlier than the earliest filing date of the '236 patent.

96. Bethel discloses methods for treating a subject with T2D, obesity, or overweight with at least one weight related comorbidity using a glucagon-like peptide-1 (GLP-1) receptor non-peptide agonist (NPA), Compound 1, by oral administration. (Id.) Compound 1 is chemically identical to orforglipron. (Id. at 4.) Example 1 describes preparation of Spray-Dried Dispersion (SDD) of ½ Ca salt of orforglipron, Example 2 describes preparation of a capsule formulation of ½ Ca salt of orforglipron, and Example 3 describes preparation of tablet formulation of ½ Ca salt of orforglipron. (Id. at 46-53.) Examples 4A-4B report "Phase 2 Clinical Data" from patients with obesity or overweight treated with dose levels (12 mg, 24 mg, 36 mg and 45 mg) of orforglipron ½ Ca salt. (Id. at 53-66.) Bethel further reports that, "Compound la was well tolerated across all arms. Liver function tests were not significantly increased in participants receiving Compound la compared with placebo," and "The percentages of participants achieving HbAlc and weight loss

targets in the various groups are shown in Fig. 7." (Id. at 57, 59.) Examples 5 and 7-12 describe phase 3 clinical studies using orforglipron ½ Ca salt. (Id. at 66-70, 71-74.)

## IX. OVERVIEW OF THE '236 PATENT

### A. The Specification and Claims of the '236 patent

97. I have read the '236 patent, titled "GLP-1R agonist and therapeutic method thereof," and reviewed the relevant portions of the prosecution history of the '236 patent (EX1003). The '236 patent issued from U.S. Non-Provisional Patent Application No. 18/884,965 ("the '965 Application"), filed on September 13, 2024, which claims the benefit of fourteen prior applications, including ten Chinese provisional patent applications and four US provisional patent applications, which are further discussed in Section IX.C below. (EX1001 at 1, 1:1-45.)

98. The cover page of the '236 patent lists Bin Liang, Jinzi Jason Wu, and Bailing Yang as the inventors and Ascletis Pharma (China) Co., Limited as the Applicant and Assignee. (Id. at 1.)

99. The background of the '236 patent states "GLP-1R agonists are currently being investigated in connection with diabetes, obesity, and NASH" and recognizes "[t]here remains a need for compounds, such as agonists of GLP-1R, with desirable therapeutic properties, metabolic properties, and/or easy administration in the treatment of GLP-1R-mediated diseases and conditions." (Id. at 2:6-7, 2:17-20.)

100. The ’236 patent discloses a broad genus of compounds represented by Formulas (I)–(XI), as well as (Ia), (Ib), (Ic), (Id), (Ie), (If), and (Ig). (EX1001 at 2:23–10:17, 28:51–56.)

101. Example 1 describes the synthesis and/or characterization of certain compounds within the scope of Formula I. (Id. at Example 1.) Example 2 reports the results of in vitro activity testing using an hGLP-1R cAMP assay. (Id. at Example 2, Table 2.) Example 3 presents pharmacokinetic (PK) data from studies conducted in Sprague-Dawley (SD) rats. (Id. at Example 3, Tables 3 and 4.) Example 4 describes an in vivo pharmacodynamics study and states that “[t]he compound of the present disclosure significantly increased the secretion of insulin and C-peptide in cynomolgus monkeys, while blood glucose levels were reduced as well.” However, no actual data are provided to support this statement. (Id. at Example 4, 203:62–67.) Although Example 4 is written in the past tense, it appears to be a prophetic example.

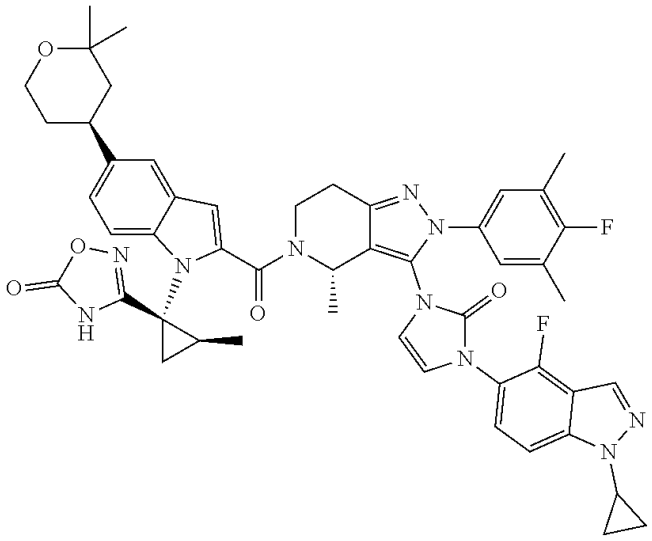
102. The ’236 patent has two independent claims (claims 1 and 24) and 23 dependent claims (claims 2-23 and 25). Independent claim 1 is directed to a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of Compounds 1, 13, 18, 19, 20, 21, and 65, each defined by its respective chemical structure. Independent claim 24 is similarly directed to a compound selected from the same group of seven compounds. Dependent claims 2–23 are directed to subsets of these seven compounds, or

pharmaceutically acceptable salts thereof. Claim 25 is directed to a pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof of claim 1, and a pharmaceutically acceptable excipient.

103. More specifically, independent claim 1 of the ’236 patent recites:

> 1. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

1



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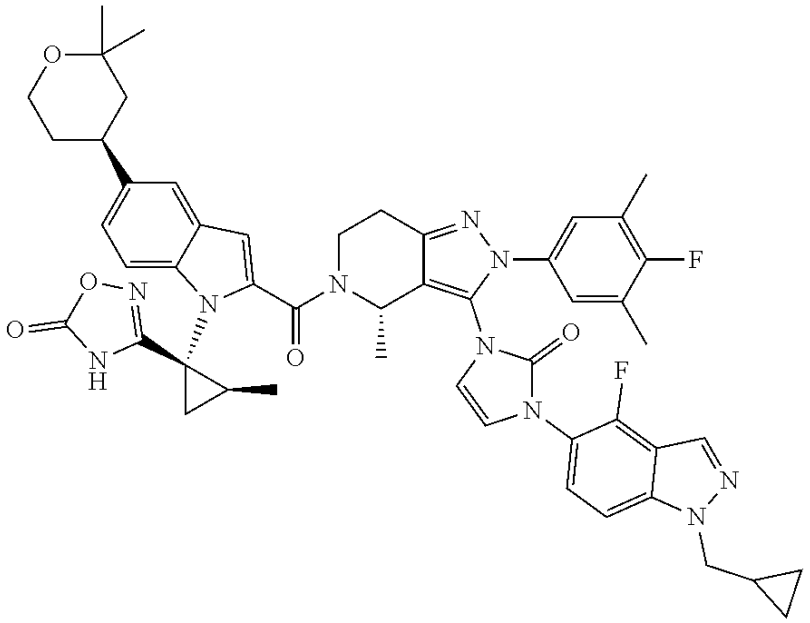

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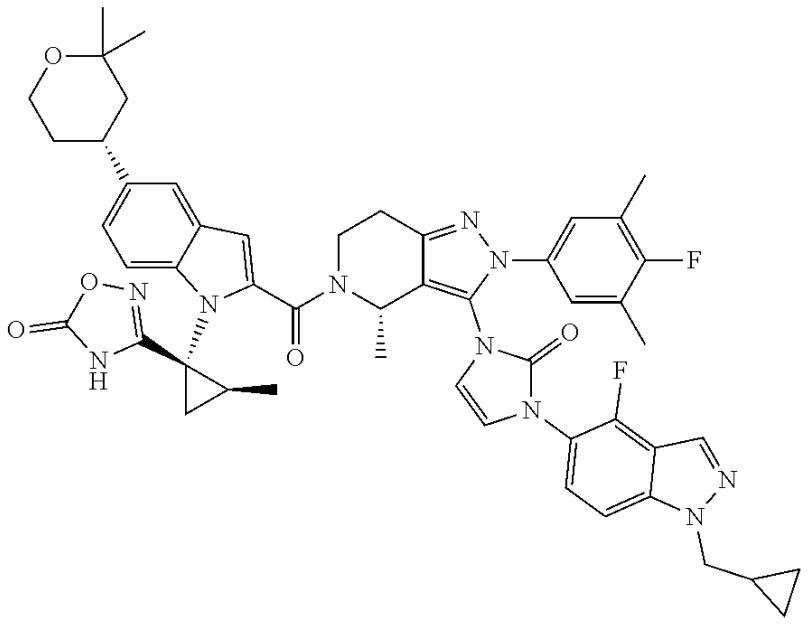

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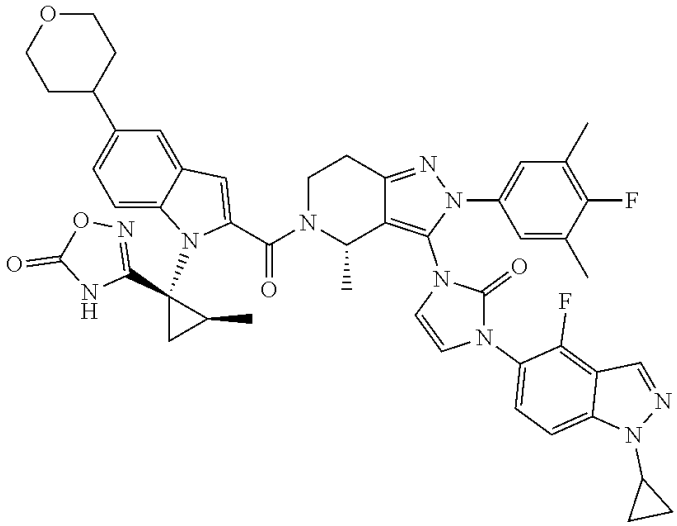

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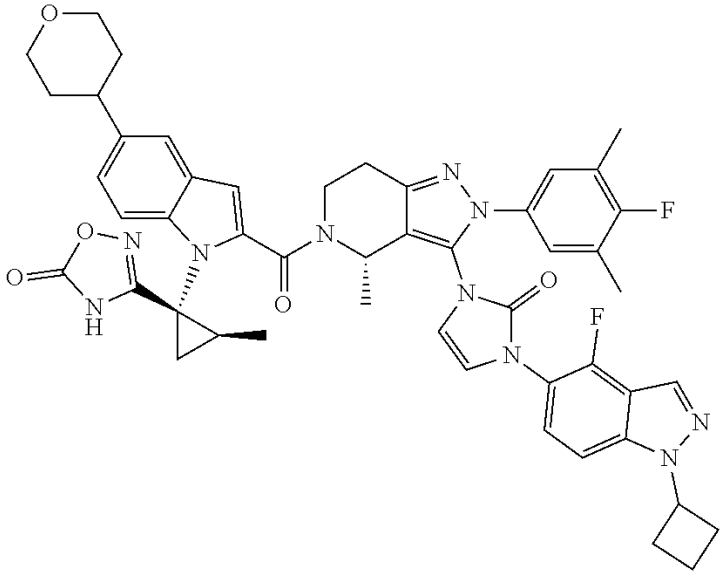

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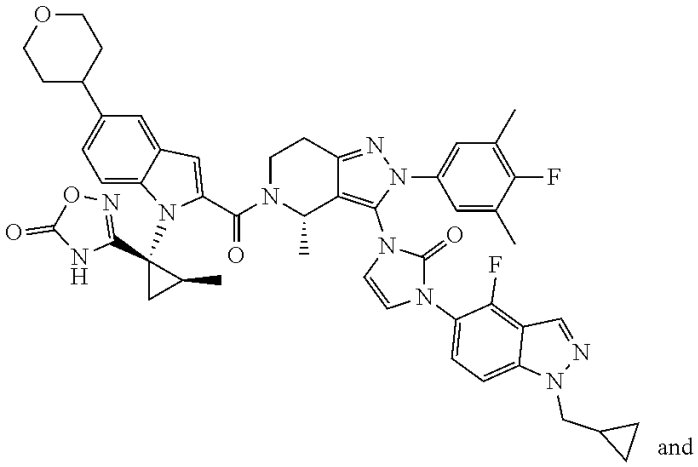
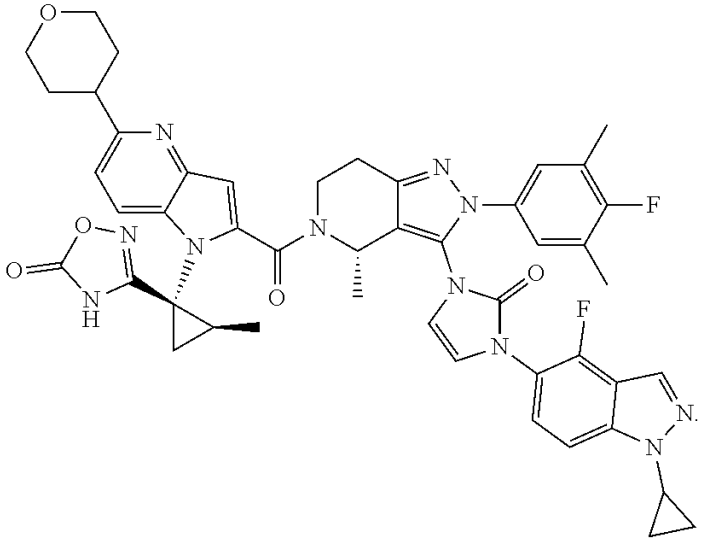


and

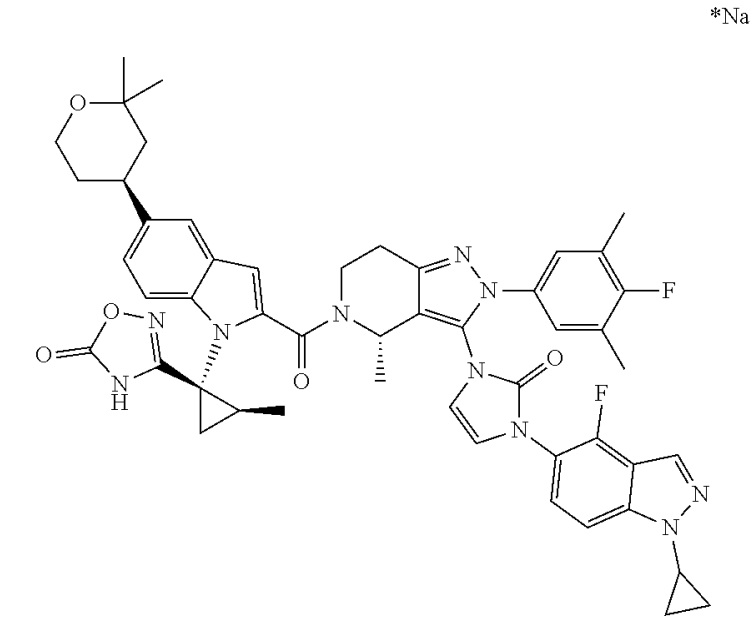
65

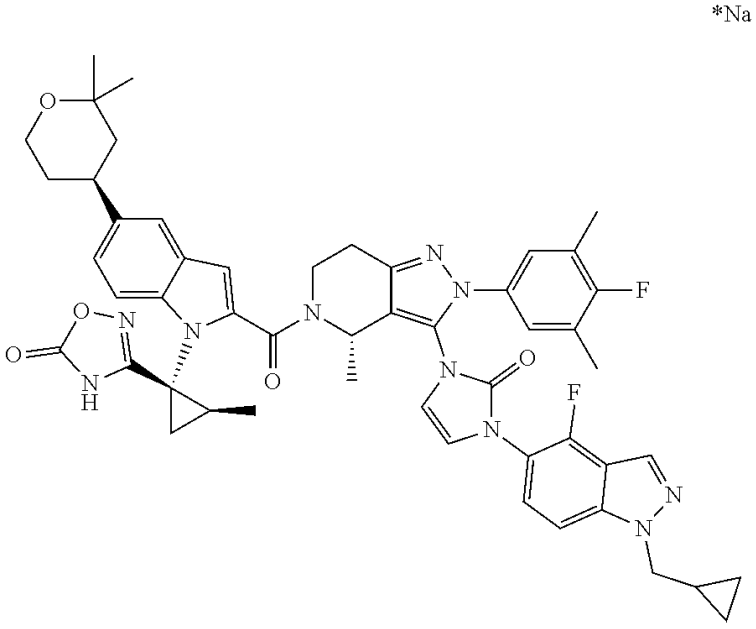


104. Claim 2 depends from claim 1 and recites "the pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, a calcium salt, a potassium salt, a magnesium salt and a lithium salt."

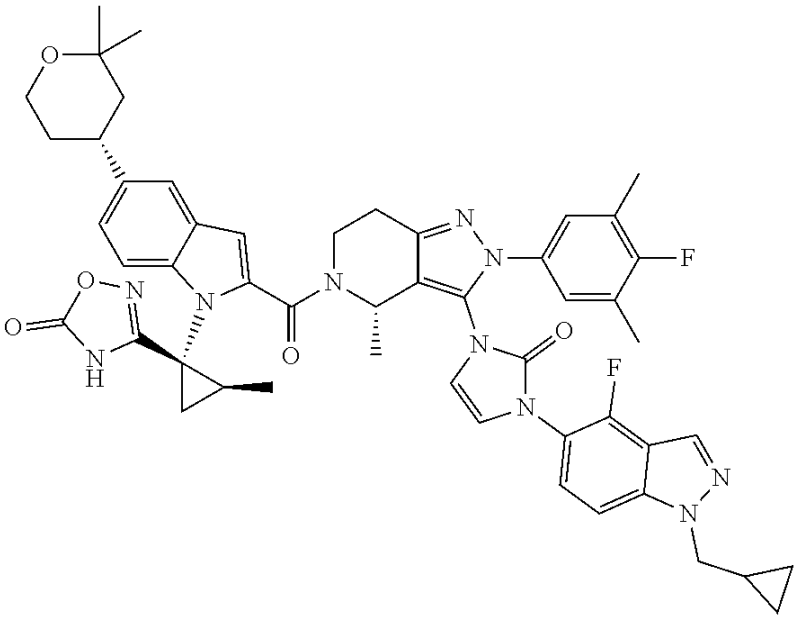
105. Claim 3 depends from claim 1 and recites:

the pharmaceutically acceptable salt is selected from the group consisting of:

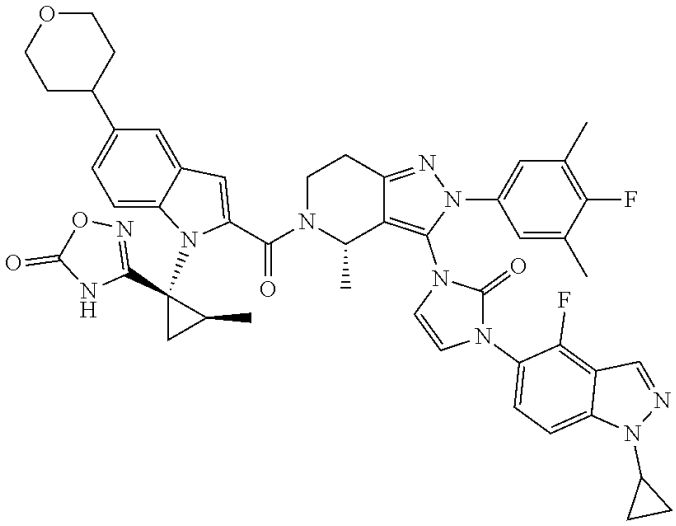


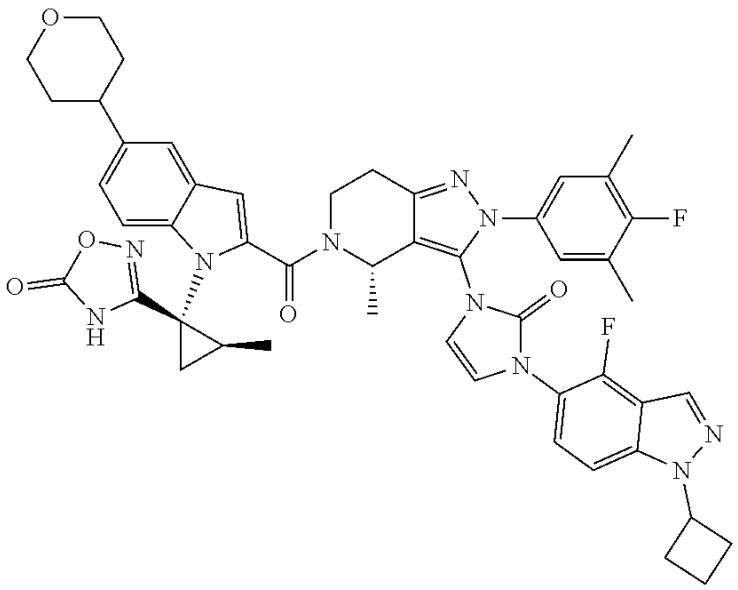
*Na



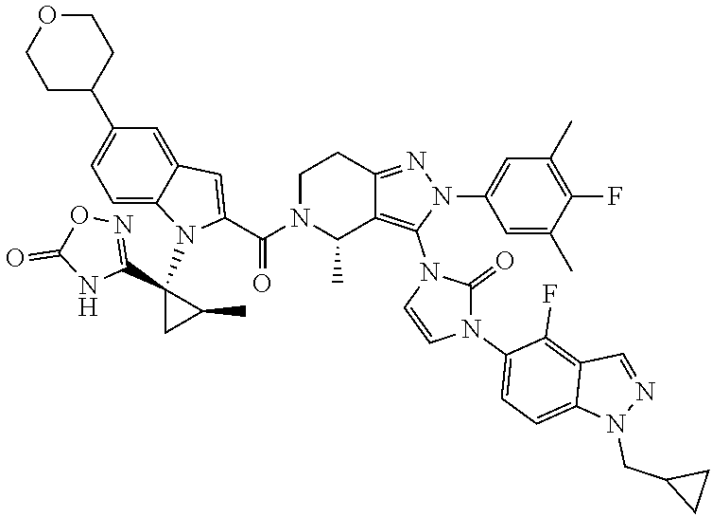
*Na



*Na

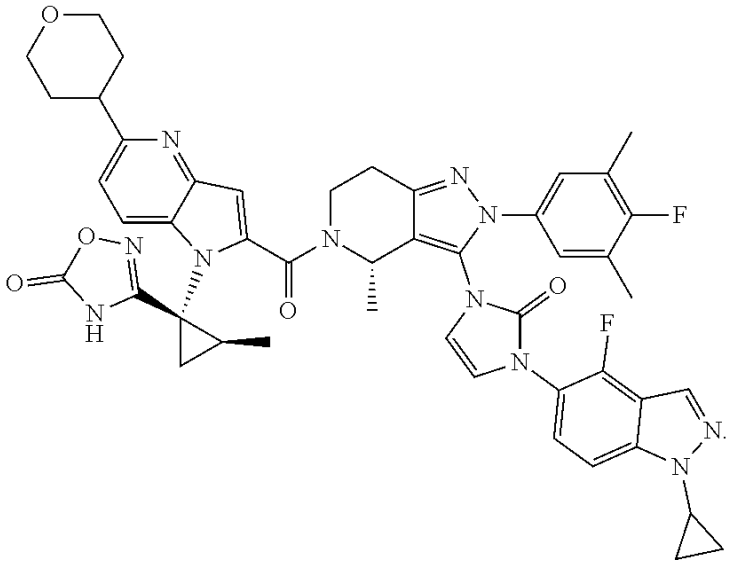


*Na



and

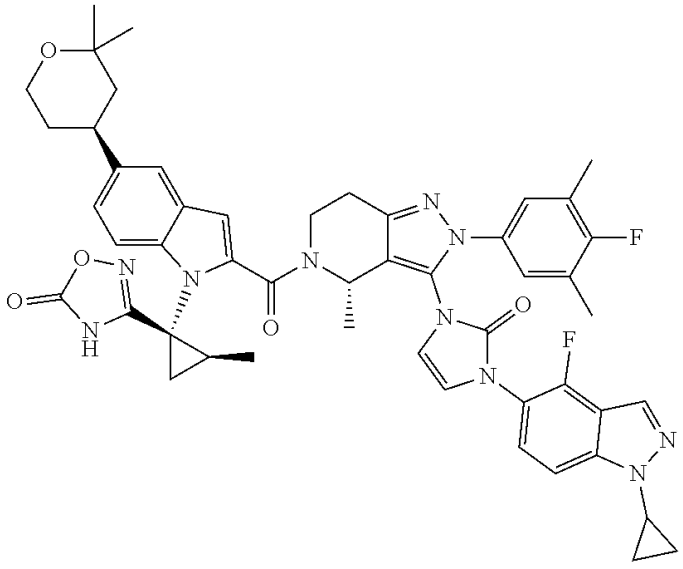
*Na



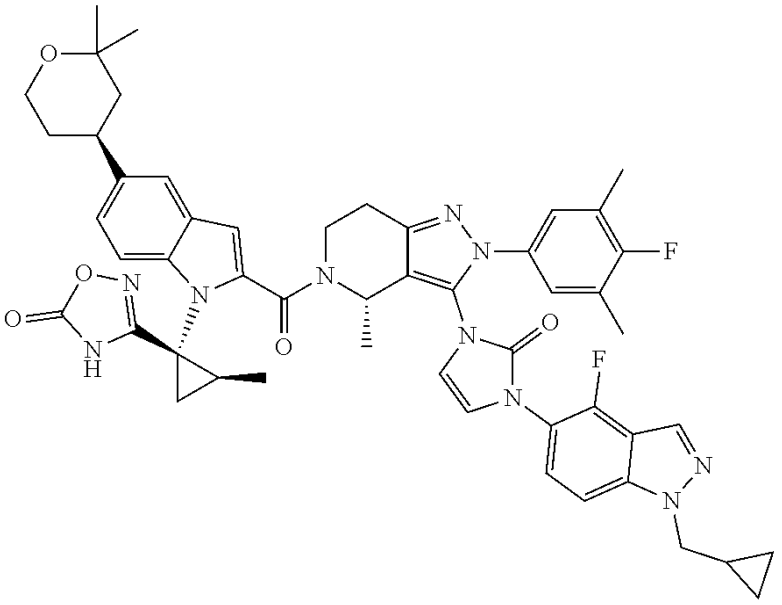
106. Claim 4 depends from claim 1 and recites:

the pharmaceutically acceptable salt is selected from the group consisting of:

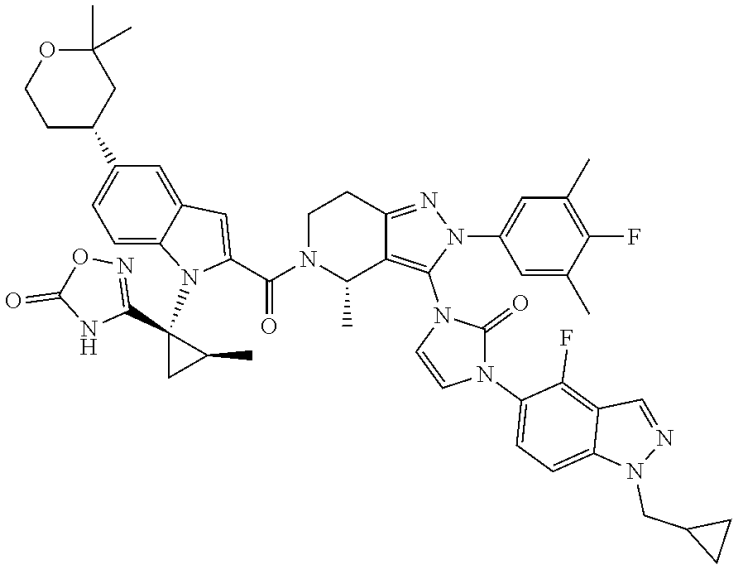
*1/2 Ca



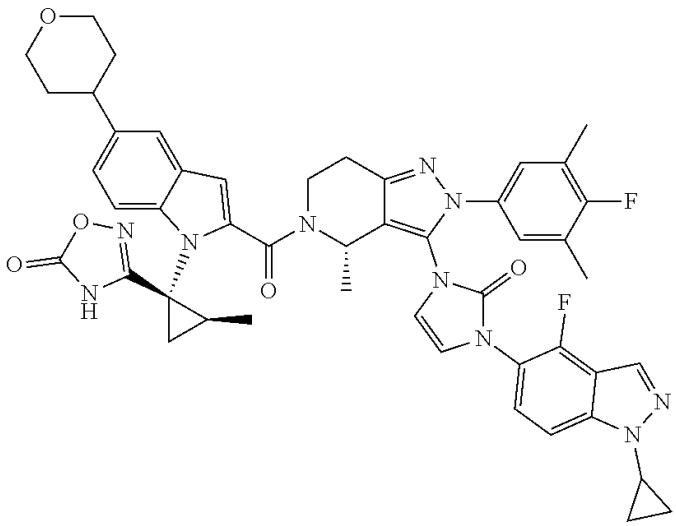
*1/2 Ca



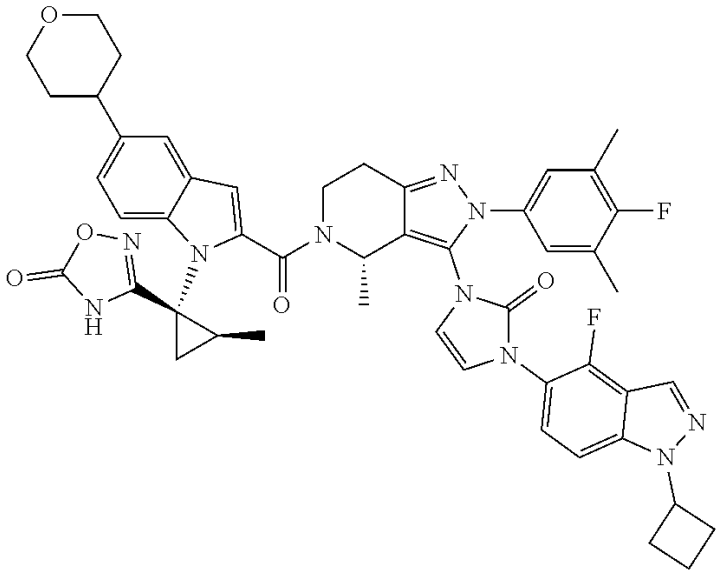
*1/2 Ca



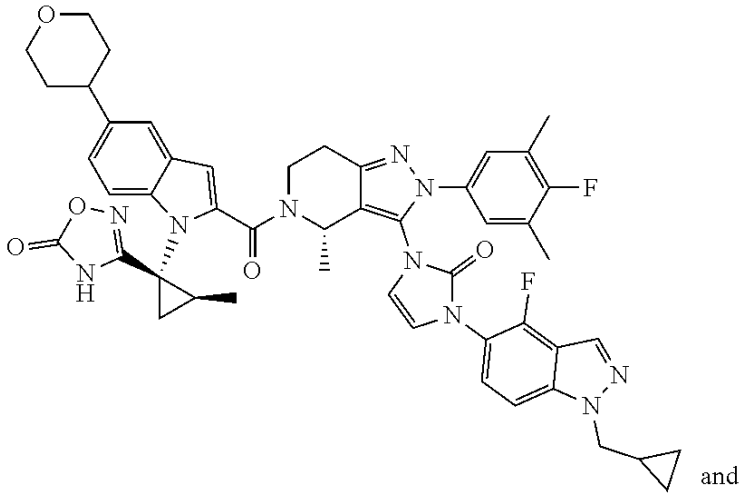
*1/2 Ca



*1/2 Ca

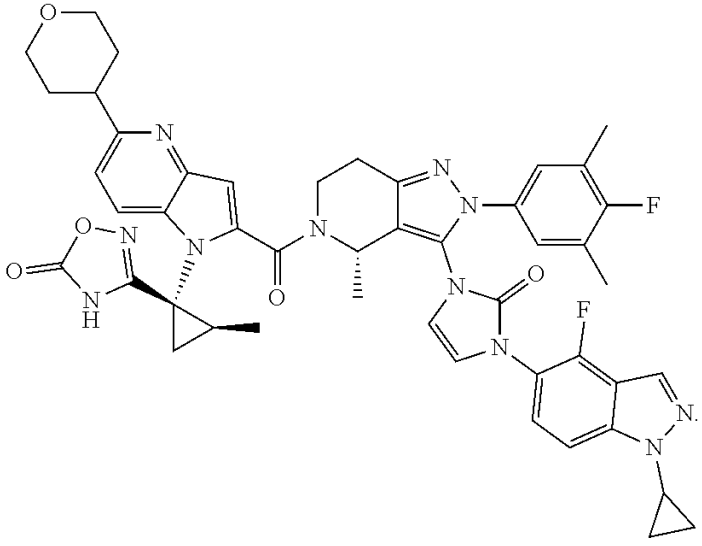


*1/2 Ca



and

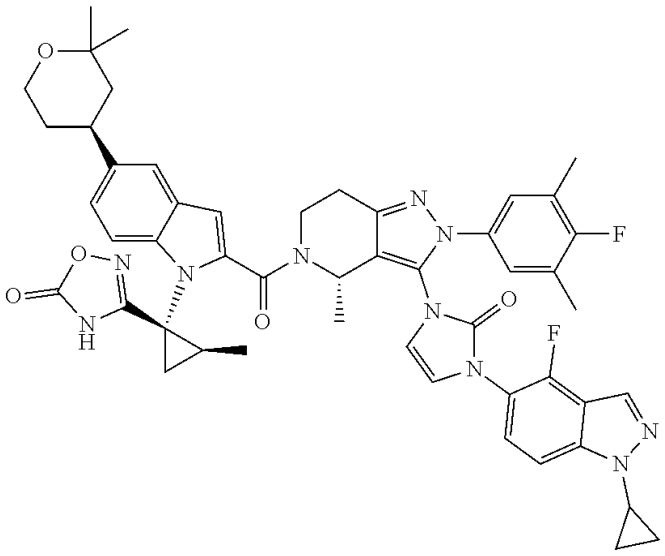
*1/2 Ca



107. Claim 5 depends from claim 1 and recites:

the compound is selected from the group consisting of:

1



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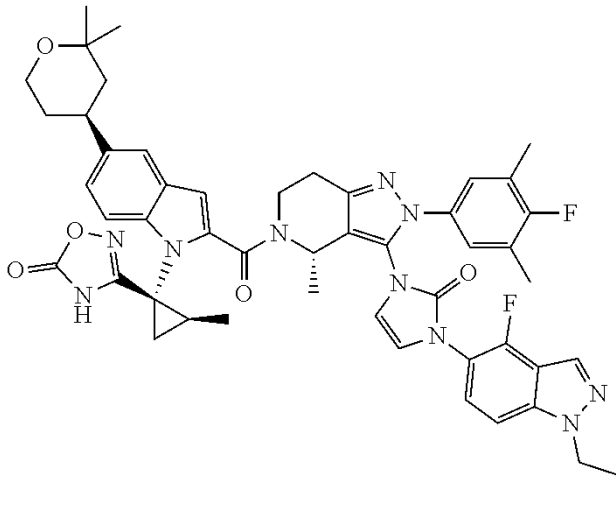

and

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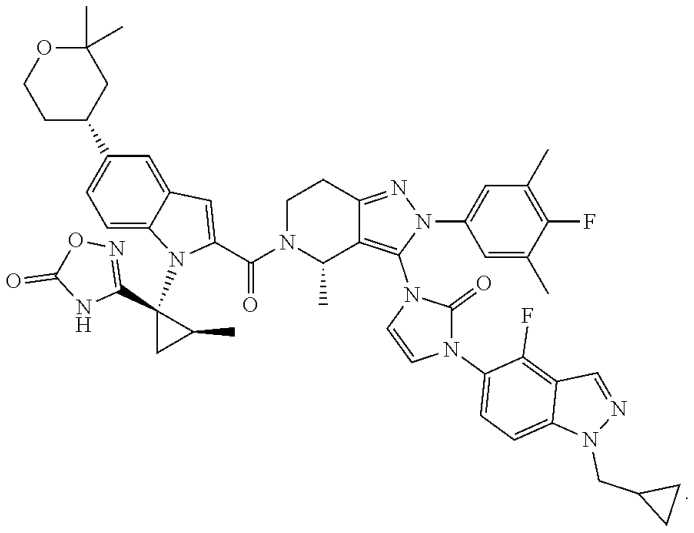
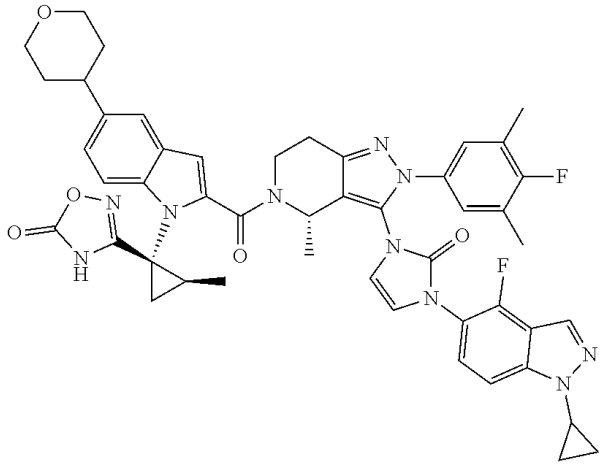


108. Claim 6 depends from claim 1 and recites:

the compound is selected from the group consisting of:

19



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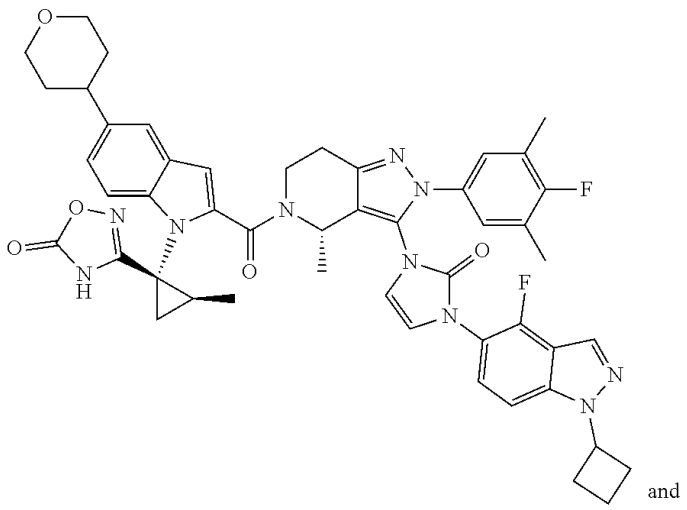

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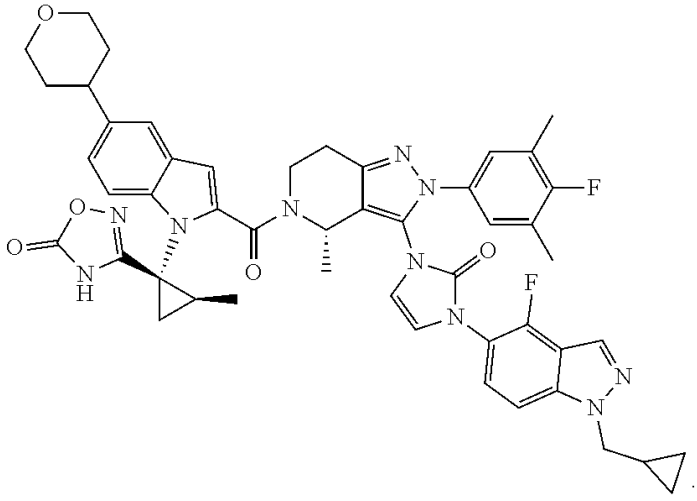
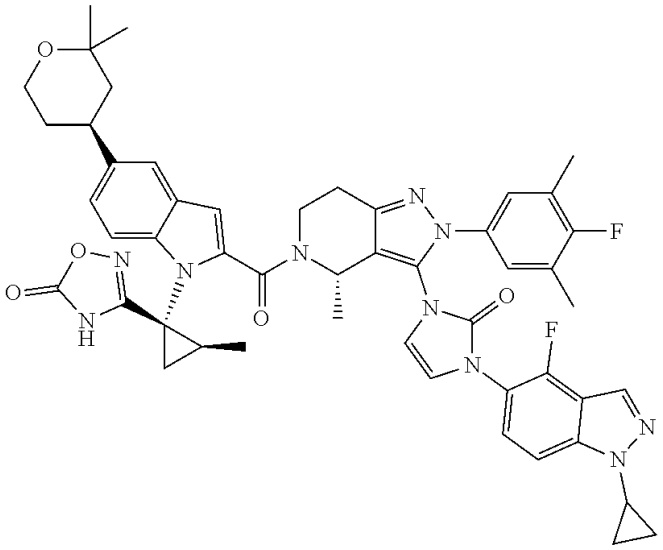


109. Claim 7 depends from claim 1 and recites:

the compound is

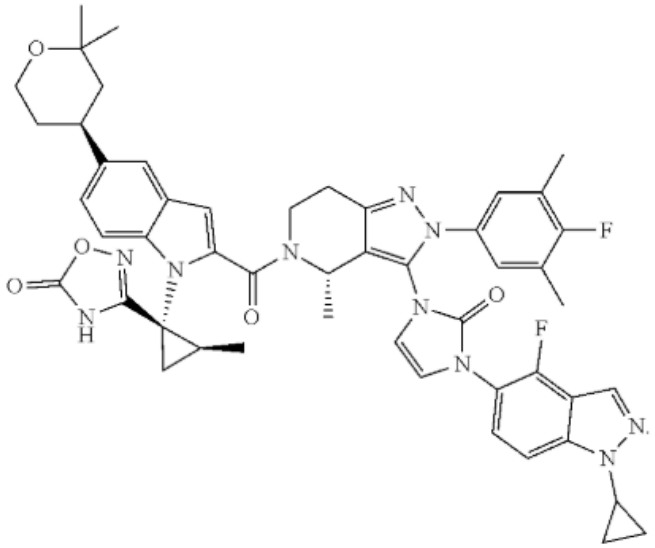
1



110. Claim 8 depends from claim 1 and recites:

the pharmaceutically acceptable salt is

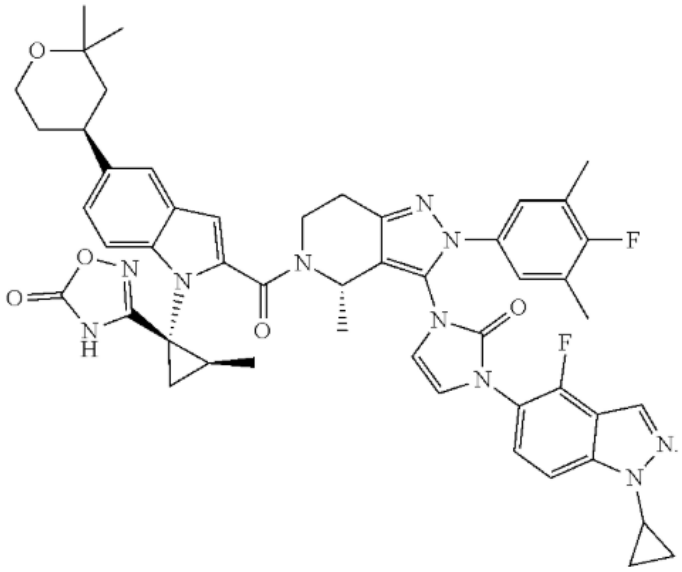
*Na



111. Claim 9 depends from claim 1 and recites:

the pharmaceutically acceptable salt is

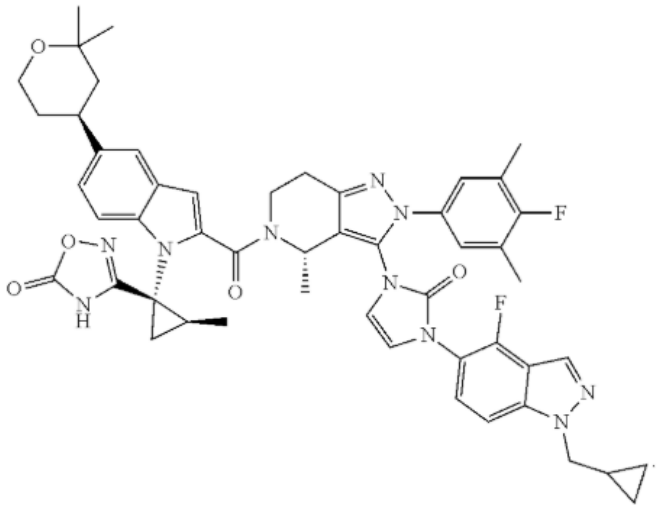
*1/2 Ca



112. Claim 10 depends from claim 1 and recites,

the compound is

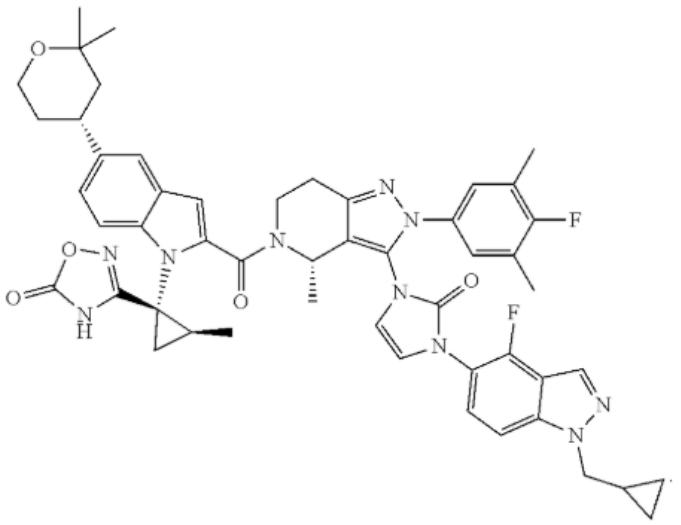
13



113. Claim 11 depends from claim 1 and recites,

the compound is

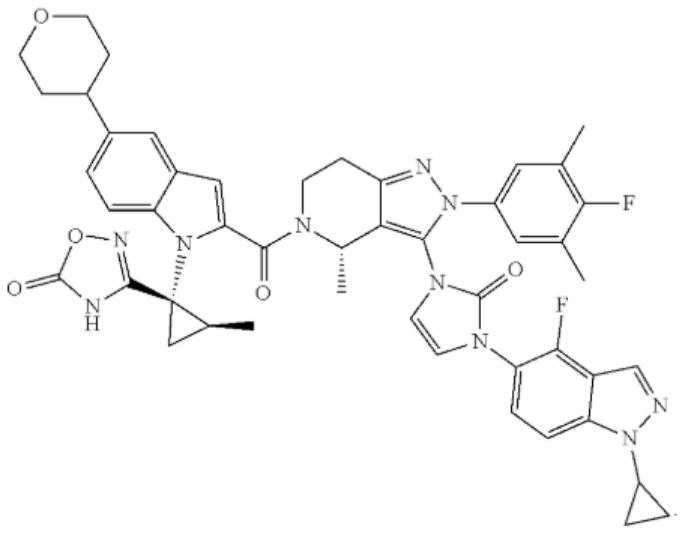
18



114. Claim 12 depends from claim 1 and recites,

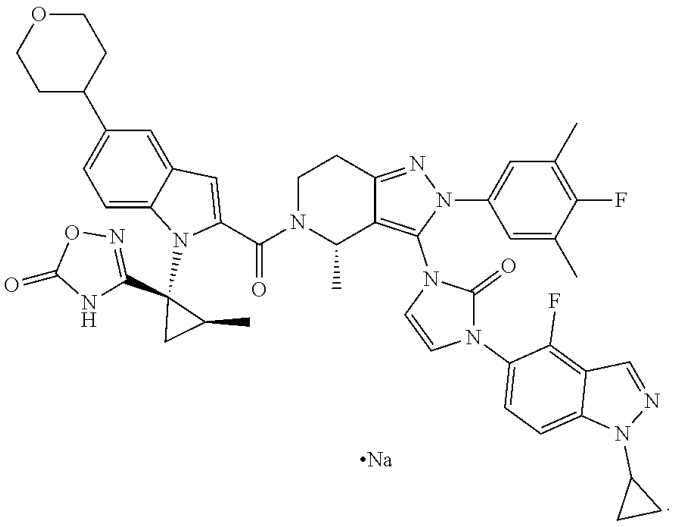
the compound is

19



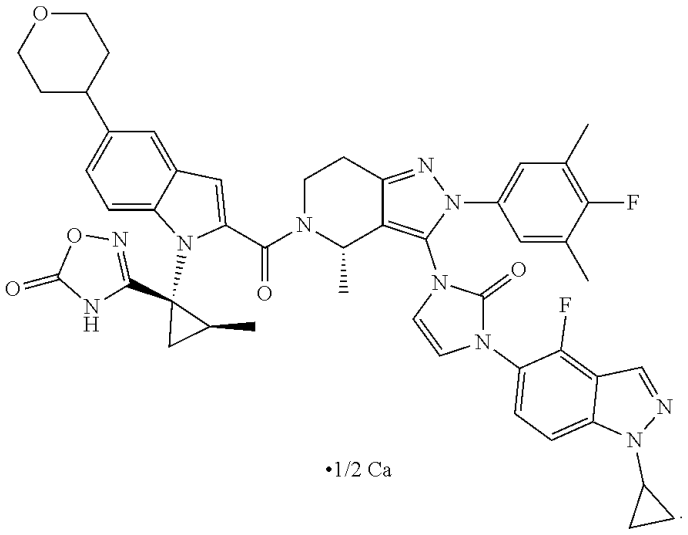
115. Claim 13 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



116. Claim 14 depends from claim 1 and recites:

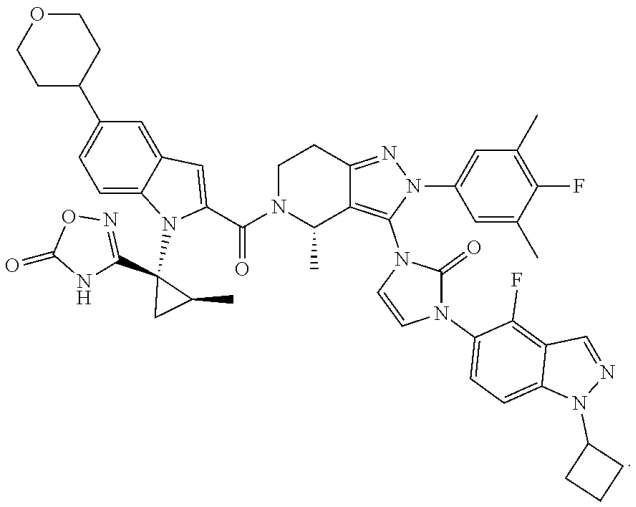
the pharmaceutically acceptable salt is



117. Claim 15 depends from claim 1 and recites:

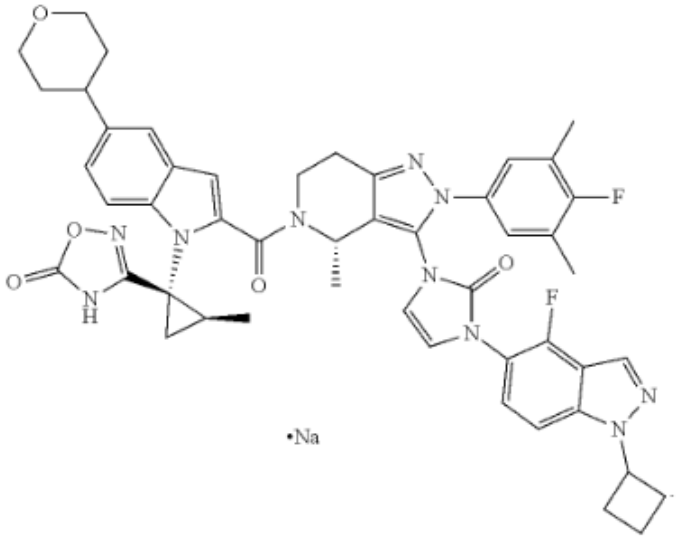
the compound is

20



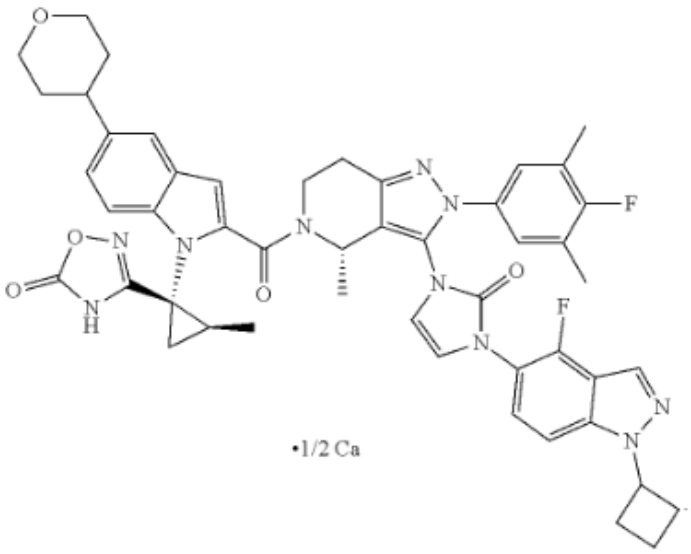
118. Claim 16 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



119. Claim 17 depends from claim 1 and recites:

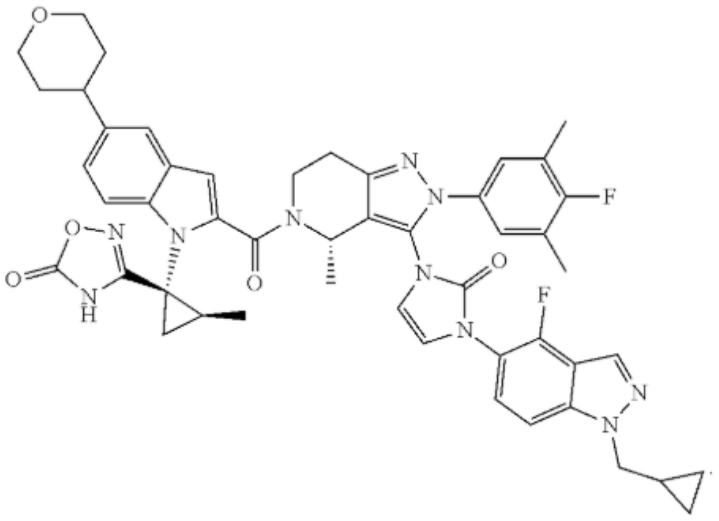
the pharmaceutically acceptable salt is




120. Claim 18 depends from claim 1 and recites:

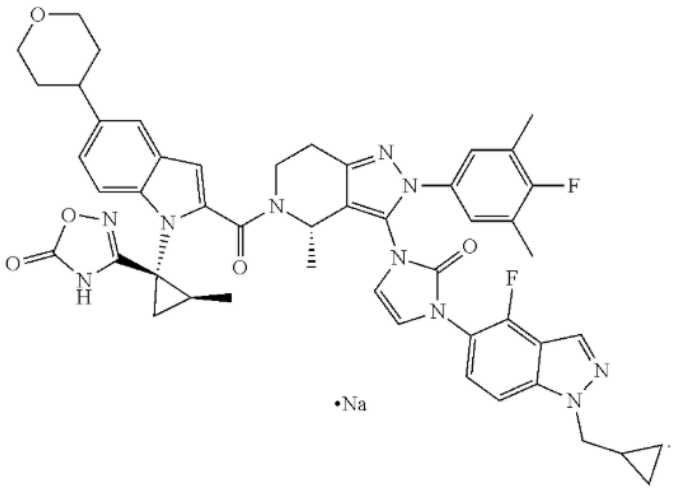
the compound is

21



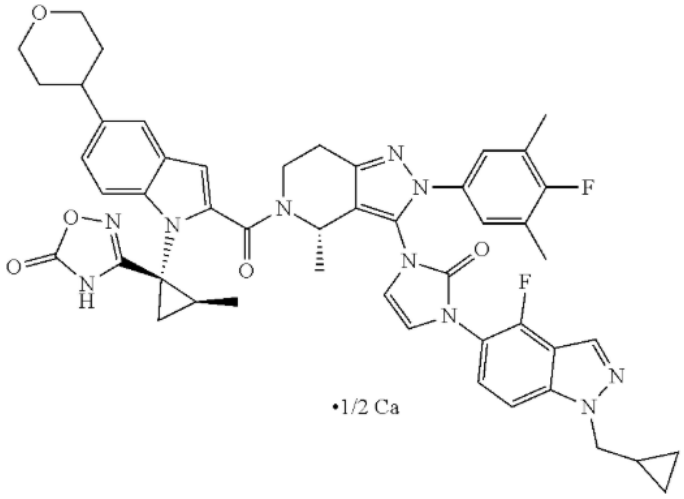
121. Claim 19 depends from claim 1 and recites:

the pharmaceutically acceptable salt is




122. Claim 20 depends from claim 1 and recites:

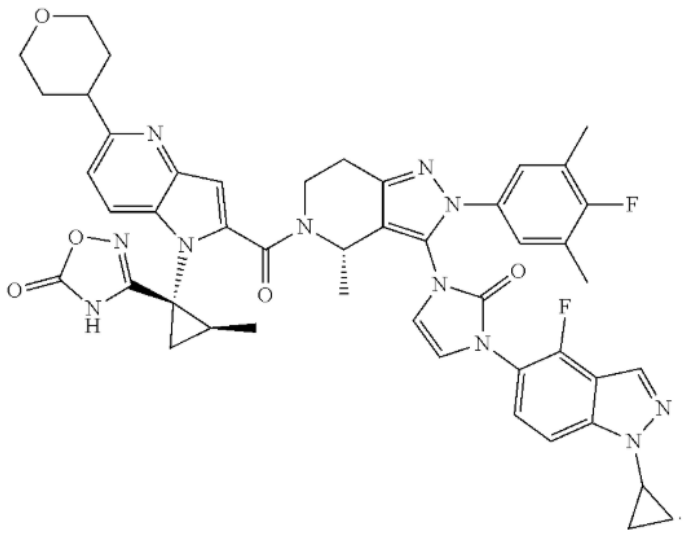
the pharmaceutically acceptable salt is




123. Claim 21 depends from claim 1 and recites:

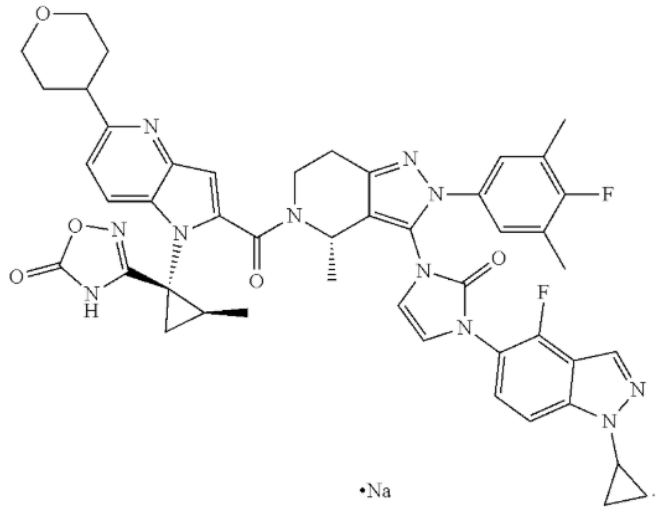
the compound is

65



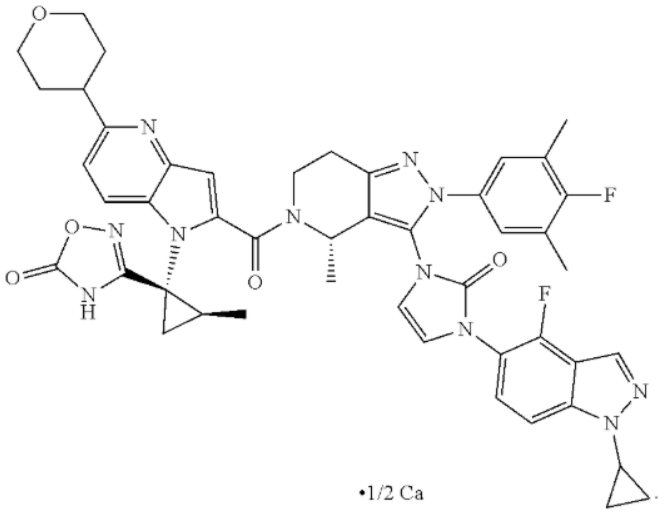
124. Claim 22 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



125. Claim 23 depends from claim 1 and recites:

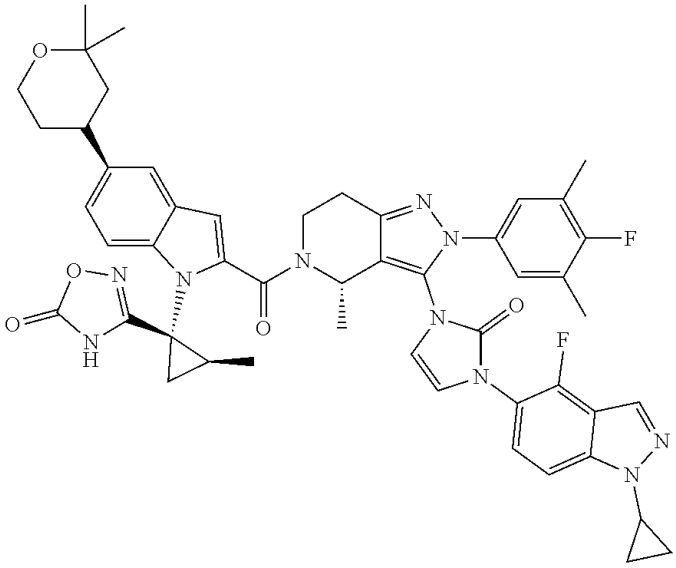
the pharmaceutically acceptable salt is




126. Independent claim 24 recites:

A compound, selected from the group consisting of:

1



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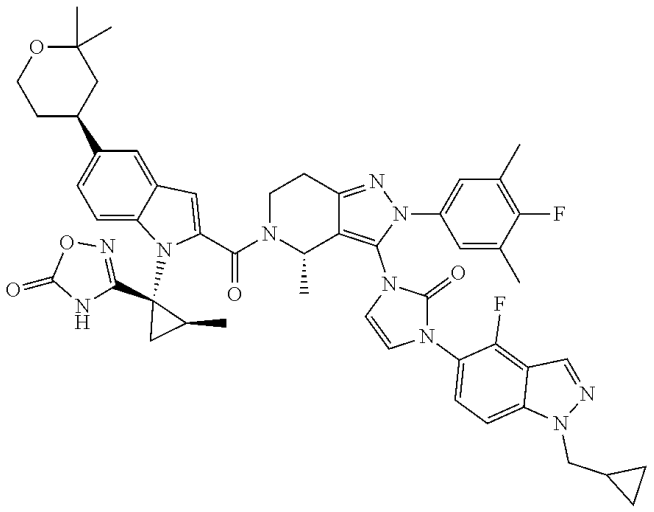

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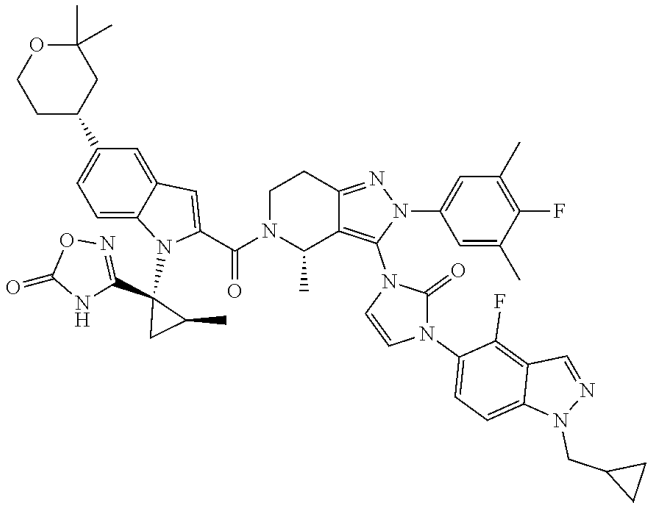

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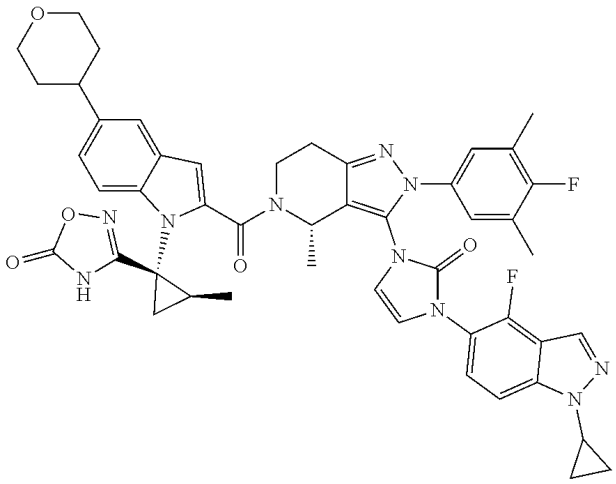

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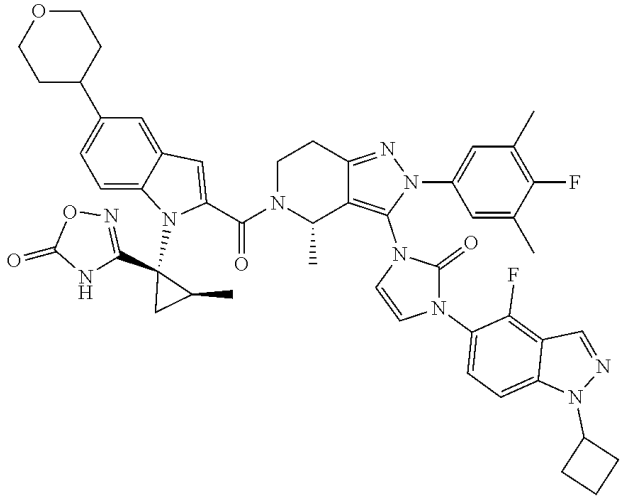

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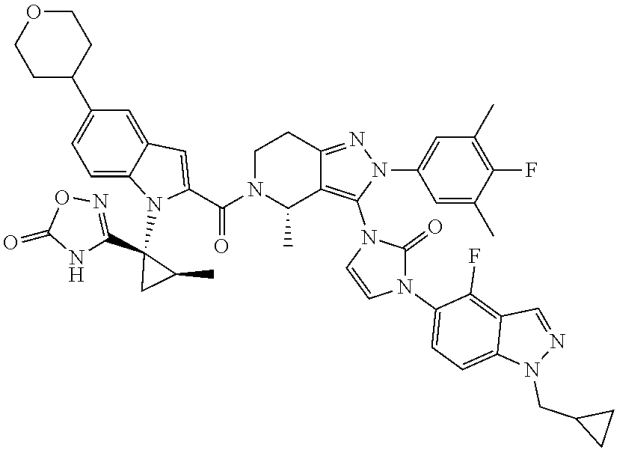
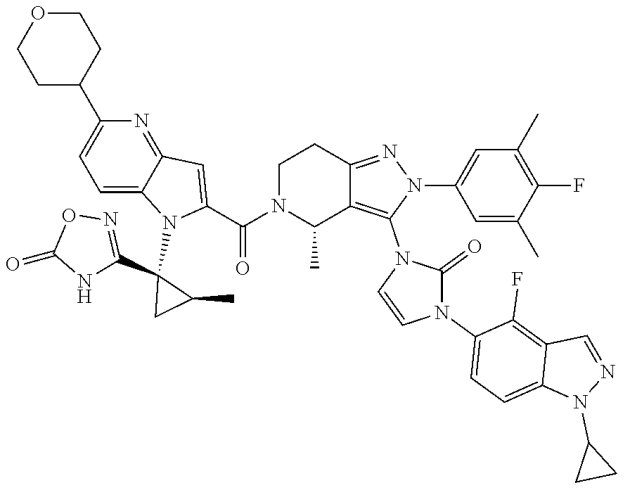


and

65



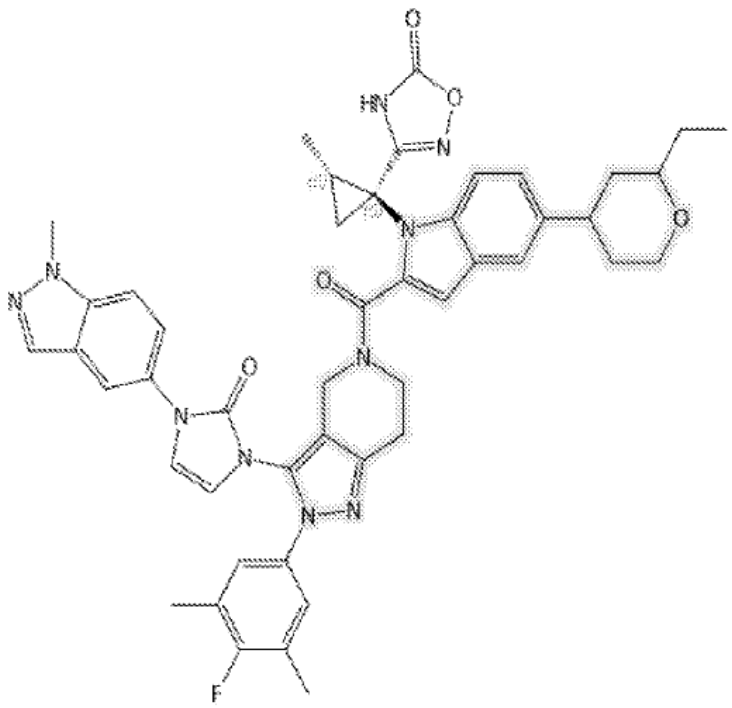
127. Claim 25 depends from claim 1 and recites, "A pharmaceutical composition, comprising the compound or the pharmaceutically acceptable salt thereof of claim 1, and a pharmaceutically acceptable excipient."

**B. The Prosecution History of the '236 patent**

128. The '965 Application that issued as the '236 patent was filed on September 13, 2024 with 25 claims, including independent claim 1 that recited Compounds 1, 13, 18, 19, 20, 21, and 65, each defined by its respective chemical structure. (EX1003 at 1, 152-162.)

129. On November 5, 2024, the USPTO issued a Notice of Allowance, indicating that claims 1–25 were allowed. (Id. at 168.) The Notice of Allowance contains the following examiner's statement of reasons for allowance:

> Claims 1-25 are patentable over Yoshino et al., US 10858356, which includes the exemplified compound:



, which has [a] different structure. Therefore, the claims are free of prior art. (Id.)

130. However, the Examiner did not address any other compounds disclosed in this reference and any additional prior art references or their combinations that could potentially render the claims of the ’965 Application obvious.

### C. The Priority Date of the ’236 patent

131. I understand that under the “Cross-reference to Related Application” of the ’236 patent, the ’965 Application from which the ’236 patent was issued claims the benefit of the following fourteen prior applications, including ten Chinese provisional patent applications: CN 202311189557.X, filed on September 14, 2023; CN 202311371725.7, filed on October 23, 2023; CN 202311582240.2, filed on November 24, 2023; CN 202311686034.6, filed on December 8, 2023; CN

202410142451.2, filed on January 31, 2024; CN 202410202078.5, filed on February 22, 2024; CN 202410398964.X, filed on April 2, 2024; CN 202410584679.7, filed on May 11, 2024; CN 202410963587.X, filed on July 17, 2024; CN 202411237048.4, filed on September 4, 2024; and four US provisional patent applications: US 63/538,892, filed on September 18, 2023; US 63/545,615, filed on October 25, 2023; US 63/603,854, filed on November 29, 2023; US 63/673,453, filed on July 19, 2024. (Id. at 4.)

132. I was told that to establish priority, the earlier application must describe the later-claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought—which I understand to mean that the earlier disclosure must describe and enable the later-claimed invention with all of its limitations. I further understand that a plan to obtain or achieve the claimed invention in the future is insufficient to show possession at the time of filing.

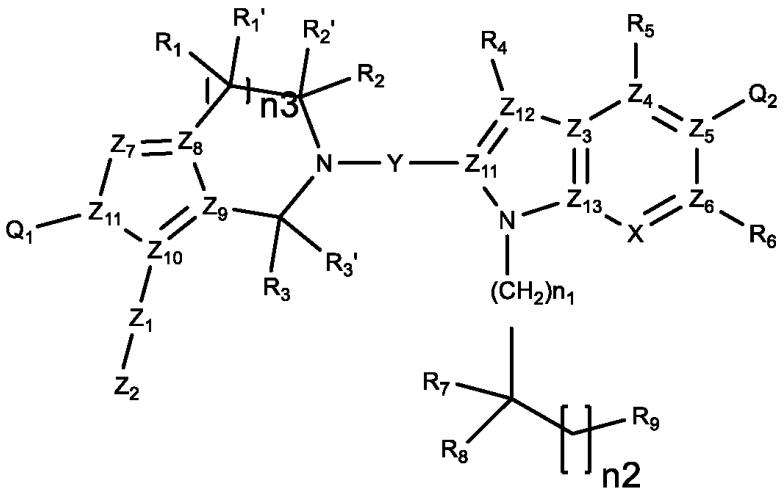
133. I was asked to determine whether the priority documents to which the ’236 patent claims benefit sufficiently describes and enables the full scope of the Challenged Claims of the ’236 patent.

134. As the ’236 patent claims benefit to fourteen priority documents, including four U.S. provisional patent applications and ten Chinese priority applications, I was asked to assess which of these priority documents first provides

a written description of one or more of the seven claimed compounds. As discussed in further detail below, it is my opinion that the Challenged Claims are not entitled to the earliest asserted priority date. For purposes of illustration, I will focus on Compounds 19, 20, 21, and 65 in assessing the disclosure of these compounds across the priority documents.

135. The chemical structures of Compounds 19, 20, and 21 were only first disclosed in CN 202311371725.7, filed on October 23, 2023 ("the '725 Provisional"). (EXS. 1013, 1014) In contrast, the earlier-filed applications, including CN 202311189557.X, filed on September 14, 2023 ("the '557 Provisional") and US 63/538,892, filed on September 18, 2023 ("the '892 Provisional"), do not disclose the specific chemical structures of at least Compounds 19, 20, and 21. (EXS. 1015, 1016, 1017.)

136. The '892 Provisional and the '557 Provisional disclose the following chemical genus encompassing millions of compounds (EX1016 at claim 1; EX1017 at claim 1). None of the exemplified compounds contains an unsubstituted tetrahydropyran ring.




137. However, in my opinion, the two earlier-filed provisional applications fail to adequately describe Compounds 19, 20, and 21, as each variable in the disclosed structural formula encompasses an unduly broad and diverse range of atoms or chemical groups. For example, the variables $Q_2$ and $Z_2$ are defined as follows:

> wherein $Q_2$ is selected from the group consisting of 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl are optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy and $-NR^{Qa}R^{Qb}$, wherein two $C_{1-6}$ alkyl groups together with the carbon atoms to which they are attached form a $C_{3-8}$ carbocyclic ring; wherein $R^{Qa}$ and $R^{Qb}$ are independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl and ($C_{1-6}$ alkyl) carbonyl;
>
> $Z_2$ is selected from the group consisting of $C_{1-6}$ alkyl, $C_{3-15}$ cycloalkyl, 3 to 12-membered heterocyclic, $C_{6-10}$ aryl and 5 to 10-membered heteroaryl, wherein the $C_{3-15}$

cycloalkyl, and 3 to 12-membered heterocyclic group are independently optionally substituted with one to five G's;

wherein G's is selected from the group consisting of:

a. Oxygen;

b. Halogen;

c. Cyano;

d. $-NR^{zd}R^{ze}$; wherein $R^{zd}$ and $R^{ze}$ are independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl and ($C_{1-6}$ alkyl) carbonyl; wherein $C_{1-6}$ alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and $C_{1-6}$ alkoxy;

e. $-C(=O)-NR^{zf}R^{zg}$; wherein $R^{zf}$ and $R^{zg}$ are independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl and ($C_{1-6}$ alkyl) carbonyl; wherein $C_{1-6}$ alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and $C_{1-6}$ alkoxy;

f. $-S(=O)_{n7}-R^{zh}$; wherein n7 is 0, 1 or 2; $R^{zh}$ is selected from the group consisting of hydrogen and $C_{1-6}$ alkyl;

g. $C_{1-6}$ alkyl; wherein $C_{1-6}$ alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, $-NR^{zi}R^{zj}$, $C_{1-6}$ alkoxy, C1-6 alkoxy and 3- to 12-membered heterocyclic groups; wherein each of $R^{zi}$ and $R^{zj}$ is independently selected from the group consisting of hydrogen or $C_{1-6}$ alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, $C_{1-6}$ alkyl and 3 to 12-membered heterocyclic;

h. $C_{1-6}$ alkoxy; wherein $C_{1-6}$ alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and $C_{1-6}$ alkoxy;

> i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic is optionally substituted by one or more substituents independently selected from $C_{1-6}$ alkyl and ($C_{1-6}$ alkyl) carbonyl;
>
> j. $C_{6-10}$ aryl; wherein $C_{6-10}$ aryl is optionally substituted by one or more ($C_{1-6}$ alkyl) carbonyl;
>
> k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $-NR^{zk}R^{zl}$, and 3- to 12-membered heterocyclic; wherein $R^{zk}$ and $R^{zl}$ are independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, and ($C_{1-6}$ alkyl)carbonyl and wherein the 3- to 12-membered heterocyclic is optionally substituted with one or more substituents independently selected from the group consisting of $C_{1-6}$ alkyl, and $C_{1-6}$ alkoxy;
>
> l. $-C_3$-$C_{15}$ cycloalkyl or $-C_1$-$C_6$ alkyl- $C_3$-$C_{15}$ cycloalkyl; wherein $-C_3$-$C_{15}$ cycloalkyl or - $C_1$-$C_6$ alkyl-$C_3$-$C_{15}$ cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and ($C_{1-6}$ alkyl) carbonyl, wherein each of $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and ($C_{1-6}$ alkyl) carbonyl is optionally substituted by halogen.

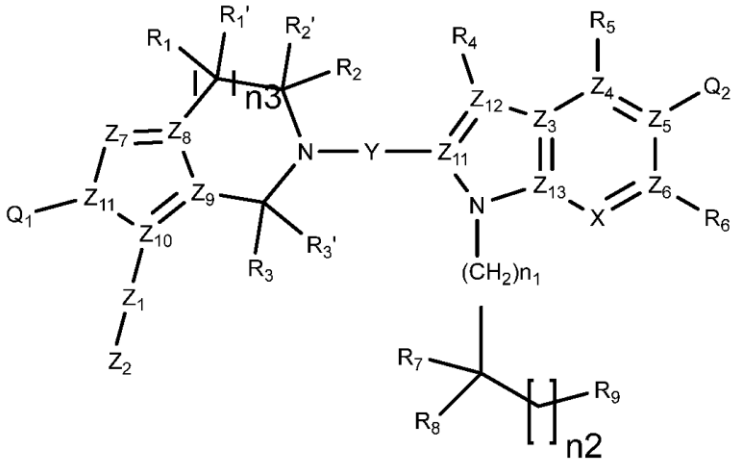
(EX1017 at 14, 16-17.)

138. It is impossible to visualize individual compounds, such as Compounds 19, 20, and 21, due at least in part to the existence of hundreds of millions of possible permutations for the $Q_2$ and $Z_2$ substituents. Moreover, because the exemplified compounds consistently include substituents on the tetrahydropyran ring, there lacks any guidance towards the particular unsubstituted tetrahydropyran ring as in

Compounds 19, 20, and 21. Accordingly, in my opinion, the Challenged Claims are not entitled to a priority date earlier than October 23, 2023, at least with respect to the subject matter relating to Compounds 19, 20, and 21.

139. The chemical structure of Compound 65 was only first disclosed in CN 202410142451.2, filed on January 31, 2024 ("the '451 Provisional"). (EXS. 1018, 1019.) In contrast, the earlier-filed applications, including the '725 Provisional, the '892 Provisional, US 63/545,615, filed October 25, 2023 ("the '615 Provisional") (EX1024), CN 202311582240, filed November 24, 2023 ("the '240 Provisional") (EXS. 1020, 1021), US 63/603,854, filed November 29, 2023 ("the '854 Provisional") (EX1025), and CN 202311686034, filed December 8, 2023 ("the '034 Provisional") (EXS. 1022, 1023) do not disclose the specific chemical structures of at least Compound 65.

140. The '725 Provisional, the '892 Provisional, the '615 Provisional, the '240 Provisional, the '854 Provisional", and the '034 Provisional" only disclose



> Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, Z12, and Z13 are selected from N or C;

(See EX1013 at 3; EX1014 at 3; EX1017 at 7; EX1024 at 8; EX1020 at 3; EX1021 at 3; EX1025 at 9; EX1022 at 4; EX1023 at 4.)

141. However, in my opinion, these earlier-filed provisional applications fail to provide a sufficiently specific description of Compound 65. The variables defined in the disclosed generic formula encompass a broad and diverse array of atoms and chemical substituents. For example, the atoms comprising the bicyclic ring of the core scaffold are defined in highly variable terms. This bicyclic ring alone permits thousands of structural permutations, and when considered in combination with the other variable positions in the formula, the resulting number of potential compounds extends into the billions.

> wherein each of Z3, Z4, Zs, Z6, Z1, Zs, Z9, Z10, Z11, Z12 and Z13 is independently selected from the group consisting of N and C;

(See id.)

142. Moreover, none of the exemplified compounds disclosed in these provisional applications include a pyrrolo-pyridine ring within their core scaffold, as found in Compound 65. Accordingly, the specific structure of Compound 65 cannot be reasonably discerned from the disclosures of these provisional applications. Thus, in my opinion, the Challenged Claims are not entitled to a priority date earlier than January 31, 2024, at least with respect to the subject matter relating to Compound 65.

143. Claims 4, 9, 14, 17, 20, and 23 depend from claim 1 and are directed to ½ Ca salt of one or more compounds recited in claim 1. However, my review of Su (EX1031) and at least the prior documents filed on and before January 31, 2024 (i.e., EX1014, EX1016, EX1017, EX1019, EX1021, EX1023, EX1024, EX1025) suggests that none of these documents discloses a ½ Ca salt of any of the compounds recited in claim 1. Accordingly, at least claims 4, 9, 14, 17, 20, and 23 are not entitled to an earlier priority date than 2024.

144. Therefore, it is my opinion that a POSA would recognize that the claims of the ’236 patent are not entitled to the filing date of September 14, 2023 of the ’557 Provisional.

## X. UNPATENTABILITY OF THE ’236 PATENT

145. As explained below, in my opinion, claims 1-9, 12-17, 24, and 25 of the ’236 patent would have been obvious over the references discussed below and the general knowledge of a POSA before the effective filing date of the ’236 patent.

### A. GROUND 1: CLAIMS 1-4, 6, 12-14, 24, and 25 WOULD HAVE BEEN OBVIOUS OVER SU, YOSHINO, AND KAIWAI IN VIEW OF TALELE

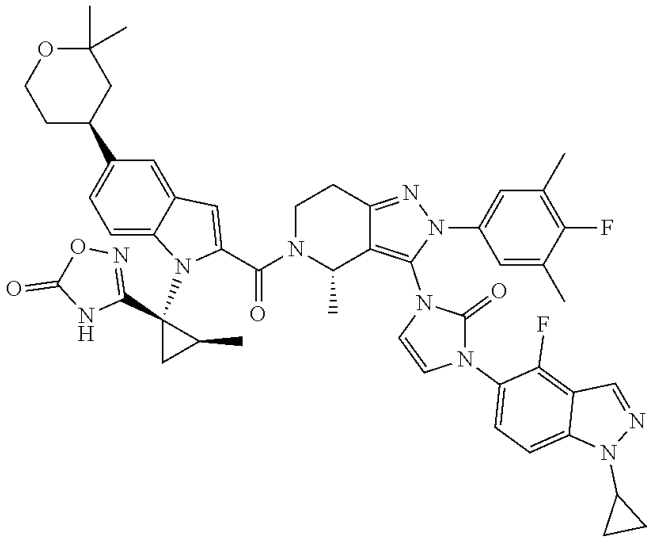
146. As detailed in Section IX.C, claims 1–4, 6, 12–14, 24, and 25, with respect to Compound 19, are not entitled to a priority date earlier than October 23, 2023. Accordingly, each of Su, Yoshino, Kawai, and Talele qualifies as prior art for these claims. As discussed below, in my opinion, claims 1-4, 6, 12-14, 24, and 25

would have been obvious at least with respect to Compound 19 in view of the state of the art and the general knowledge of a POSA before the effective filing date of the ’236 patent, in particular, Su, Yoshino, and Kawai in view of Talele. The teachings of Su, Yoshino, Kaiwai, and Talele are detailed above in Section VIII.

### 1. Claim 1

147. Independent claim 1 recites:

> A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:
>
> 1



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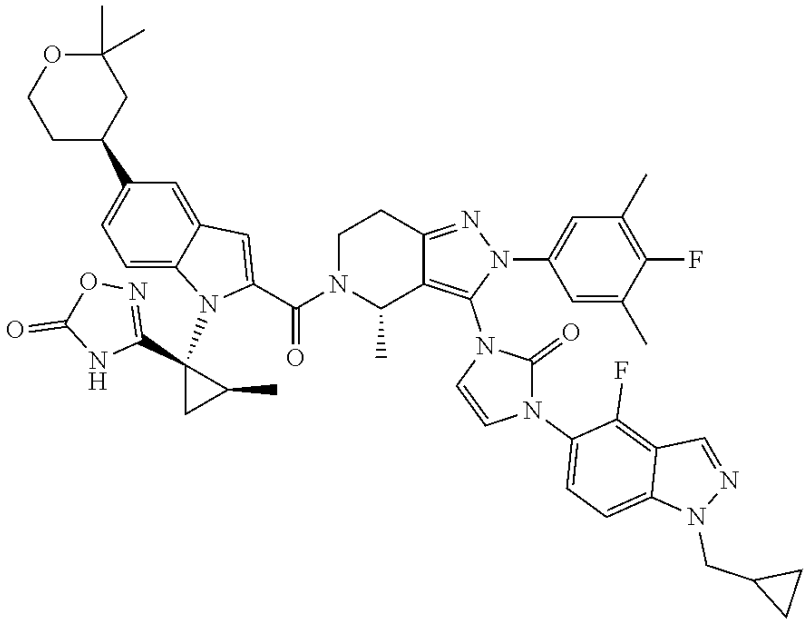

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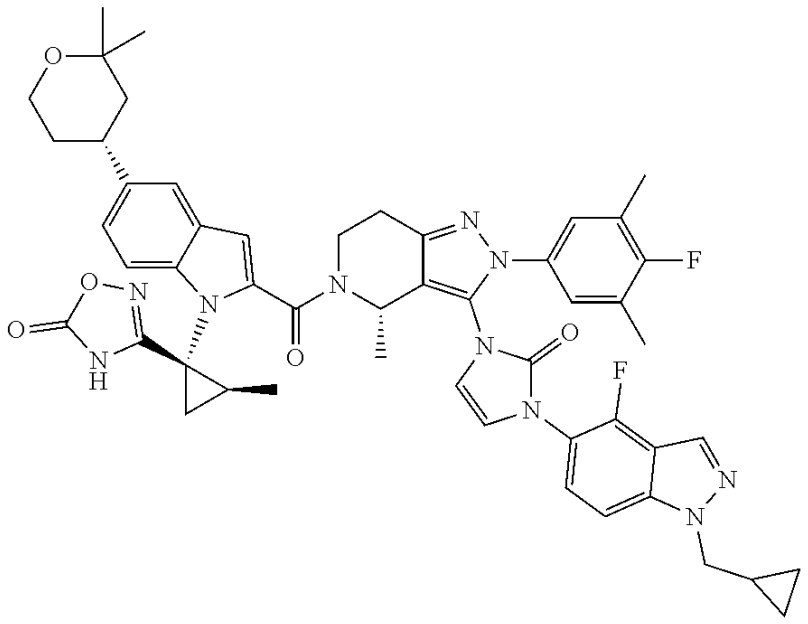

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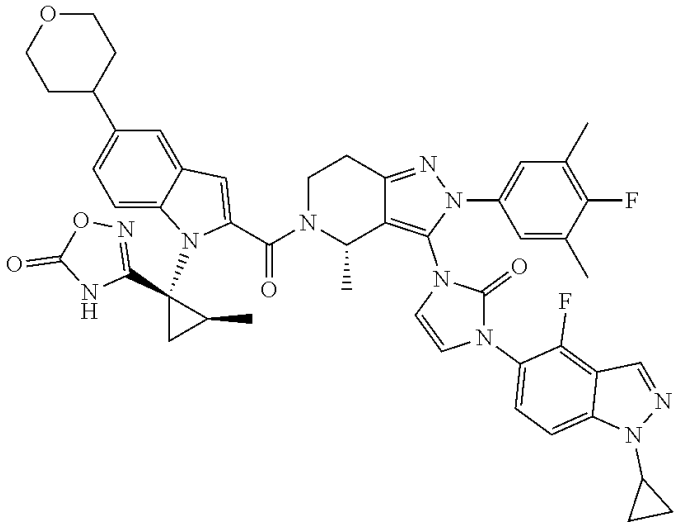

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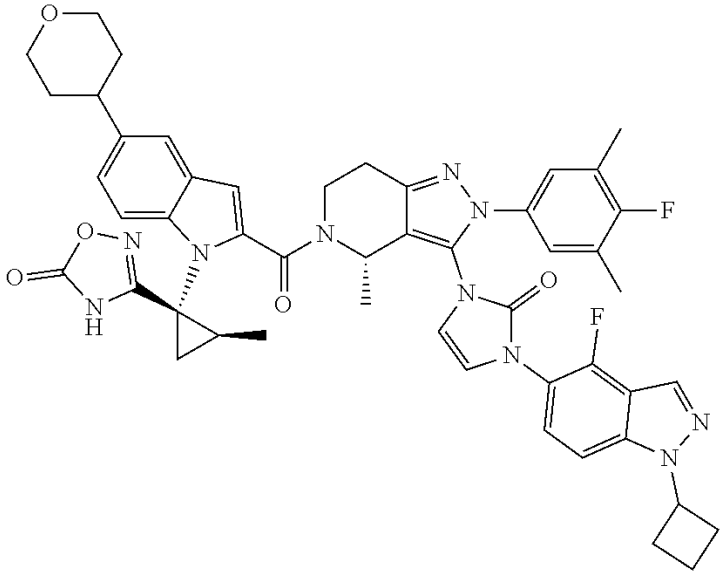

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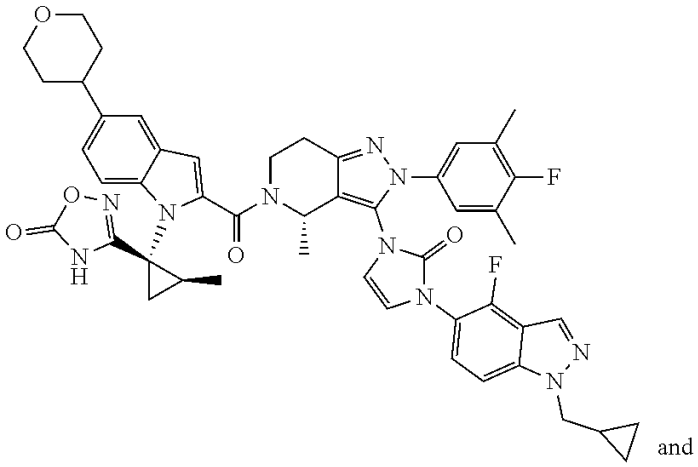
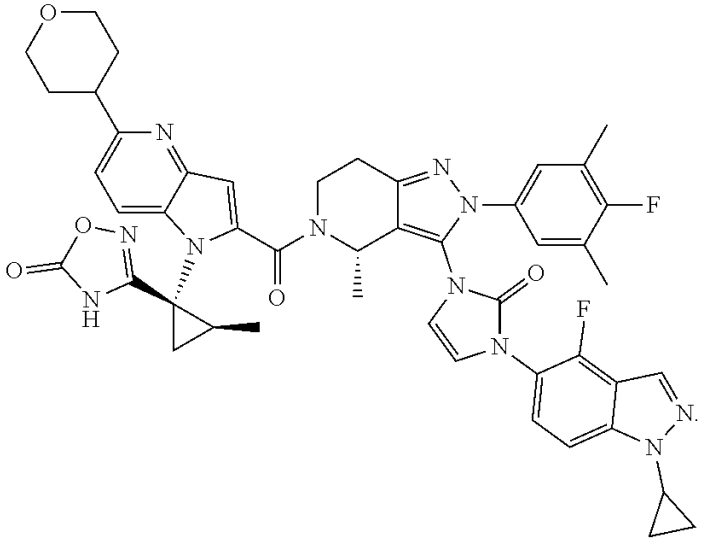
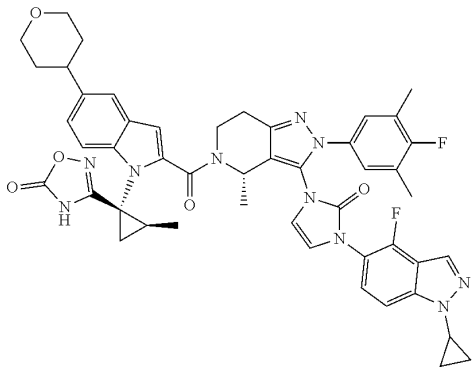
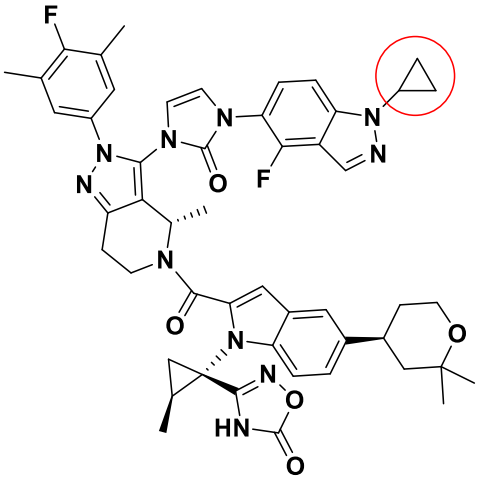
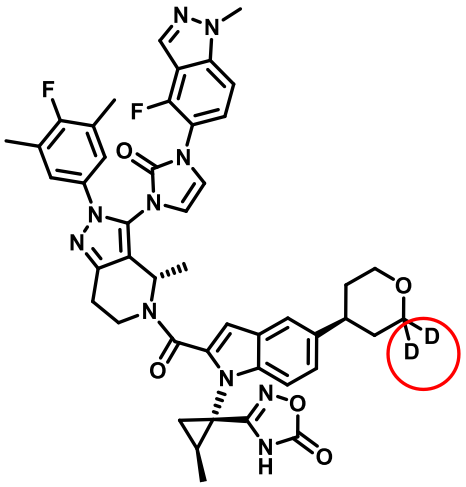


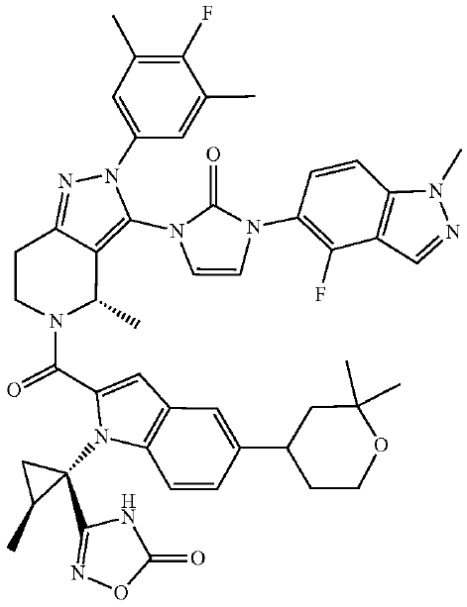
and

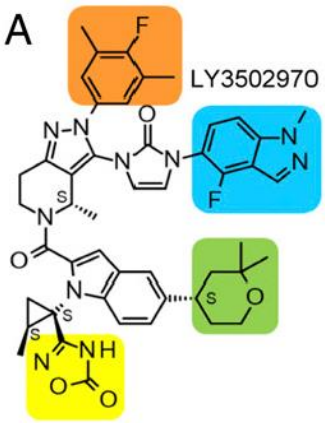
65

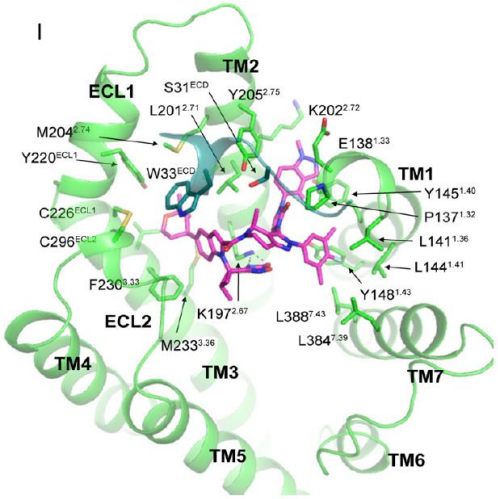


148. In my opinion, claim 1 would have been obvious over Su, Yoshino, and Kawai in view of Talele, at least with respect to Compound 19. A comparison between Compound 19 of claim 1 and the teachings of Su, Yoshino, Kawai, and Talele is provided in the chart below:

| Compound 19 of the ’236 patent | Prior Art |
|---|---|
| 19<br><br>**Compound 19** | **Su** discloses and claims:<br>Deuterated Compounds 176, its non-deuterated parent Compound 175, and Compound 44, as illustrated below, maintain the scaffold of orforglipron (see also Compound 67 as disclosed in Yoshino) and contain only peripheral modifications (as depicted with red circles) with respect to orforglipron. (EX1006 at 327, 328 and claim 12; EX1007 at 327, 328, and claim 12.)<br><br>**non-deuterated compound 175**<br><br>Compound 44 |

| | |
|---|---|
| | **Yoshino** discloses and claims:<br><br>(Compound 67)<br><br>Yoshino also teaches that replacement of methyl with a ring moiety and removal of dimethyl results in improved or comparable activities as measured by $EC_{50}$ values. (EX1008 at claims 13 and 14, 183:1-65, Table 2-5).<br><br>**Kawai** discloses:<br>structural basis for GLP-1 receptor activation by orforglipron. (EX1004 at 1.) In particular, Kawai discloses a high resolution cryo-EM structure of orforglipron bound to the GLP-1 receptor, along with a detailed three-dimensional protein-ligand interaction model illustrating the ligand-binding pocket surrounding orforglipron, as shown below: |




(Id. at FIGS. 1A and 1I)

Kawai further teaches that the region of the ligand-binding pocket formed by transmembrane helices TM1, TM2, TM6, and TM7 lies in close proximity to the 4-fluoro-1-methyl-indazole moiety, and that this region exhibits conformational flexibility. (Id. at 4.) Accordingly, a POSA would have understood that modifications to the indazole moiety would not be expected to cause significant structural disturbance to the ligand-binding pocket, and thus would likely maintain binding potency.

| | |
|---|---|
| | In addition, the binding pocket adjacent to the methyl group of the indazole moiety is shown as being surrounded by a spacious hydrophobic environment, suggesting that the pocket could reasonably accommodate a compound bearing a bulkier ring substituent in place of the methyl group.<br><br>**Talele** teaches:<br>Cyclopropyl is known to enhance metabolic stability and decrease plasma clearance and substitution of a methyl group with cyclopropyl will enhance metabolic stability. (EX1009 at 1.) |

149. Su discloses 218 working examples but describes only seven deuterated stereoisomerically pure compounds—Compounds 35, 44, 123, 139, 176, 188, and 212. (EX1006 at 303, 309, 327, 328, 365, and claim 12; EX1007 at 303, 309, 327, 328, 365, and claims 12 and 27.) Su also discloses the deuterated non-stereoisomerically pure counterpart of Compounds 35, 44, and 176 (EX1006 at 327, 328, and claim 12; EX1007 at 326-329, and claim 12). Further, Compound 175, the non-deuterated parent of Compound 176, and the non-stereoisomerically pure form of Compound 175 are specifically described (EX1006 at 328, 329, and claim 12; EX1007 at 328, 329, and claim 12).

150. Additionally, a POSA would have understood that the selection of specific compounds for deuteration studies reflects their heightened potential for lead optimization. It is generally impractical to deuterate every compound within a

series, due to limitations imposed by time, synthetic complexity, and resource constraints. For instance, the synthesis of deuterated Compound 176 requires a more extended and complex synthetic route compared to its non-deuterated parent, Compound 175.

151. Thus, a POSA would have recognized that the stereoisomerically pure compounds for which deuterated analogs are disclosed, namely, Compounds 35, 44, 123, 139, 176, 188, and 212, are of particular significance and likely represent promising candidates for further development. Notably, Compound 176 is one of a limited number of deuterated stereoisomerically pure compounds disclosed and is the deuterated form of stereoisomerically pure Compound 175 (see EX1006 at 328, claim 12; EX1007 at 328, claim 12). Additionally, Su discloses the non-stereoisomerically pure form of Compound 175, along with its corresponding deuterated analog, thereby further highlighting the structural and developmental significance of this compound series. (See EX1006 at 329, claim 12; EX1007 at 329, claim 12.)

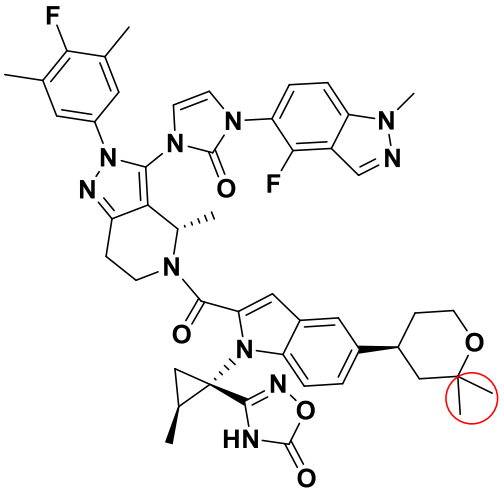
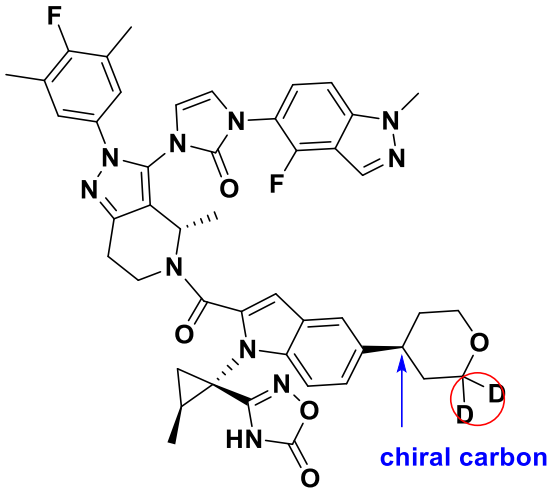
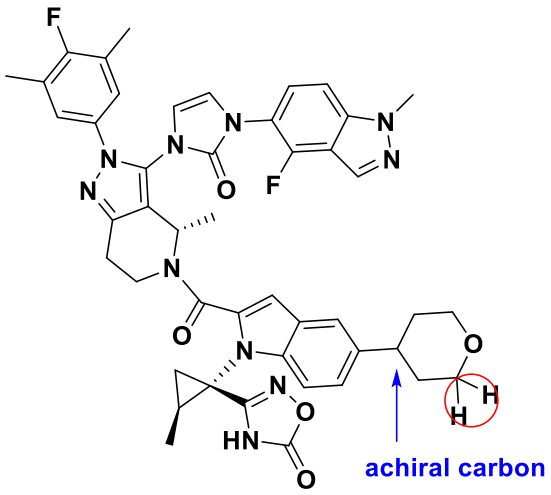
152. As discussed above, orforglipron is currently in clinical trials to assess its efficacy and safety in patient populations with type 2 diabetes and obesity. (EX1012 at 2.) In view of the advanced clinical development stage of this compound and the structural insights provided by the molecular model discussed above, it is my opinion that a POSA, when contemplating modifications to orforglipron, would

have been motivated to first make only peripheral modifications while maintaining the core scaffold of the molecule.

153. Here, Compound 175, in its stereoisomerically pure form as well as in its non-stereoisomerically pure form, was selected for deuteration, underscoring the significance of this structure to potential drug development. Notably, Compound 175 retains the same core scaffold as orforglipron, differing only by the presence of a peripheral cyclopropyl substitution. The inclusion of this modification in this candidate underscores the relevance of the cyclopropyl group to its pharmacological properties and potential for drug optimization and development.

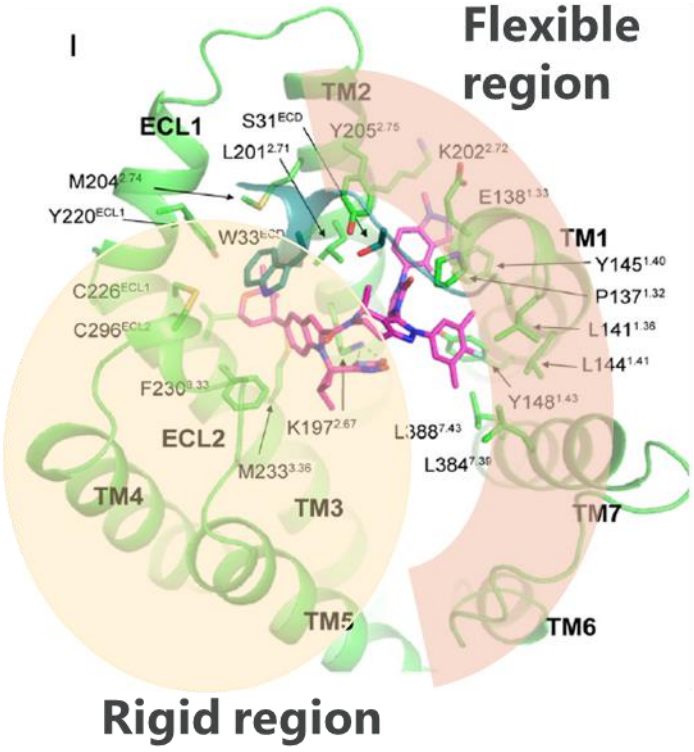
154. Compound 44, in its stereoisomerically pure form as well as in its non-stereoisomerically pure form, is disclosed in Su and displays the same core scaffold as orforglipron, with the exception of the absence of two methyl groups on the tetrahydropyran ring. (EX1006 at 327; EX1007 at 327.) This structural variation indicates that the dimethyl substitution is not essential for pharmacological activity. Moreover, the closest structural analog to Compound 44 is its non-deuterated counterpart, which offers practical advantages, including greater synthetic simplicity and the absence of a chiral center in the tetrahydropyran moiety. Accordingly, Compound 44, and its deuterated non-stereoisomerically pure counterpart, and their non-deuterated counterparts collectively support the teaching that a dimethyl-substituted tetrahydropyran ring can be effectively replaced with a non-substituted,

achiral tetrahydropyran ring, thereby providing a clear rationale for such a modification.

| **Orforglipron** | **Compound 44** |
|---|---|
|  | <br>Non-deuterated counterpart of Compound 44<br> |

155. In my opinion, Yoshino and Kawai further support the above conclusion that a POSA would have been motivated to pursue the peripheral modifications as taught by Su.

156. Kawai provides the structural basis for GLP-1 receptor activation by orforglipron through high-resolution cryo-EM analysis. (EX1004 at 1.) Specifically, Kawai presents a three-dimensional structure that reveals key interactions of orforglipron with surrounding residues in the ligand-binding pocket of GLP-1 receptor, as shown below. In my opinion, the structural data disclosed by Kawai offer a valuable framework for structure-based drug design. A POSA would have utilized this model to assess which regions of the ligand-binding pocket exhibit sufficient conformational flexibility to tolerate chemical modifications, particularly bulkier substituents, without disrupting drug binding.




(EX1004 at FIG. 1, 1-9 (emphases added to indicate the flexible and rigid regions).)

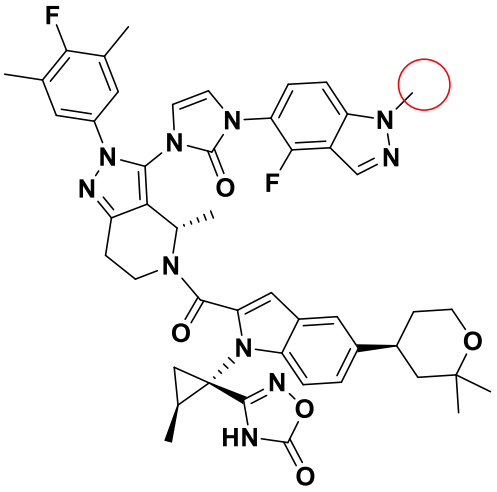
157. In my opinion, the structural data disclosed by Kawai offer a valuable framework for structure-based drug design. A POSA would have utilized this model to assess which regions of the ligand-binding pocket exhibit sufficient conformational flexibility to tolerate chemical modifications, particularly bulkier substituents, without disrupting drug binding.

158. Kawai identifies that the ligand-binding region formed by transmembrane helices TM1, TM2, TM6, and TM7, adjacent to the 4-fluoro-1-methyl-indazole moiety, exhibits conformational flexibility, as illustrated in

annotated FIG. 1I above. (Id. at 4.). In contrast, the region formed by TM3, TM4, and TM5 is described as structurally rigid. (Id.) Based on these findings, a POSA would have understood that structural modifications to the 4-fluoro-1-methyl-indazole moiety are unlikely to destabilize the binding pocket and would likely preserve receptor binding affinity.

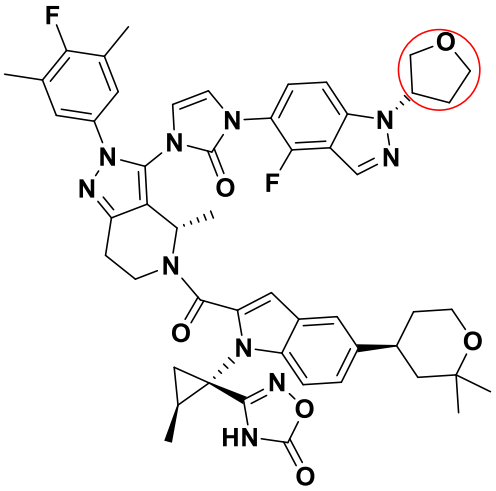
159. In my view, the methyl group of the indazole moiety is located in a spacious, hydrophobic pocket formed by the side chain of Y205 and carbon atoms of K202 and E318, as shown in the three-dimensional structure model. A POSA would have recognized this environment as amenable to substitution with larger hydrophobic groups, such as three- to five-membered rings.

160. Yoshino supports this observation by demonstrating that substitution of the methyl group with a tetrahydrofuran ring yields compounds with retained biological activity. For instance, Compound 40, in which the methyl group of Compound 67 is replaced by a tetrahydrofuran ring, exhibits comparable activity. (EX1008 at 50, 99, Table 3.)



Compound 67

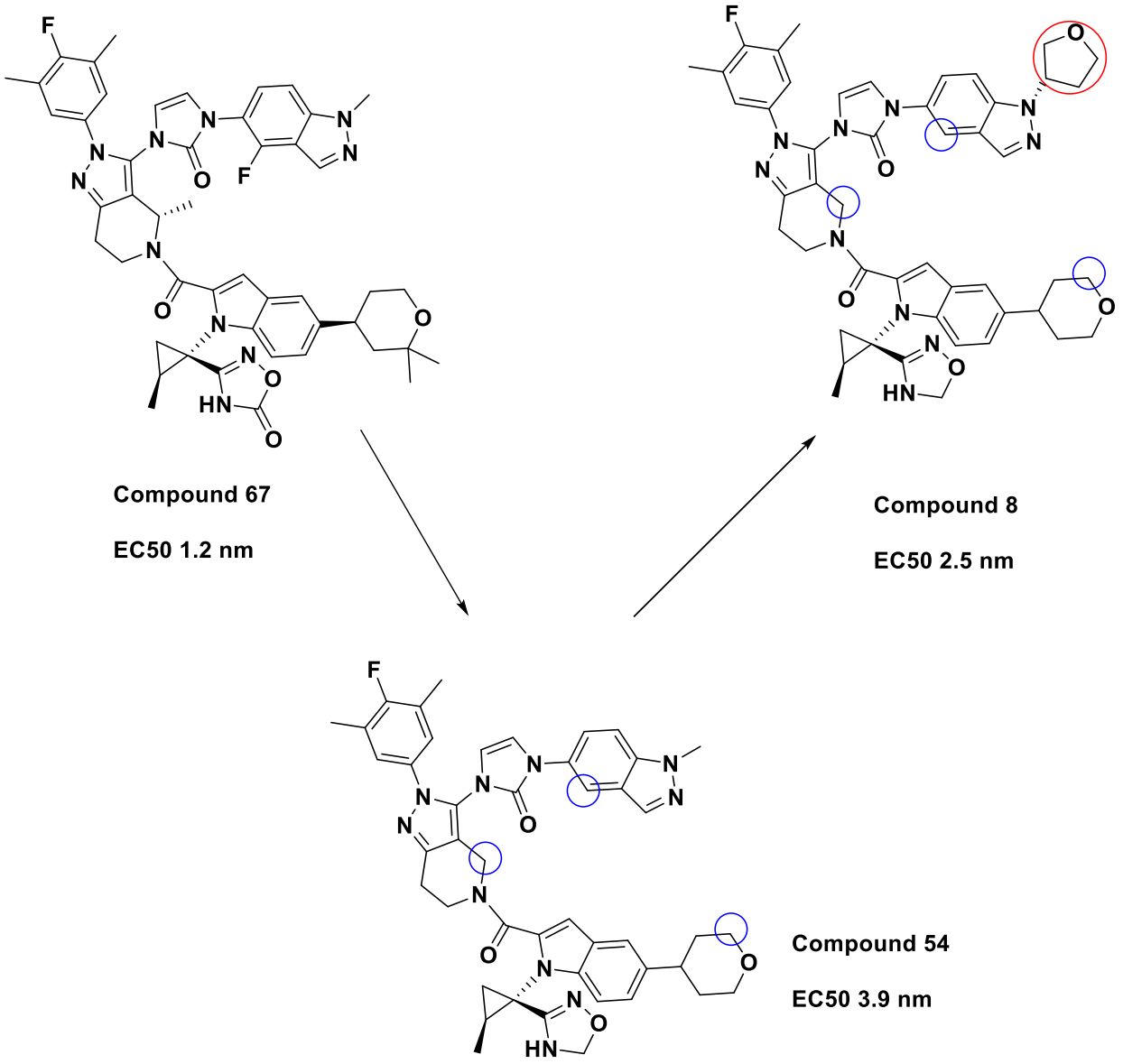
EC50 1.2 nm



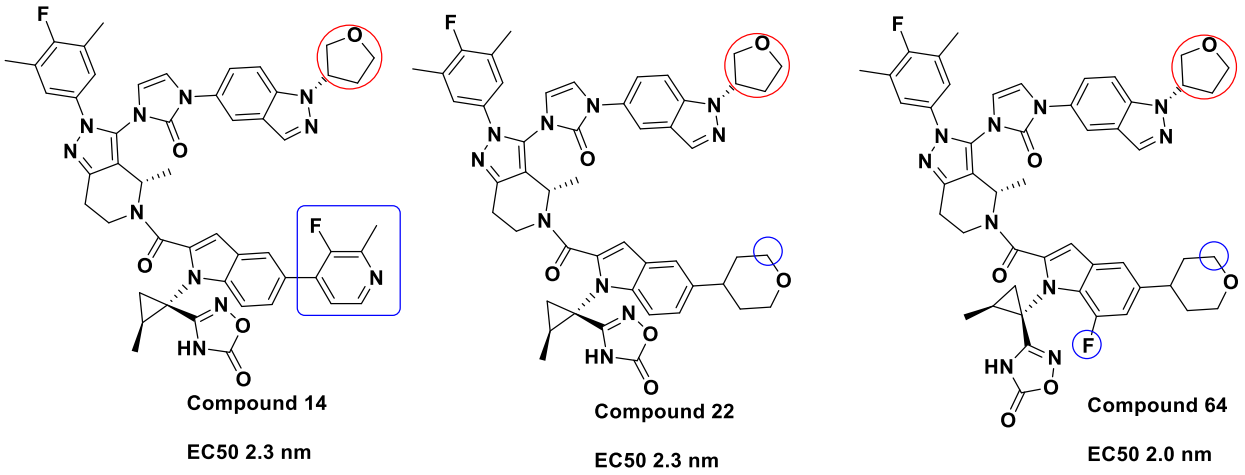
Compound 40

EC50 2.2 nm

161. Moreover, while the removal of multiple substituents, as exemplified by Compound 54, led to a reduction in the biological activity of the lead compound, the substitution of the methyl group with a tetrahydrofuran moiety was found to partially restore or mitigate this loss of activity, as demonstrated below. (EX1008 at 34, 92, 99, Table 3.)




162. Consistent with these observations, several additional analogs disclosed in Yoshino, each containing a tetrahydrofuran ring, also retained activity levels comparable to that of the lead compound. (EX1008 at 37, 41, 97, Table 3.)




163. Accordingly, when considered as a whole, Yoshino suggests that replacement of the methyl group with a ring structure can maintain the biological activity of the lead compound. As explained above, the hydrophobic character of the binding pocket favors the incorporation of a carbocyclic ring as a suitable replacement for the original methyl group. Additionally, carbocycles are preferred to simple alkyl groups because they have fewer rotational degrees of freedom, meaning they pay smaller entropic penalties when they achieve their bound confirmations, which restricts their rotation. Among potential carbocycles, cyclopropyl represents the simplest and most structurally analogous to a methyl group, offering minimal steric deviation while providing favorable physicochemical properties consistent with the binding environment. Additionally, in my opinion, a cycloalkyl ring would be favored over a heterocyclic ring, at least in part due to the absence of chirality, which simplifies the synthesis.

164. Talele also supports a substitution with the cyclopropyl ring. Talele teaches that "the cyclopropyl fragment is a versatile player," and that "from the 1960s to the present, the cyclopropyl ring has appeared frequently in U.S. FDA-approved drugs and is likely to continue to play a significant role in the development of new drugs to meet specific therapeutic goals." (EX1009 at 1.) Talele further notes that "it is striking to find that eight of the 200 best-selling drugs approved by the U.S. FDA contain a cyclopropyl ring," and that "at present, there are about 65 unique cyclopropane-containing compounds in various stages of clinical trials and about 55 in preclinical stages." (Id. at 2.)

165. Talele further states:

> Collectively, it is clearly evident that **the cyclopropane ring system has a positive impact** on the biological actions of drugs approved by the FDA for a wide range of human diseases. Consequently, the number of cyclopropyl-containing drugs will continue to rise. **These facts point toward the firm establishment of the sp3-hybridized three carbon ring system in modern drug discovery research**.
>
> Consequently, the cyclopropyl ring addresses multiple roadblocks that can occur during drug discovery such as (a) enhancing potency, (b) reducing off-target effects, (c) **increasing metabolic stability**, (d) increasing brain permeability, (e) **decreasing plasma clearance**, (f) contributing to an entropically more favorable binding to the receptor, (g) conformational restriction of peptides/peptidomimetics to prevent proteolytic hydrolysis, and (h) altering drug pKa to reduce its P-glycoprotein efflux ratio.

(Id. at 1, 2 (emphases added).)

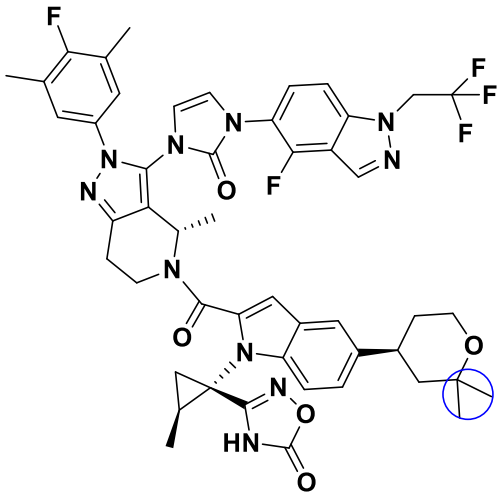
166. In particular, with regard to a methyl to cyclopropyl substitution, Talele discloses that:

> The C−H bonds in the cyclopropane ring are shorter and stronger (106 kcal/mol) compared to the C−H bonds in ethane (101 kcal/mol). On the basis of this observation, **one can expect to achieve a metabolically stable derivative upon replacement of the methyl group with a cyclopropane ring**. This latter property occurs as proton abstraction from a cyclopropane ring would be more difficult than from a methyl group, which is required for oxidative metabolism to proceed.
>
> (Id. (emphasis added))

167. Thus, Talele teaches that substitution with a cyclopropyl ring is a well-established strategy in medicinal chemistry for enhancing metabolic stability, improving pharmacokinetic properties, or modulating the biological activity of a drug molecule.

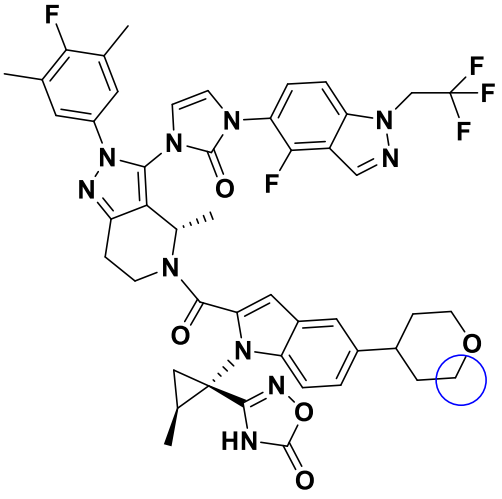
168. With regard to the modification on the tetrahydropyran moiety, Yoshino teaches that removal of the dimethyl group from the 2,2-dimethyl-tetrahydropyran moiety can result in comparable biological activity. As illustrated in the comparison below, removal of the dimethyl groups from Compound 35 yielded Compound 28, which retained comparable activity. (EX1008 at 44, 48, Table 3.) Similarly, Compound 30, which lacks dimethyl groups on the

tetrahydropyran ring, exhibited the same level of activity as Compound 38. (EX1008 at 45, 49, Table 3.)



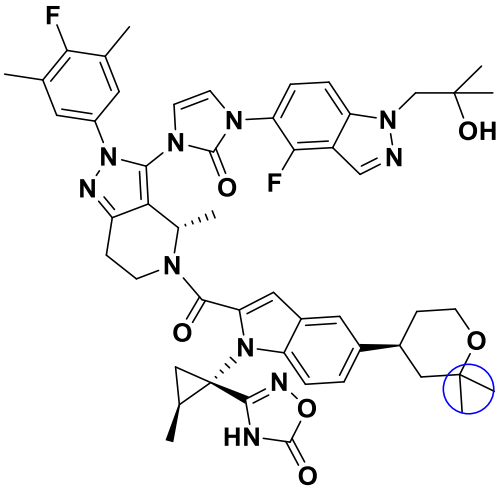
Compound 35

EC50 3.2 nm



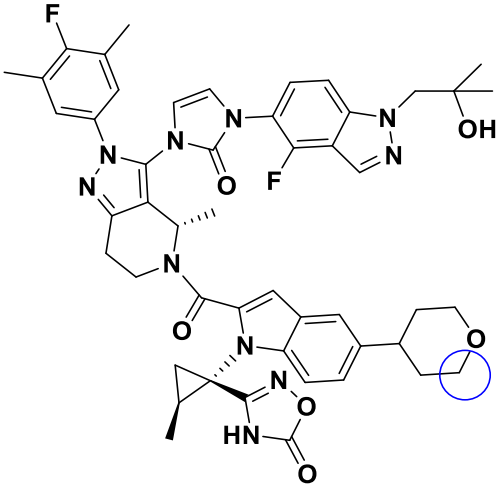
Compound 28

EC50 1.9 nm



Compound 38

EC50 1.7 nm



Compound 30

EC50 1.4 nm

169. Notably, of the 80 compounds listed in Table 3 of Yoshino with reported biological activity, more than 30 incorporate a non-substituted, achiral tetrahydropyran ring. Considering both the biological activity data discussed above

and the prevalence of the achiral tetrahydropyran ring among active compounds, a POSA would have been motivated to remove the dimethyl groups from the 2,2-dimethyl-tetrahydropyran moiety.

170. Accordingly, in my opinion, a POSA seeking to modify orforglipron would have been motivated to incorporate peripheral modifications guided by Compounds 175 and 44. Specifically, Compound 175 demonstrates a substitution of the methyl group on the indazole moiety with a cyclopropyl group, while Compound 44 illustrates the removal of the dimethyl substituents on the 2,2-dimethyl-pyran ring, resulting in an achiral tetrahydropyran ring. These specific structural modifications provide clear guidance to a POSA, would reasonably be expected to retain or improve activity, and, in combination, would have led the POSA to arrive at Compound 19 as claimed in the ’236 patent.

171. With regard to “a pharmaceutically acceptable salt thereof” recited in claim 1, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including “a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt.” (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Su also discloses GLP-1 receptor

agonists and pharmaceutically acceptable salts thereof. (EX. 1007 at 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.)

172. Therefore, for at least the above reasons, claim 1 would have been obvious over the cited references.

**2. Claim 2**

173. In my opinion, claim 2 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 2 depends from claim 1 and recites “the pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, a calcium salt, a potassium salt, a magnesium salt and a lithium salt.”

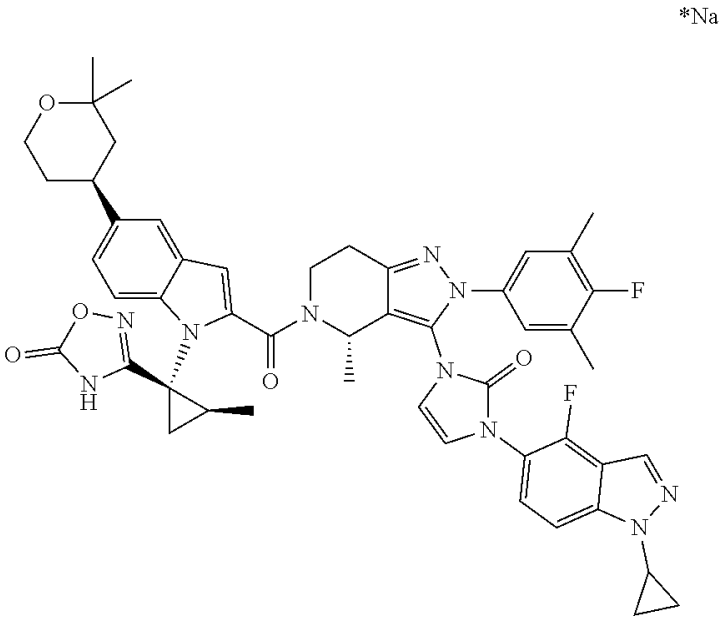
174. Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including “a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt.” (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) In view of the teaching of Yoshino, it would have been obvious for a POSA to prepare a sodium salt or a calcium salt of Compound 19 as recited in claim 2 of the ’236 patent.

175. Accordingly, claim 2 of the ’236 patent would have been obvious to a POSA over the prior art.

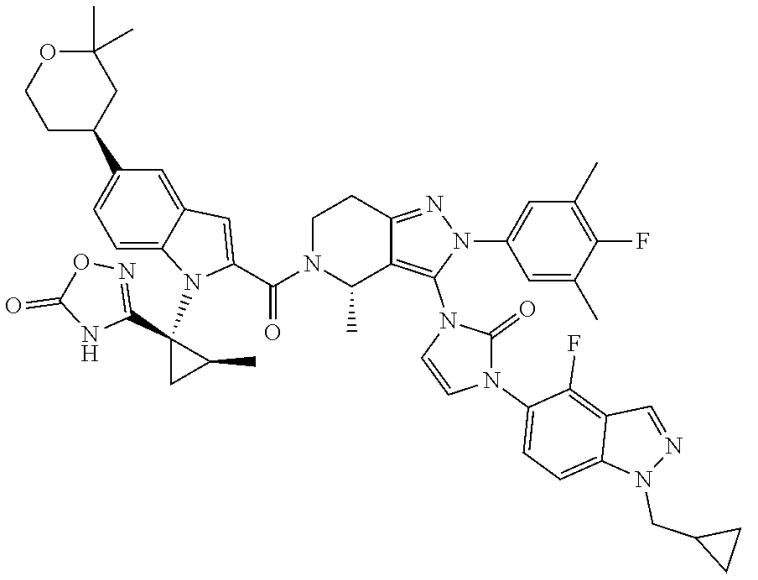
### 3. Claim 3

176. In my opinion, claim 3 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 3 depends from claim 1 and recites:

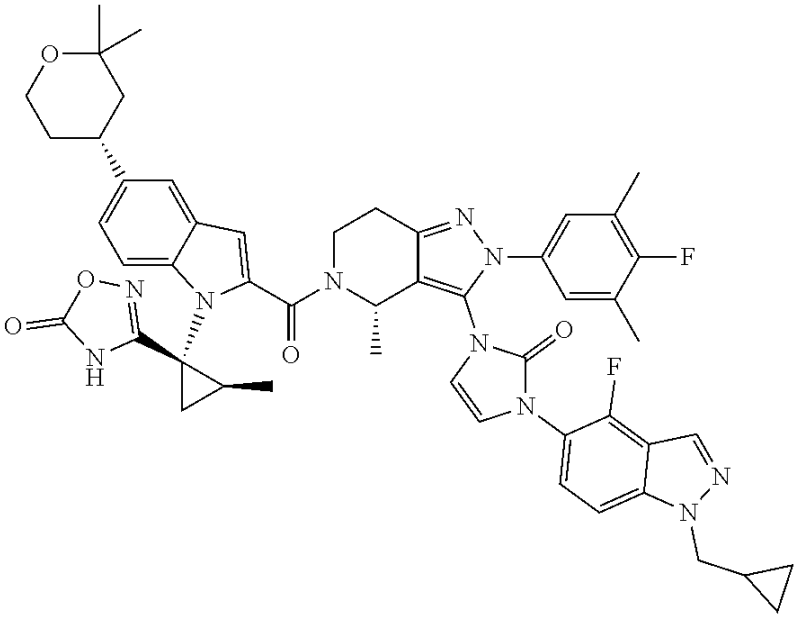
> the pharmaceutically acceptable salt is selected from the group consisting of:



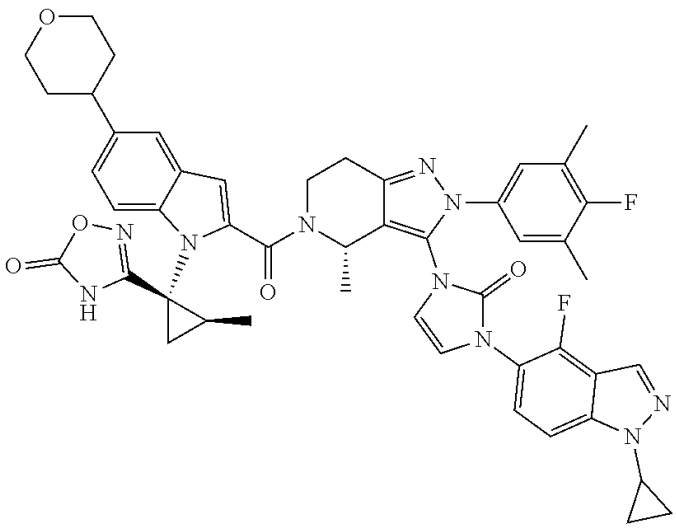
*Na



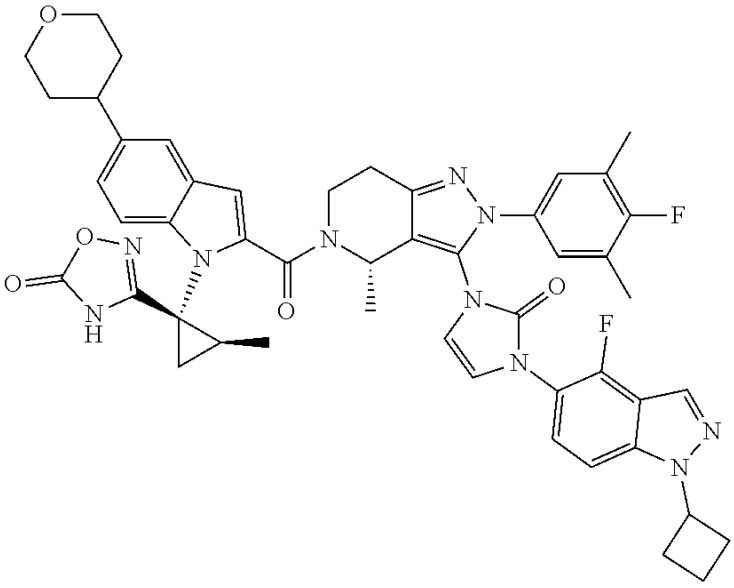
*Na



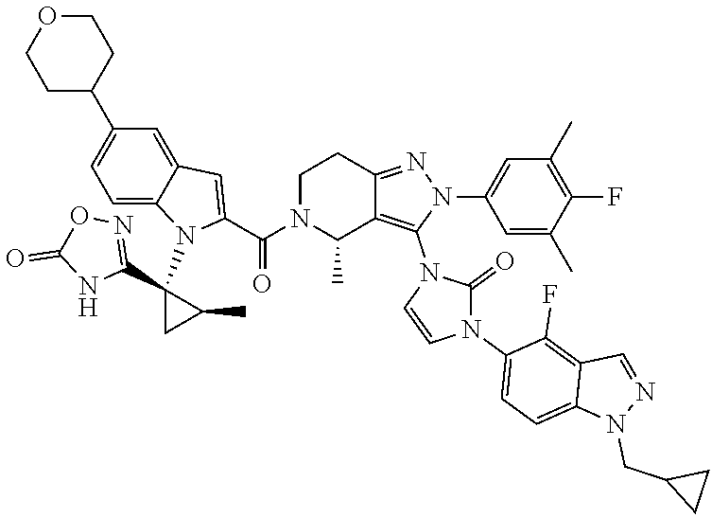
*Na



*Na

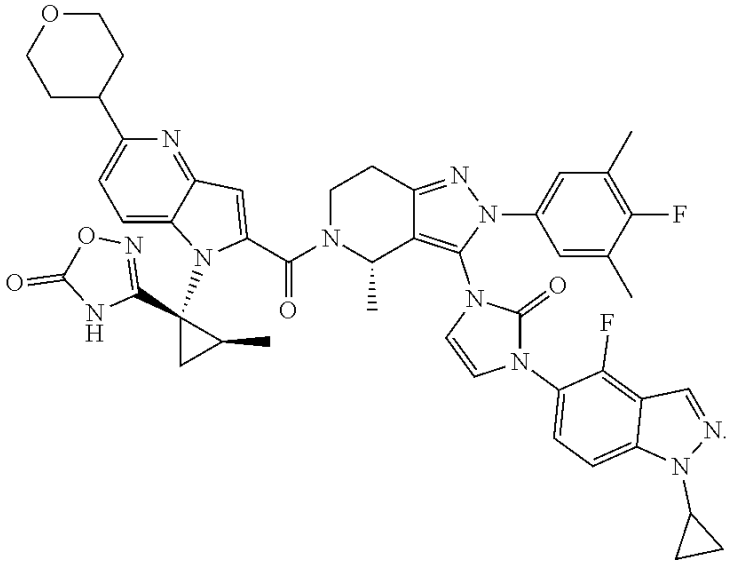


*Na



and

*Na



177. Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including "a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably,

a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt." (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) As discussed above with respect to claims 1 and 2, it would have been obvious for a POSA to prepare a sodium salt or a calcium salt of Compound 19 as recited in claim 3 of the '236 patent.

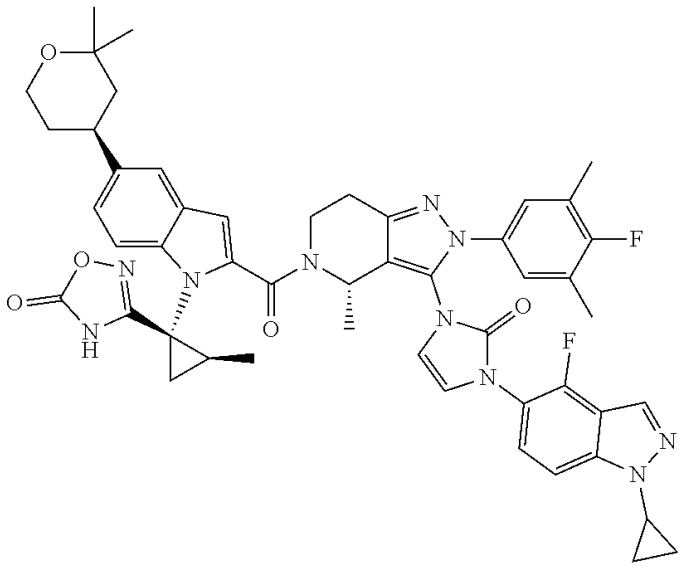
178. Accordingly, claim 3 of the '236 patent would have been obvious to a POSA over the prior art.

**4. Claim 4**

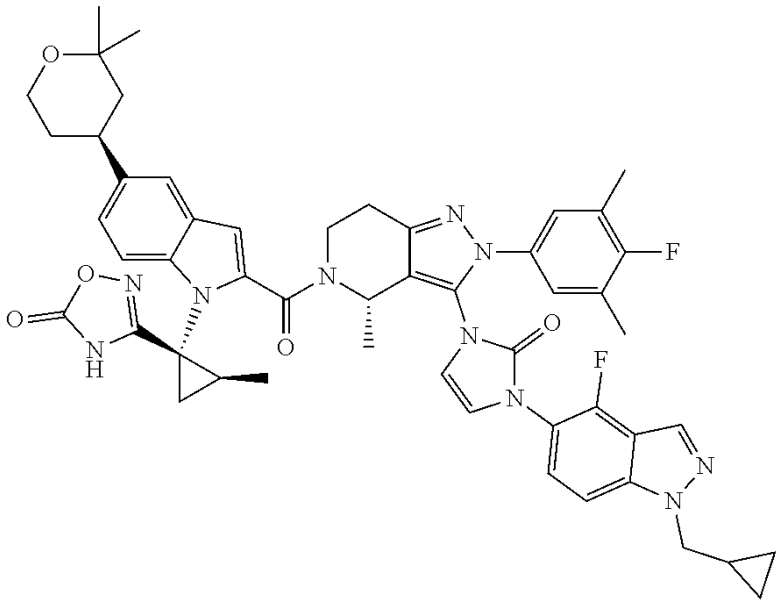
179. In my opinion, claim 4 of the '236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 4 depends from claim 1 and recites:

> the pharmaceutically acceptable salt is selected from the group consisting of:

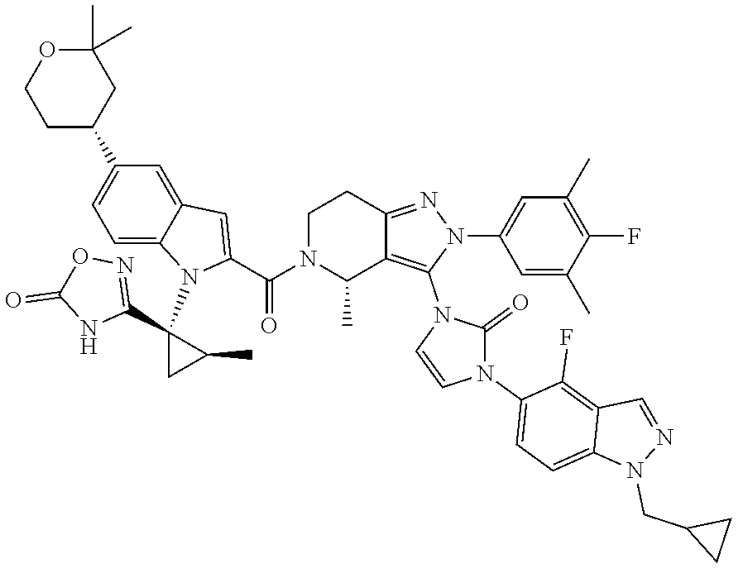
*1/2 Ca



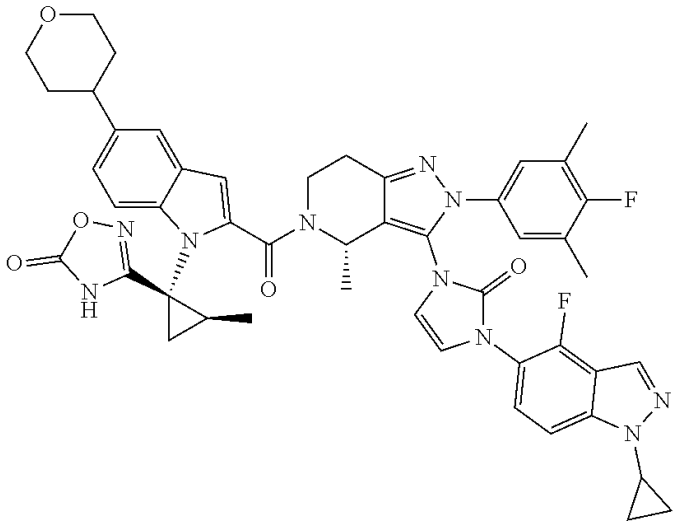
*1/2 Ca



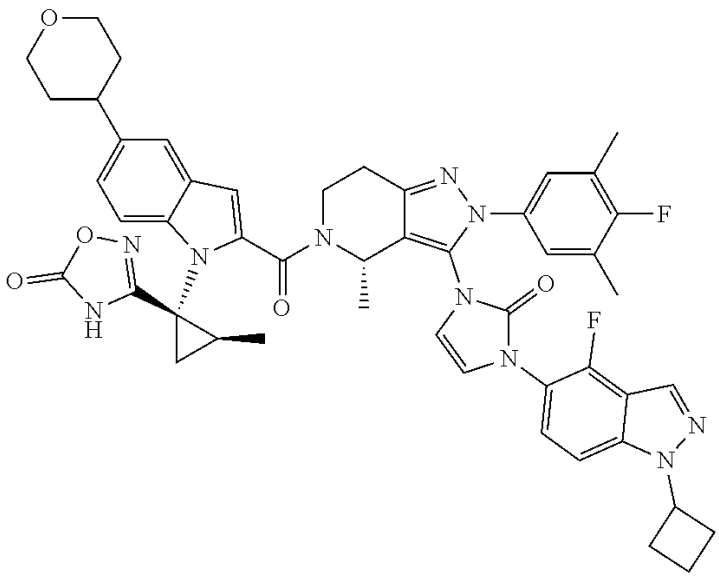
*1/2 Ca



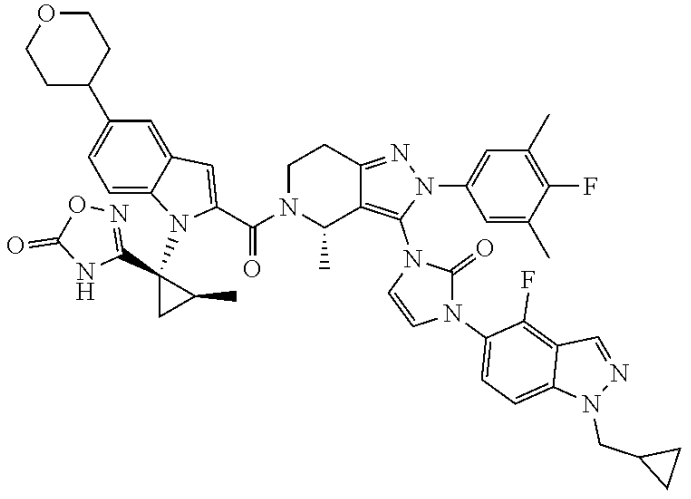
*1/2 Ca



*1/2 Ca

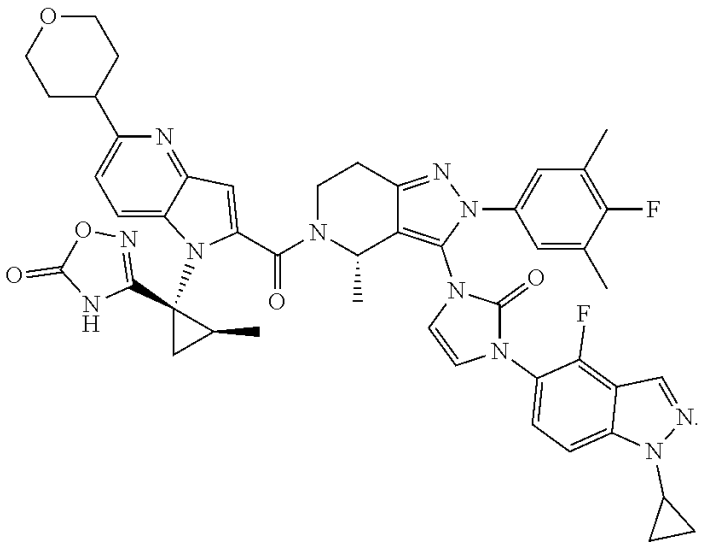


*1/2 Ca



and

*1/2 Ca



180. As discussed above with respect to claim 2, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a calcium salt thereof, including a calcium salt of the free form and a hydrate of the calcium salt. (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare a calcium salt of Compound 19 as recited in claim 4 of the '236 patent.

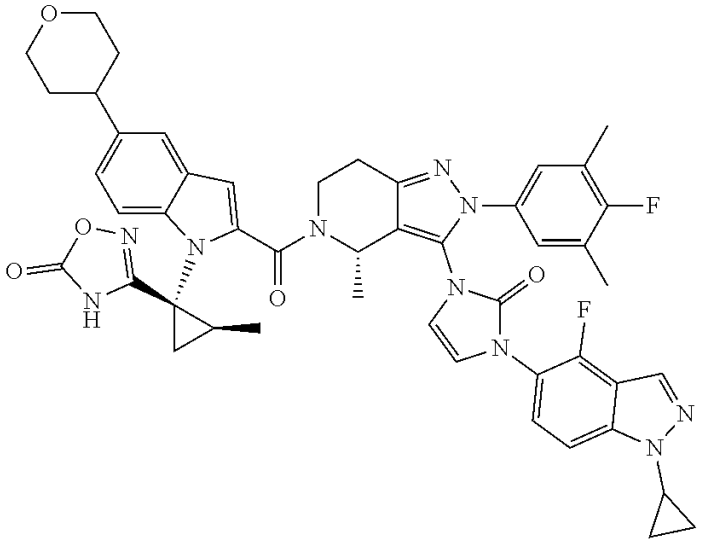
181. Accordingly, claim 4 of the '236 patent would have been obvious to a POSA over the prior art.

### 5. Claim 6

182. In my opinion, claim 6 of the '236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 6 depends from claim 1 and recites:

the compound is selected from the group consisting of:

19



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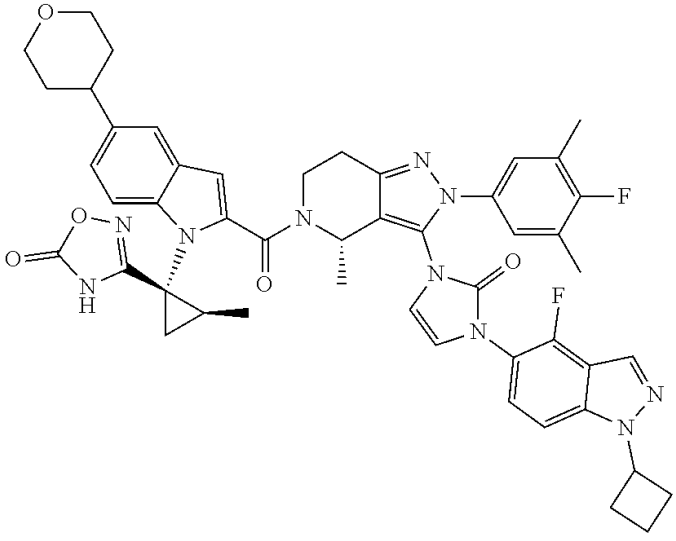

and

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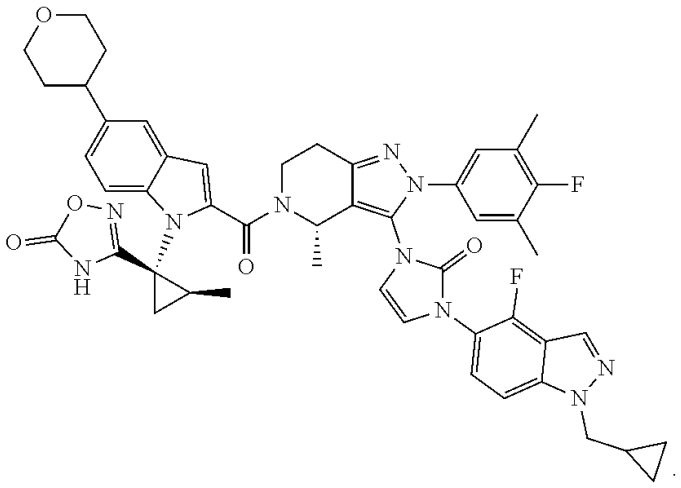


183. As discussed above with respect to claim 1, it would have been obvious for a POSA to arrive at Compound 19 as recited in claim 6 of the ’236 patent in view of the teachings of Su and Yoshino.

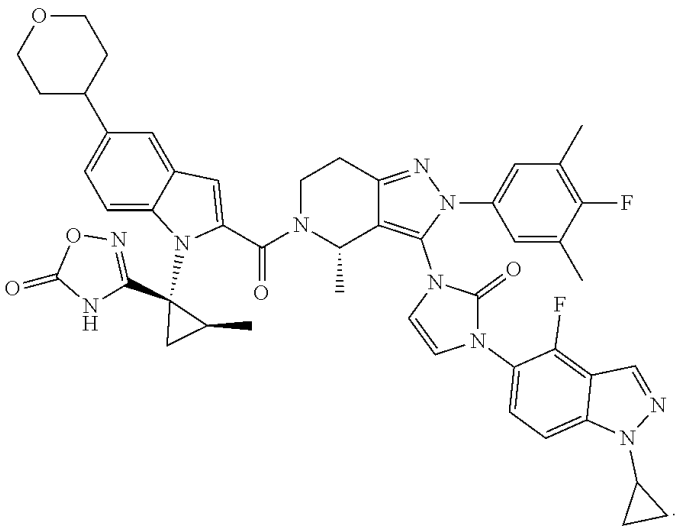
184. Accordingly, claim 6 of the ’236 patent would have been obvious to a POSA over the prior art.

**6. Claim 12**

185. In my opinion, claim 12 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 6. Claim 12 depends from claim 1 and recites:

the compound is

19



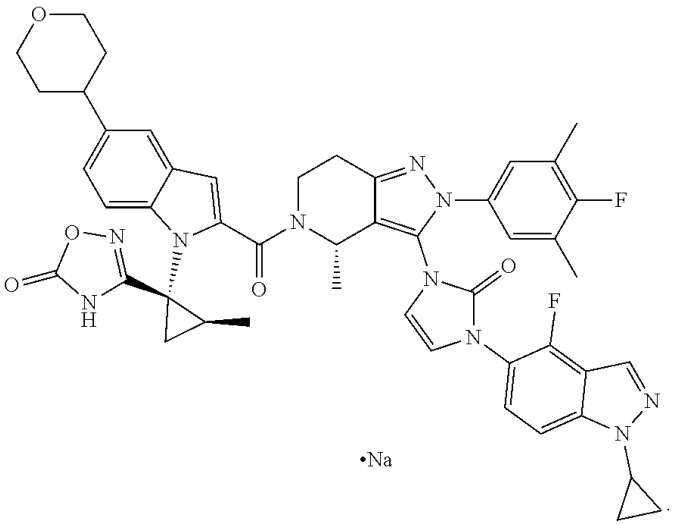
186. As discussed above with respect to claim 1, it would have been obvious for a POSA to arrive at Compound 19 as recited in claim 6 of the ’236 patent.

187. Accordingly, claim 12 of the ’236 patent would have been obvious to a POSA over the prior art.

### 7. Claim 13

188. In my opinion, claim 13 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1-3. Claim 13 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



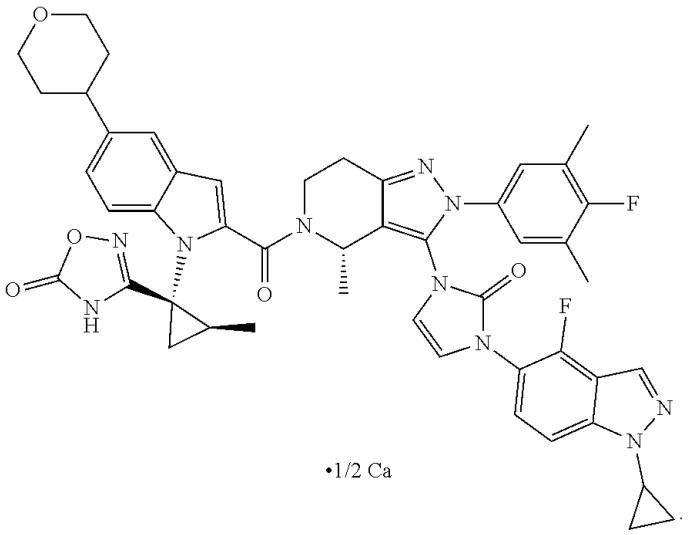

189. As discussed above with respect to claims 2 and 3, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof, including a sodium salt of the free form and a hydrate of the sodium salt. (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare a sodium salt of Compound 19 as recited in claim 13 of the ’236 patent.

190. Accordingly, claim 13 of the ’236 patent would have been obvious to a POSA over the prior art.

### 8. Claim 14

191. In my opinion, claim 14 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 2, and 4. Claim 14 depends from claim 1 and recites:

> the pharmaceutically acceptable salt is




192. As discussed above with respect to claims 1, 2, and 4, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a calcium salt thereof, including a calcium salt of the free form and a hydrate of the calcium salt. (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare a calcium salt of Compound 19 as recited in claim 14 of the ’236 patent.

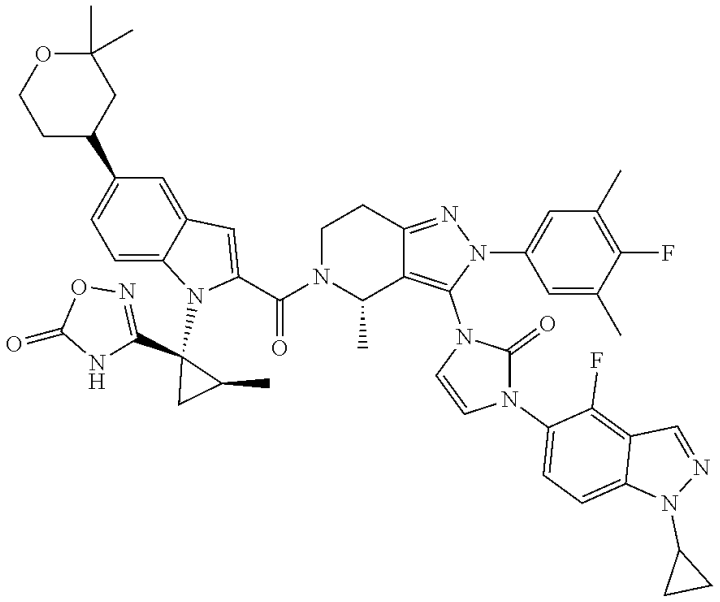
193. Accordingly, claim 14 of the ’236 patent would have been obvious to a POSA over the prior art.

### 9. Claim 24

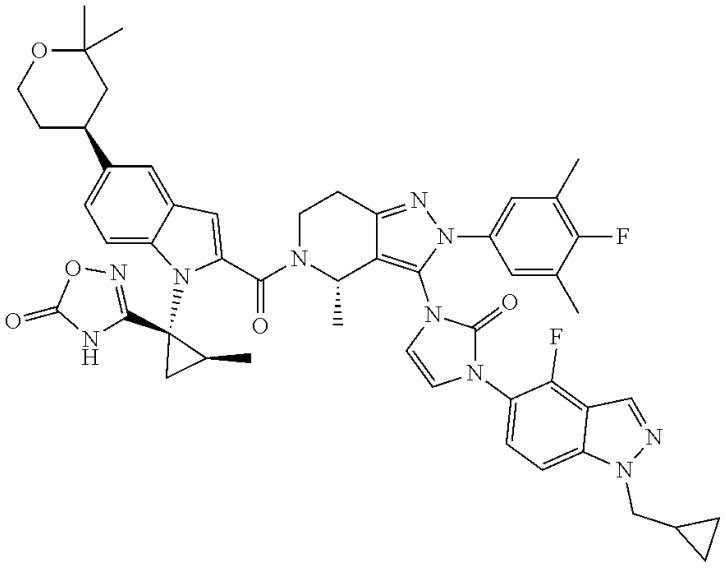
194. In my opinion, independent claim 24 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 6, and 12. Claim 24 recites:

A compound, selected from the group consisting of:

1



13



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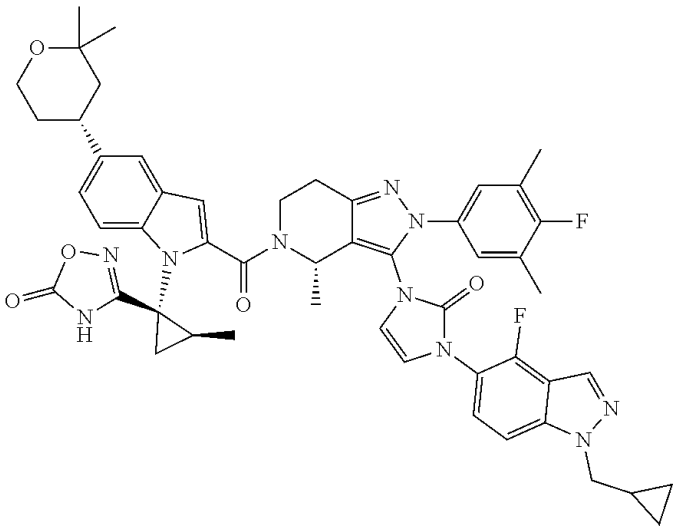
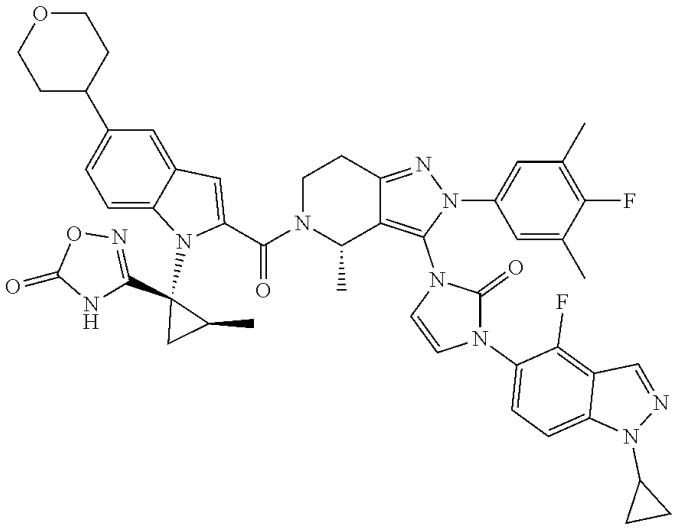


19



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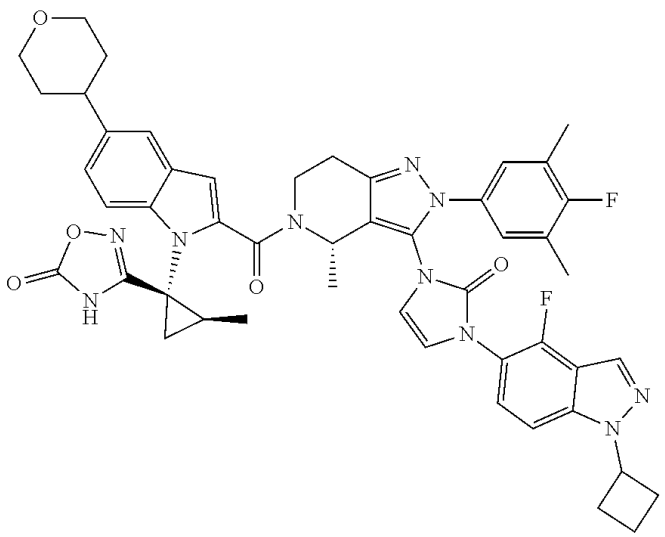
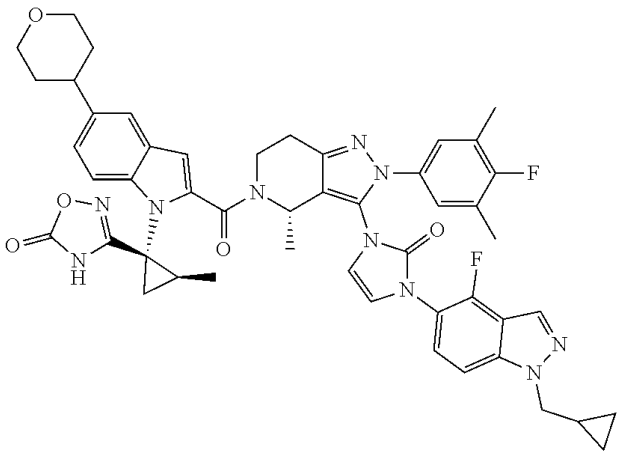
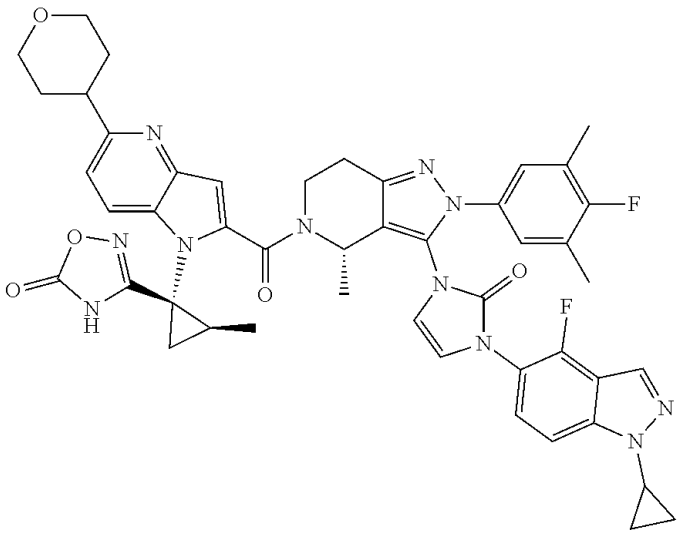


21



and

65



195. As discussed above with respect to claims 1 and 12, it is obvious for a POSA to arrive at Compound 19.

196. Accordingly, claim 24 of the ’236 patent would have been obvious to a POSA over the prior art.

### 10. Claim 25

197. In my opinion, claim 25 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 25 depends from claim 1 and recites, “A pharmaceutical composition, comprising the compound or the pharmaceutically acceptable salt thereof of claim 1, and a pharmaceutically acceptable excipient.”

198. Yoshino discloses various pharmaceutical formulations and a pharmaceutically acceptable additive that includes an excipient. (EX1008 at 35:45-

67.) Su also discloses pharmaceutical formulations and a pharmaceutically acceptable additive that includes an excipient. (EX1006 at 80:12-14; EX1007 at 80:15-17.)

199. Accordingly, claim 25 of the ’236 patent would have been obvious to a POSA over the prior art.

## B. GROUND 2: CLAIMS 1-9, 12-17, 24, and 25 WOULD HAVE BEEN OBVIOUS OVER YOSHINO AND KAWAI IN VIEW OF TALELE

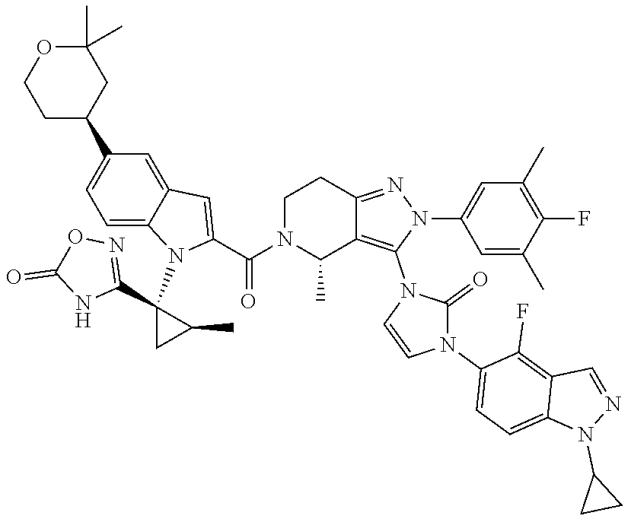
200. For the reasons discussed below, it is my opinion that claims 1-9, 12-17, 24, and 25 would have been obvious, at least with respect to Compounds 1, 19, or 20, based on the state of the art and the general knowledge of a POSA before the effective filing date of the ’236 patent, in particular, in view of Yoshino and Kawai combined with Talele. The relevant teachings of Yoshino, Kawai, and Talele are detailed above in Section VIII.

### 1. Claim 1

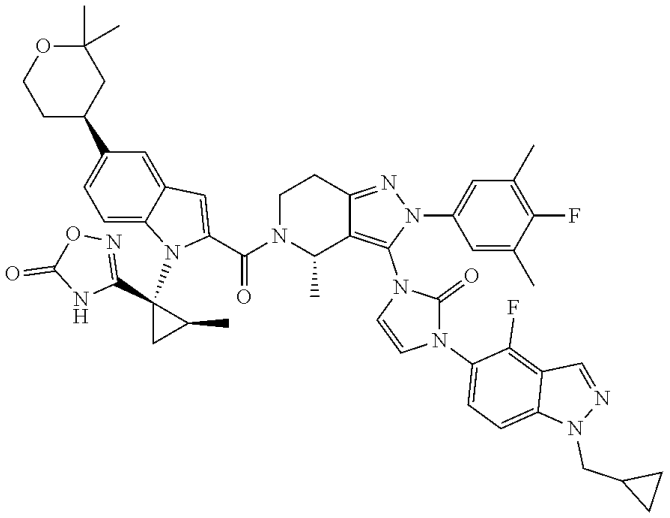
201. Independent claim 1 recites:

> A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

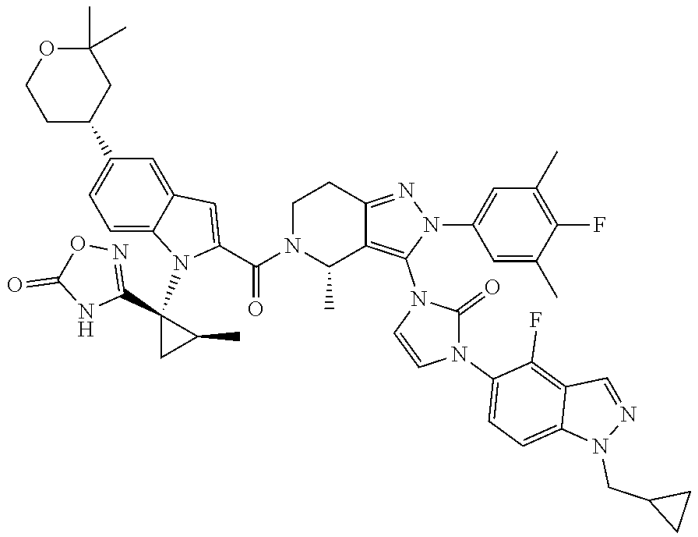
1



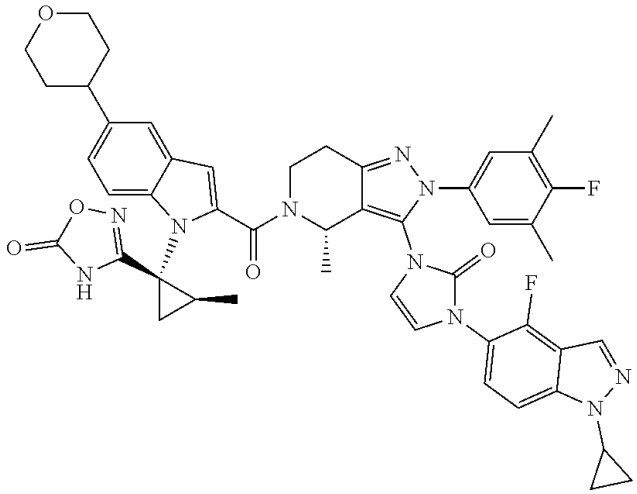
13



18



19



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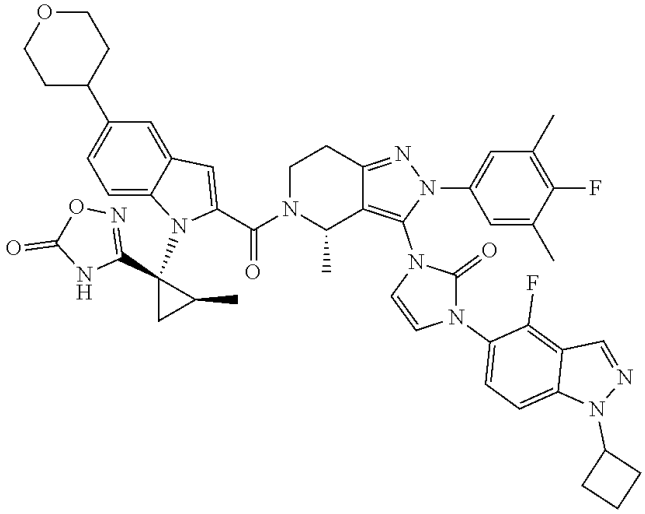

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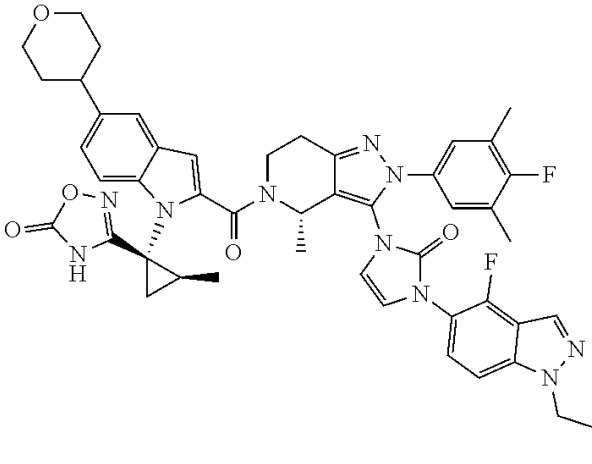
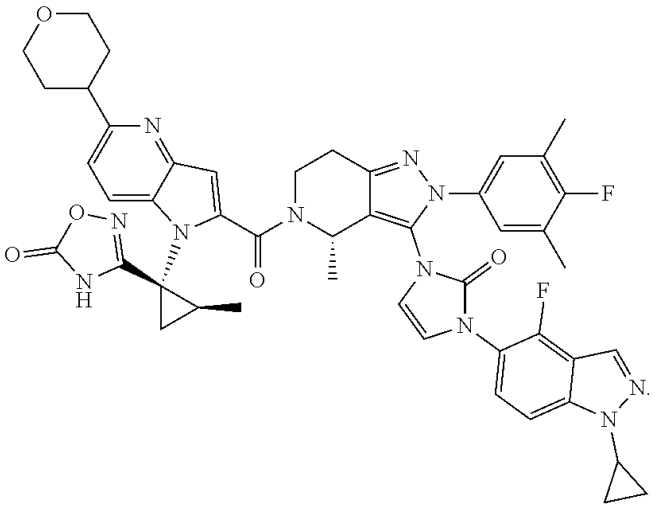


and

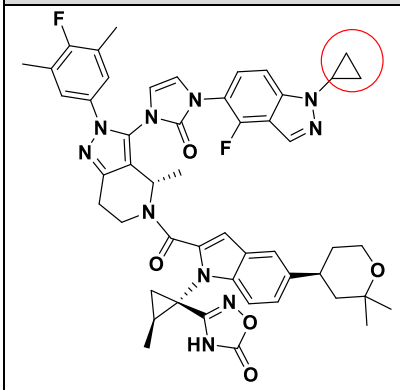
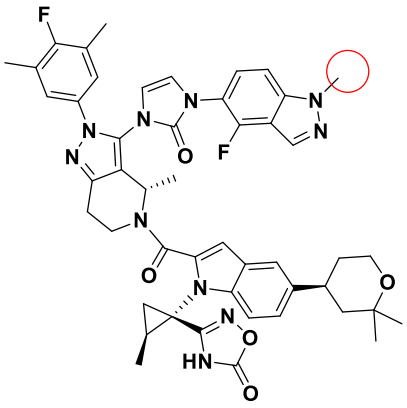
65

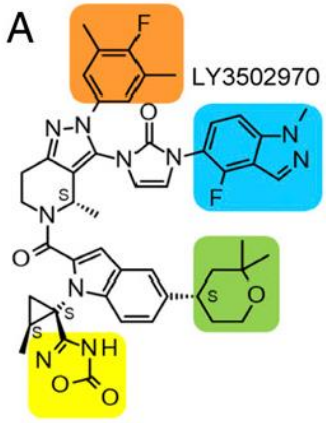


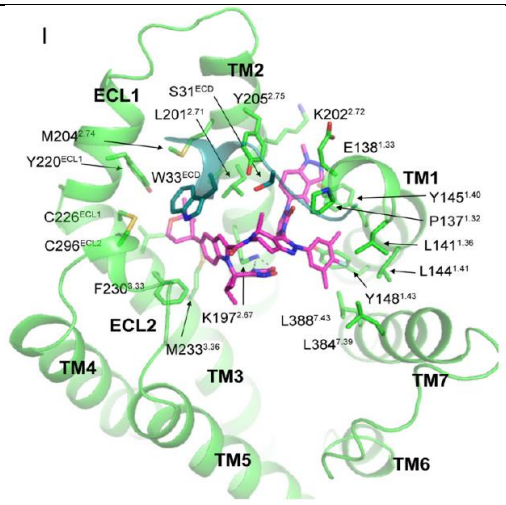
202. In my opinion, claim 1 would have been obvious over Yoshino and Kawai in combination with Talele, at least with respect to Compounds 1, 19, or 20.

**(a) Compound 1**

203. A comparison between Compound 1 and the teachings of Yoshino, Kawai, and Talele are provided in the chart below:

| **Compound 1 of the '236 patent** | **Prior Art** |
|---|---|
|  **Compound 1** | **Yoshino** discloses and claims:  (Compound 67, also known as orforglipron; the difference between |

| | |
|---|---|
| | claimed Compound 1 and orforglipron is highlighted in the red circle) (EX1008 at 99.)<br><br>Yoshino further teaches that modifications involving substitution of the methyl group on the 4-fluoro-1-methyl-indazole moiety generally preserve the biological activity of the compounds. (Id. at Table 3.)<br><br>**Kawai** discloses:<br>structural basis for GLP-1 receptor activation by orforglipron. (EX1004 at 1.) In particular, Kawai discloses a high resolution cryo-EM structure of orforglipron in complex with the GLP-1 receptor, along with a detailed three dimensional protein-ligand interaction model illustrating the ligand-binding pocket surrounding orforglipron, as shown below:<br><br> |



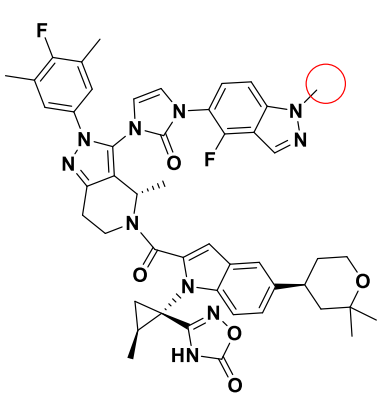

(EX1004 at FIGS. 1A and 1I)

Kawai further teaches that the region of the ligand-binding pocket formed by transmembrane helices TM1, TM2, TM6, and TM7 lies in close proximity to the 4-fluoro-1-methyl-indazole moiety, and that this region exhibits conformational flexibility. (Id. at 4.) Accordingly, a POSA would have understood that modifications to the 4-fluoro-1-methyl-indazole moiety would not be expected to cause significant structural disturbance to the ligand-binding pocket, and thus would likely maintain binding potency.

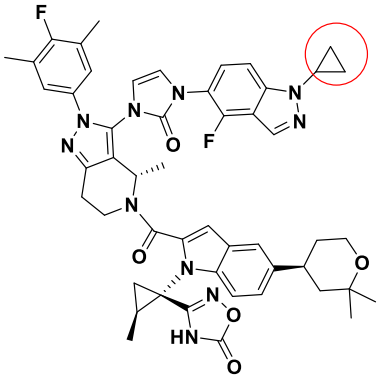
In addition, the binding pocket adjacent to the methyl group of the 4-fluoro-1-methyl-indazolemoiety is shown as being surrounded by a spacious hydrophobic environment, suggesting that the pocket could reasonably accommodate a compound bearing a bulkier ring substituent in place of the methyl group.

| | |
|---|---|
| | **Talele** teaches:<br>Cyclopropyl is known to enhance metabolic stability and decrease plasma clearance and substitution of a methyl group with cyclopropyl will enhance metabolic stability. (EX1009 at 1.) |

204. As illustrated in the chart above, Yoshino discloses orforglipron (Compound 67), which differs from claimed Compound 1 only in that it contains a methyl group, rather than a cyclopropyl group, on the 4-fluoro-1-methyl-indazole moiety, as highlighted by the red circle.

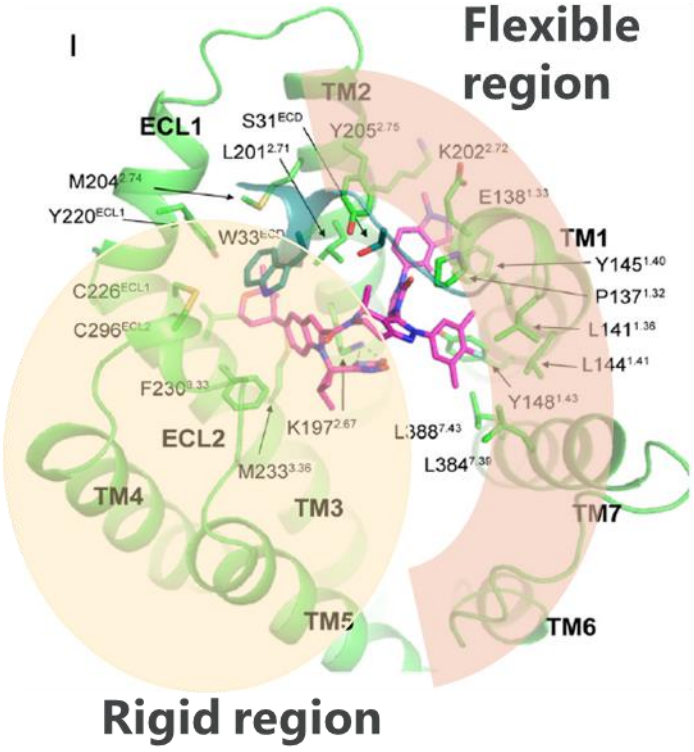


Compound 67 (Lilly prior art)



Compound 1

205. Kawai discloses the structural basis for GLP-1 receptor activation by orforglipron. In particular, Kawai presents a high resolution cryo-EM structure of orforglipron bound to the N-terminal extracellular domain (ECD) of the GLP-1 receptor, revealing the ligand-binding pocket surrounding orforglipron and providing a detailed three-dimensional protein-ligand interaction model, as shown below:




(EX1004 at FIG. 1, 1-9 (emphases added to indicate the flexible and rigid regions).)

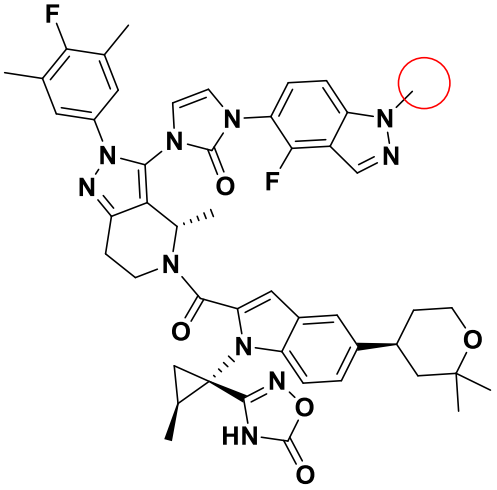
206. In my opinion, the detailed three-dimensional protein-ligand interaction model disclosed by Kawai provides a valuable framework for structure-based drug design, particularly with respect to potential modifications of orforglipron. For example, based on this model, a POSA would have understood which regions of the ligand-binding pocket exhibit conformational flexibility and could accommodate a bulkier substituent without significantly disrupting the overall structure of the binding pocket.

207. Indeed, Kawai further teaches that the region of the ligand-binding pocket formed by transmembrane helices TM1, TM2, TM6, and TM7 is in close proximity to the 4-fluoro-1-methyl-indazole moiety, and that this region exhibits conformational flexibility, as illustrated in annotated FIG. 1I above. (Id. at 4.) In contrast, the region formed by transmembrane helices TM3, TM4, and TM5 is described as being relatively rigid. (Id.)

208. Accordingly, a POSA would have understood that modifications to the 4-fluoro-1-methyl-indazole moiety, which interact with the flexible region of the ligand-binding pocket, would not be expected to cause significant structural perturbation to the pocket and, therefore, would likely preserve binding potency.

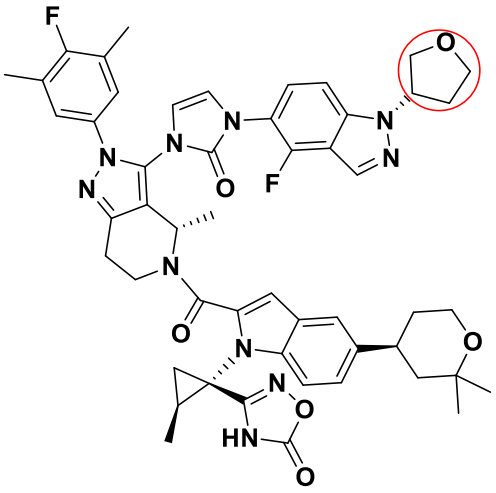
209. In considering modifications to the 4-fluoro-1-methyl-indazole moiety of orforglipron, a POSA would have understood that the region of the ligand-binding pocket where the methyl group resides is spacious and characterized by a hydrophobic environment. (Id. at FIG. 1I.) This environment is formed by the side chain of tyrosine at position 205 (Y205) and the carbon atoms of the lysine at position 202 (K202) and glutamate at position 318 (E318) residues, as shown in the three-dimensional structural model. (Id.) Accordingly, a POSA would have envisioned that the methyl group on the 4-fluoro-1-methyl-indazole moiety of orforglipron could be substituted with a bulkier substituent, such as a three-, four-, or five-membered ring.

210. Indeed, Yoshino teaches that the methyl group may be replaced with a tetrahydrofuran ring without compromising biological activity. For example, replacement of the methyl group in Compound 67 with a tetrahydrofuran ring yielded Compound 40, which demonstrated comparable biological activity. (EX1008 at 50, 99, Table 3.)



**Compound 67**

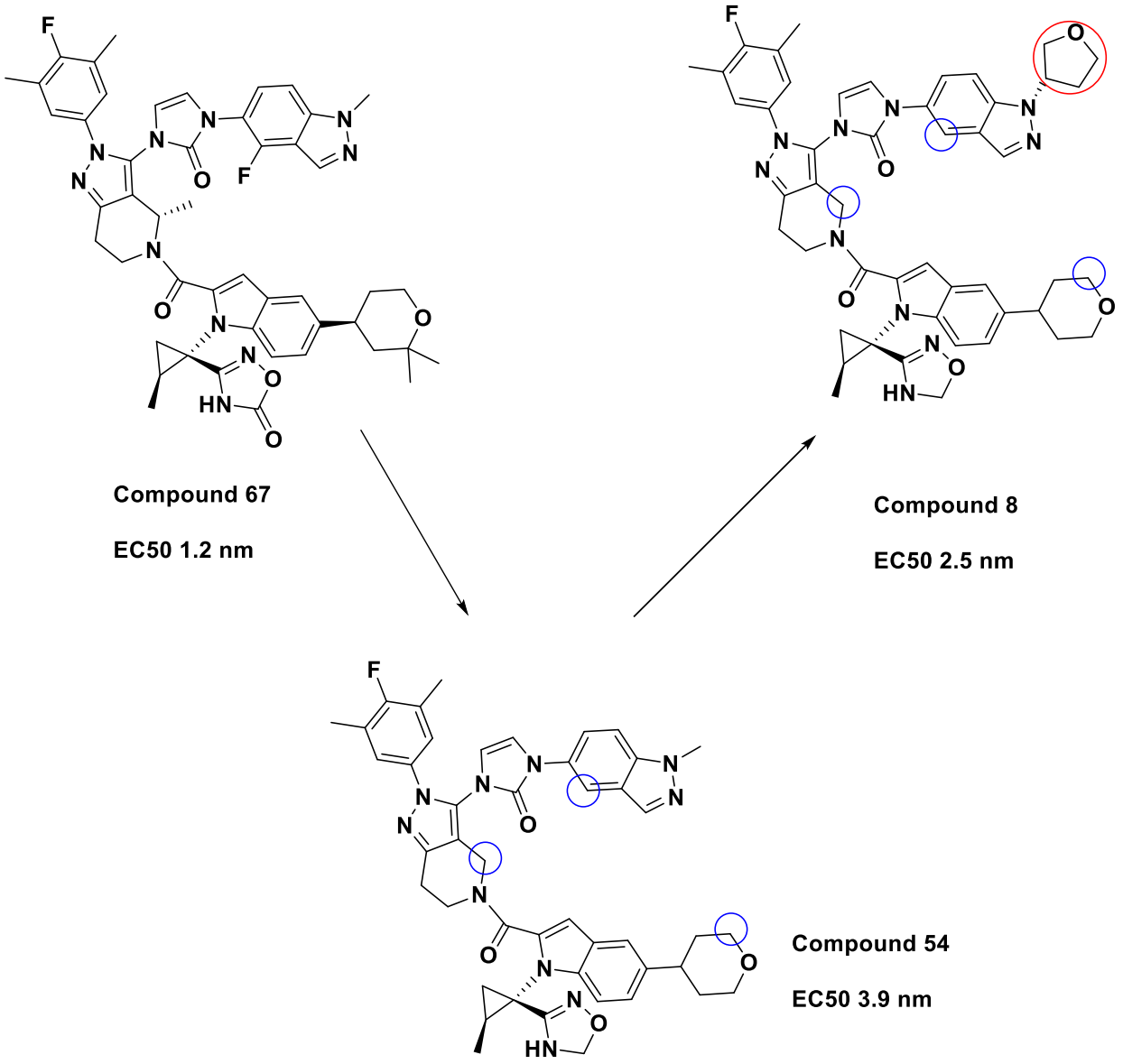
**EC50 1.2 nm**



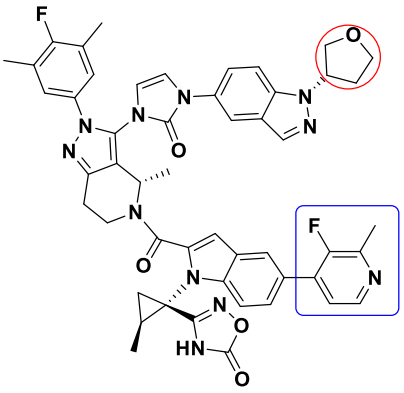
**Compound 40**

**EC50 2.2 nm**

211. Moreover, while the removal of multiple substituents, as exemplified by Compound 54, led to a reduction in the biological activity of the lead compound, the substitution of the methyl group with a tetrahydrofuran moiety was found to partially restore or mitigate this loss of activity, as demonstrated below. (Id. at 34, 92, 99, Table 3.)

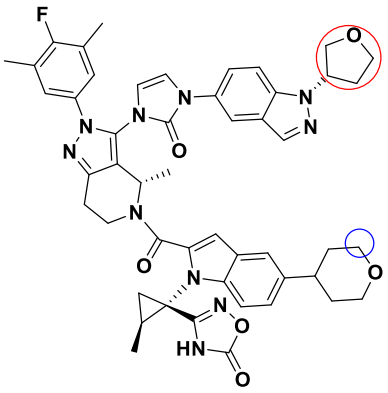



212. Consistent with these observations, several additional analogs disclosed in Yoshino, each containing a tetrahydrofuran ring, also retained activity levels comparable to that of the lead compound. (Id. at 37, 41, 97, Table 3.)



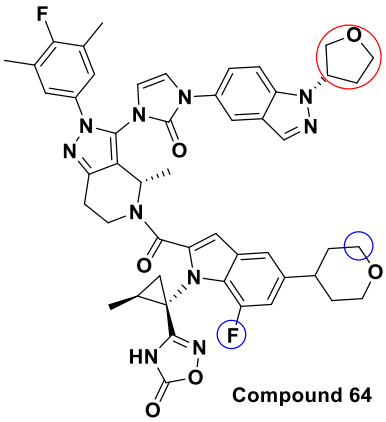
Compound 14

EC50 2.3 nm



Compound 22

EC50 2.3 nm



Compound 64

EC50 2.0 nm

213. Accordingly, when considered as a whole, Yoshino suggests that replacement of the methyl group with a ring structure can maintain the biological activity of the lead compound. As explained above, the hydrophobic character of the binding pocket favors the incorporation of a carbocyclic ring as a suitable replacement for the original methyl group. Additionally, carbocycles are preferred to simple alkyl groups because they have fewer rotational degrees of freedom, meaning they pay smaller entropic penalties when they achieve their bound confirmations, which restricts their rotation. Among potential carbocycles, cyclopropyl represents the simplest and most structurally analogous to a methyl group, offering minimal steric deviation while providing favorable physicochemical properties consistent with the binding environment. Additionally, in my opinion, a cycloalkyl ring would be favored over a heterocyclic ring, at least in part due to the absence of chirality, which simplifies the synthesis.

214. Talele further supports a substitution with the cyclopropyl ring, as discussed in detail with respect to claim 1 in Ground 1. Specifically, Talele teaches that "the cyclopropyl fragment is a versatile player" in drug design, noting that "it is striking to find that eight of the 200 best-selling drugs approved by the U.S. FDA contain a cyclopropyl ring" and that "approximately 65 unique cyclopropane-containing compounds are in various stages of clinical development, with about 55 in preclinical stages." (EX1009 at 1-2.)

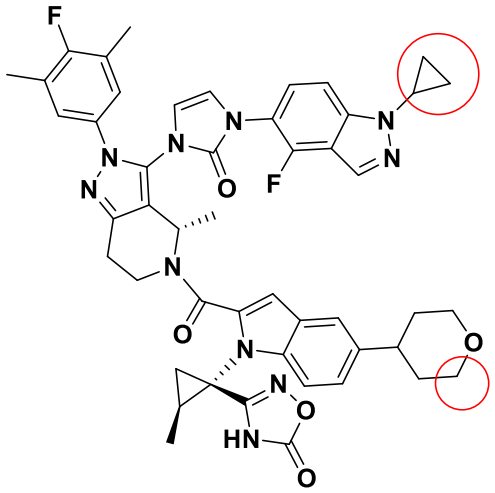
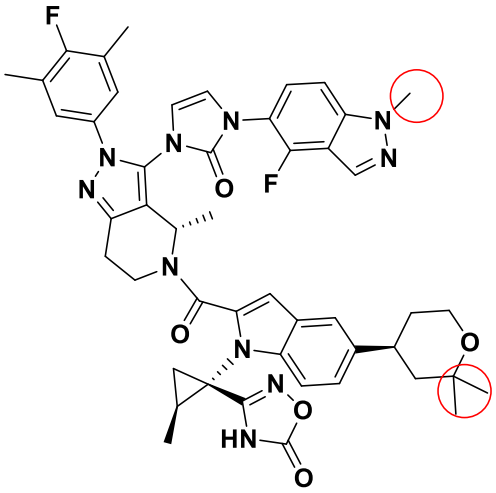
215. In particular, with regard to a methyl to cyclopropyl substitution, Talele discloses that "**one can expect to achieve a metabolically stable derivative upon replacement of the methyl group with a cyclopropane ring**." (Id. at 2 (emphasis added))

216. Thus, Talele teaches that substitution with a cyclopropyl ring is a well-established strategy in medicinal chemistry for enhancing metabolic stability, improving pharmacokinetic properties, or modulating the biological activity of a drug molecule. In light of this teaching, a POSA would have been motivated to substitute the methyl group on the 4-fluoro-1-methyl-indazole moiety of orforglipron with a cyclopropyl group, thereby arriving at claimed Compound 1 of the '236 patent.

217. In view of the prior art teachings as discussed above, claim 1 would have been obvious for a POSA, at least with respect to claimed Compound 1.

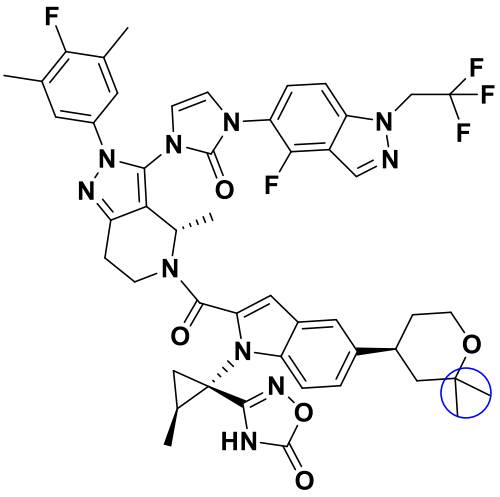
### (b) Compound 19

218. A comparison between Compound 19 and orforglipron as disclosed in Yoshino is provided in the chart below:

| Compound 19 of the '236 patent | Prior Art |
|---|---|
| <br>**Compound 19** | **Yoshino** discloses and claims:<br><br>(Compound 67, also known as orforglipron; the differences between claimed Compound 19 and orforglipron are highlighted in the red circle) |

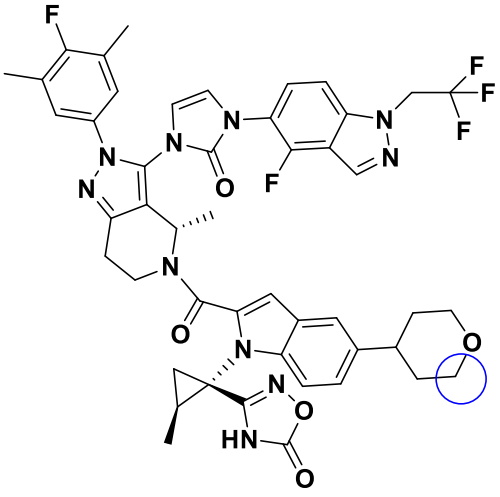
219. As discussed above with respect to claimed Compound 1, a POSA would have been motivated to substitute the methyl group on the 4-fluoro-1-methyl-indazole moiety of orforglipron with a cyclopropyl group. As further explained below, a POSA would also have been motivated to remove the dimethyl group from the 2,2-dimethyl-tetrahydropyran moiety of orforglipron, thereby arriving at claimed Compound 19.

220. Indeed, Yoshino teaches that removal of the dimethyl group from the 2,2-dimethyl-tetrahydropyran moiety results in improved or comparable biological activity. As illustrated in the comparison below, removal of the dimethyl groups from Compound 35 yields Compound 28, which retains comparable activity. (EX1008 at 44, 48, Table 3.) Similarly, Compound 30, which lacks dimethyl groups on the tetrahydropyran ring, exhibits a similar level of activity as Compound 38. (EX1008 at 45, 49, Table 3.)



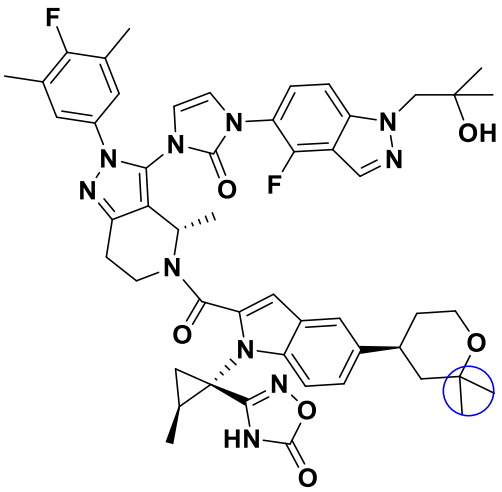
**Compound 35**

**EC50 3.2 nm**



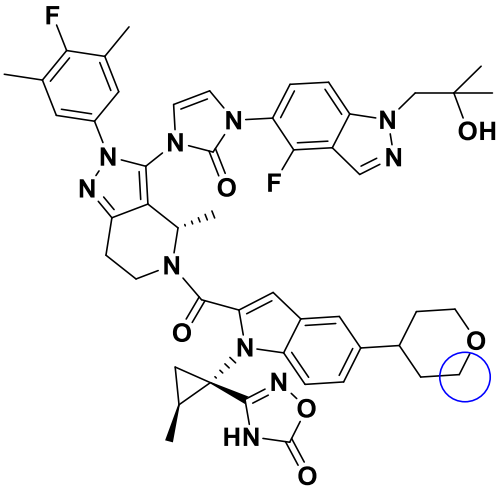
**Compound 28**

**EC50 1.9 nm**



Compound 38

EC50 1.7 nm



Compound 30

EC50 1.4 nm

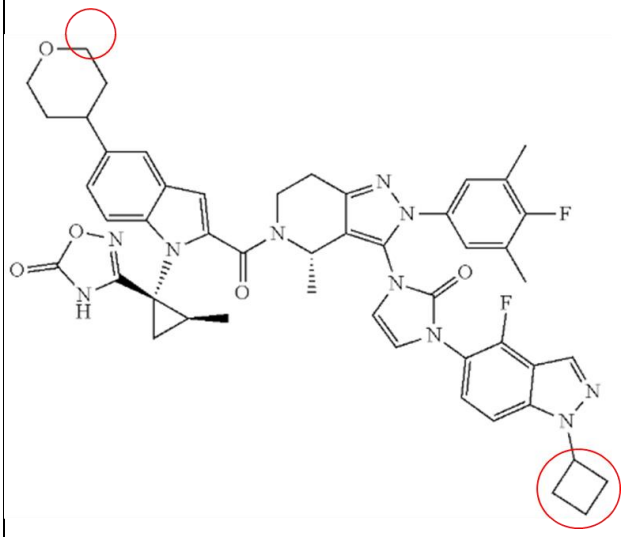
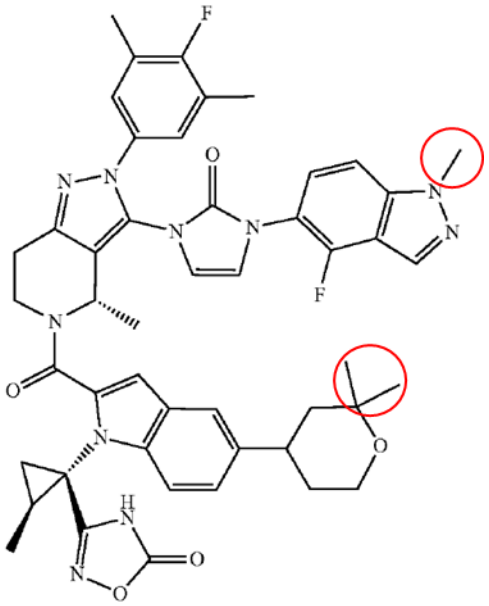
221. Notably, among the 80 compounds with biological activity reported in Table 3 of Yoshino, over 30 feature a non-substituted, achiral tetrahydropyran ring. Considering both the biological activity data discussed above and the prevalence of the achiral tetrahydropyran ring among active compounds, a POSA would have been motivated to remove the dimethyl groups from the 2,2-dimethyl-tetrahydropyran moiety, thus arriving at claimed Compound 19.

222. Therefore, in view of the prior art teachings discussed above, claim 1 would have been obvious to a POSA, at least with respect to claimed Compound 19.

**(c) Compound 20**

223. A comparison between Compound 20 and orforglipron as disclosed in Yoshino is provided in the chart below:

| **Compound 20 of the ’236 patent** | **Prior Art** |
|---|---|

| | |
|---|---|
| <br>**Compound 20** | **Yoshino** discloses and claims:<br><br>(Compound 67, also known as orforglipron; the differences between claimed Compound 20 and orforglipron are highlighted in the red circles) |

224. As discussed above with respect to claimed Compound 19, a POSA would have been motivated to remove the dimethyl group from the 2,2-dimethyl-tetrahydropyran moiety of orforglipron. As further explained below, it would also have been obvious for a POSA to substitute the methyl group on the 4-fluoro-1-methyl-indazole moiety of orforglipron with a carbocycle such as a cyclopropyl or cyclobutyl group, thereby arriving at claimed Compound 20.

225. As discussed above with respect to claimed Compounds 1 and 19, a POSA would have been motivated to substitute the methyl group on the 4-fluoro-1-

methyl-indazole moiety of orforglipron with a three- or four-membered cycloalkyl ring. Moreover, a cycloalkyl ring would have been preferred over a heterocyclic ring, at least in part due to the absence of chirality, which simplifies the synthesis. It is well known in organic chemistry that the strain of the four-membered ring confers similar strong C-H bonds as were discussed in Talele for the three-membered cyclopropane ring. This characteristic renders the four-membered ring cycloalkyl group similarly more resistant to metabolism than simple alkyl groups. It is also well recognized in medicinal chemistry that simple structural modifications of alkane groupings (by addition of $CH_2$ groups) are routine, as the trite "methyl, ethyl, propyl, butyl" recited even by novice medicinal chemists attests. The four-membered cycloalkyl ring in Compound 20 can be formally produced by addition of a $CH_2$ group into a cyclopropane structure.

226. Accordingly, it would have been obvious to a POSA, seeking to substitute the methyl group with a three- or four-membered cycloalkyl ring, to modify the 4-fluoro-1-methyl-indazole moiety of orforglipron in such a manner, thereby arriving at claimed Compound 20. Therefore, in view of the prior art teachings discussed above, claim 1 would have been obvious to a POSA, at least with respect to claimed Compound 20.

227. With regard to "a pharmaceutically acceptable salt thereof" recited in claim 1, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt

thereof, such as a sodium salt thereof or a calcium salt thereof, including "a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt." (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.)

228. Therefore, for at least the above reasons, claim 1 would have been obvious over the prior art.

**2. Claim 2**

229. In my opinion, claim 2 of the '236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 2 depends from claim 1 and recites "the pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, a calcium salt, a potassium salt, a magnesium salt and a lithium salt."

230. Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including "a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt." (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) In view of the teaching

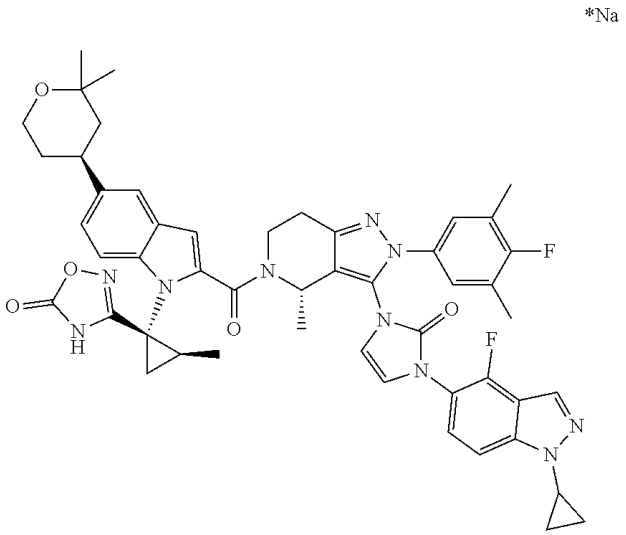
of Yoshino, it would have been obvious for a POSA to prepare a sodium salt or a calcium salt of Compounds 1, 19, or 20 as recited in claim 2 of the ’236 patent.

231. Accordingly, claim 2 of the ’236 patent would have been obvious to a POSA over the prior art.

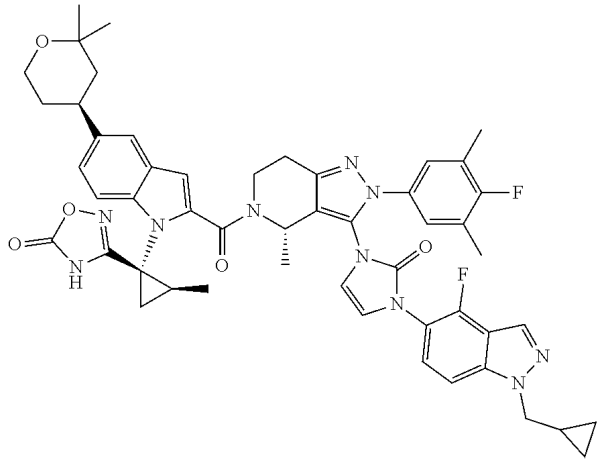
### 3. Claim 3

232. In my opinion, claim 3 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 3 depends from claim 1 and recites:

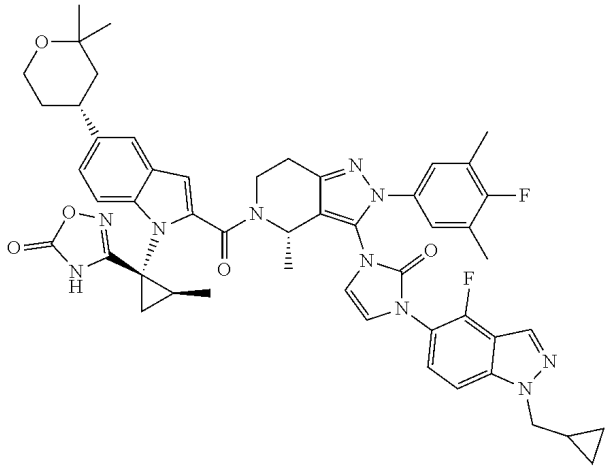
> the pharmaceutically acceptable salt is selected from the group consisting of:



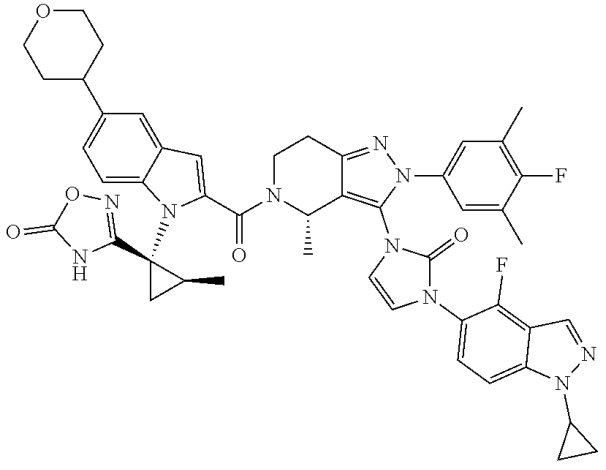
*Na



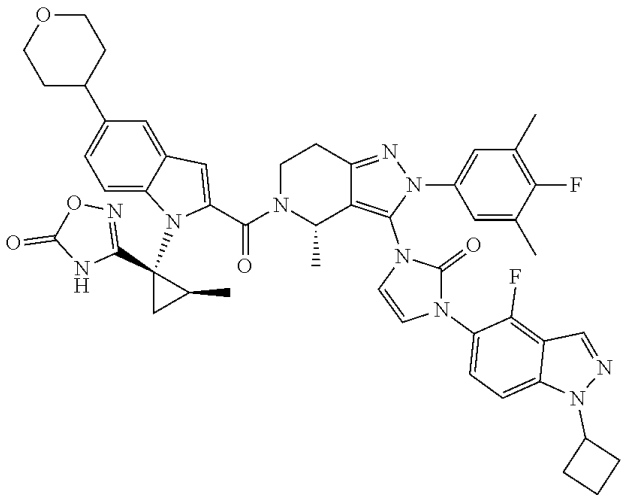
*Na



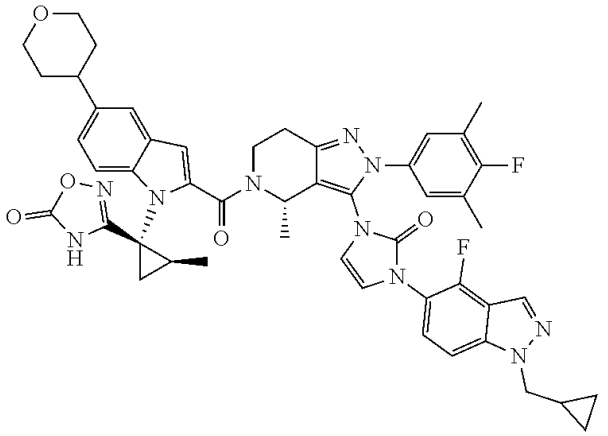
*Na



*Na

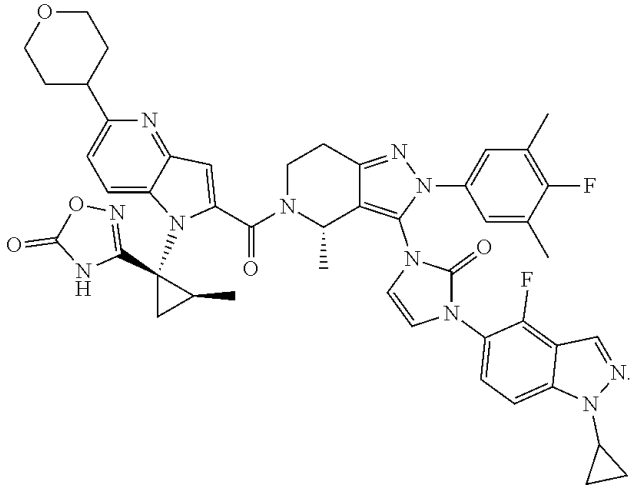


*Na



and

*Na



233. Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including "a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt." (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) As discussed above with respect to claims 1 and 2, it would have been obvious for a POSA to prepare a sodium salt or a calcium salt of Compounds 1, 19, and 20 as recited in claim 3 of the '236 patent.

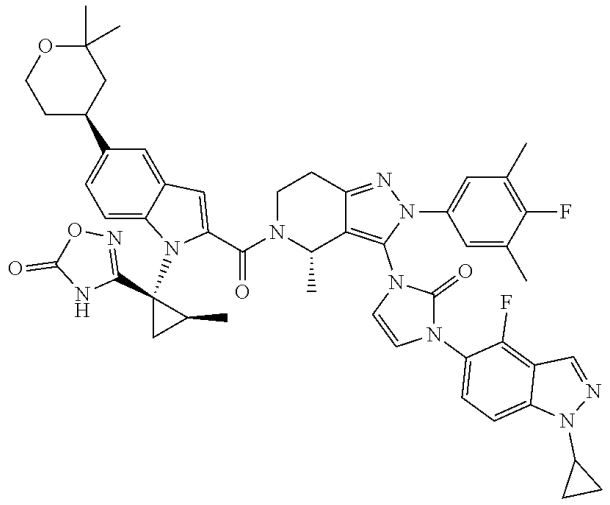
234. Accordingly, claim 3 of the '236 patent would have been obvious to a POSA over the prior art.

**4. Claim 4**

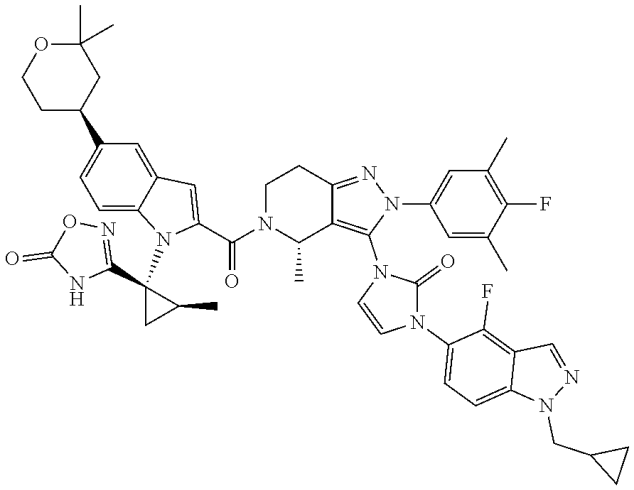
235. In my opinion, claim 4 of the '236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 4 depends from claim 1 and recites:

> the pharmaceutically acceptable salt is selected from the group consisting of:

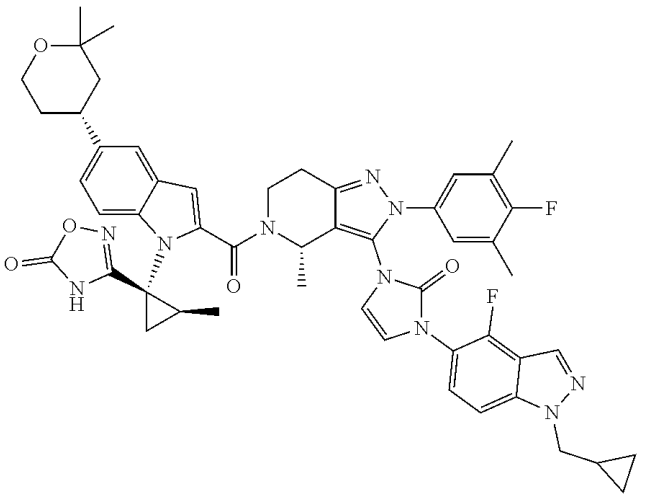
*1/2 Ca



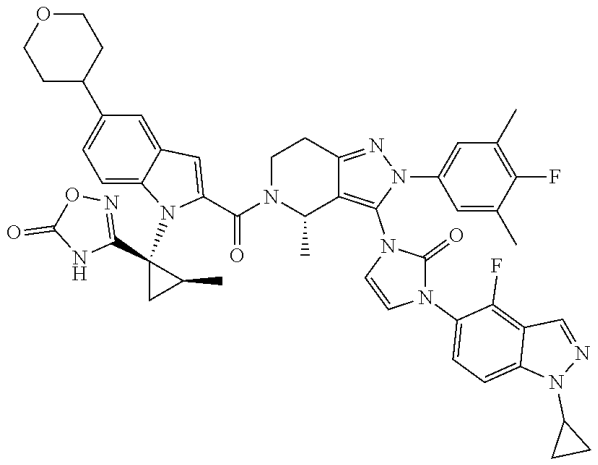
*1/2 Ca



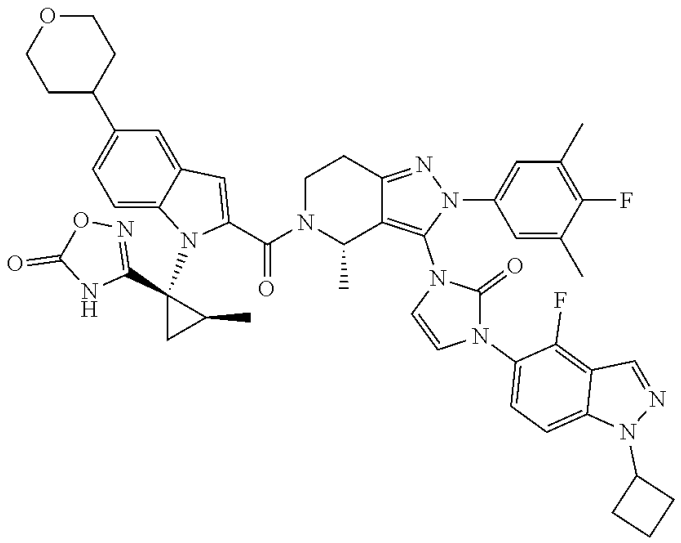
*1/2 Ca



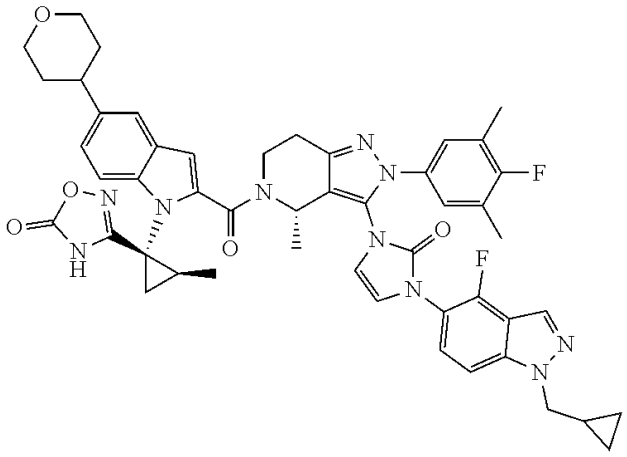
*1/2 Ca



*1/2 Ca

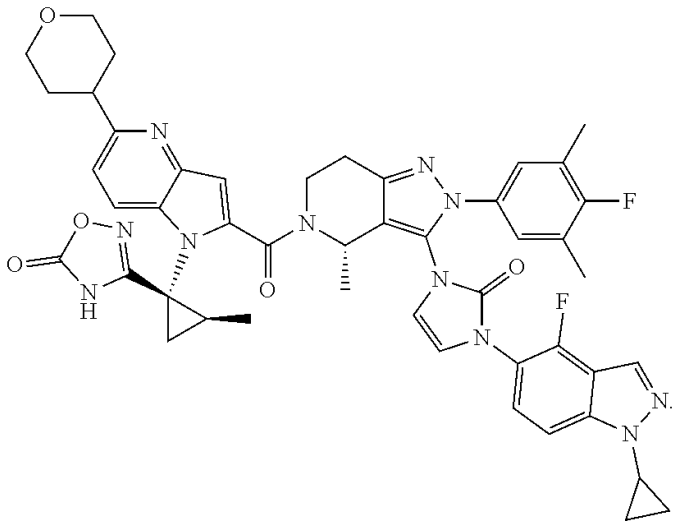


*1/2 Ca



and

*1/2 Ca



236. As discussed above with respect to claim 2, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a calcium salt thereof, including a calcium salt of the free form and a hydrate of the calcium salt. (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare a calcium salt of Compounds 1, 19, and 20 as recited in claim 4 of the ’236 patent.

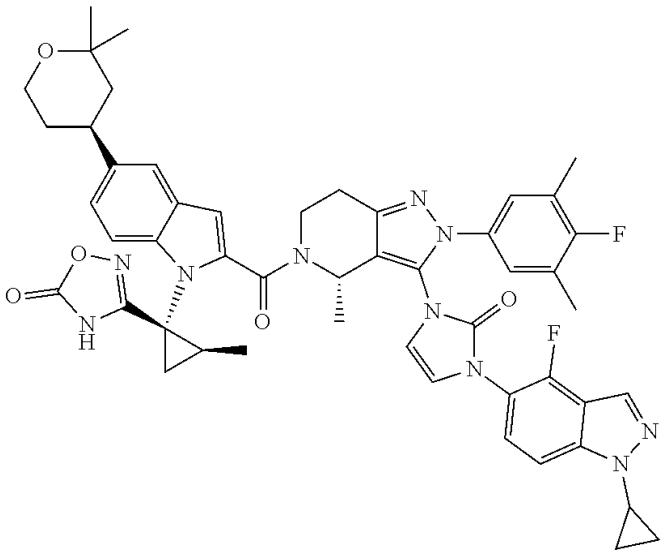
237. Accordingly, claim 4 of the ’236 patent would have been obvious to a POSA over the prior art.

**5. Claim 5**

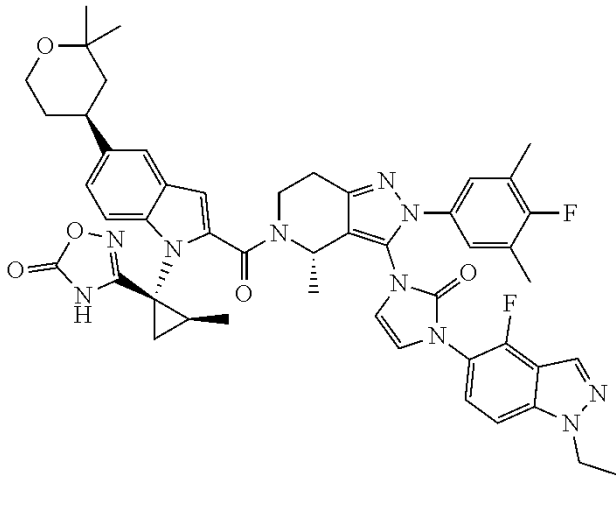
238. In my opinion, claim 5 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 5 depends from claim 1 and recites:

the compound is selected from the group consisting of:

1

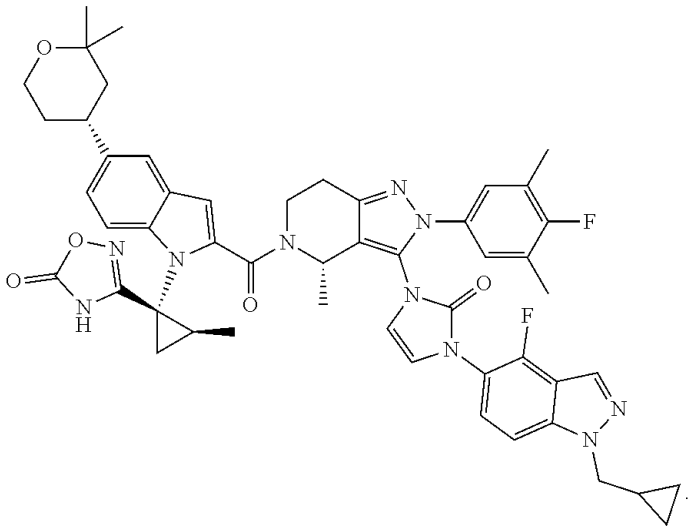


13



and

18



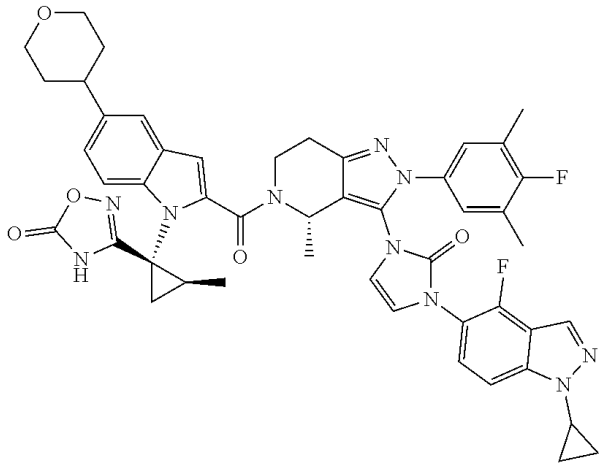
239. As discussed above with respect to claim 1, it would have been obvious for a POSA to arrive at Compound 1 as recited in claim 5 of the ’236 patent.

### 6. Claim 6

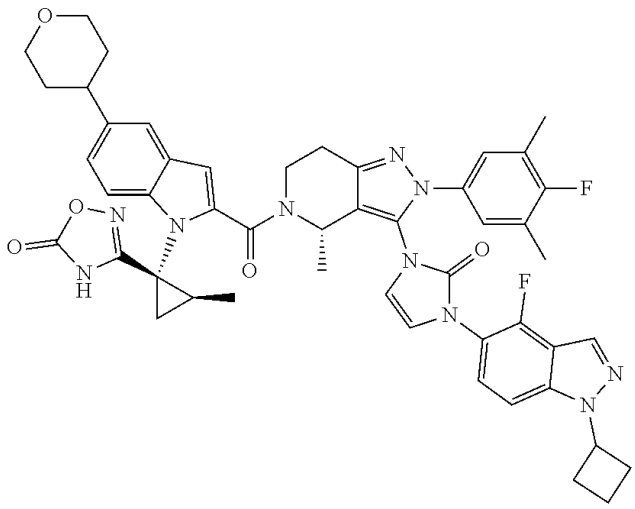
240. In my opinion, claim 6 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 6 depends from claim 1 and recites:

the compound is selected from the group consisting of:

19

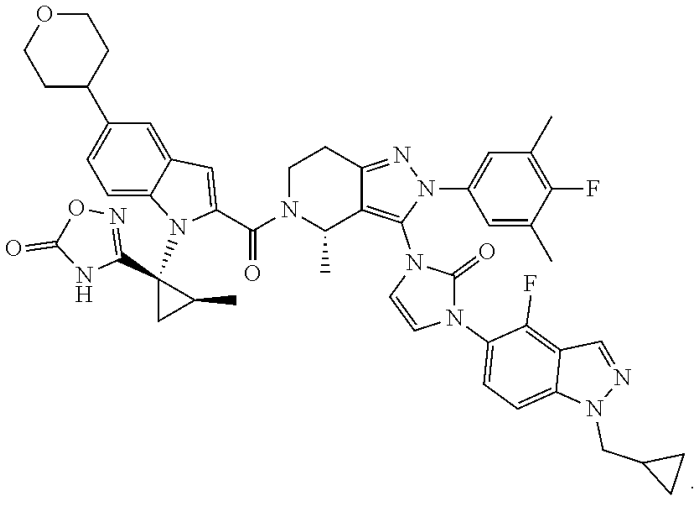


20



and

21



.

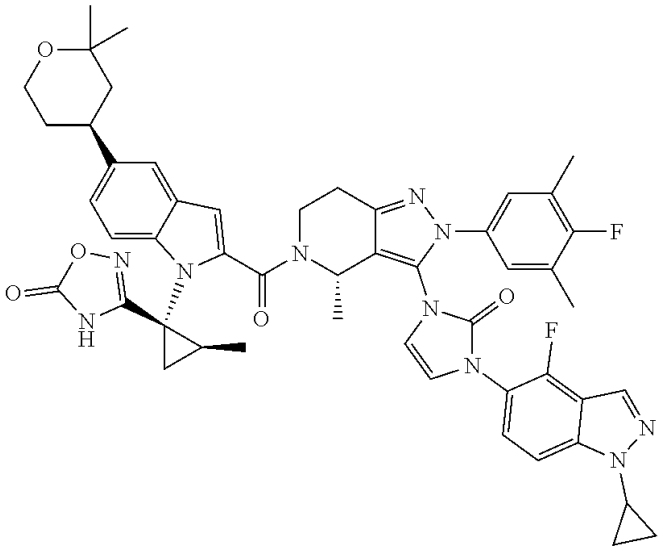
241. As discussed above with respect to claim 1, it would have been obvious for a POSA to arrive at Compounds 19 and 20 as recited in claim 6 of the ’236 patent.

### 7. Claim 7

242. In my opinion, claim 7 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 7 depends from claim 1 and recites:

the compound is

1

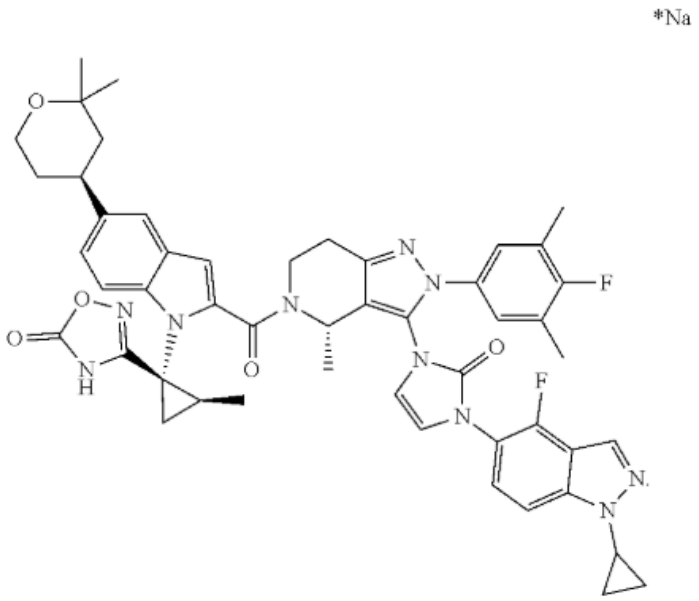


243. As discussed above with respect to claim 1, it would have been obvious for a POSA to arrive at Compound 1 as recited in claim 7 of the ’236 patent.

### 8. Claim 8

244. In my opinion, claim 8 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1-3. Claim 8 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



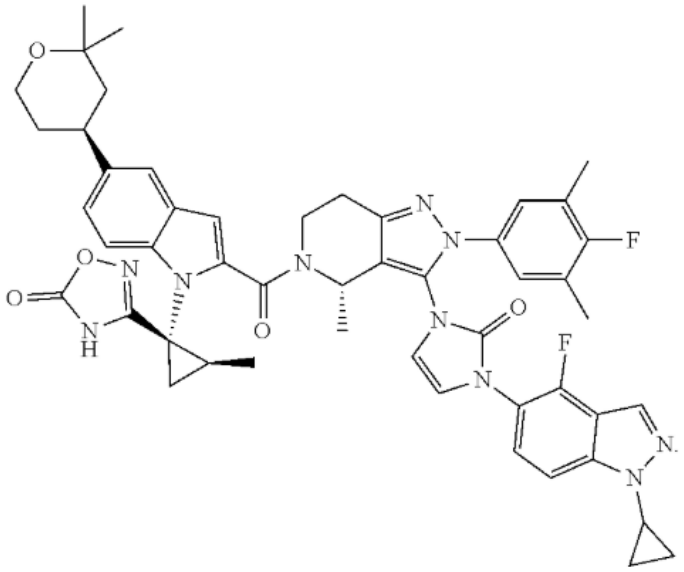

245. As discussed above with respect to claims 1-3, it would have been obvious for a POSA to arrive at Compound 1 as recited in claim 8 of the ’236 patent.

### 9. Claim 9

246. In my opinion, claim 9 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 2, and 4. Claim 9 depends from claim 1 and recites:

the pharmaceutically acceptable salt is

*1/2 Ca



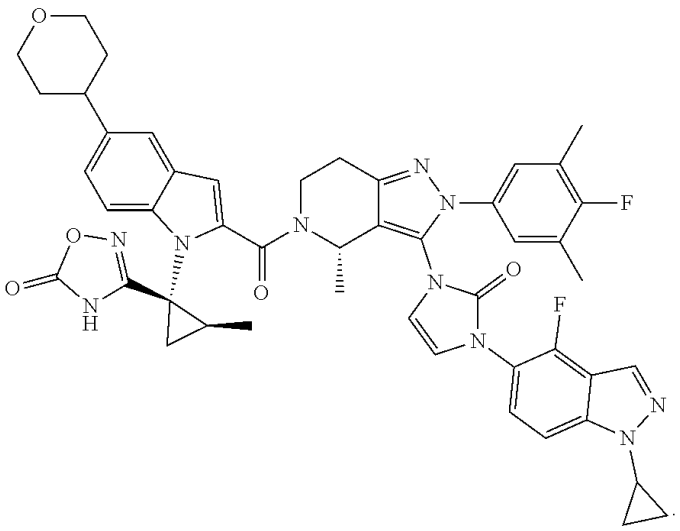
247. As discussed above with respect to claims 1, 2, and 4, it would have been obvious for a POSA to arrive at Compound 1 as recited in claim 9 of the ’236 patent.

### 10. Claim 12

248. In my opinion, claim 12 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 6. Claim 12 depends from claim 1 and recites:

the compound is

19

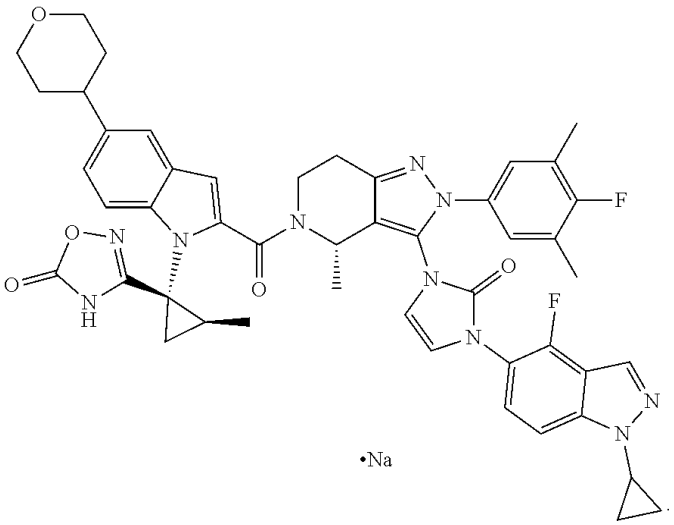


249. As discussed above with respect to claim 1, it would have been obvious to a POSA to arrive at Compound 19 as recited in claim 12 of the ’236 patent. Accordingly, claim 12 of the ’236 patent would have been obvious to a POSA in view of the prior art.

### 11. Claim 13

250. In my opinion, claim 13 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1-3. Claim 13 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



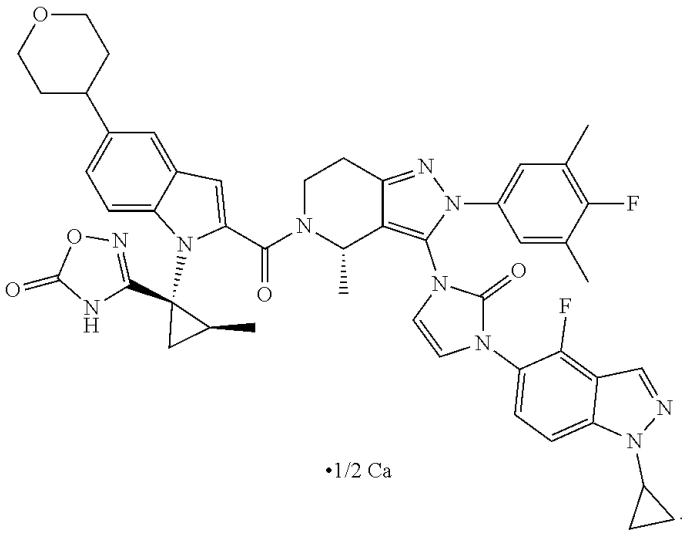

251. As discussed above with respect to claims 2 and 3, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof, including a sodium salt of the free form and a hydrate of the sodium salt. (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare a sodium salt of Compound 19 as recited in claim 13 of the ’236 patent.

252. Accordingly, claim 13 of the ’236 patent would have been obvious to a POSA over the prior art.

### 12. Claim 14

253. In my opinion, claim 14 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 2, and 4. Claim 14 depends from claim 1 and recites:

> the pharmaceutically acceptable salt is




254. As discussed above with respect to claims 1, 2, and 4, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a calcium salt thereof, including a calcium salt of the free form and a hydrate of the calcium salt. (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare a calcium salt of Compound 19 as recited in claim 14 of the ’236 patent.

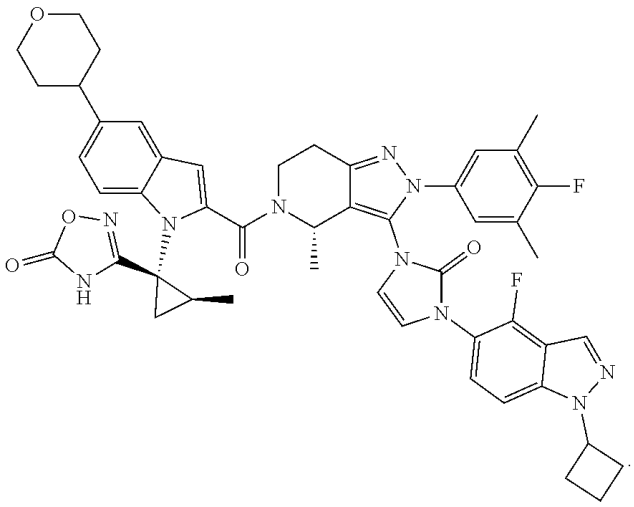
255. Accordingly, claim 14 of the ’236 patent would have been obvious to a POSA over the prior art.

### 13. Claim 15

256. In my opinion, claim 15 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 6. Claim 15 depends from claim 1 and recites:

the compound is

20

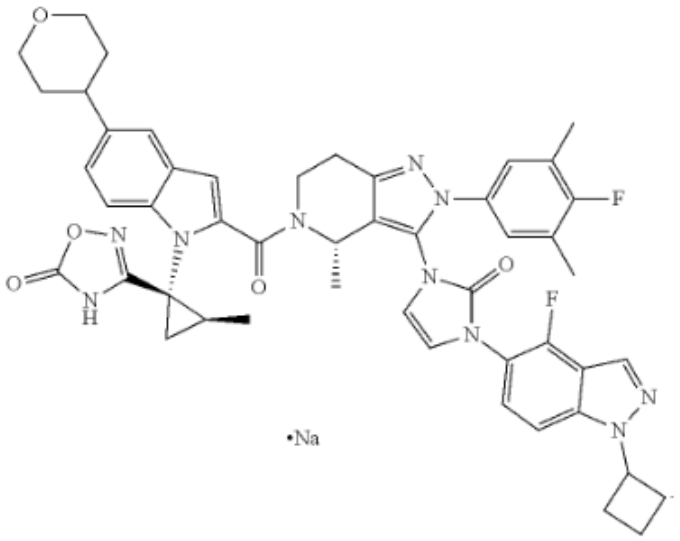


257. As discussed above with respect to claims 1 and 6, it would have been obvious to a POSA to arrive at Compound 20 as recited in claim 15 of the ’236 patent. Accordingly, claim 15 of the ’236 patent would have been obvious to a POSA in view of the prior art.

### 14. Claim 16

258. In my opinion, claim 16 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1-3 and 6. Claim 16 depends from claim 1 and recites:

the pharmaceutically acceptable salt is

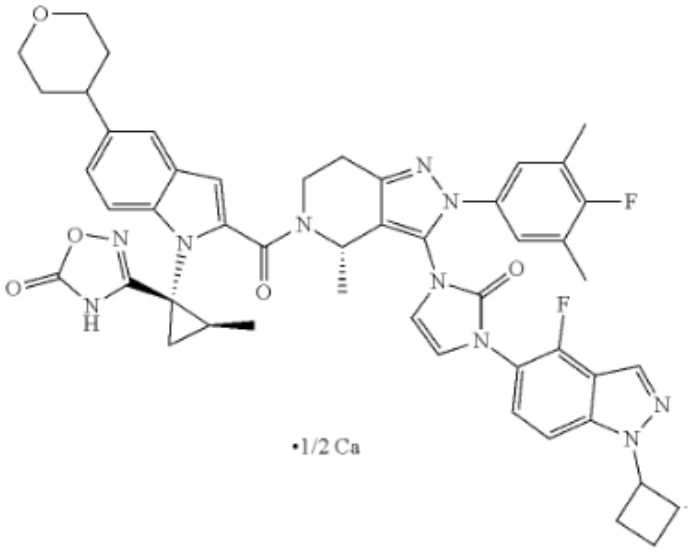



259. As discussed above with respect to claims 1-3 and 6, it would have been obvious to a POSA to arrive at Compound 20 as recited in claim 16 of the ’236 patent. Accordingly, claim 16 of the ’236 patent would have been obvious to a POSA in view of the prior art.

### 15. Claim 17

260. In my opinion, claim 17 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 2, 4, and 6. Claim 17 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



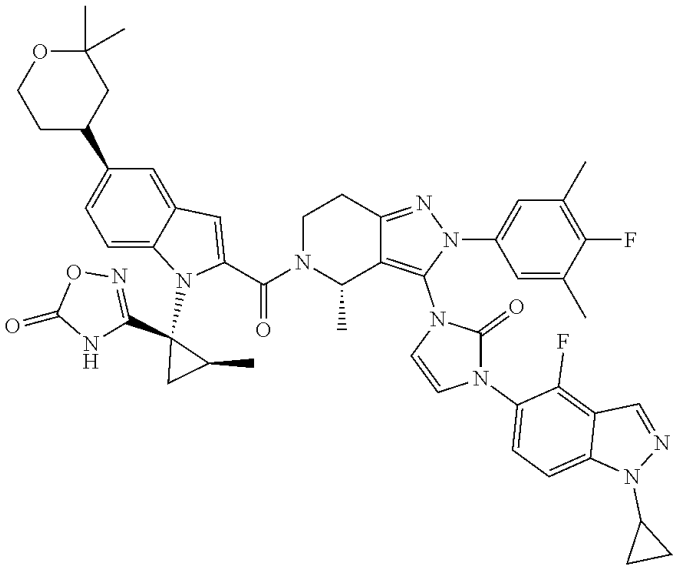

261. As discussed above with respect to claims 1, 2, 4, and 6, it would have been obvious to a POSA to arrive at Compound 20 as recited in claim 17 of the ’236 patent. Accordingly, claim 17 of the ’236 patent would have been obvious to a POSA in view of the prior art.

### 16. Claim 24

262. In my opinion, independent claim 24 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 6, and 12. Claim 24 recites:

A compound, selected from the group consisting of:

1



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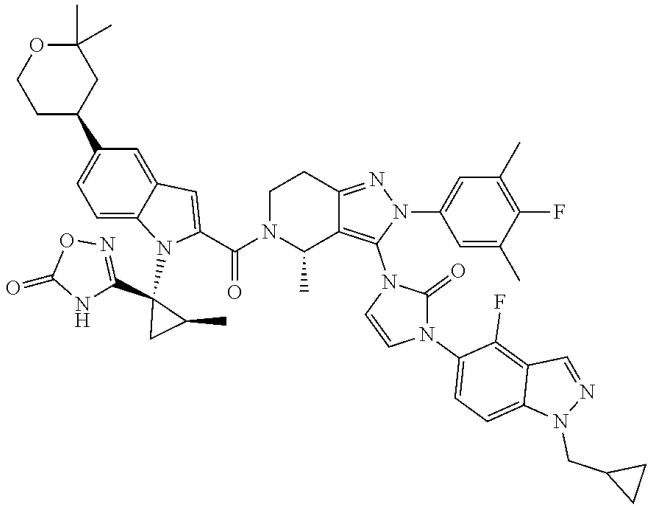

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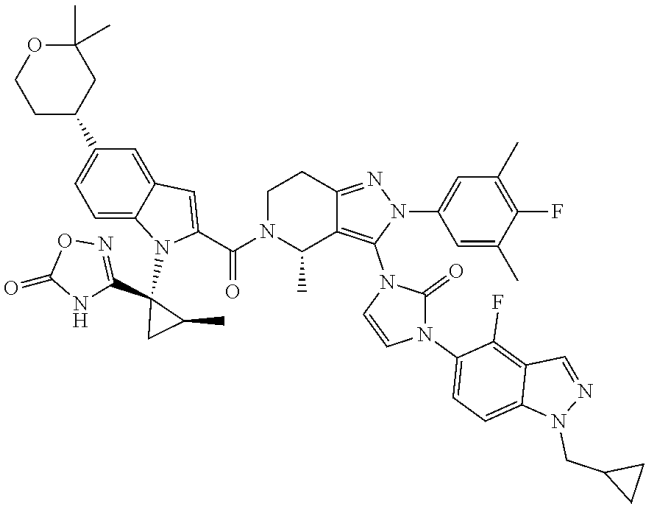

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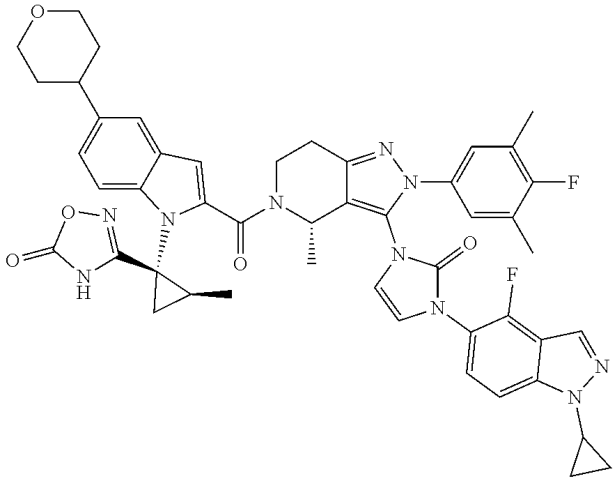

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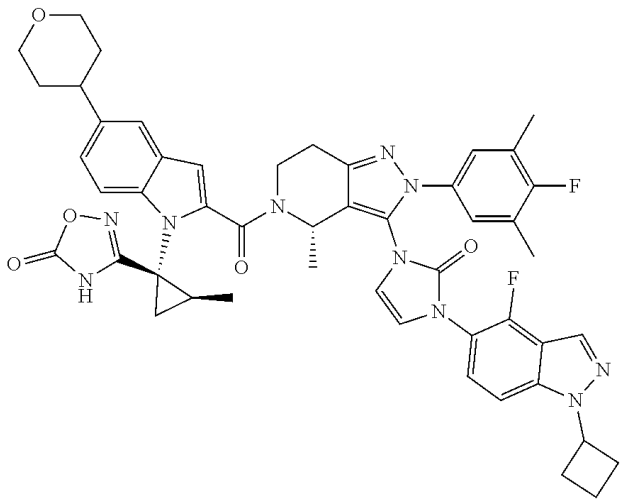

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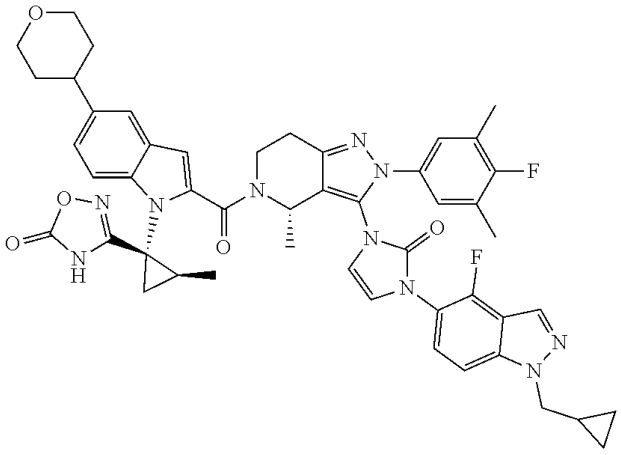
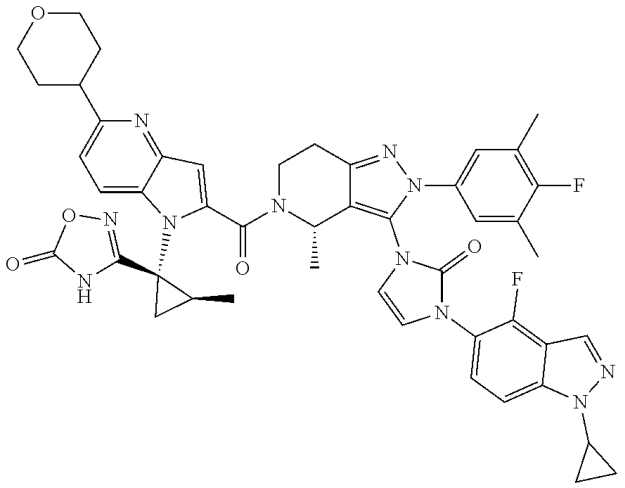


and

65



263. As discussed above with respect to claims 1, 6, and 12, it is obvious for a POSA to arrive at Compounds 1, 19, and 20.

264. Accordingly, claim 24 of the ’236 patent would have been obvious to a POSA over the prior art.

### 17. Claim 25

265. In my opinion, claim 25 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 25 depends from claim 1 and recites, “A pharmaceutical composition, comprising the compound or the pharmaceutically acceptable salt thereof of claim 1, and a pharmaceutically acceptable excipient.”

266. Yoshino discloses various pharmaceutical formulations and a pharmaceutically acceptable additive that includes an excipient. (EX1008 at 35:45-67.)

267. Accordingly, claim 25 of the ’236 patent would have been obvious to a POSA over the prior art.

### C. GROUND 3: CLAIMS 1-4 AND 21-25 WOULD HAVE BEEN OBVIOUS OVER SU, YOSHINO, KAWAI, TALELE, AND MENG IN VIEW OF PATEL AND REN

268. As discussed in Section IX.C, claims 1–4 and 24–25, at least with respect to Compound 65, are not entitled to a priority date earlier than January 31, 2024. Accordingly, Su, Yoshino, Kawai, Talele, Meng, Patel, and Ren each qualify as prior art for these claims. Based on my review of the prior art and the state of the field as it existed prior to the effective filing date of the ’236 patent, it is my opinion that claims 1–4 and 21–25 would have been obvious to a POSA, at least with respect to Compound 65. This conclusion is grounded in a comprehensive analysis of the structural features and pharmacological properties disclosed in the prior art and supported by well-established principles of medicinal chemistry known to a POSA at the time.

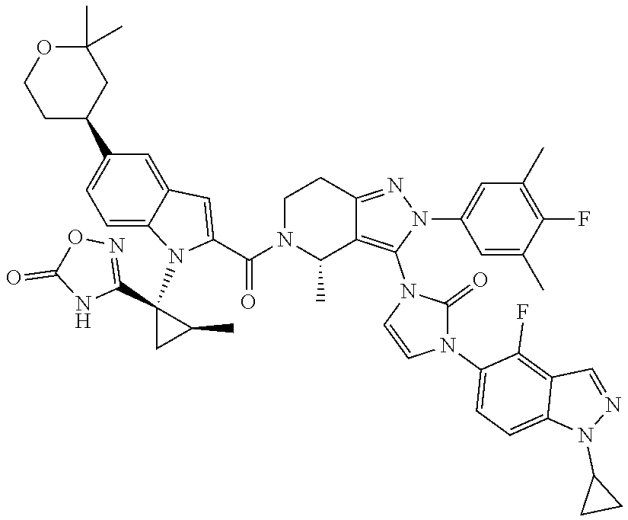
269. In particular, the combination of Su, Yoshino, Kawai, Talele, and Meng, when further considered in view of Patel and Ren, renders claims 1-4 and 21-25 obvious. Each of these references contributes teachings that would have guided a POSA in making the specific structural modifications reflected in Compound 65 of the ’236 patent, including the incorporation of nitrogen atoms into aromatic systems to improve potency, solubility, metabolic stability, and oral bioavailability.

270. The specific teachings of these references, individually and in combination, and their relevance to the Challenged Claims, are discussed in detail above in Section VIII. As elaborated below, the references collectively provide not only a clear motivation for the modification of Compound 19 (previously addressed in Grounds 1 and 2) into Compound 65, but also a reasonable expectation of success in achieving the desired pharmacological improvements.

### 1. Claim 1

271. Independent claim 1 recites:

> A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:
>
> 1



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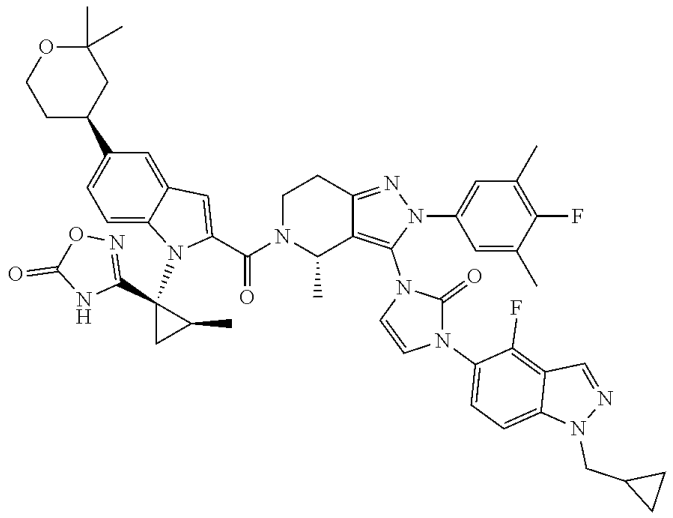

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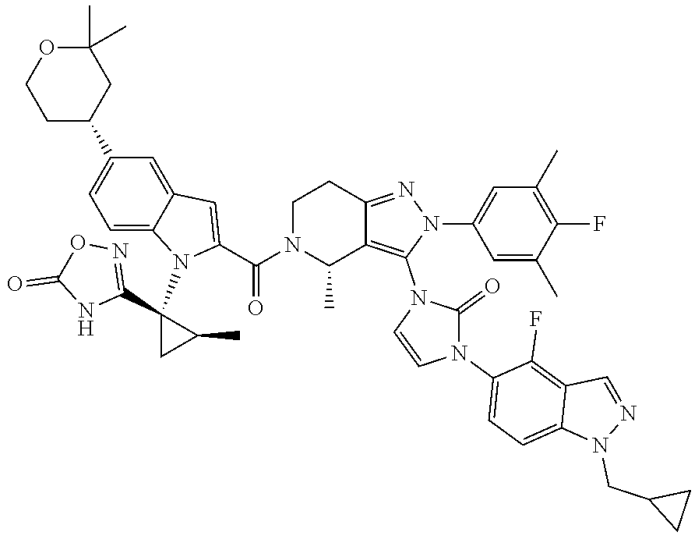

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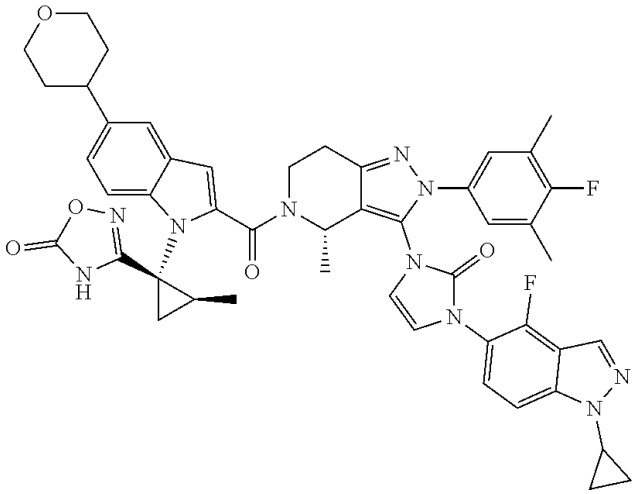

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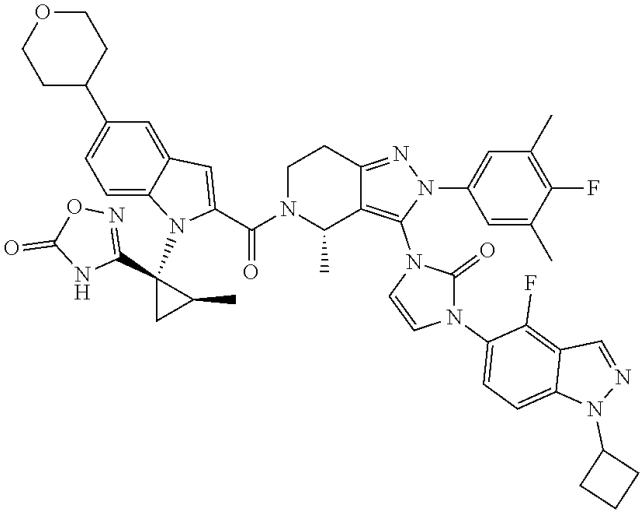

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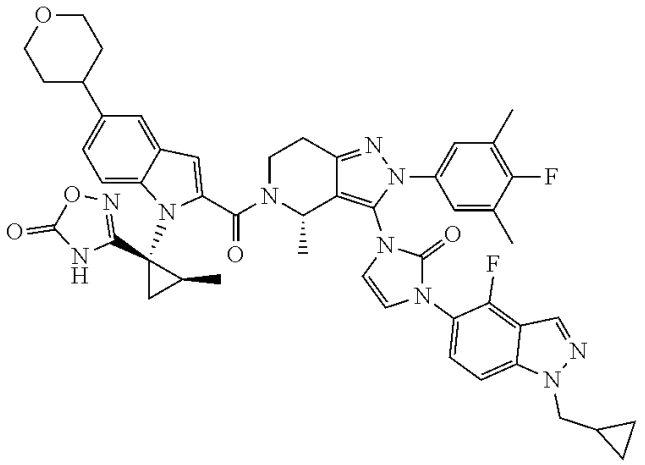
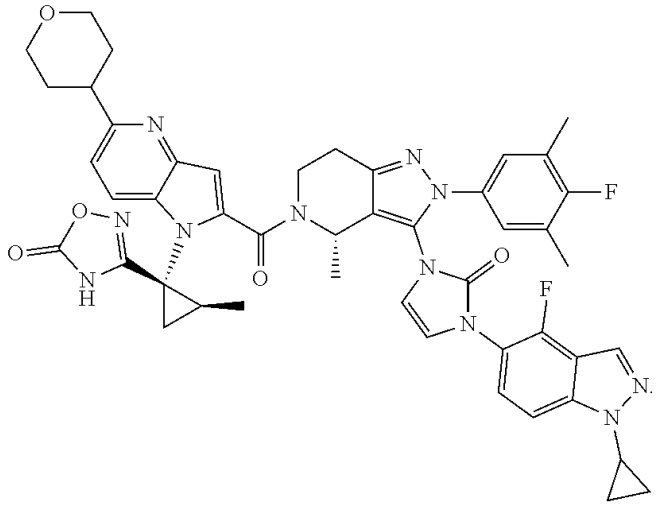


and

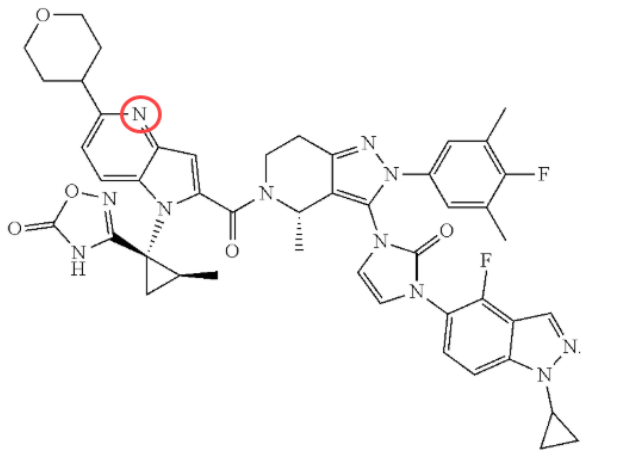
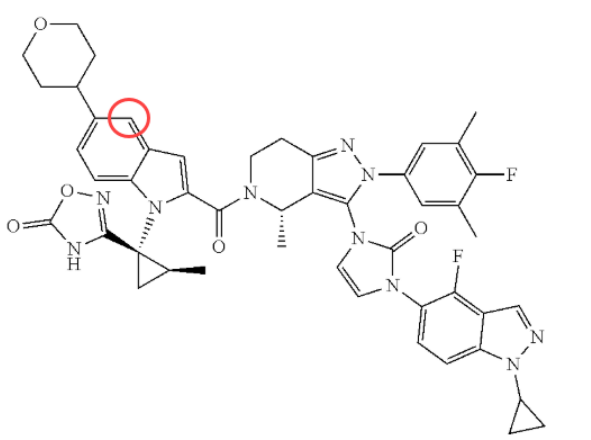
65



272. In my opinion, claim 1 would have been obvious over the prior art, at least with respect to Compound 65.

273. Compound 65 of the ’236 patent differs from Compound 19—previously addressed in Grounds 1 and 2—by the substitution of a nitrogen atom into the aromatic ring that is fused to the pyran moiety. Specifically, whereas

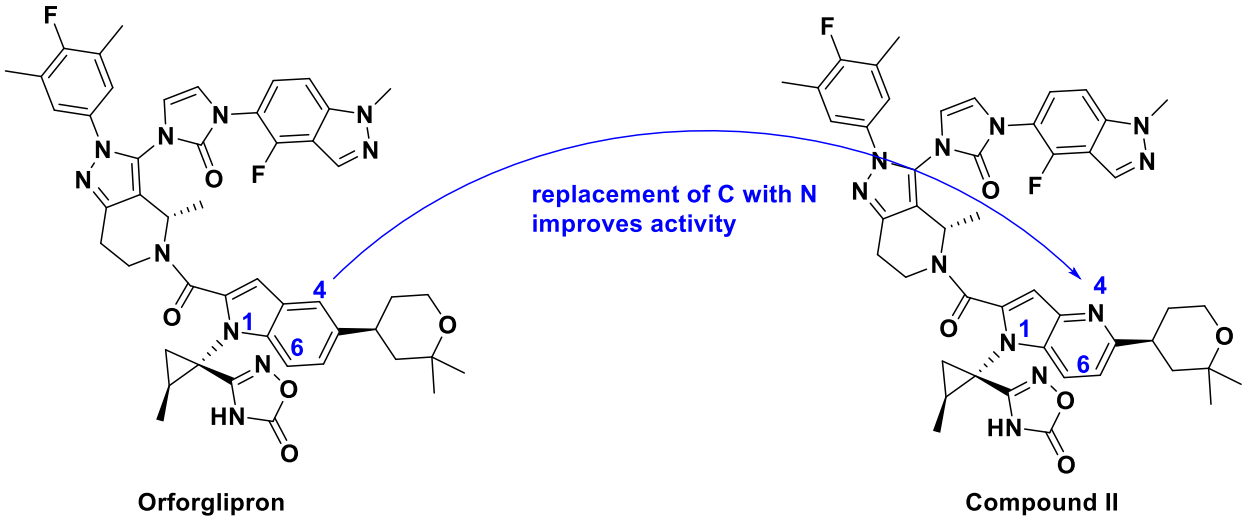
Compound 19 contains a benzene ring, Compound 65 incorporates a nitrogen atom within this same ring, effectively converting it to a pyridine derivative. This seemingly modest structural modification is highlighted below and reflects a well-established medicinal chemistry approach used to optimize pharmacokinetic and pharmacodynamic properties.

| **Compound 65 of the '236 patent** | **Compound 19 of the '236 patent** |
|---|---|
| 65  | 19  |

274. As previously discussed in Grounds 1 and 2, it would have been obvious for a POSA to arrive at Compound 19 in view of the combined teachings of Su, Yoshino, Kawai, and Talele.

275. Building upon the structure of Compound 19, Meng teaches the rational incorporation of an additional nitrogen atom into the aromatic core of orforglipron analogs. In particular, Meng discloses and claims Compound (II) which incorporate an additional nitrogen atom relative to the core scaffold of orforglipron. (See

EX1028 at 2–3, claim 5, ¶¶ [0020]–[0025]; Examples 1–3; EX1029 at 2–3, claim 5, ¶¶ [0020]–[0025].) Structurally, Compound (II) is nearly identical to orforglipron, differing only by the presence and location of an additional nitrogen atom within the aromatic ring. A comparison between orforglipron and Compound (II) is shown below.




(See id.)

276. Notably, Compound (II) is one of the only two compounds in Meng that are structurally and functionally characterized. (Id. at ¶¶[0027]–[0192]; Examples 1–3.) Meng also reports a comparative study evaluating these compounds against a reference compound, identified as Compound 67 of TW201827426. (Id. at ¶¶[0186]-[0192].) I understand that TW201827426 is the Taiwanese counterpart of Yoshino, and that Compound 67 disclosed therein is the same as Compound 67 of Yoshino—chemically identical to orforglipron. The data from the comparative study reported in Meng demonstrate that the introduction of a nitrogen atom into the

aromatic core of orforglipron analogs can significantly enhance GLP-1 receptor potency. (Id.) Specifically, Compound (II) is 1.6-fold more potent than orforglipron, as evidenced by its lower $EC_{50}$ value. (Id.) A POSA, reviewing this data, would reasonably infer that such nitrogen incorporation is a viable and advantageous strategy for improving agonist efficacy.

277. In my opinion, a POSA presented with the teachings of Meng and the known structure of Compound 19 would have been motivated to apply the structural optimization strategies disclosed in Meng. The modification of Compound 19 to include a nitrogen atom at the aromatic ring—positions shown by Compound (II) of Meng to confer enhanced potency—would have been a logical and predictable design choice. The resulting structure corresponds to Compound 65 of the ’236 patent.

278. Furthermore, the strategy of introducing nitrogen atoms into aromatic systems is deeply embedded in medicinal chemistry practice. Patel, for example, explains that pyridine is not only the most common aromatic heterocycle in FDA-approved drugs, but also a widely used isostere for benzene due to its ability to modulate lipophilicity, solubility, metabolic stability, and hydrogen-bonding potential—all while maintaining desirable features such as planarity and π-stacking capability. (Patel at 1.) Patel notes:

> **Pyridine is the most common aromatic heterocycle and the second most common heterocycle found in FDA-**

> **approved drugs in the United States. It is known as an important benzene isostere and used to modulate lipophilicity and improve aqueous solubility, metabolic stability, and hydrogen-bond capability, while still maintaining benzene-like characteristics such as planarity and π-stacking, attributes which saturated carbocyclic isosteres dramatically disrupt.** Indeed, drug discovery programs routinely undergo systematic nitrogen atom scans (N-scans), **wherein a CH unit in a lead compound is replaced with a nitrogen atom in an effort to improve molecular and physicochemical properties**. This so-called "**necessary nitrogen atom**" effect has been shown to improve a variety of key pharmacological parameters including potency anywhere from 10- to 1000-fold.

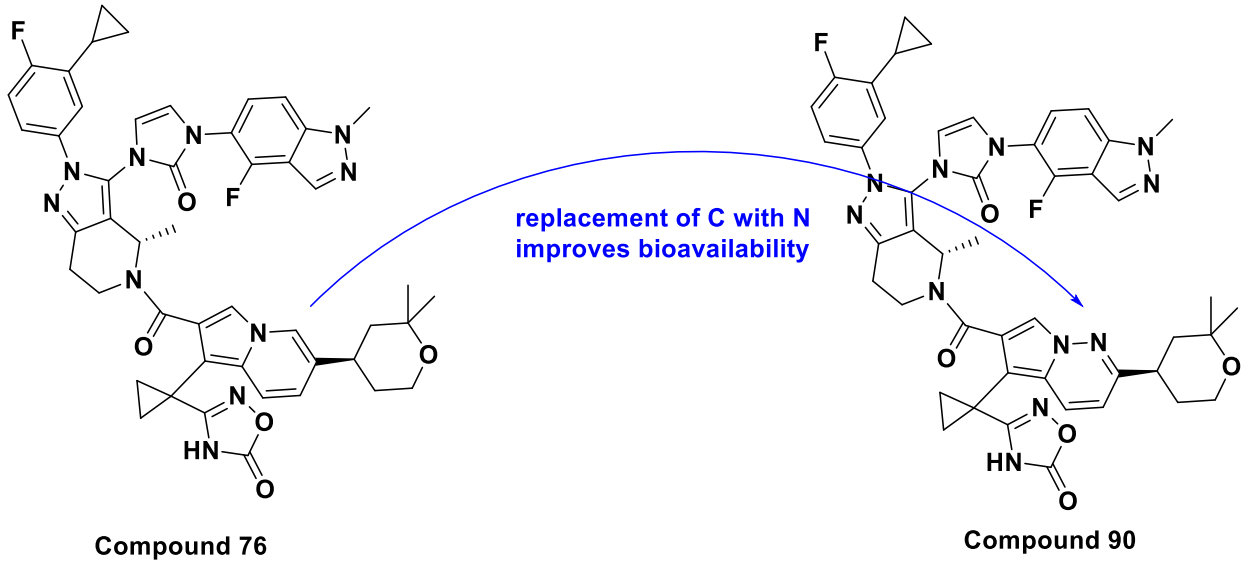
(Id. (emphases added))

279. The concept of the "necessary nitrogen atom" was introduced in a 2017 review article by Pennington et al. as a high-impact structural feature in medicinal chemistry. (EX1027) As described in the abstract of the article, the "necessary nitrogen atom" is a "versatile high-impact design element for multiparameter optimization," capable of yielding "≥10-, 100-, or 1000-fold improvement in a variety of key pharmacological parameters." (Id. at 1.)

280. Therefore, a POSA seeking to further enhance the drug-like characteristics of Compound 19—already a reasonable design choice per Grounds 1 and 2—would have been strongly motivated to introduce a nitrogen atom into the aromatic ring as a rational and predictable optimization step. Such a modification would be expected to improve solubility, potency, metabolic stability, and

ultimately, oral bioavailability. The resulting compound—Compound 65—reflects the application of this well-known medicinal chemistry strategy.

281. Additional support for the beneficial effects of nitrogen substitution is found in Ren, which discloses Compounds 76 and 90, as shown below. (EX1030 at 393:1-67, 445:1-67.) These compounds differ solely in that Compound 90 incorporates an additional nitrogen atom at the aromatic ring. (Id.)




Compound 76 Compound 90

282. Ren provides pharmacokinetic data in Table 30 below for only four disclosed compounds including Compound 90 and 76, demonstrating that Compound 90, which contains the additional nitrogen atom, exhibits substantially improved oral bioavailability compared to Compound 76. (Id. at 459:46–460:30, Example 81.) Specifically, the bioavailability (F%) of Compound 90 is reported as 59%, compared to only 30% for Compound 76, a nearly two-fold improvement attributed to the nitrogen substitution. (Id.)

TABLE 30-continued

| | PO parameters | | | |
|---|---|---|---|---|
| Cmpd No. | Dose (mg/kg) | $C_{max}$ (ng/mL) | AUC (ng hr/mL) | F (%) |
| 73 | 5 | 1700 | 10193 | 90 |
| 76 | 5 | 962 | 5321 | 30 |
| 90 | 5 | 1370 | 3338 | 59 |
| 91 | 5 | 738 | 2661 | 22 |

283. These data would have reinforced to a POSA the practical benefit of introducing nitrogen atoms into aromatic systems. In the case of Compound 19, incorporating a nitrogen at the position—consistent with Compound (II) of Meng and Compound 90 of Ren—would have been viewed as a rational strategy to enhance potency, bioavailability, and overall pharmacological profile. Thus, Compound 65 represents a predictable optimization of Compound 19 using well-established principles and concrete prior art teachings.

284. With regard to "a pharmaceutically acceptable salt thereof" recited in claim 1, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including "a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt." (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Su also discloses GLP-1 receptor

agonists and pharmaceutically acceptable salts thereof. (EX. 1007 at 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.)

285. Accordingly, in view of the teachings of Su, Yoshino, Kawai, and Talele, claim 1 of the ’236 patent would have been obvious to a POSA, at least with respect to Compound 65.

**2. Claim 2**

286. In my opinion, claim 2 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 2 depends from claim 1 and recites “the pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, a calcium salt, a potassium salt, a magnesium salt and a lithium salt.”

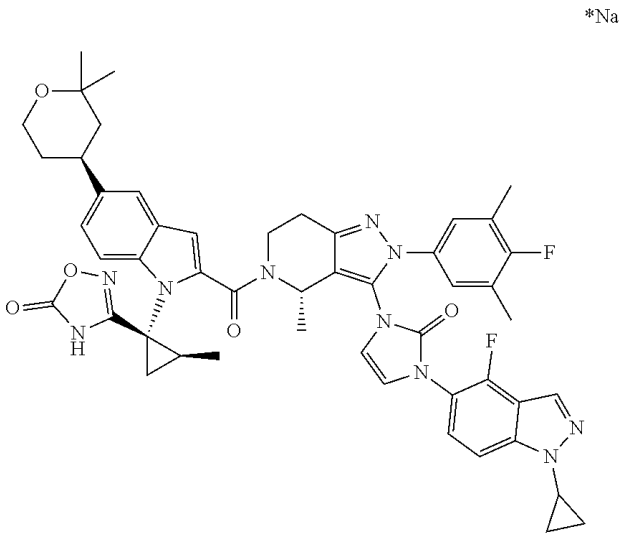
287. Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including “a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt.” (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) In view of the teaching of Yoshino, it would have been obvious for a POSA to prepare a sodium salt or a calcium salt of Compound 65 as recited in claim 2 of the ’236 patent.

288. Accordingly, claim 2 of the ’236 patent would have been obvious to a POSA over the prior art.

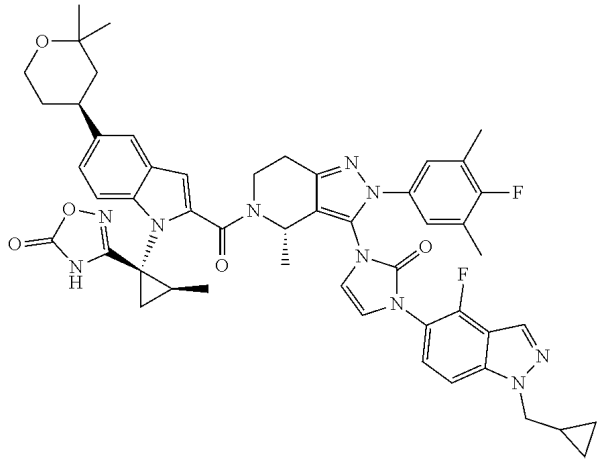
### 3. Claim 3

289. In my opinion, claim 3 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 3 depends from claim 1 and recites:

> the pharmaceutically acceptable salt is selected from the group consisting of:



*Na



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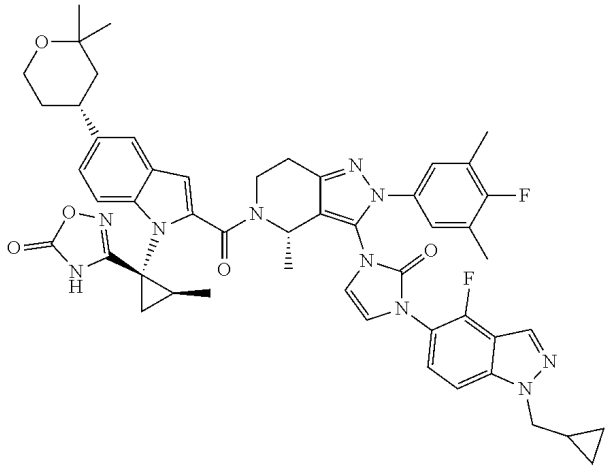
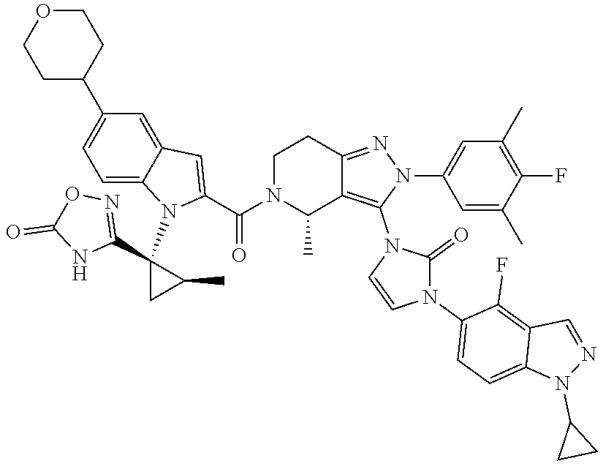
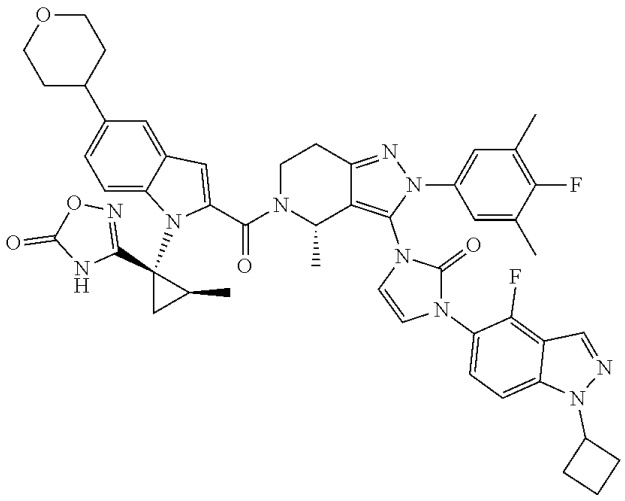


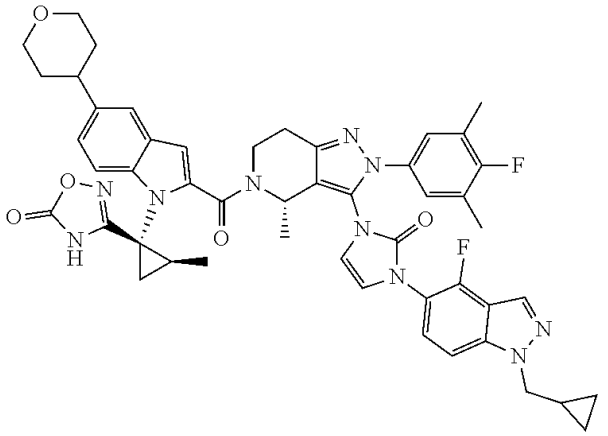
*Na



*Na

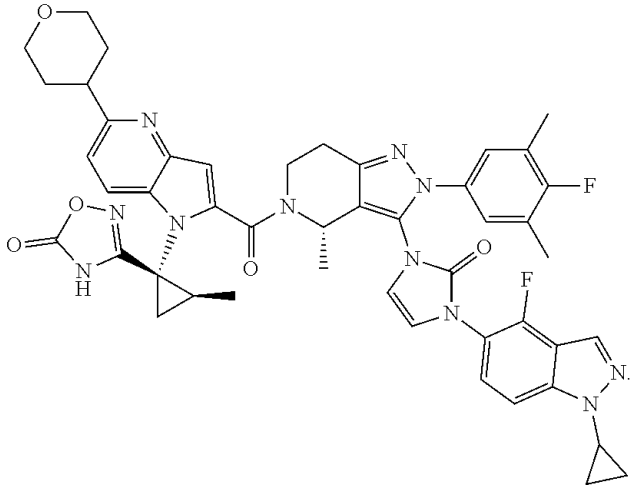


*Na



and

*Na



290. Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof or a calcium salt thereof, including "a hydrate of the free form, a salt of the free form, and a hydrate of salt, more preferably, a free form, a hydrate of the free form, a sodium salt of the free form, a hydrate of a sodium salt, a calcium salt of the free form, and a hydrate of the calcium salt." (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) As discussed above with respect to claims 1 and 2, it would have been obvious for a POSA to prepare a sodium salt or a calcium salt of Compound 65 as recited in claim 3 of the '236 patent.

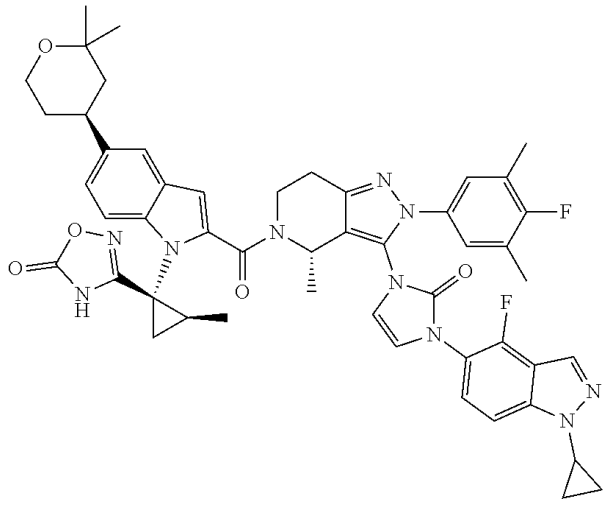
291. Accordingly, claim 3 of the '236 patent would have been obvious to a POSA over the prior art.

**4. Claim 4**

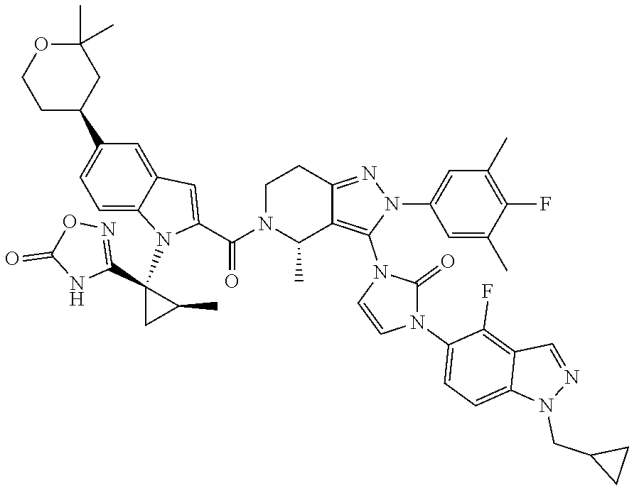
292. In my opinion, claim 4 of the '236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 4 depends from claim 1 and recites:

> the pharmaceutically acceptable salt is selected from the group consisting of:

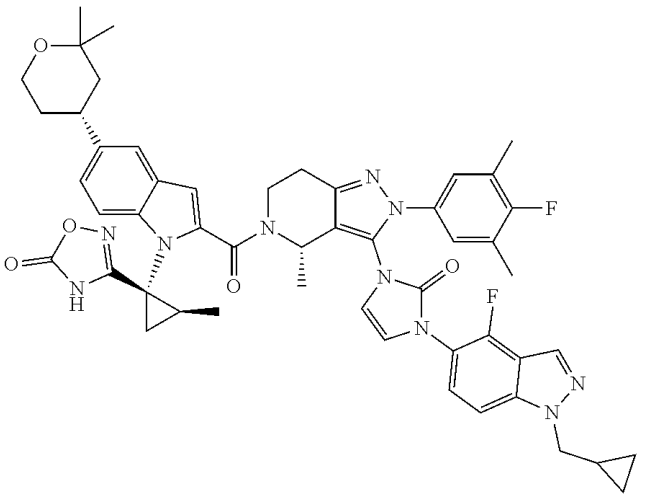
*1/2 Ca



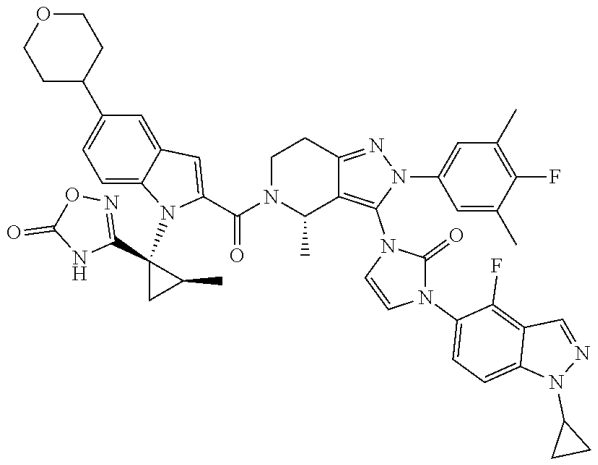
*1/2 Ca



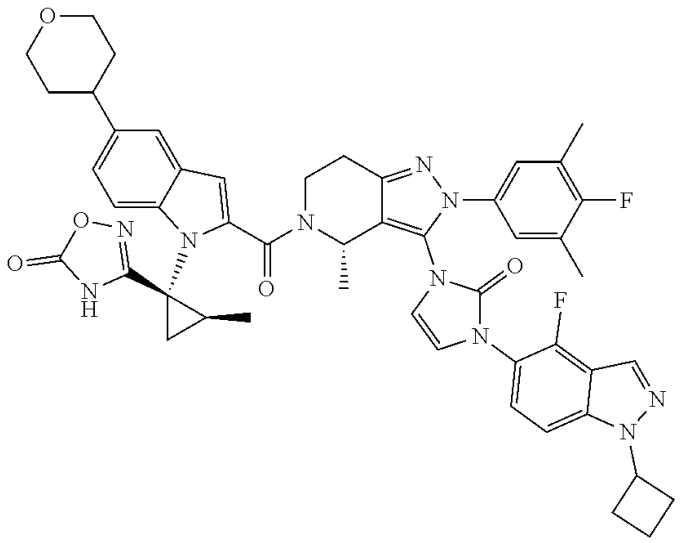
*1/2 Ca



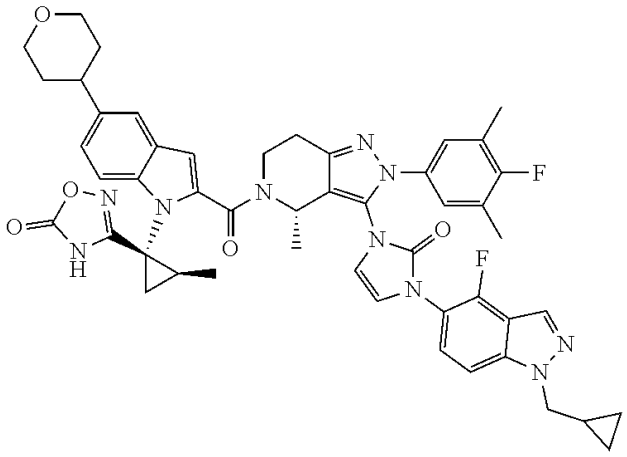
*1/2 Ca



*1/2 Ca

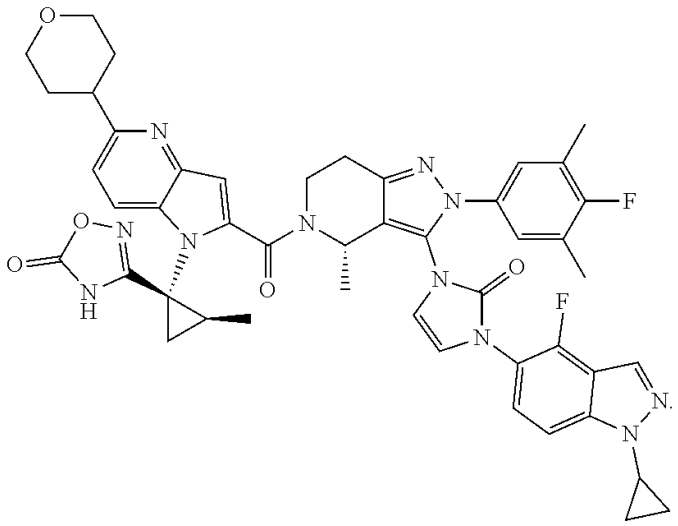


*1/2 Ca



and

*1/2 Ca



293. As discussed above with respect to claim 2, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a calcium salt thereof, including a calcium salt of the free form and a hydrate of the calcium salt. (EX1008 at 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare a calcium salt of Compound 65 as recited in claim 4 of the '236 patent.

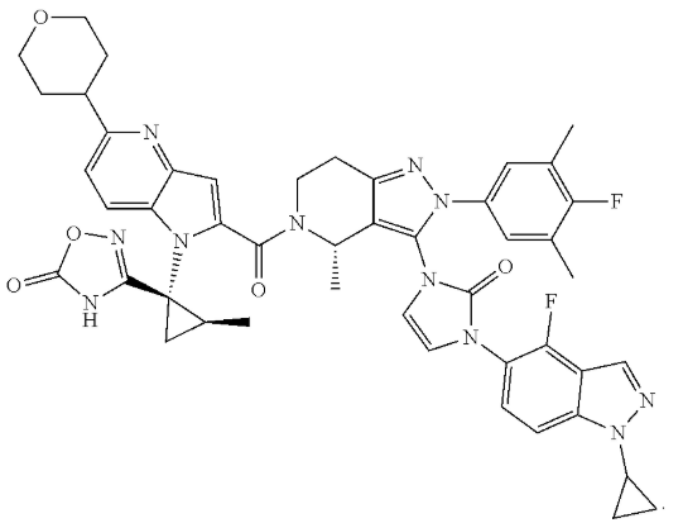
294. Accordingly, claim 4 of the '236 patent would have been obvious to a POSA over the prior art.

**5. Claim 21**

295. In my opinion, claim 21 of the '236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 21 depends from claim 1 and recites:

wherein the compound is

65

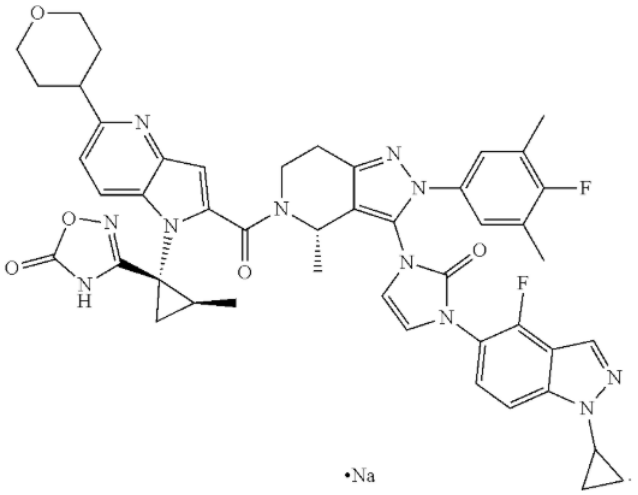


296. As discussed above with respect to claim 1, it would have been obvious to a POSA to arrive at Compound 65 as recited in claim 21 of the ’236 patent. Accordingly, claim 21 of the ’236 patent would have been obvious to a POSA in view of the prior art.

### 6. Claim 22

297. In my opinion, claim 22 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1-3. Claim 22 depends from claim 1 and recites:

the pharmaceutically acceptable salt is

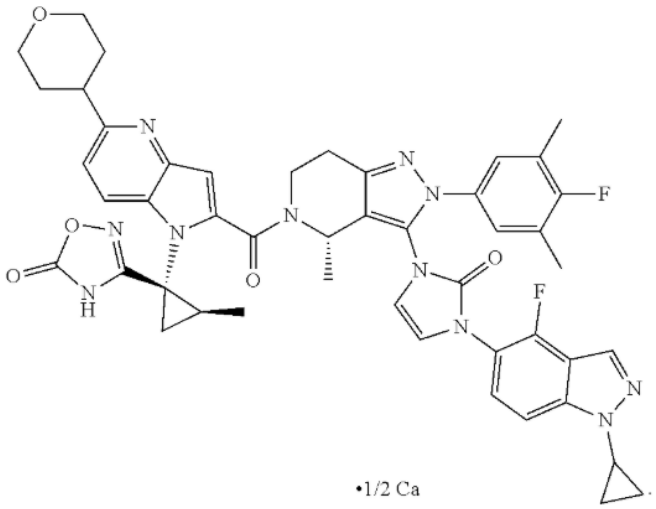



298. As discussed above with respect to claims 1-3, it would have been obvious to a POSA to prepare a sodium salt of Compound 65 as recited in claim 22 of the ’236 patent. Accordingly, claim 22 of the ’236 patent would have been obvious to a POSA in view of the prior art.

### 7. Claim 23

299. In my opinion, claim 23 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 2, and 4. Claim 23 depends from claim 1 and recites:

> the pharmaceutically acceptable salt is



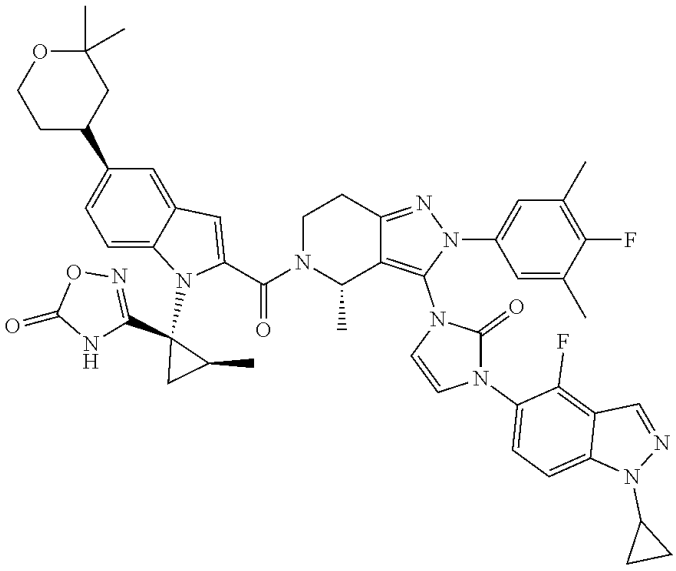

300. As discussed above with respect to claims 1, 2, and 4, it would have been obvious to a POSA to prepare a calcium salt of Compound 65 as recited in claim 23 of the ’236 patent. Accordingly, claim 23 of the ’236 patent would have been obvious to a POSA in view of the prior art.

**8. Claim 24**

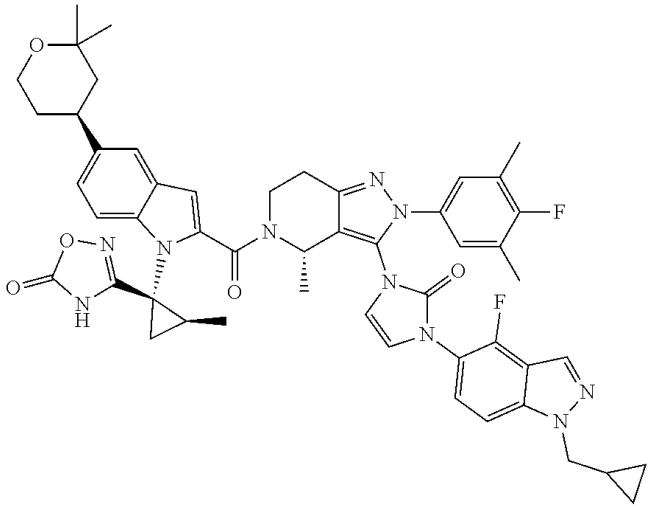
301. In my opinion, independent claim 24 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 21. Claim 24 recites:

A compound, selected from the group consisting of:

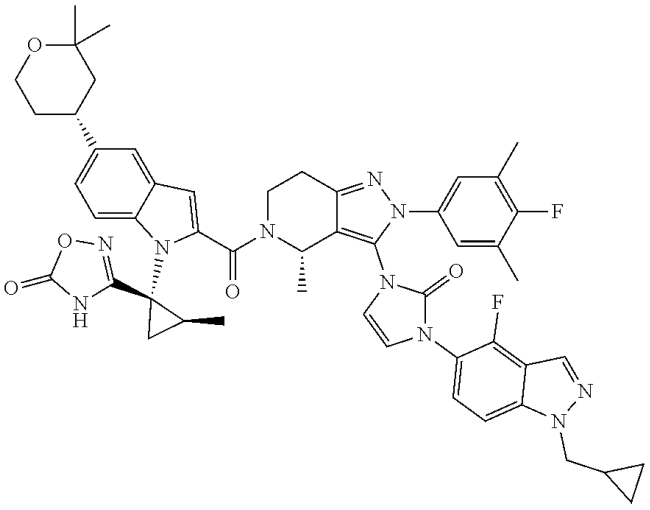
1



13



18



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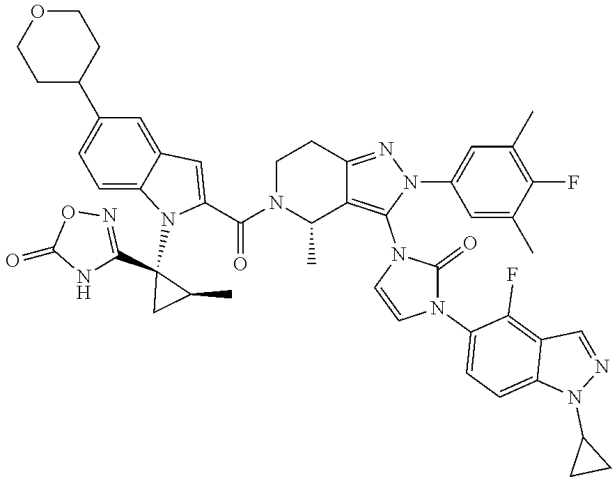
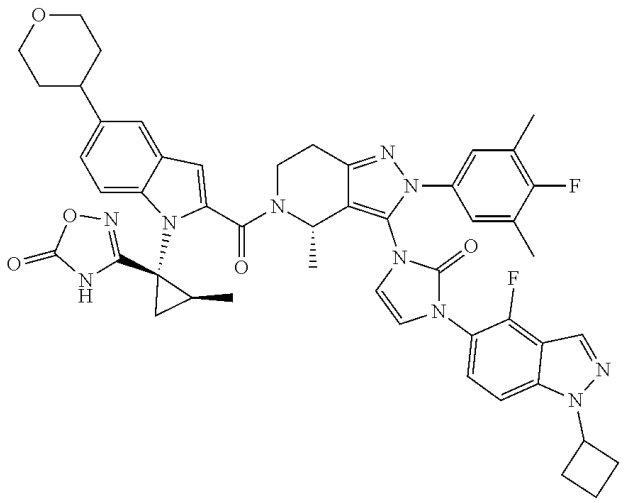
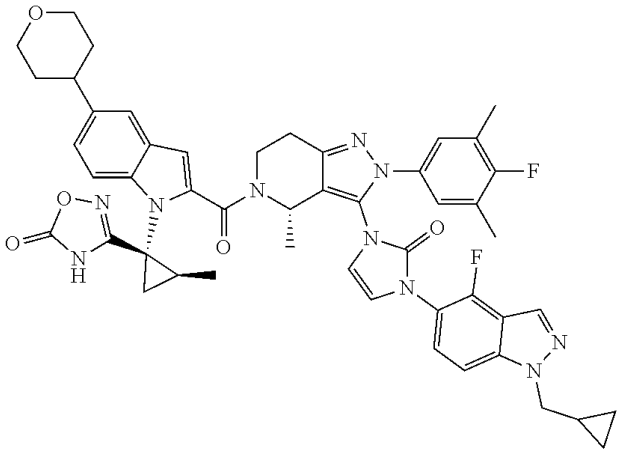


20

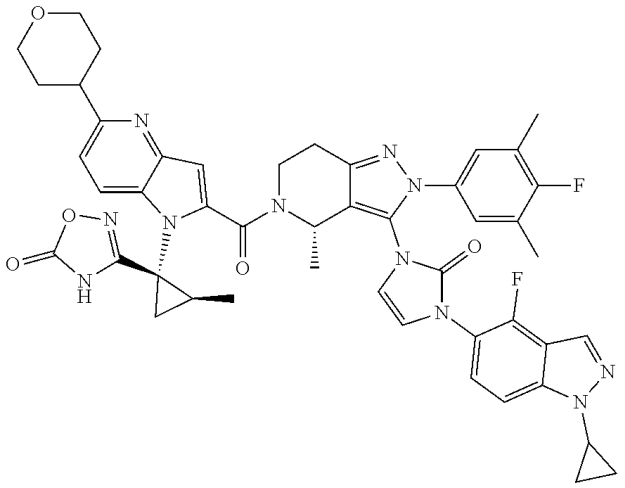


21



and

65



302. As discussed above with respect to claims 1 and 21, it is obvious for a POSA to arrive at Compound 65.

303. Accordingly, claim 24 of the ’236 patent would have been obvious to a POSA over the prior art.

### 9. Claim 25

304. In my opinion, claim 25 of the ’236 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 25 depends from claim 1 and recites, “A pharmaceutical composition, comprising the compound or the pharmaceutically acceptable salt thereof of claim 1, and a pharmaceutically acceptable excipient.”

305. Yoshino discloses various pharmaceutical formulations and a pharmaceutically acceptable additive that includes an excipient. (EX1008 at 35:45-

67.) Su also discloses GLP-1 receptor agonists and pharmaceutically acceptable salts thereof. (EX. 1007 at 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.)

306. Accordingly, claim 25 of the ’236 patent would have been obvious to a POSA over the prior art.

### D. GROUND 4: CLAIMS 4 and 9 WOULD HAVE BEEN OBVIOUS OVER SU AND BETHEL

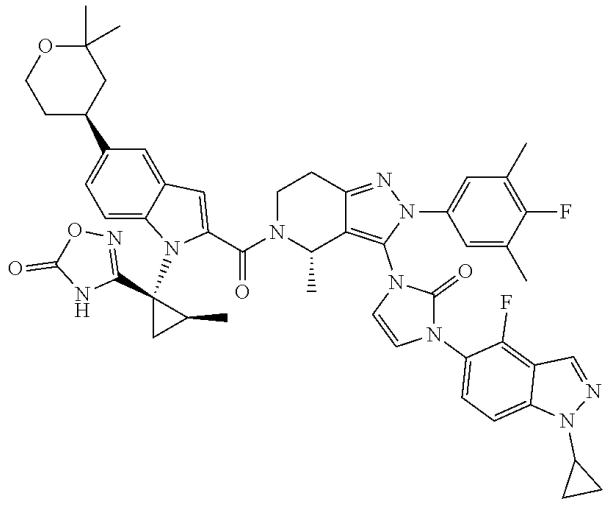
307. As addressed in Section IX.C, claims 4 and 9 are not entitled to an earlier priority date than 2024. Accordingly, Su and Bethel qualify as prior art with respect to at least claims 4 and 9. As discussed below, in my opinion, claims 4 and 9 would have been obvious at least with respect to ½ calcium salt of Compound 1 in view of the state of the art and the general knowledge of a POSA before the effective filing date of the ’236 patent, in particular, Su and Bethel. In particular, the teachings of Su and Bethel, which are discussed in detail above in Section VIII, provide a clear motivation and reasonable expectation of success for the claimed subject matter.

#### 1. Claim 4

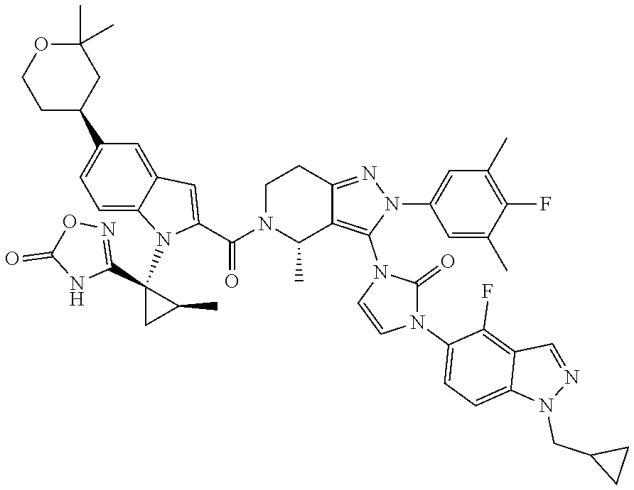
308. In my opinion, claim 4 of the ’236 patent would also have been obvious in view of Su and Yoshino. Claim 4 depends from claim 1 and recites:

the pharmaceutically acceptable salt is selected from the group consisting of:

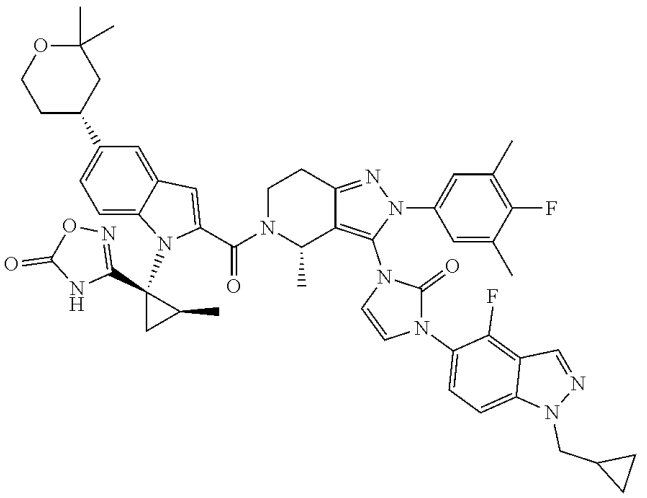
*1/2 Ca



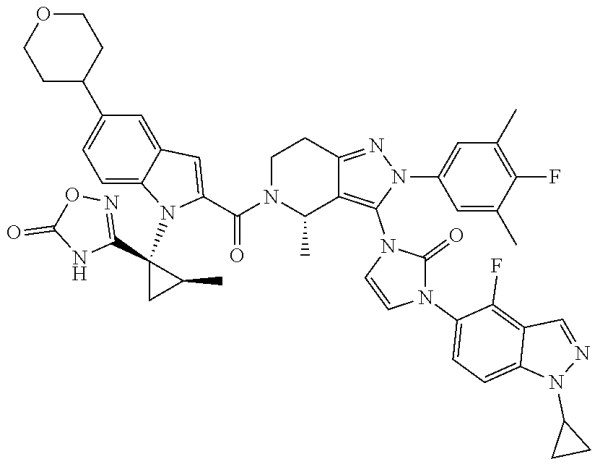
*1/2 Ca



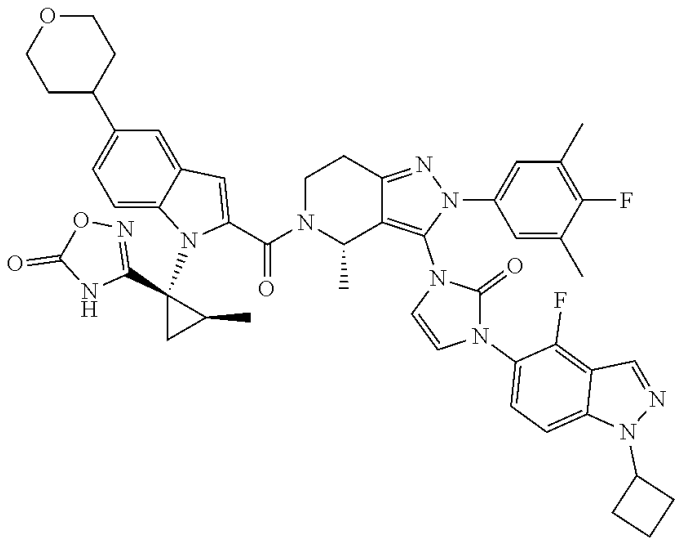
*1/2 Ca



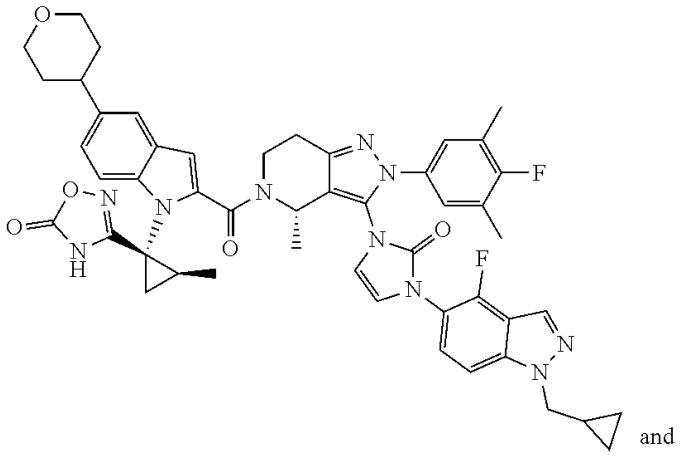
*1/2 Ca



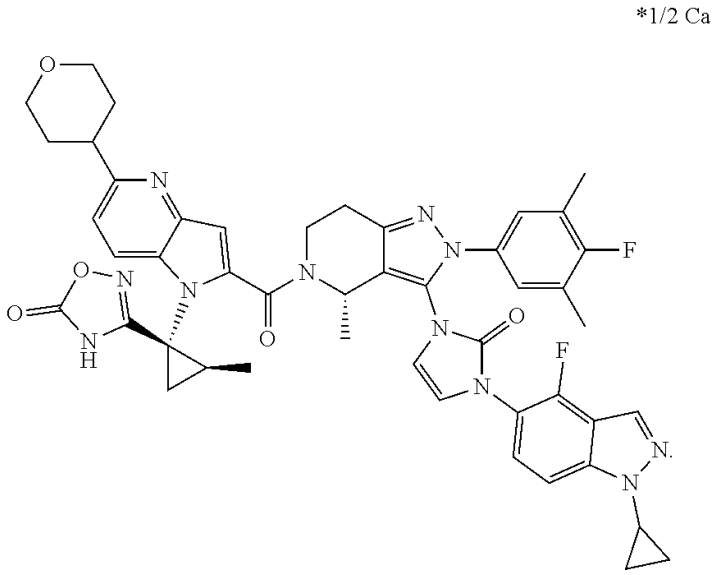
*1/2 Ca



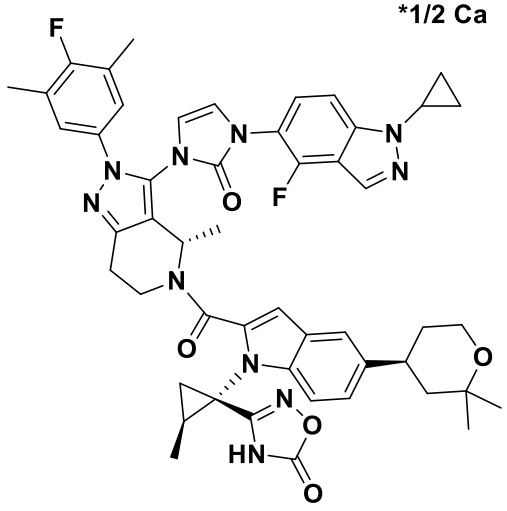
*1/2 Ca

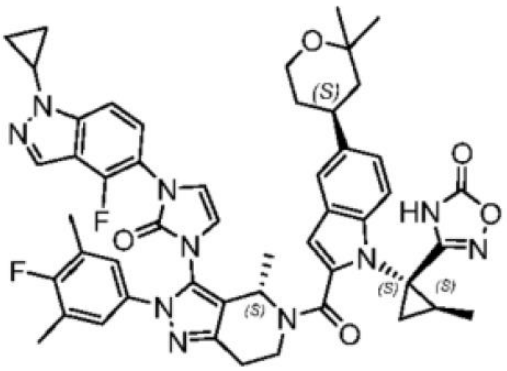


and




309. A comparison between ½ Ca salt of Compound 1 and the teachings of Su and Yoshino are provided in the chart below:

| | |
|---|---|
|   **Compound 1** | **Su** discloses and claims: Compound 175 (see below), which is chemically identical to Compound 1 of the '236 patent. (See EX1006 at 328, 329, and claim 12; EX1007 at 328, 329, and claim 12.) As discussed in Ground 1, a POSA would have recognized Compound 175 as particularly significant for potential drug development, at least because it was specifically selected for deuteration, indicating its value as a lead compound. |

| | |
|---|---|
| | <br>**Compound 175**<br><br>**Bethel** discloses preparation of capsule and tablet formulation of the ½ calcium salt of orforglipron and positive clinical outcomes for the ½ calcium salt of orforglipron in late-stage studies. (EX1032 at 46-74.)<br><br>In view of the combined teachings of Su and Bethel, it would have been obvious to a POSA to prepare a calcium salt of Compound 175, thereby arriving at the ½ calcium salt form of Compound 1 as recited in Claims 4 and 9 of the '236 patent. |

310. Su discloses and claims Compound 175, which is chemically identical to Compound 1 of the '236 patent. (See EX1006 at 328, 329, and claim 12; EX1007 at 328, 329, and claim 12.) As explained in Ground 1, a person of ordinary skill in the art ("POSA") would have recognized Compound 175 as a promising lead compound for drug development, in part because it was specifically chosen for deuteration, signaling its importance for further optimization.

311. Bethel discloses methods of treating subjects with type 2 diabetes (T2D), obesity, or overweight with at least one weight-related comorbidity using Compound 1a, a non-peptide GLP-1 receptor agonist (NPA), administered orally. (Id.) Compound 1a is chemically identical to orforglipron. (Id. at 4.) Example 1 describes preparation of Spray-Dried Dispersion (SDD) of ½ Ca salt of orforglipron, Example 2 describes preparation of a capsule formulation of ½ Ca salt of orforglipron, and Example 3 describes a tablet formulation of the same salt. (Id. at 46–53.) Examples 4A and 4B present Phase 2 clinical data involving patients with obesity or overweight who received various oral doses of the ½ calcium salt of orforglipron. (Id. at 53–66.) Bethel further reports that, "Compound la was well tolerated across all arms. Liver function tests were not significantly increased in participants receiving Compound la compared with placebo," and "The percentages of participants achieving HbAlc and weight loss targets in the various groups are shown in Fig. 7." (Id. at 55, 59.) Examples 5 and 7–12 further describe Phase 3 clinical trials using the ½ calcium salt formulation of orforglipron. (Id. at 66–70, 71–74.)

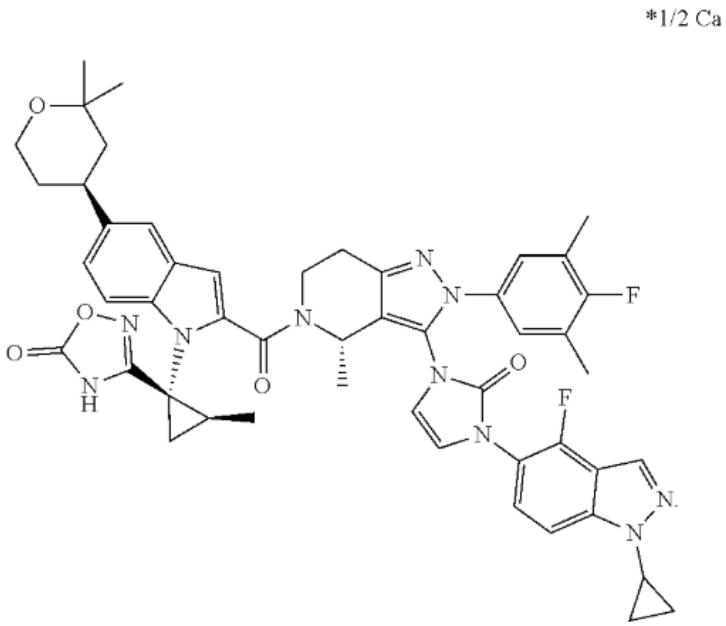
312. In my opinion, given the positive clinical outcomes reported by Bethel for the ½ calcium salt of orforglipron in late-stage studies, a POSA would have been motivated to prepare a calcium salt of Compound 175, which is chemically identical to Compound 1 as recited in claim 4. The combined teachings of Su and Bethel

provide a clear rationale for selecting a calcium salt in this context. Moreover, Bethel demonstrates that the ½ calcium salt of orforglipron can be successfully prepared, supporting a reasonable expectation of success. Accordingly, it would have been obvious to a POSA to prepare a calcium salt of Compound 175, thereby arriving at the ½ calcium salt of Compound 1 as claimed in claims 4 and 9 of the '236 patent.

**2. Claim 9**

313. In my opinion, for the same reasons discussed above for claim 4, claim 9 of the '236 patent would also have been obvious in view of Su and Yoshino. Claim 9 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



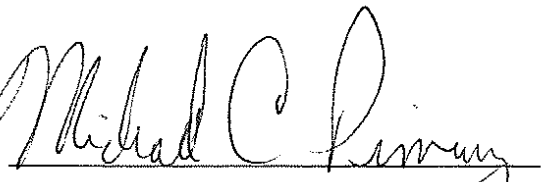

314. As discussed above for claim 4, based on the combined teachings of Su and Yoshino, it would have been obvious to a POSA to prepare a calcium salt of

Compound 175, thereby arriving at the ½ calcium salt of Compound 1 as claimed in Claim 9 of the '236 patent.

## XI. CONCLUSION

315. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

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

Signature: 

Michael C. Pirrung, Ph.D.

Date: June 15, 2025

# APPENDIX A

# Curriculum Vitae

## MICHAEL C. PIRRUNG

April, 2025

Department of Chemistry
University of California
Riverside, CA 92521-0403

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EDUCATION: University of Texas, Austin, September 1973-December 1975
B.A. in Chemistry with Highest Honors.
University of California, Berkeley, September 1976-June 1980
Ph.D. in Organic Chemistry (with C. H. Heathcock).
Columbia University, 1980-81
NSF Postdoctoral Fellow in Organic Chemistry (with G. Stork).

HONORS: Phi Beta Kappa, December 1975.
Fellow, Fannie and John Hertz Foundation, 1978-80.
Award for Newly-Appointed Faculty, Dreyfus Foundation, 1982-87.
Grantee, Eli Lilly, 1984-86.
Presidential Young Investigator, NSF, 1985-90.
Research Fellow, Alfred P. Sloan Foundation, 1986-88.
Newcomb Cleveland Prize, AAAS, 1991 (best paper in *Science*).
Distinguished Inventor Award, Intellectual Property Owners, 1993.
Fellow, John Simon Guggenheim Memorial Foundation, 1994-95.
Outstanding Young Texas Ex Award, University of
Texas Ex-Student's Association, 1995.
Fellow, American Association for the Advancement of Science, 1996.
Chemical Pioneer Award, American Institute of Chemists, 2004.
UC Presidential Chair in Chemistry, UC-Riverside, 2004-09.
European Inventor of the Year, European Patent Office, 2006.
Fellow, National Academy of Inventors, 2016.

POSITIONS: Assistant Professor of Chemistry, Stanford University, 1981-1989.
Senior Scientist, Affymax Research Institute, Palo Alto, CA, 1989.
Associate Professor of Chemistry, Duke University, 1989-94.
Director, University Program in Biological Chemistry, 1994-2004.
Founder and Director, Biotechnology for Business, 1993-2013.
Professor of Chemistry, Duke University, 1994-2004.
Professor of Chemistry, UC-Riverside, 2004-2012.
Distinguished Professor of Chemistry, UC-Riverside, 2012-.
Professor of Pharmaceutical Sciences (WOS), UC-Irvine, 2013-.

VISITING PROFESSORSHIPS: UC-Berkeley, 1988 (with P. A. Bartlett).
Department of Molecular and Human Genetics,
Baylor College of Medicine, 1994-5 (with C. T. Caskey).
Burroughs Wellcome Professor, Dyson Perrins Laboratory,
University of Oxford, 1995 (with Sir J. E. Baldwin).
UC-San Diego, 1998.
UC-Irvine, 2002.
Caltech, 2002.

RESEARCH: Chemical Biology.

RESEARCH INFO: https://profiles.ucr.edu/michael.pirrung

CURRENT AREAS
OF INTEREST: Organic Synthesis, Medicinal Chemistry, Molecular Diversity, Nucleic Acids, Bioorganic Chemistry, Photochemistry.

TOPICS OF
PAST RESEARCH
CONTRIBUTIONS: Photochemistry in Organic Synthesis, Ethylene Biosynthesis, Rhodium Carbenoids, Microarray Fabrication.

EDITORIAL BOARDS: *Journal of Combinatorial Chemistry*, 1998-2003.
*QSAR and Combinatorial Science*, 2002-2009.
*Cell Chemical Biology*, 2004-2020.
*H1 Connect*, 2012-2022.
*BioTech*, 2016-.

ADVISORY BOARDS: Genta, 1993-97.
Affymax Research Institute, 1994-95.
ChromaXome, 1995-9.
Oasis Biosciences, 1998-2002.
Orchid Biosciences, 1997-2003 (President's Fellow, 1999-2003).
Genicon Sciences, 2000-2003.
NimbleGen Systems, 2001-2005.
Hibiskus Biopharma, 2017-2020 (co-founder).
Lodo Therapeutics, 2020-2021.

CONSULTANCIES: DowElanco, 1985-1992.
Abbott Laboratories, 1991-94.
American Cyanamid, 1992-98.
Affymax Research Institute, 1990-98.
A. M. Pappas & Associates, 1997-2004.
Wyeth Pharmaceuticals, 1995-2009.

SELECT PLENARY/
NAMED LECTURES: ACS Nobel Laureate Signature Award Symposium, Miami, 1985.
Oregon/Oregon State Snow Symposium, Bend, 1986.
ACS Guenther Award Symposium, Boston, 1989.
Pfizer Distinguished Lecturer, Colorado State University, 1993.
Suddath Symposium, Georgia Institute of Technology, 1995.
Round Table, Rhône-Poulenc Rorer, 1996.
ACS N. Alabama Section, Madison Marshall Award Symposium, 1996.
5th Visions in Chemistry Symposium, Rhône-Poulenc Rorer, 1997.
Seminaire Hors-Ville, 3ème Cycle en Chimie, Champéry, 1997.
VII International Meeting, Human Genome Project, Valencia, 2000.
Bayer Seminar, University of Pennsylvania, 2001.
Roche Colorado Distinguished Lecturer, CU-Boulder, 2001.
German Chemical Society, Würzburg, 2001.
*Organic Syntheses* Lecturer, Wayne State University, 2008.

MEMBERSHIPS: American Chemical Society (ORGN, MEDI, CHAS).
Fellow, American Association for the Advancement of Science.
Fellow, American Institute of Chemists (FAIC).
Fellow and Life Member, National Academy of Inventors (FNAI).
The Author’s Guild.

RESEARCH STUDENTS:

| Name | Current position | Training |
|---|---|---|
| Steven Dunlap | Eli Lilly & Co. | M.S., 1985 |
| Jerry McGeehan | Syndax Pharmaceuticals | Ph.D., 1985 |
| Richard Graham | Allergan | Postdoctoral |
| Michelle Gerard | Family leave | Postdoctoral |
| Nicholas Webster | UC-San Diego Medical School | Ph.D., 1986 |
| John Werner | Eli Lilly & Co. (ret'd) | Ph.D., 1987 |
| Steve Thomson | Ten63 Therapeutics | Ph.D., 1987 |
| Carl DeAmicis | Dow AgroSciences | Ph.D., 1987 |
| Paul Kenney | ThermoFisher | Postdoctoral |
| David Nunn | | Ph.D., 1991 |
| Virginia Chang | Family leave | M.S., 1988 |
| Chris Holmes | Regado Biosciences | Postdoctoral |
| Hyun-Joon Ha | Hankuk University | Postdoctoral |
| Uwe Trinks | IQVIA | Postdoctoral |
| Pierre Laughton | Medical Clinic of North Texas | Postdoctoral |
| Daniel Horowitz | US Chemical Safety Board | M.S., 1989 |
| William Brown | ASTRA Montreal | Postdoctoral |
| Sushil Rege | Abbott Molecular | Postdoctoral |
| Murthy Nacharaju | ThermoFisher | Postdoctoral |
| Larry Zhang | Guangzhou Institute of Biomedicine | Postdoctoral |
| Elizabeth Rowley | Princeton Innovation Center | Postdoctoral |
| Ronald Tepper | R.T. Vanderbilt Co. | Postdoctoral |
| Richard Ludwig | Bristol Myers Squibb | Postdoctoral |
| Karen Lackey | Evotec | M.S., 1994 |
| David Lever | Ohio Wesleyan University | Postdoctoral |
| Steve Shuey | DuPont | Postdoctoral |
| Hyunsoo Han | University of Texas-San Antonio | Postdoctoral |
| J.-C. Bradley | Deceased | Postdoctoral |
| Jun Cao | | M.S., 1994 |
| Yong Rok Lee | Yeung Nam University | Postdoctoral |
| Muthukumar Ramaswamy | Wyeth Biotech | Postdoctoral |
| Joyce Huang | Genesis Drug Discovery | Postdoctoral |
| William Hawe | Shopzilla | Postdoctoral |
| William Sherwin | AUS Therapeutic Goods Administration | Postdoctoral |
| Joseph H.-L. Chau | Chau Pharma Consulting | Postdoctoral |
| N. Chidambaram | US Food and Drug Administration | Postdoctoral |
| Sara Nauhaus Birbaum | Parexel | M.S., 1995 |
| Andrew Morehead | East Carolina University | Ph.D., 1996 |
| Shin Han | Shin Poong Pharma | Postdoctoral |
| James Springer | Graham High School, NC | Postdoctoral |
| Jrlung Chen | SETI Institute | Postdoctoral |
| Thomas Oliver | US Food and Drug Administration | Postdoctoral |
| Lara Fallon | Pfizer-Montreal | Ph.D., 1997 |
| M. Montague-Smith | University of Maryland (ret'd) | Postdoctoral |
| Richard Connors | Grand Canyon University | Postdoctoral |
| Michael Campbell | Lakehead University, Thunder Bay, Ont. | Postdoctoral |
| Robb Nicewonger | Eisai, Inc. | Postdoctoral |
| Florian Blume | EUROAPI, Frankfurt | M.S., 1997 |
| Xiaodong Zhao | Abbott-San Diego | Postdoctoral |
| Wolfgang Pieper | SAP | Postdoctoral |
| Kurt Gothelf | Aarhus University | Postdoctoral |
| Tao Pei | Arrowhead Pharmaceuticals | M.S., 1999 |
| Xiaoming Zhou | Purdue Pharmaceuticals | Postdoctoral |
| Kenneth James | Seachaid Pharmaceuticals | Postdoctoral |
| Shannon Harris | Cardinal Health | Postdoctoral |
| Laixin Wang | Chongqing Denali Medpharma | Postdoctoral |

| | | |
|---|---|---|
| Irina Gazaryan | Burke Institute | Visiting Scholar |
| Sandra Drabik | Southwest Research Institute | Postdoctoral |
| Amy Odenbaugh | Jenkins, Wilson, Taylor & Hunt | Postdoctoral |
| Hunwoo Shin | SK Life Science-US | Postdoctoral |
| Romuald Baudelle | Chem-X-Infinity | Postdoctoral |
| Jin Zhu | Eckert Seamans Cherin & Mellott | Postdoctoral |
| Krishna Kaliappan | IIT, Bombay | Postdoctoral |
| Andrea Saurage | Glen Raven | Postdoctoral |
| Lisa Ford | Metabolon | Ph.D., 2001 |
| Kaapjoo Park | RedGene Korea | Postdoctoral |
| Sunil Pansare | Memorial University of Newfoundland | Visiting Scholar |
| Chaozhong Cai | Abzena | Postdoctoral |
| Zheng Zhou | | M.S., 2001 |
| Nathan Tumey | Binghamton University (SUNY) | Ph.D., 2001 |
| Michael Wedel | Boehringer Ingelheim | Postdoctoral |
| Debasis Das | Arromax Pharmatech | Postdoctoral |
| Yufa Liu | ACB SciTech | Postdoctoral |
| Hao Liu | Scynexis | Ph.D., 2002 |
| M. Dhananjeyan | Hospira | Postdoctoral |
| Koichi Fujita | Ajinomoto Pharmaceuticals | Visiting Scholar |
| Zhitao Li | Eastman Chemical | Ph.D., 2003 |
| Koushik Das Sharma | Sudarshan | Postdoctoral |
| Daniel Lim | Bristol Myers Squibb | M.S., 2004 |
| Liu Deng | Eastman Chemical | Ph.D., 2005 |
| Sankar Guchhait | NIPER Mohali | Postdoctoral |
| Chiyi Xiong | M.D. Anderson Cancer Center | Postdoctoral |
| Vipul Rana | Innovassynth Technologies India | Postdoctoral |
| Aparna Tanksale | Family leave | Postdoctoral |
| Yunfan Zou | UC-Riverside | Ph.D., 2006 |
| Irwin Loh | Clinical Research Compliance | M.S., 2006 |
| Walter Affo | University of Ghana | Postdoctoral |
| Subir Ghorai | Aldrich Chemical | Postdoctoral |
| Dennis Xiong | Novartis China | Postdoctoral |
| Hyunsoo Kim | Sequenom | Postdoctoral |
| Jianmei Wang | Amphastar Pharmaceuticals | Ph.D., 2007 |
| Yaodong Huang | Frontage Laboratories | Postdoctoral |
| Suvadeep Nath | Syngene | Postdoctoral |
| Surendra Gadamsetty | Aurigene Discovery Technologies | Postdoctoral |
| Biswajit Roy | Sikkim University | Postdoctoral |
| Andrei Kochegarov | UCLA-Medical School | Postdoctoral |
| Theresa Massoud | University of Balamand Dubai | Ph.D., 2010 |
| Tannya Ibarra | Autonomous University, Nuevo León | Postdoctoral |
| Goutam Biswas | Cooch Behar Panchanan Barma University | Postdoctoral |
| Yongfeng Zhao | Jackson State University | Postdoctoral |
| Gangadhara Rao | UMass-Dartmouth | Postdoctoral |
| Fa Zhang | Postdoctoral Fellow | Indiana University |
| Jenifer Nalbandian | California Baptist University | Ph.D., 2013 |
| Andrew Defries | 710 Vermont | Ph.D., 2013 |
| Sudhakar Ambadi | Sai Life Science Hyderabad | Postdoctoral |
| Yangfan Zheng | Ningbo | Postdoctoral |
| Allyson Dorsey | GT Medical Technologies | M.S., 2015 |
| Luca Gambini | Johnson & Johnson-Milan | Postdoctoral |
| Narendar Reddy Gade | Dalriada Drug Discovery | Postdoctoral |
| Nicole Bakas | RayzeBio | Ph.D., 2017 |
| Natalie de Howitt | Cell Care Therapeutics | Ph.D., 2018 |
| Ryan Schreihans | | M.S., 2018 |
| Alon Agua | City of Hope | Ph.D., 2021 |
| Ryan Stanton | | M.S., 2022 |

SELECT INVITED PRESENTATIONS, MAJOR MEETINGS:

02/19/2013 International Conference of Drug Discovery and Therapy, Dubai, UAE, "Synthesis and Biology of Natural Proteasome-Inhibiting Anticancer Agents"
12/17/2015 Pacifichem 2015, Honolulu, HI, "Structural Variations Enhancing the Bioluminescence of Luciferin"
12/12/2016 IUPAC International Conference on Organic Synthesis-21, Mumbai, "Serine Peptide Assembly (SPA) for Complex Polypeptide Synthesis"
12/17/2021 Pacifichem 2020, Honolulu, HI, "Peptide Hormone Assembly at Serine"

RECENT RESEARCH FUNDING:

07/21-06/26 NSF CHE 2109271 "Biosynthesis of Triplet States via Luciferase" $107,941/yr.
10/23-09/26 UC CRCC "Small Molecule Immuno-Oncology" $79,500/yr.

ACTIVE COLLABORATIONS:

| | | |
|---|---|---|
| Jiayu Liao | Bioengineering, UCR | Bioluminescence |
| Christopher Bardeen | Chemistry, UCR | Bioluminescence |

RECENT PROFESSIONAL SERVICE:

01/2017-12/2025 American Chemical Society, Committee on Patents and Related Matters
12/2021 Organizer, Pacifichem 2020 Symposium,
New Technologies in Peptide/Protein Synthesis
11/2021- American Chemical Society, Division of Organic Chemistry, Exec Comm
Manuscripts reviewed (2016-2025) 220
Nobel Prize, Macarthur Fellow, Lasker Award (invited nominations) 4

RECENT UNIVERSITY SERVICE:

2021-22: Molecular Medicine Program, Steering Committee
Chemistry Department, Organic and Organic Materials Search Committee, Chair

2022-23: Molecular Medicine Program, Steering Committee
Chemistry Department, Organic and Organic Materials Search Committee, Chair

2021-24: Faculty Senate, Committee on Memorial Resolutions

2024-25: Molecular Medicine Program, Steering Committee

RECENT COURSES TAUGHT:

| | | |
|---|---|---|
| 2022-23: | Chemistry 242. | Pharmaceutical Chemistry (graduate) |
| | Chemistry 8BH. | Introductory Organic Chemistry (honors lecture) |
| | Chemistry 8B. | Introductory Organic Chemistry (lecture) |
| 2023-24: | Chemistry 211C. | Synthetic Methods in Organic Chemistry (graduate) |
| | Chemistry 8BH. | Introductory Organic Chemistry (honors lecture) |
| | Chemistry 8CH. | Introductory Organic Chemistry (honors lecture) |
| 2024-25: | Chemistry 211C. | Synthetic Methods in Organic Chemistry (graduate) |
| | Chemistry 8CH. | Introductory Organic Chemistry (honors lecture) |

## Publications

(as a graduate student)

1. Clayton Heathcock, Michael Pirrung, and John Sohn, "Acyclic Stereoselection. 4. Assignment of Stereostructure to β-Hydroxy Carbonyl Compounds by Carbon-13 Nuclear Magnetic Resonance," *J. Org. Chem.*, **44**, 4294 (1979).
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9. Clayton Heathcock, Michael Pirrung, Steven Young, James Hagen, Esa Jarvi, Ulrich Badertscher, Hans-Peter Marki, and Stephen H. Montgomery, "Acyclic

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10. Stephen H. Montgomery, Michael Pirrung, and Clayton H. Heathcock, "(2*SR*,3*SR*)-2,4-Dimethyl-3-hydroxypentanoic acid [pentanoic acid, 3-hydroxy-2,4-dimethyl-, (*R**,*R**)-]," *Org. Synth.*, **63**, 99 (1985).

11. Stephen H. Montgomery, Michael Pirrung, and Clayton H. Heathcock, "De Novo Synthesis of Carbohydrates by Stereoselective Aldol Reaction: L-Cladinose," *Carbohyd. Res.*, **202**, 13 (1990).

(as an independent investigator)

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13. Michael C. Pirrung, "Total Synthesis of 2,4-Methanoproline," *Tetrahedron Lett.*, 4577 (1980).

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