

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CONJUPRO BIOTHERAPEUTICS, INC.,
Petitioner,

v.

Ascletis Pharma China Co Ltd,
Patent Owner.

Case No. PGR2025-00057

Patent No. 12,234,236

Title: GLP-1R agonist and therapeutic method thereof

**PETITION FOR POST GRANT REVIEW OF Claims 1-9, 12-17, and 21-25
OF U.S. PATENT NO. 12,234,236**

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

Page

TABLE OF EXHIBITS.....	vii
I. INTRODUCTION	1
II. MANDATORY NOTICES	5
III. PAYMENT OF FEES	6
IV. GROUNDS FOR STANDING	6
V. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. § 42.204(b)	6
VI. BACKGROUND	8
VII. THE '236 PATENT	10
A. The Prosecution of the '236 Patent	10
B. The Effective Filing Date	12
VIII. SUMMARY OF THE PRIOR ART REFERENCES.....	20
A. Yoshino (EX1008).....	20
B. Su (EX1005).....	25
C. Kawai (EX1004).....	31
D. Talele (EX1009)	35
E. Meng (EX1028).....	38
F. Patel (EX1026)	40
G. Ren (EX1030).....	41
H. Bethel (EX1032).....	43
IX. PERSON OF ORDINARY SKILL IN THE ART	44
X. CLAIM CONSTRUCTION	45

XI.	LEGAL STANDARDS.....	45
XIII.	DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY	46
A.	GROUND 1: CLAIMS 1-4, 6, 12-14, 24, AND 25 ARE OBVIOUS OVER SU, YOSHINO, AND KAWAI IN VIEW OF TALELE	46
	Claim 1:	46
	Claim 2:	65
	Claim 3:	66
	Claim 4:	69
	Claim 6:	73
	Claim 12:	75
	Claim 13:	76
	Claim 14:	77
	Claim 24:	78
	Claim 25:	82
B.	GROUND 2: CLAIMS 1-9, 12-17, 24, AND 25 ARE OBVIOUS OVER YOSHINO AND KAWAI IN VIEW OF TALELE	83
	(i) Compound 1	83
	(ii) Compound 19	94
	(iii) Compound 20	98
	Claim 2:	101
	Claim 3:	101
	Claim 4:	101
	Claim 5:	101

Claim 6:	102
Claim 7:	102
Claim 8:	102
Claim 9:	102
Claim 12:	103
Claim 13:	103
Claim 14:	103
Claim 15:	103
Claim 16:	104
Claim 17:	104
Claim 24:	104
Claim 25:	104
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	105
Claim 1:	105
Claim 2:	112
Claim 3:	112
Claim 4:	113
Claim 21:	113
Claim 22:	113
Claim 23:	114
Claim 24:	114
Claim 25:	114

D. GROUND 4: CLAIMS 4 and 9 ARE OBVIOUS OVER SU AND
BETHEL.....115

 Claim 9:116

XIV. DISCRETIONARY DENIAL UNDER 35 U.S.C. §325(d)116

XV. CONCLUSION.....120

TABLE OF AUTHORITIES

Page(s)

Cases

<i>Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH,</i> IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020).....	117
<i>Graham v. John Deere Co. of Kansas City,</i> 383 U.S. 1 (1966).....	45
<i>KSR Int’l v. Teleflex Inc.,</i> 550 U.S. 398 (2007)	45
<i>Phillips v. AWH Corp.,</i> 415 F.3d 1303 (Fed. Cir. 2005)	45
<i>Wellman, Inc. v. Eastman Chem. Co.,</i> 642 F.3d 1355 (Fed. Cir. 2001)	45
<i>ZUP, LLC v. Nash Mfg., Inc.,</i> 896 F.3d 1365 (Fed. Cir. 2018)	46

Statutes

35 U.S.C. § 102(a)	<i>passim</i>
35 U.S.C. § 102(a)(2).....	26, 43
35 U.S.C. § 102(b)	<i>passim</i>
35 U.S.C. § 103	6, 7, 45
35 U.S.C. §325(d)	116, 120

Other Authorities

37 C.F.R. § 42.8(b)(1).....	5
37 C.F.R. § 42.8(b)(2).....	5
37 C.F.R. § 42.8 (b)(3).....	5

37 C.F.R. § 42.8 (b)(4).....5

37 C.F.R. § 42.15(a).....6

37 C.F.R. § 42.2026

37 C.F.R. § 42.203(a).....6

37 C.F.R. § 42.204(a).....6

37 C.F.R. § 42.204(b)6

U.S. Patent No. 10,858,356.....7, 20

U.S. Patent No. 12,037,339.....7, 41

U.S. Patent No. 12,234,236.....*passim*

TABLE OF EXHIBITS

Exhibit	Description
EX1001	U.S. Patent No. 12,234,236 (“the ’236 Patent”)
EX1002	Declaration of Michael C. Pirrung, Ph.D.
EX1003	Excerpts of File History of U.S. Patent No. 12,234,236
EX1004	Kawai, <i>et al.</i> , 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 to Yoshino, et al (“Yoshino”)
EX1009	Talele, Journal of Medicinal Chemistry, 59(19):8712–8756 (2016) (“Talele”)
EX1010	Liu, <i>et al.</i> , Expert Opinion on Therapeutic Patents, 30(10):781-794 (2020)
EX1011	Pratt, <i>et al.</i> , Diabetes Obes Metab., 25(9):2642-2649 (2023)
EX1012	Frias, <i>et al.</i> , 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
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

Exhibit	Description
	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 & Burns, J Am Chem Soc., 144(39):17797-17802 (2022) (“Patel”)
EX1027	Pennington & Moustakas, J Med Chem., 60(9):3552-3579 (2017)
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”)

I. INTRODUCTION

Conjupro Biotherapeutics, Inc. (“Petitioner”) requests post grant review of claims 1-9, 12-17, and 21-25 (the “Challenged Claims”) of U.S. Patent No. 12,234,236 (“the ’236 Patent”) (EX1001), assigned to Ascletis Pharma China Co Ltd. (“Patent Owner”). For the reasons set forth below and in the accompanying Declaration of Dr. Michael C. Pirrung (EX1002), it is more likely than not that at least one of the Challenged Claims is unpatentable as being obvious over the prior art.

The Challenged Claims are directed to a class of compounds that function as modulators of the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R). The ’236 Patent has two independent Markush claims, claims 1 and 24, both of which claim—among other compounds—Compound 1, Compound 19, Compound 20, and Compound 65. (*See* EX1001, 204:1-220:58.)

As of the relevant priority date, it was well known that orforglipron was an orally bioavailable, non-peptidic small-molecule GLP-1R agonist developed by Eli Lilly & Co. (EX1002, ¶48.) This compound exhibited full agonist efficacy, promoting cAMP accumulation at levels comparable to native GLP-1, with an EC₅₀ of 1.1 nM at both human and cynomolgus monkey GLP-1 receptors. (*Id.*, ¶49 (citing EX1010, 4).) Unlike traditional peptide-based GLP-1R agonists, orforglipron was structurally optimized for once-daily oral administration, addressing compliance

issues associated with injectable therapies for type 2 diabetes and obesity. (*Id.* (citing EX1011, 2); EX1004.)

Kawai (EX1004) provides a detailed structural analysis of orforglipron binding to the GLP-1 receptor, revealing that the region surrounding the methyl group on the indazole moiety is both flexible and hydrophobic, and can accommodate bulkier substituents without compromising receptor engagement. (EX1002, ¶58 (citing EX1004, FIG. 1I).) A person of ordinary skill in the art (POSA), armed with this structural insight, would have been motivated to explore alternative substituents for the methyl group. (*Id.*, ¶¶58-59.)

Yoshino (EX1008) further confirms that replacing the methyl group, such as with a tetrahydrofuran ring, preserves biological activity, thereby validating that small ring substitutions, including carbocyclic moieties like cyclopropyl, are viable alternatives. (EX1002, ¶73 (citing EX1008, 50, 99, Table 3).) Cyclopropyl rings, in particular, are well-established in medicinal chemistry for enhancing drug properties such as metabolic stability and receptor binding affinity. (*Id.*, ¶81.) Talele (EX1009) underscores the prevalence and utility of cyclopropyl substitution in pharmaceutical design, where such rings are often employed to replace methyl groups for improved pharmacokinetics and resistance to metabolic degradation. (EX1002, ¶¶82-84 (citing EX1009, 1, 2).)

Accordingly, based on the combined teachings of Yoshino, Kawai, and Talele, a POSA would have had clear motivation to replace the methyl group in orforglipron with a cyclopropyl group, thereby arriving at the structure of claimed Compound 1. (*Id.*, ¶¶208-219.)

As to claimed Compound 19, its structure would have been obvious in view of the combined teachings of Su (EX1006) and Yoshino. Su discloses more than 200 working examples but selects only seven stereoisomerically pure compounds and in some cases their respective stereoisomeric mixtures for deuteration, underscoring their potential as development leads. (EX1002, ¶¶61-62; *infra* Section VIII.B.) This selective deuteration, given the time and resource-intensive nature of the process, suggests a belief in the value of the unique substitution on the underlying scaffolds. (*Id.*, ¶¶62-64.)

Su discloses a Compound 175 (as well as its deuterated analog, Compound 176) that share the same core scaffold as orforglipron, differing only in a peripheral cyclopropyl substitution for the original methyl group. (*Id.*, ¶¶63-65.) Similarly, Su's Compound 44 maintains the same core scaffold but lacks the two peripheral methyl groups on the tetrahydropyran ring. (*Id.*, ¶¶66.) The structural proximity of Su's Compounds 175/176 and 44 to orforglipron, coupled with their selection for deuteration, would have led a POSA to identify them as lead compounds. (*Id.*, ¶¶63-64.) By applying the peripheral modifications observed in these compounds, namely,

the introduction of a cyclopropyl group to Su's Compound 175 or the removal of the dimethyl substituents from Su's Compound 44, a POSA would have arrived at the structure of claimed Compound 19. (*Id.*, ¶69.)

A POSA would also have found claimed Compound 20 to be obvious. As explained by Dr. Pirrung, minor structural modifications—such as elongating alkyl chains or cyclizing them—are routine in medicinal chemistry. (*Id.*, ¶¶223-226.) A POSA would have reasonably found it obvious to replace the methyl group on the 4-fluoro-1-methyl-indazole moiety of orforglipron with a small cycloalkyl group, such as cyclobutyl, leading directly to the structure of Compound 20. (*Id.*)

Claimed Compound 65 would likewise have been obvious. A POSA seeking to improve the potency and/or pharmacokinetic profile of Compound 19 would have been motivated to introduce a nitrogen atom at the corresponding position—consistent with the structural modifications disclosed in Compound (II) of Meng (EX1028) and Compound 90 of Ren (EX1030). (EX1002, ¶¶268-287.) Such a substitution would have been understood as a rational and routine medicinal chemistry strategy to enhance potency, oral bioavailability, and the overall pharmacological profile of the compound. (*Id.*) Accordingly, Compound 65 represents nothing more than a predictable variation of Compound 19, derived through the application of well-established design principles in view of express teachings in the prior art. (*Id.*)

Accordingly, the claimed subject matter, when considered as a whole, would have been obvious to a POSA in view of the prior art and the general knowledge in the field. Petitioner therefore requests that this Petition be granted and that the Challenged Claims be canceled as unpatentable.

II. MANDATORY NOTICES

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

The real parties-in-interest are CSPC Pharmaceutical Group Limited, CSPC Baike (Shandong) Bio-Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc.

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

Petitioner is unaware of any judicial or administrative proceedings that would either affect or be affected by a decision regarding this Petition.

C. Counsel and Service Information (37 C.F.R. §§ 42.8 (b)(3) and (4))

Petitioner identifies its lead and backup counsel as shown below:

Lead Counsel	Backup Counsel
Jin Zhu, Ph.D. (Reg. No. 62,869) jzhu@foxrothschild.com Fox Rothschild LLP 212 Carnegie Center, Suite 400 Princeton, NJ 08540 Tel: (609) 895-6297 Fax: (609) 896-1469	Joe G. Chen, Ph.D. (Reg. No. 70,066) joechen@foxrothschild.com Fox Rothschild LLP 212 Carnegie Center, Suite 400 Princeton, NJ 08540 Tel: (609) 844-3024 Fax: (609) 896-1469 Luke Toft (Reg. No. 75,311) ltoft@foxrothschild.com Fox Rothschild LLP 33 South 6th Street, Suite 3600 Minneapolis, MN 55402

	Tel: (612) 607-7336 Fax: (612) 607-7100
--	--

Please address all correspondence to the lead and backup counsel at the above addresses. Petitioner consents to electronic service to the e-mail addresses above for lead and backup counsel (jzhu@foxrothschild.com, joechen@foxrothschild.com, ltoft@foxrothschild.com) with a copy to ipdocket@foxrothschild.com (referencing Attorney Docket No. 340008.00025).

III. PAYMENT OF FEES

Pursuant to 37 C.F.R. §§ 42.203(a) and 42.15(a), the required fees are submitted herewith. If additional fees are due during this proceeding, the Office is authorized to charge Deposit Account 50-1943.

IV. GROUNDS FOR STANDING

Petitioner certifies, pursuant to 37 C.F.R. § 42.204(a), that the '236 Patent is available for PGR, and that Petitioner is not the patent owner nor barred or estopped from requesting PGR of the Challenged Claims on the grounds identified in this Petition. This Petition is filed within nine months of the '236 Patent issuance, February 25, 2025. *See* 37 C.F.R. § 42.202.

V. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. § 42.204(b)

The Challenged Claims are unpatentable under 35 U.S.C. § 103.

The following is a list of prior art that renders obvious the Challenged Claims:

Exhibit	Description	Publication/Filing Date
EX1004	Kawai, <i>et al.</i> , Proc Natl Acad Sci U S A., 117(47):29959-29967 (2020) (“Kawai”)	Published on November 11, 2020
EX1007	PCT/CN2024/108192 (published as WO 2025/026270) to Su Yidong <i>et al.</i> (“Su”)	Published on February 6, 2025
EX1008	U.S. Patent No. 10,858,356 to Yoshino <i>et al.</i> (“Yoshino”)	Published on December 8, 2020
EX1009	Talele, Journal of Medicinal Chemistry, 59(19):8712–8756 (2016) (“Talele”)	Published on June 14, 2016
EX1026	Patel & Burns, J Am Chem Soc., 144(39):17797-17802 (2022) (“Patel”)	Published on September 22, 2022
EX1028	Chinese Patent Publication No. CN117069743A (“Meng”)	Published on November 17, 2023
EX1030	U.S. Patent No. 12,037,339 (“Ren”)	Published on February 16, 2023
EX1032	PCT/CN2024/108192 (published as WO 2025/026270) to Mary Angelyn Bethel <i>et al.</i> (“Bethel”)	Published on June 20, 2024

Petitioner requests cancellation of claims 1-9, 12-17, and 21-25 on the following grounds:

Ground	Claims	Description
1	1-4, 6, 12-14, 24, and 25	Obvious under 35 U.S.C. § 103 over Su, Yoshino, and Kawai, in view of Talele.
2	1-9, 12-17, 24, and 25	Obvious under 35 U.S.C. § 103 over Yoshino and Kawai in view of Talele.
3	1-4 and 21-25	Obvious under 35 U.S.C. § 103 over Su, Yoshino, Kawai, Talele, and Meng in view of Patel and Ren
4	4 and 9	Obvious under 35 U.S.C. § 103 over Su and Bethel

VI. BACKGROUND

Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone secreted predominantly by enteroendocrine L-cells in the distal intestine in response to nutrient ingestion. (*See, e.g.*, EX1010, 1; EX1002, ¶38.) Through activation of the GLP-1 receptor (GLP-1R), GLP-1 exerts multiple metabolic effects, including glucose-dependent stimulation of insulin secretion, inhibition of glucagon release, promotion of satiety, delayed gastric emptying, and a reduction in energy intake. (EX1010, 1.) Several years prior to the earliest filing date of the '236 Patent, pharmacological GLP-1R agonists were known to replicate these effects and demonstrated substantial clinical benefit in managing hyperglycemia and promoting weight loss in both diabetic and non-diabetic populations. (*Id.*)

Obesity, a chronic metabolic disorder affecting over 10% of the global adult population, is primarily driven by sustained caloric excess—often from high-fat and high-carbohydrate diets—and is further exacerbated by psychosocial stress, sedentary lifestyles, and disordered eating behaviors. (EX1010, 1; EX1002, ¶39.) Obesity is closely associated with a range of chronic diseases, including diabetes, nonalcoholic fatty liver disease, heart disease, and cancer. (EX1010, 1; EX1002, ¶39.)

GLP-1R agonists have emerged as a transformative class of therapeutics for the treatment of those who are obese and overweight, offering durable weight loss

and improvement in metabolic parameters. (EX1010, 1; EX1002, ¶40.) Originally approved for type 2 diabetes, these agents are now recognized for their weight-reducing properties, driven primarily by appetite suppression and thus decreased caloric intake through central and peripheral mechanisms. (EX1010, 1; EX1002, ¶41-42.) Mechanistic studies show that GLP-1R agonists activate both hypothalamic pathways and gastrointestinal signaling via vagal afferents, reinforcing satiety and reducing food consumption. (EX1010, 1; EX1002, ¶41-42.)

Although under clinical evaluation for weight loss efficacy, several small-molecule GLP-1R agonists have demonstrated *in vitro* and *in vivo* activity comparable to peptide-based counterparts. (EX1010, 4; EX1002, ¶44.) Orforglipron, also known as LY3502970 and formerly designated OWL-833 (initially discovered by Chugai Pharmaceutical), was regarded as a next-generation, non-peptidic small-molecule GLP-1R agonist being developed by Eli Lilly & Co. (EX1010, 4; EX1002, ¶48.) Engineered for once-daily oral administration, orforglipron addresses adherence challenges inherent to injectable peptide therapies. (EX1004; EX1011, 2.)

Orforglipron exhibits full agonist activity, promoting cAMP accumulation to levels comparable to native GLP-1, with EC₅₀ values of 1.1 nM for both human and cynomolgus monkey GLP-1 receptors. (EX1010, 4; EX1002, ¶49.) Unlike conventional peptide-based agonists, orforglipron binds the GLP-1R at a distinct allosteric site and displays biased agonism, preferentially activating G protein

pathways while minimizing β -arrestin recruitment. (EX1004, 2.) Clinical data confirm that orforglipron significantly improves glycemic control and reduces body weight. (Id; EX1002, ¶51.) Eli Lilly initiated its first Phase 3 study for orforglipron in April 2023 to evaluate the safety and efficacy of once-daily oral orforglipron (<https://clinicaltrials.gov/study/NCT05803421>).

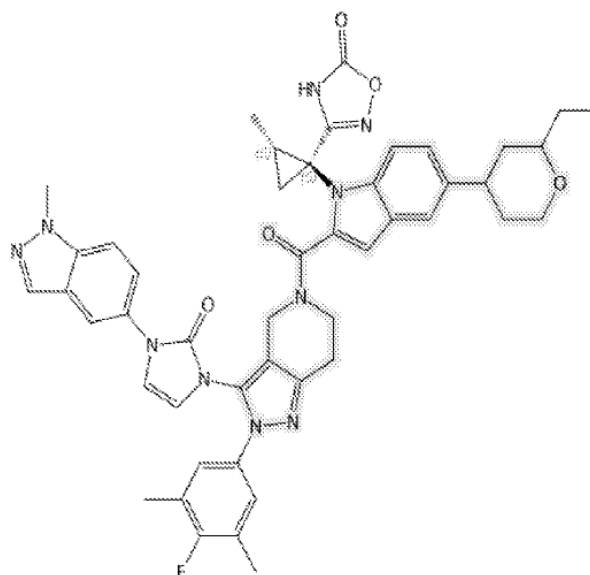
VII. THE '236 PATENT

A. The Prosecution of the '236 Patent

The application that issued as the '236 Patent, U.S. Patent Application No. 18/884,965 (“the '965 Application”), was filed on September 13, 2024. The '965 Application was filed with a total of 25 claims. Between November 2 and November 4, 2024, Patent Owner submitted six different information disclosure statements (IDSs) that *disclosed more than 250 prior art references*. (EX1003, 704-812.)

On November 6, 2024, less than two months after the filing of the '965 Application and just *a couple days after the disclosure of hundreds of prior art references*, the U.S. Patent and Trademark Office issued a Notice of Allowance citing only one reference and allowing all claims 1–25. (*Id.*, 168-170.) The Notice of Allowance contains only the following Examiner’s statement for the reason 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.*, 168.)

Notably, the image of the compound cited in the Notice of Allowance (and reproduced above) came directly from the October 28, 2024 search report Examiner's search strategy and results. (*Compare* EX1003, 547 with generally EX1008 (which does not disclose the image reproduced above).) This report, run just a week before the Examiner issued the Notice of Allowance, identified hundreds of compounds from dozens of references, including Yoshino and Kawai, but did not otherwise include information about the disclosures in the references. (EX1003, 176-703.)

That is, the Examiner considered and cited just one compound in Yoshino, (one of at least 159 compounds in Yoshino, *see* EX1008), and, it appears, did not address *or even consider* other disclosures in any of the prior art references or

whether additional prior art references, or combinations thereof, could potentially render the claims of the '965 Application obvious. For instance, the Examiner did not consider the multitude of other compounds disclosed in Yoshino *et al.*, such as Compound 67, which the Petitioner relies upon as a reference compound against claimed Compounds 1 and 19 in Ground 2.

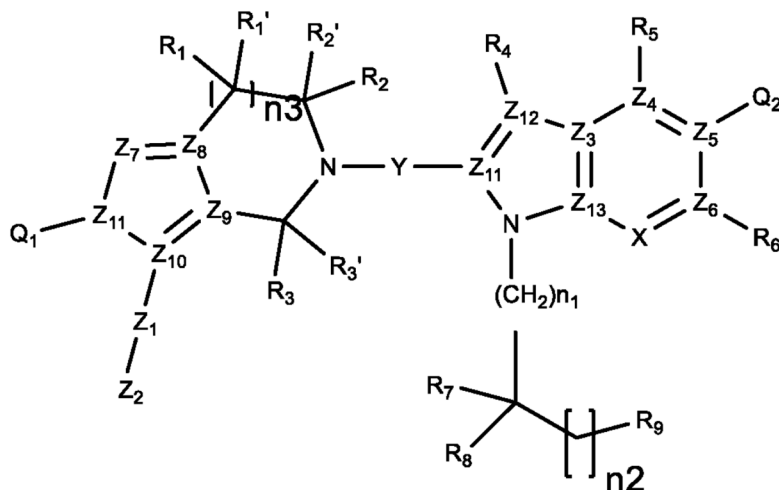
B. The Effective Filing Date

Under the “Cross-Reference to Related Application” section of the '236 Patent, the '965 Application, from which the '236 Patent issued, claims the benefit of the following fourteen prior applications, including ten Chinese provisional patent applications and four U.S. provisional patent applications, as summarized in the table below (EX1001, 1:1-45):

Country Code	Appl. No.	Filing Date
CN	202311189557	9/14/2023
US	63/538,892	9/18/2023
CN	202311371725	10/23/2023
US	63/545,615	10/25/2023
CN	202311582240	11/24/2023
US	63/603,854	11/29/2023
CN	202311686034	12/8/2023
CN	202410142451	1/31/2024
CN	202410202078	2/22/2024
CN	202410398964	4/2/2024
CN	202410584679	5/11/2024
CN	202410963587	7/17/2024
US	63/673,453	7/19/2024
CN	202411237048	9/4/2024

As Dr. Pirrung explains, the written description of one or more of the seven compounds recited in the Challenged Claims was not provided in the priority documents to which they claim priority. (EX1024, ¶¶128-140.) For example, the chemical structures of Compounds 19, 20, and 21 were only first disclosed in CN 202311371725, filed on October 23, 2023 (“the ’725 Provisional”). (EX1002, ¶¶135-138; EX1013, EX1014.) 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. (EX1002, ¶¶135-138; EXS. 1015, 1016, 1017.)

As Dr. Pirrung explains, both the ’892 Provisional and the ’557 Provisional disclose the following chemical genus encompassing millions of compounds (*see, e.g.,* claim 1 of both the ’892 Provisional and the ’557 Provisional). (EX.1002, ¶¶135-137; EX1016, claim 1; EX1017, claim 1.) Notably, none of the exemplified compounds disclosed in either application includes an unsubstituted tetrahydropyran ring.



These earlier-filed provisional applications fail to provide an adequate written description of Compounds 19, 20, and 21. (EX1002, ¶¶135-138.) Specifically, the structural formulas disclosed therein define each variable in terms of an unduly broad and diverse range of atoms or chemical groups. (*Id.*) As a result, a person of ordinary skill in the art would not have reasonably concluded that the inventors were in possession of the specific compounds as of the filing dates of those provisional applications. For example, the variables Q₂ and Z₂ are defined as follows:

wherein Q₂ 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, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy and –NR^{Qa}R^{Qb}, wherein two C₁₋₆ alkyl groups together with the carbon atoms to which they are attached form a C₃₋₈ carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and (C₁₋₆ 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, C_{1-6} 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. C₁₋₆ alkoxy; wherein C₁₋₆ alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and C₁₋₆ alkoxy;
- i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic is optionally substituted by one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl) carbonyl;
- j. C₆₋₁₀ aryl; wherein C₆₋₁₀ aryl is optionally substituted by one or more (C₁₋₆ 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 C₁₋₆ alkyl, C₁₋₆ 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, C₁₋₆ alkyl, and (C₁₋₆ 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 C₁₋₆ alkyl, and C₁₋₆ alkoxy;
- l. -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl- C₃-C₁₅ cycloalkyl; wherein -C₃-C₁₅ cycloalkyl or - C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl, wherein each of C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl is optionally substituted by halogen.

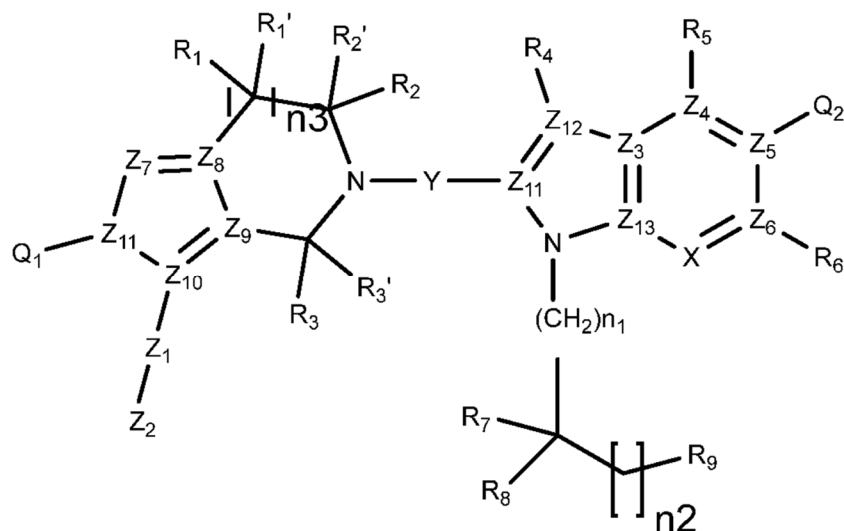
(EX1002, ¶¶135-138; EX1017, 14, 16-17.)

It would not have been possible for a POSA to visualize individual compounds, such as Compounds 19, 20, and 21, in light of the disclosure, at least in part due to the existence of hundreds of millions of potential permutations for the Q²

and Z² substituents. (EX1002, ¶138.) Furthermore, the consistent inclusion of substituents on the tetrahydropyran ring in the exemplified compounds fails to provide any direction or motivation toward the specific unsubstituted tetrahydropyran ring present in Compounds 19, 20, and 21. (*Id.*) Accordingly, the Challenged Claims cannot properly claim priority to any date earlier than October 23, 2023, with respect to the subject matter encompassing Compounds 19, 20, and 21. (*Id.*)

The chemical structure of Compound 65 is first disclosed in Chinese Patent Application No. 202410142451.2, filed on January 31, 2024 (“the ’451 Provisional”). (EX1002, ¶¶139-142; EXS. 1018, 1019.) By contrast, none of the earlier-filed provisional applications, including CN 202311371725.7, filed on October 23, 2023 (“the ’725 Provisional”); U.S. Provisional Application No. 63/538,892, filed on September 18, 2023 (“the ’892 Provisional”); U.S. Provisional Application No. 63/545,615, filed on October 25, 2023 (“the ’615 Provisional”) (EX1024); CN 202311582240.2, filed on November 24, 2023 (“the ’240 Provisional”) (EXS. 1020, 1021); U.S. Provisional Application No. 63/603,854, filed on November 29, 2023 (“the ’854 Provisional”) (EX1025); or CN 202311686034.6, filed on December 8, 2023 (“the ’034 Provisional”) (EXS. 1022, 1023), contains a disclosure of the specific chemical structure of Compound 65. (EX1002, ¶¶139-142.)

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;

(EX1002, ¶140; *see* EX1013, 3; EX1014, 3; EX1017, 7; EX1024, 8; EX1020, 3; EX1021, 3; EX1025, 9; EX1022, 4; EX1023, 4.)

However, as Dr. Pirrung explains, these earlier-filed provisional applications fail to provide a sufficiently specific description of Compound 65. (*Id.*) The generic chemical formulae presented in the provisional applications define variables that encompass an exceedingly broad and diverse range of atoms and substituents. (*Id.*) For instance, the atoms forming the bicyclic ring of the core scaffold are described in highly generalized terms, allowing for a wide range of structural alternatives. (*Id.*) The breadth of these definitions permits thousands of distinct permutations of the bicyclic core alone. (*Id.*) When considered in conjunction with the numerous other variable positions in the generic formula, the total number of potential compounds

encompassed by the disclosure reaches into the billions. (*Id.*) Accordingly, the provisional applications do not convey possession of Compound 65 with the specificity and clarity necessary to satisfy the written description requirement. (*Id.*)

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* EX1013, 3; EX1014, 3; EX1017, 7; EX1024, 8; EX1020, 3; EX1021, 3; EX1025, 9; EX1022, 4; EX1023, 4.)

Moreover, none of the exemplified compounds disclosed in the referenced provisional applications include a pyrrolo-pyridine ring within the core scaffold, as recited in Compound 65. (EX1002, ¶142.) As such, the specific structure of Compound 65 is not reasonably discernible from the disclosures of these provisional applications. (*Id.*) Accordingly, the Challenged Claims cannot properly claim priority earlier than January 31, 2024, with respect to the subject matter pertaining to Compound 65. (*Id.*)

Claims 4, 9, 14, 17, 20, and 23 each depend from claim 1 and are directed to a ½ calcium salt of one or more of the compounds recited therein. (*Id.*, ¶143.) However, neither Su (EX1031) nor any of the prior art documents filed on or before January 31, 2024, including EX1014, EX1016, EX1017, EX1019, EX1021, EX1023, EX1024, and EX1025, discloses a ½ calcium salt of any compound encompassed by claim 1. (*Id.*) Accordingly, claims 4, 9, 14, 17, 20, and 23 are not entitled to a priority date earlier than 2024. (*Id.*)

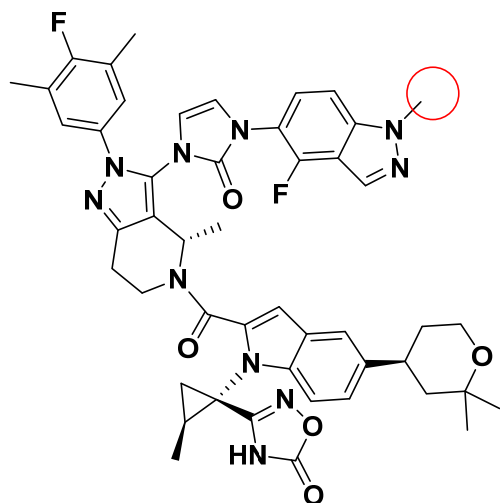
Therefore, a POSA would have recognized that the claims of the '236 Patent are not entitled to the filing date of September 14, 2023 of the '557 Provisional. (*Id.*, ¶144.)

VIII. SUMMARY OF THE PRIOR ART REFERENCES

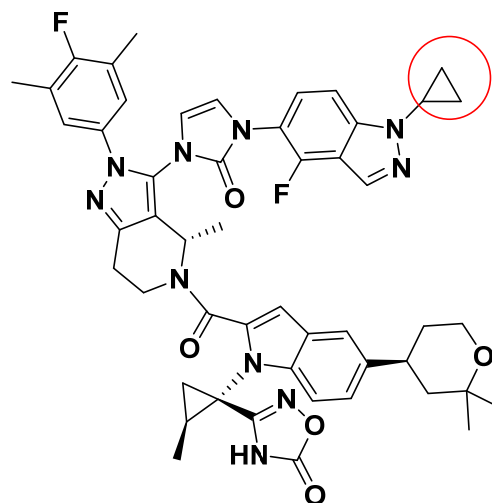
A. Yoshino (EX1008)

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”) on December 8, 2020. (EX1008, 1.) Yoshino is prior art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the '236 Patent, and none of the exceptions of 35 U.S.C. § 102(b) apply.

Yoshino discloses and claims Compound 67 in claims 13 and 14. Compound 67 is identical to orforglipron evaluated in Kawai and is the only compound in Yoshino that was advanced to pharmacokinetic studies. (*Id.*, 166, claims 13, 14; EX1002, ¶72.) As Dr. Pirrung explains, Compound 67 can be reasonably identified as a lead compound based on its demonstrated potential for further development. The only structural distinction between Compound 67 (orforglipron) and claimed Compound 1 of the '236 Patent is highlighted in the red circle shown below. (EX1002, ¶72.)

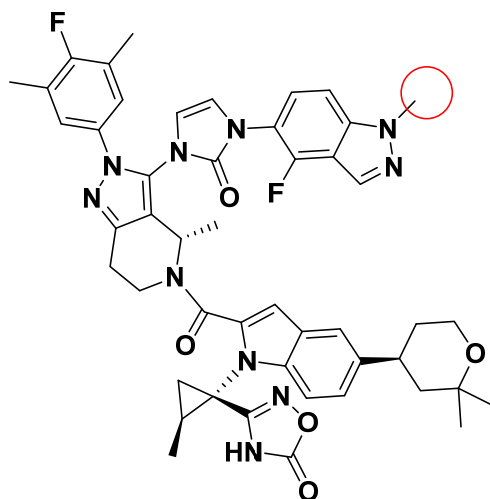


Compound 67 (orforglipron)



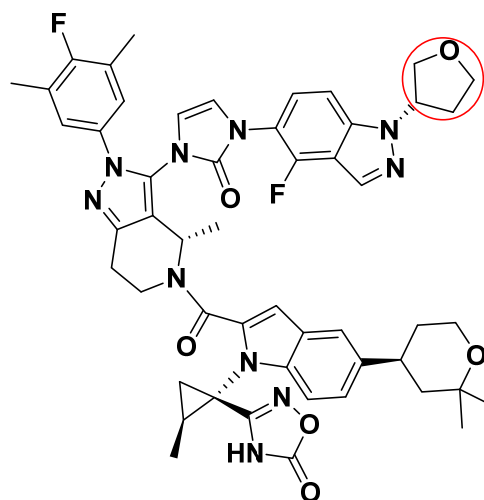
Compound 1

In modifying lead Compound 67, Yoshino discloses that the methyl group may be substituted with a tetrahydrofuran ring without adversely affecting biological activity. Specifically, substitution of the methyl group in Compound 67 with a tetrahydrofuran ring resulted in Compound 40, which demonstrated a comparable level of activity. (*Id.*, ¶73; EX1008, 50, 99, Table 3.)



Compound 67

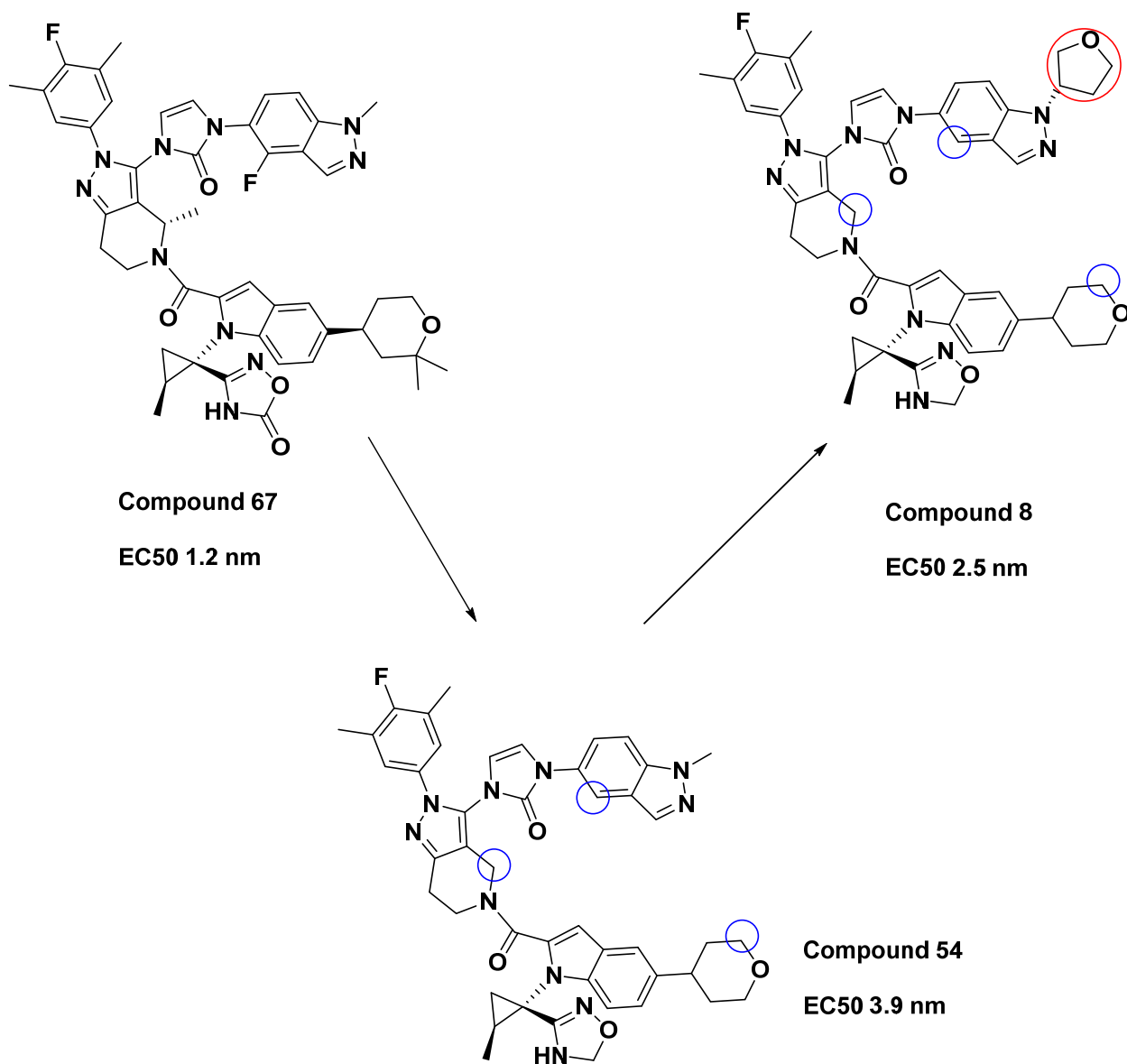
EC50 1.2 nm



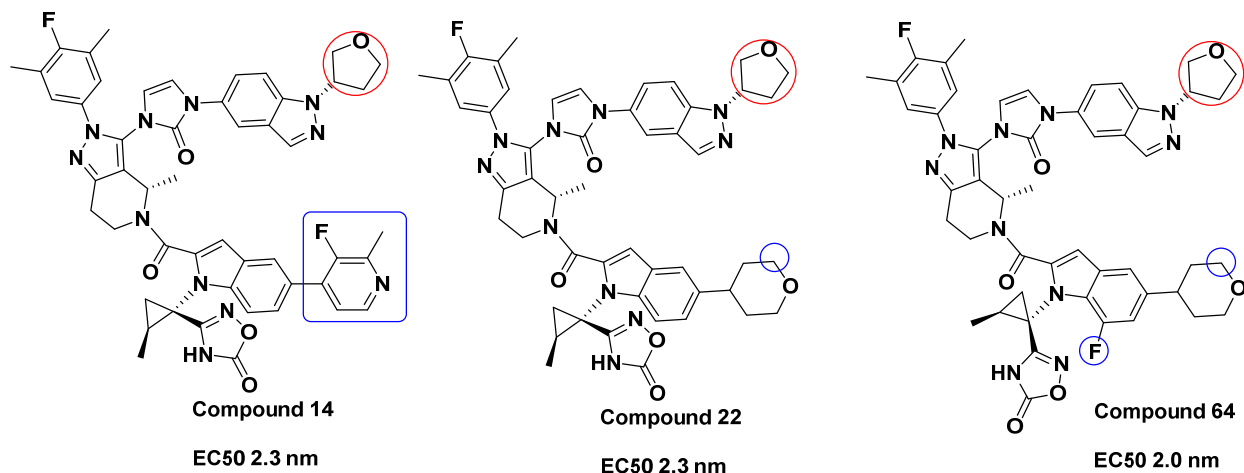
Compound 40

EC50 2.2 nm

In addition, and as illustrated below, while the removal of multiple substituents, as exemplified by Compound 54, resulted in diminished activity relative to the lead compound, substitution of the methyl group on Compound 54 with a tetrahydrofuran moiety was found to mitigate this loss of activity. (EX1002, ¶74; EX1008, 34, 92, 99, Table 3.)



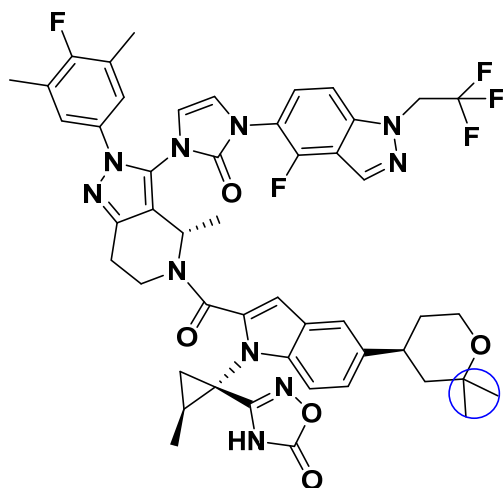
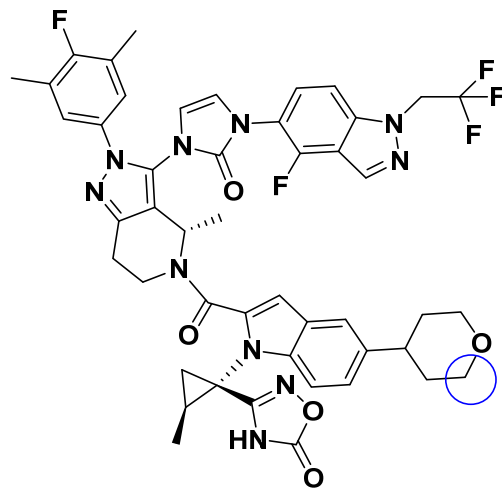
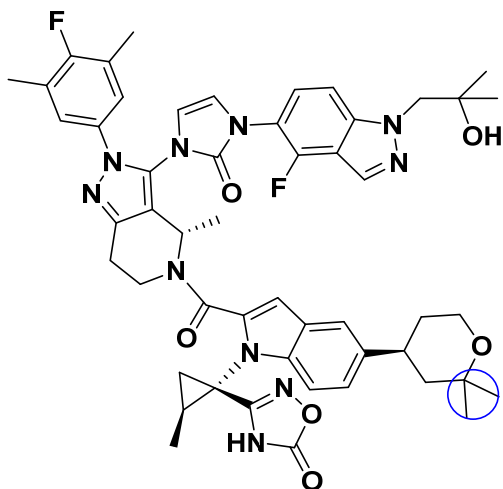
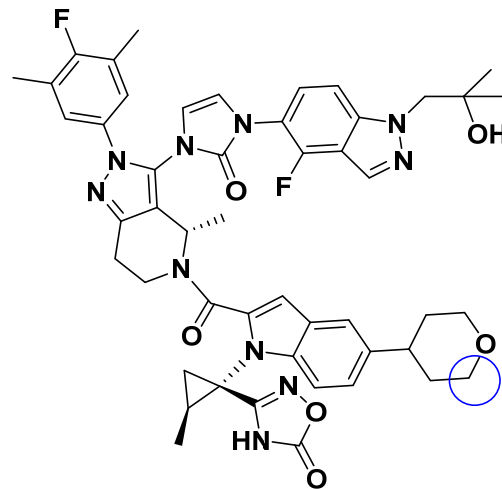
Consistent with these observations, Yoshino further discloses additional analogs containing a tetrahydrofuran ring, each of which exhibited biological activity comparable to that of the lead compound. (EX1002, ¶75; EX1008, 37, 41, 97, Table 3.)



Accordingly, Yoshino, when considered as a whole, suggests to a POSA that replacement of the methyl group with a ring structure can preserve the biological activity of the lead compound. (EX1002, ¶76.) This understanding of a POSA is consistent with the modeling study of Kawai. (See EX1004, 4, FIG. 11.)

Yoshino further teaches that modifications involving the removal of methyl groups from the tetrahydro-2H-pyran moiety generally do not compromise the biological activity of the compounds. (EX1002, ¶77.) As illustrated in the comparison below, the removal of dimethyl groups from Compound 35 resulted in Compound 28, which retained comparable biological activity. (*Id.*; EX1008, 44, 48, Table 3.) Similarly, Compound 30, which lacks dimethyl substitution on the

tetrahydropyran ring, demonstrated the same level of activity as Compound 38. (EX1002, ¶77; EX1008, 45, 49, Table 3.) Further, out of 80 compounds with reported activities in Table 3, over 30 compounds display the unsubstituted tetrahydropyran ring. (EX1008, 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**

Notably, the removal of the methyl groups from the tetrahydropyran ring eliminates the chiral center, thereby rendering the ring achiral. (EX1002, ¶78.) A POSA would understand that this structural modification facilitates a more efficient synthetic route and reduces the potential for adverse effects associated with the formation of undesired stereoisomers. (*Id.*)

Yoshino discloses a compound that functions as a GLP-1 receptor agonist or a salt thereof, including, for example, its sodium or calcium salts. (*Id.*, ¶79; EX1008, 2:45-56, 8:5-60, 34:7-15; FIGs. 1, 2, and 5-8.) Yoshino further specifies various forms, including “a hydrate of the free form, a salt of the free form, and a hydrate of the salt,” and 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.*)

B. Su (EX1005)

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,

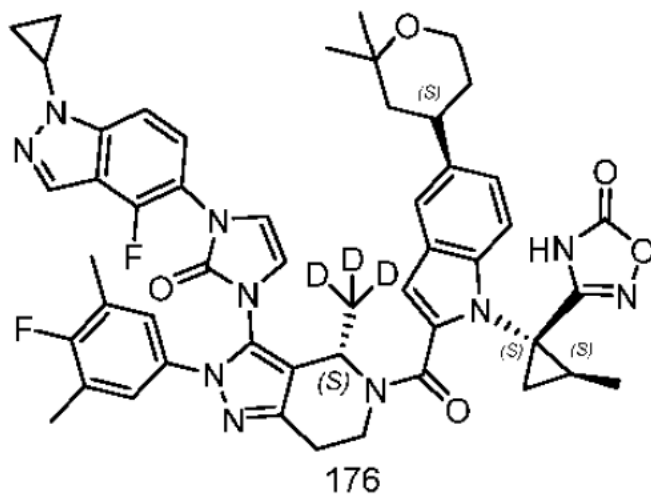
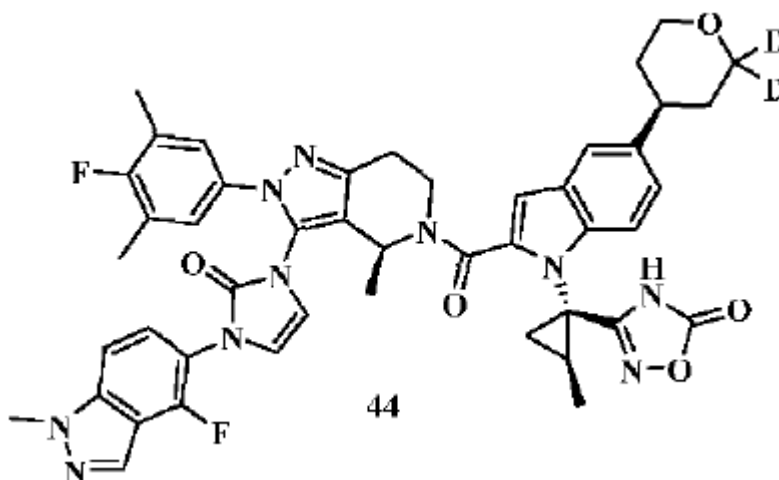
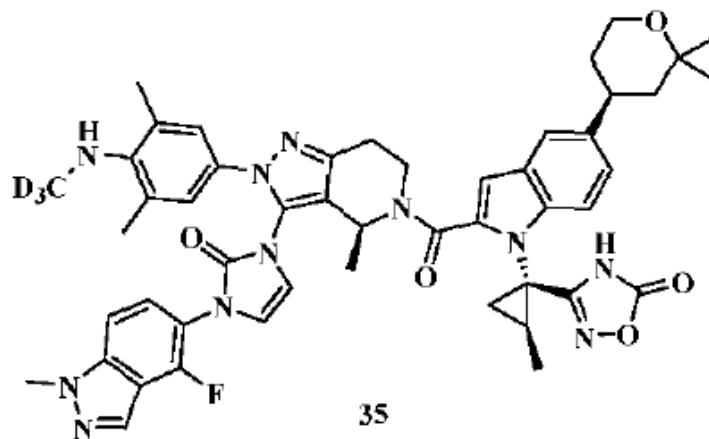
filed on August 30, 2023; CN202311269491.5, filed on September 27, 2023; CN202311372605.9, filed on October 20, 2023; CN202311546779.2, filed on November 17, 2023; CN202311690443.3, filed on December 8, 2023; CN202311866263.6, filed on December 29, 2023; CN202410140555.X, filed on January 31, 2024; CN202410241733.8, 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. (EX1005; EX1031, 1.)

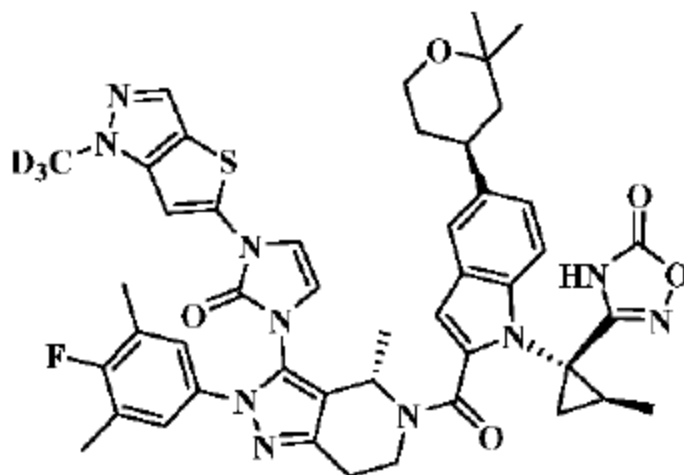
Su is prior art under 35 U.S.C. § 102(a)(2) because it has an effective filing date before the earliest possible claimed priority date of the '236 Patent's claims, and none of the exceptions of 35 U.S.C. § 102(b) apply. Unless otherwise stated, Su's disclosures discussed herein have an effective filing date of July 28, 2023 (the filing of CN202310946477.8). However, as Dr. Pirrung explains, certain disclosures in Su, for example, the description of Compounds 44, 175, and 176 discussed below, have an effective filing date of at least October 20, 2023 (the filing of Application No. CN 202311372605.9 ("Su II")). (EX1002, ¶61; EX1006.) Therefore, for ease of reference, any relevant disclosure in Su that is at least 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 only seven deuterated stereoisomerically pure compounds are specifically described—Compounds 176,

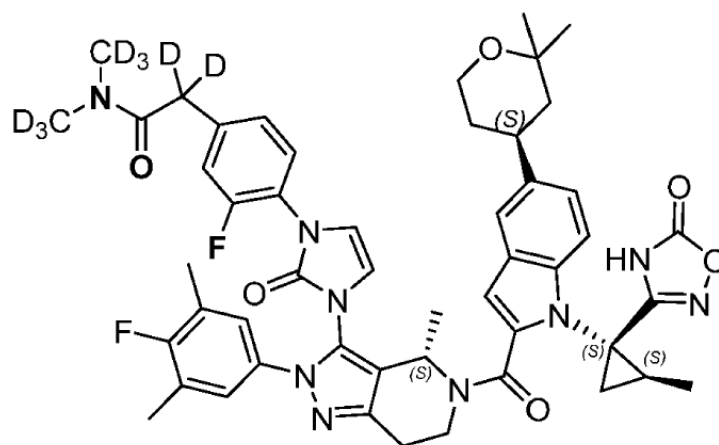
44, 35, 123, 139, 188, and 212—the chemical structures of which are shown below.

(EX1007, Examples 176, 44, 35, 123, 139, 188, and 212; EX1002, ¶61.)

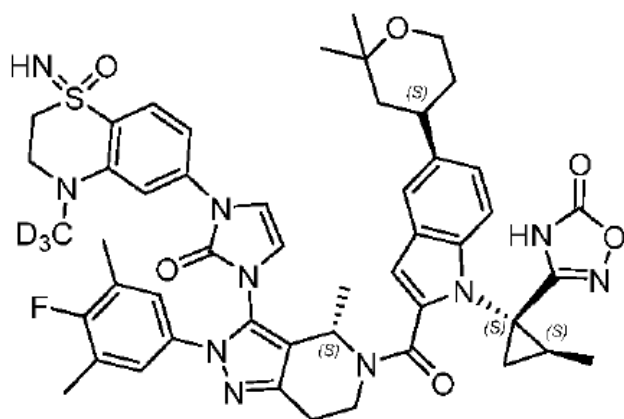




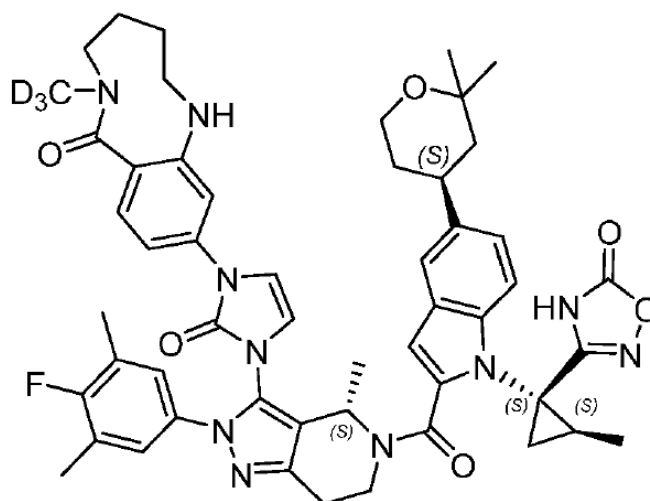
123



139



188



212

As Dr. Pirrung further explains, given the labor-intensive synthetic procedures required for deuteration (*see, e.g.*, EX1007, Example 176), particularly in the context of the limited subset of stereoisomerically pure compounds among the more than 200 compounds disclosed, a POSA would reasonably infer that the stereoisomerically pure compounds selected for deuteration were regarded as strong candidates for further development. (EX1002, ¶62.) Additionally, deuteration is often examined to enhance metabolic traits of drug candidates. (*Id.*) Thus, a POSA would have understood the deliberate undertaking of deuteration to signify that the compound was considered a lead candidate. (*Id.*)

Furthermore, among the seven deuterated stereoisomerically pure compounds, Compounds 176 (and its non-deuterated parent compound), 44, and 35, share a common scaffold ring structure, further supporting their identification as lead

candidates with an elevated likelihood of being selected for continued development. (*Id.*, ¶63.)

Notably, the well-known Lilly compound, orforglipron, shares the same scaffold structure as the original non-deuterated parent compounds, underscoring the structural significance of this scaffold and supporting the designation of these parent compounds as lead candidates. (*Id.*, ¶64.) Therefore, a POSA would consider such compounds as lead compounds for further development. (*Id.*) In contrast, the remaining deuterated compounds disclosed in Su II involve modifications to the scaffold ring and exhibit substantial structural divergence from one another. (*Id.*) Therefore, a POSA would understand these compounds were likely not great candidates as a lead compound. (*Id.*)

As Dr. Pirrung explains, the teachings derived from the very small group of deuterated stereoisomerically pure compounds and their related non-deuterated parent compounds are specific and well-defined. (EX1002, ¶68.) These include: (1) incorporation of a cyclopropyl group in both the deuterated Compound 176 and its non-deuterated parent compound 175, with respect to the orforglipron; (2) removal of methyl groups from the tetrahydropyran ring in deuterated Compound 44, with its closest analog containing only hydrogen atoms in the tetrahydropyran ring (replacing D with H for at least simplified synthesis and removal of chiral center);

and (3) substitution of a fluorine atom with an amino group, as exemplified by Compound 35. (*Id.*)

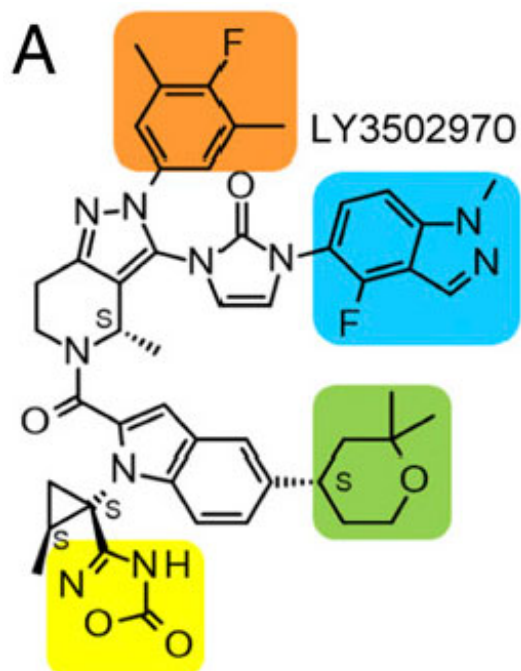
Regarding pharmaceutically acceptable salts of the disclosed compounds, Su also discloses GLP-1 receptor agonists and pharmaceutically acceptable salts thereof. (*Id.*, ¶70; EX1007, 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.)

C. Kawai (EX1004)

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). Kawai is prior art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the ’236 patent, and none of the exceptions of 35 U.S.C. § 102(b) apply. Kawai was among the references submitted through an IDS dated November 2, 2024, just four days before the issuance of the Notice of Allowance, but was not considered by the Examiner prior to issuance of said notice. (*Supra* Section VII.)

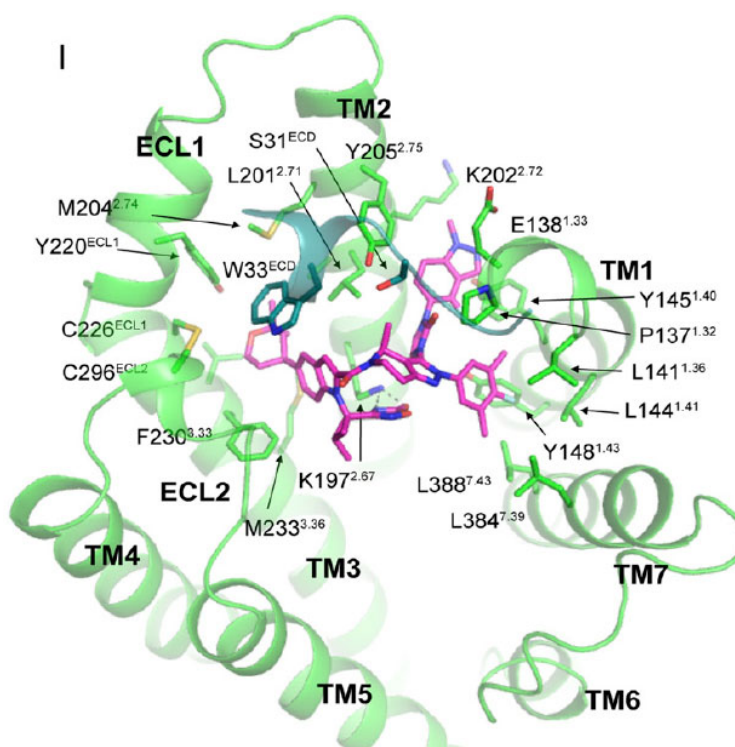
Kawai discloses the structural basis for GLP-1 receptor activation by orforglipron. Specifically, Kawai presents a high-resolution cryo-electron microscopy (cryo-EM) structure of orforglipron in complex with the N-terminal extracellular domain of the GLP-1 receptor. (EX1002, ¶53; EX1004, 1.) The chemical structure of orforglipron is shown below, with the following moieties highlighted: the 2,2-dimethyl-tetrahydropyran moiety in green, the 4-fluoro-1-

methyl-indazole moiety in blue, the 3,5-dimethyl-4-fluoro-phenyl ring in orange, and the 4H-1,2,4-oxadiazol-5-one moiety in yellow. (EX1004, FIG. 1A.)



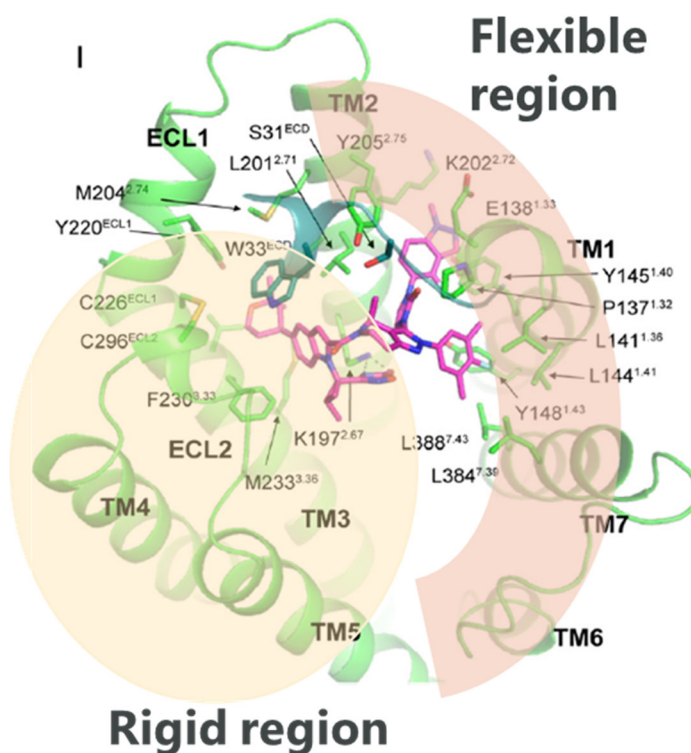
Kawai describes orforglipron as a highly potent and selective compound with respect to other class B G protein-coupled receptors (GPCRs), and possessing a pharmacokinetic profile suitable for oral administration. (EX1002, ¶54; EX1004, 1.) Kawai further discloses that oral administration of orforglipron resulted in glucose-lowering effects in humanized GLP-1 receptor transgenic mice, as well as insulinotropic and hypophagic effects in nonhuman primates. (*Id.*) According to Kawai, these findings elucidate the molecular basis for the activity of an orally administered agent then under development for the treatment of type 2 diabetes mellitus and provide insight into the activation of class B GPCRs by non-peptidic ligands. (*Id.*)

Moreover, Kawai discloses a structural analysis elucidating the ligand-binding pocket surrounding the compound and provides a detailed three-dimensional model of the protein-ligand interactions, as illustrated below:



(EX1004, FIG. 1I)

Kawai further discloses that the region of the ligand-binding pocket formed by transmembrane helices TM1, TM2, TM6, and TM7 is positioned in close proximity to the 4-fluoro-1-methyl-indazole moiety. (EX1002, ¶56; EX1004, FIG. 1I.) This region is reported to exhibit conformational flexibility, as depicted in annotated FIG. 1I above. (EX1002, ¶56; EX1004, 4.) In contrast, the region of the ligand-binding pocket formed by transmembrane helices TM3, TM4, and TM5 is characterized as relatively rigid. (*Id.*)



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

As Dr. Pirrung explains, the conformational flexibility of the region of the ligand-binding pocket formed by transmembrane helices TM1, TM2, TM6, and TM7 suggests that modifications to the 4-fluoro-1-methyl-indazole moiety would not be expected to result in significant structural disruption of the ligand-binding pocket and, accordingly, would likely preserve binding potency. (EX1002, ¶57.)

In addition, the binding pocket adjacent to the methyl group of the indazole moiety is depicted as being surrounded by a spacious hydrophobic environment,

indicating that the pocket could reasonably accommodate a bulkier substituent in place of the methyl group. (EX1002, ¶58; EX1004, FIG. 1I.)

As Dr. Pirrung explains, the detailed three-dimensional protein-ligand interaction model disclosed in Kawai provides a valuable framework for structure-based drug design, particularly in evaluating potential modifications to orforglipron. (EX1002, ¶59.) For instance, based on this model, a POSA would have understood which regions of the ligand-binding pocket exhibit conformational flexibility and, therefore, could accommodate bulkier substituents of hydrophobic nature without materially disrupting the structural integrity or functional conformation of the binding pocket. (*Id.*)

D. Talele (EX1009)

Talele, entitled “The ‘Cyclopropyl Fragment’ is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules,” is a review article published in the Journal of Medicinal Chemistry on June 14, 2016 (Ex. 1009). Talele is prior art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the ’236 Patent, and none of the exceptions of 35 U.S.C. § 102(b) apply.

As Dr. Pirrung explains, Talele teaches that substitution with a cyclopropyl ring is a well-recognized strategy in medicinal chemistry, commonly employed to

enhance metabolic stability, improve pharmacokinetic properties, and modulate the biological activity of drug molecules. (EX1002, ¶81.)

Talele states that “the cyclopropyl fragment is a versatile player,” noting 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, 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.*, 2.)

Talele provides a comprehensive review of the role of the cyclopropane ring in modulating pharmaceutical activity, emphasizing its contribution to a range of favorable drug-like properties. (EX1002, ¶¶83-84 (citing EX1009, 1-37.) These include enhanced potency, improved receptor subtype selectivity, increased oral bioavailability, prolonged half-life, greater microsomal stability, improved blood-brain barrier permeability, adaptability to dynamic or mutable binding sites, increased aqueous solubility, and entropically favorable binding interactions. (*Id.*, ¶¶83-84; EX1009, 2.) In addition, the presence of a cyclopropane ring has been associated with reduced lipophilicity, lower metabolic liability, diminished off-target pharmacology, and reduced entropic penalties upon binding, characteristics

that collectively increase the likelihood of achieving therapeutic efficacy. (*Id.*)

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 pK_a to reduce its P-glycoprotein efflux ratio.

(EX1009, 1-2 (emphases added).)

In particular, with regard to the replacement of a methyl with a cyclopropyl,

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.

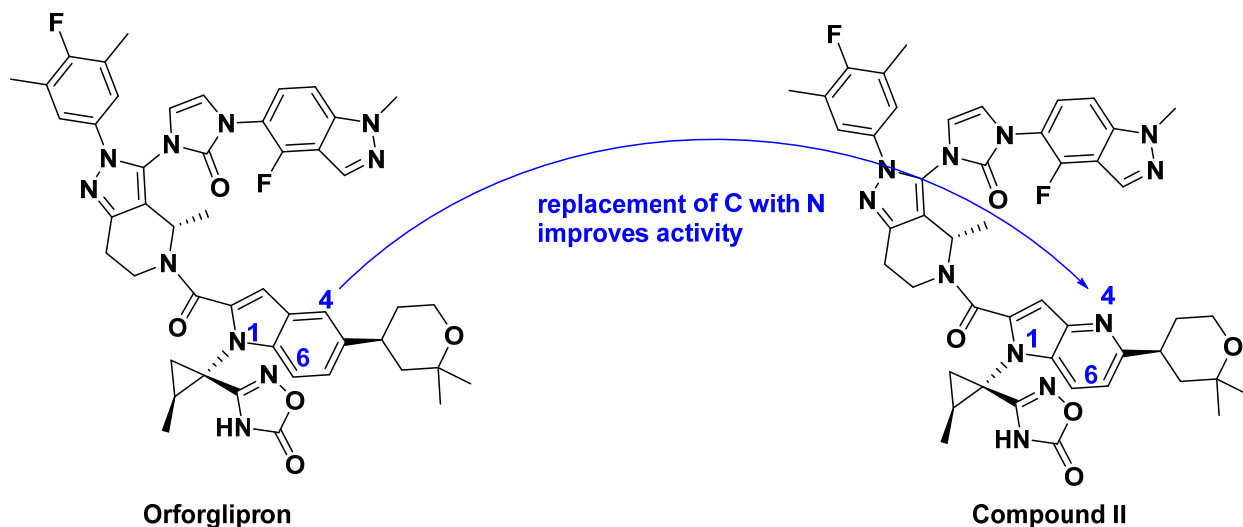
The cyclopropane scaffold may also contribute toward sp^3 disruption of overall planarity due to increased character and three-dimensionality favoring noncoplanarity, less crystal packing, low melting point, and higher aqueous solubility.

(*Id.* (emphasis added))

E. Meng (EX1028)

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. (EX1028, 1; EX1029, 1.) Meng is prior art 35 U.S.C. § 102(a) at least because it was published before the priority date of January 31, 2024 to which Compound 65 in the ’236 patent may be entitled (see Section VII), and none of the exceptions of 35 U.S.C. § 102(b) apply.

Meng discloses and claims Compound (II), which includes an additional nitrogen atom in the core scaffold compared to orforglipron. (EX1002, ¶86 (citing EX1029, 2–3, claim 5; ¶¶ [0020]–[0025]; Examples 1–3).) Structurally, Compound (II) is nearly identical to orforglipron, with the sole distinction being the presence and position of the added nitrogen atom within the aromatic ring. (*Id.*) This close structural similarity between Compound (II) and orforglipron is illustrated below.



(*Id.*)

Importantly, Compound (II) is one of only two compounds in Meng that are structurally and functionally characterized in detail. (*Id.*, ¶87 (citing EX1029, ¶¶ [0027]–[0192]; Examples 1–3).) Meng describes a comparative study evaluating Compound (II) relative to a reference compound, identified as Compound 67 of TW201827426. (*Id.* (citing EX1029, ¶¶ [0186]–[0192])). TW201827426 is the Taiwanese counterpart to Yoshino, and that Compound 67 disclosed therein is chemically identical to orforglipron. (*Id.*)

The comparative data in Meng show that introducing a nitrogen atom into the aromatic core of orforglipron analogs significantly enhances GLP-1 receptor potency. (*Id.*, ¶88 (citing EX1029, ¶¶ [0186]–[0192])). Specifically, Compound (II) demonstrates a 1.6-fold improvement in potency compared to orforglipron, as evidenced by a lower EC50 value in GLP-1 receptor activation assays. (*Id.*)

F. Patel (EX1026)

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 is prior art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the ’236 Patent, and none of the exceptions of 35 U.S.C. § 102(b) apply.

Patel describes a well-established medicinal chemistry strategy involving the substitution of a benzene ring with a pyridine ring. (EX1002, ¶90.) Specifically, Patel discloses a study demonstrating a concise synthetic approach for the direct transformation of aromatic C–H bonds into nitrogen-containing heterocycles. (*Id.*, ¶90; Ex. 1026, 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. 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

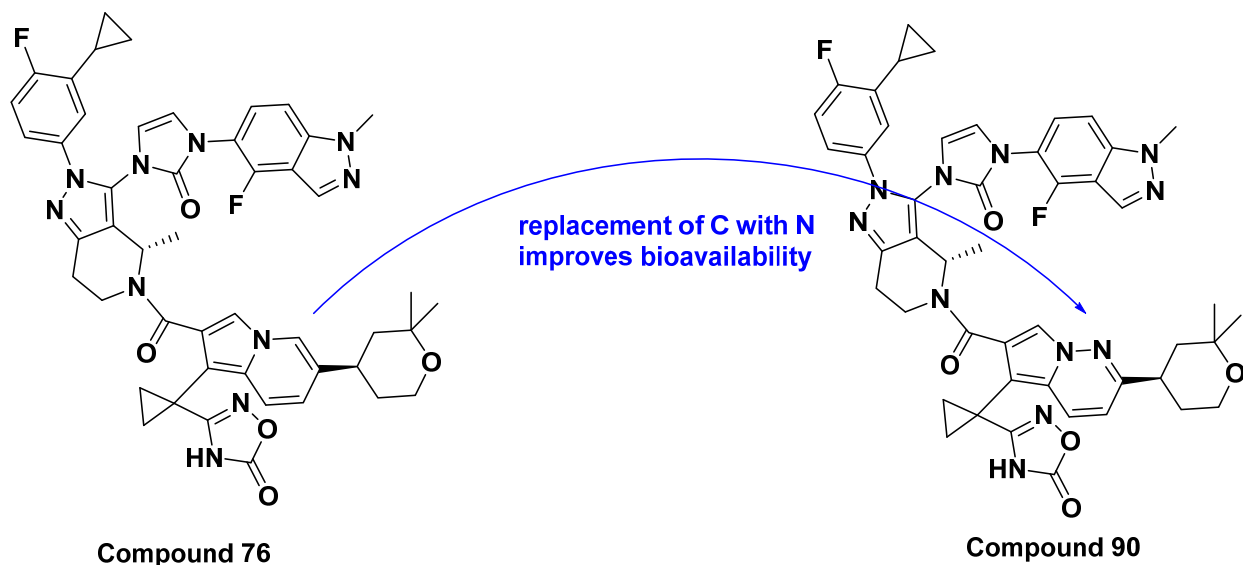
parameters including potency anywhere from 10- to 1000-fold.

(*Id.*, 1 (emphases added; international citations omitted).)

G. Ren (EX1030)

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 US 2023/0051320 A1, and subsequently issued as U.S. Patent No. 12,037,339 (“Ren”), assigned to Eccogene Inc. (EX1030, 1). Ren qualifies as prior art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the ’236 Patent, and none of the exceptions of 35 U.S.C. § 102(b) apply.

Ren discloses Compounds 76 and 90. (EX1002, ¶92 (citing EX1030, 393:1–67, 445:1–67).) These two compounds are structurally identical except that Compound 90 incorporates an additional nitrogen atom into the core aromatic ring—a modification that distinguishes it from Compound 76. (*Id.*)



Ren further provides pharmacokinetic data for both compounds in Table 30. (*Id.*, ¶93 (citing EX1030, 459:46–460:30, Example 81).) This data reveals that Compound 90, which includes the additional nitrogen atom, exhibits significantly improved oral bioavailability. (*Id.*) Specifically, Compound 90 demonstrates an oral bioavailability (F%) of 59%, compared to only 30% for Compound 76—an improvement of nearly two-fold. Ren attributes this enhancement in pharmacokinetic performance to the presence of the additional nitrogen atom in the aromatic ring. (*Id.*)

TABLE 30-continued

Cmpd No.	PO parameters			
	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

As Dr. Pirrung explained, a POSA would have recognized from Ren that introducing a nitrogen atom into the aromatic core structure—particularly at the same position as in Compound 90—was a rational and effective strategy to improve oral bioavailability. In view of these teachings, a POSA would have been motivated to modify structurally similar GLP-1 receptor agonists in the same manner to enhance their pharmacological properties. (*Id.*, ¶94.)

H. Bethel (EX1032)

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.) Bethel is prior art under 35 U.S.C. § 102(a)(2) because it has an effective filing date before the earliest possible claimed priority date of the ’236 Patent’s claims, and none of the exceptions of 35 U.S.C. § 102(b) apply.

Bethel discloses methods of treating subjects with type 2 diabetes (T2D), obesity, or overweight with at least one weight-related comorbidity using a non-

peptide glucagon-like peptide-1 (GLP-1) receptor agonist referred to as Compound 1, which is chemically identical to orforglipron. (EX1032, 4; EX1002, ¶96.) Examples 1–3 describe the preparation of capsule and tablet formulations containing the ½ calcium salt of orforglipron. (EX1032, 46–53; EX1002, ¶96.) Examples 4A and 4B report Phase 2 clinical trial results in patients with obesity or overweight who were treated with various doses of the orforglipron ½ calcium salt formulation. (EX1032, 53–66; EX1002, ¶96.) Bethel states that “Compound 1a was well tolerated across all arms,” with no significant increases in liver function tests compared to placebo. (EX1032, 57, 59; EX1002, ¶96.) Bethel also reports the percentages of participants achieving HbA1c and weight loss targets (*Id.*) In addition, Examples 5 and 7–12 describe Phase 3 clinical studies using the same orforglipron ½ calcium salt formulation. (EX1032, 66–70, 71–74; EX1002, ¶96.)

IX. PERSON OF ORDINARY SKILL IN THE ART

34. 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. (*See* EX1002, ¶¶34-35.) Such experience would include the design, chemical synthesis, and structure-activity relationship (SAR) analysis of therapeutic compounds. (*Id.*)

X. CLAIM CONSTRUCTION

For PGR proceedings, the Board applies the same claim construction standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). *See* 83 Fed. Reg. 51,340-59 (Oct. 11, 2018). “[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’” *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2001). Petitioner submits that no term of the Challenged Claims requires construction to resolve the challenges in this Petition.

XI. LEGAL STANDARDS

“[I]f the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art” a patent may not be obtained. 35 U.S.C. § 103. The obvious analysis looks at (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966); *see also KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 415 (2007) (applying *Graham* but noting it is an “expansive and flexible” standard and includes combinations that were “obvious to try” or an obvious solution to a known problem). Obviousness looks at whether a person of ordinary skill in the art would have been motivated to combine the prior art teachings and would have had a reasonable expectation of success in

doing so. *See ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018) (noting a motivation to combine “may be found explicitly or implicitly in... the interrelated teachings of multiple patents” as well as “the background knowledge, creativity, and common sense of ordinary skill.”) (citations omitted).

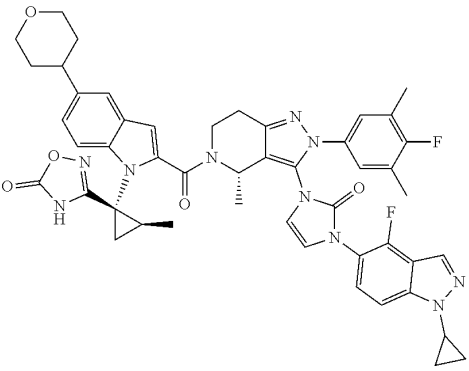
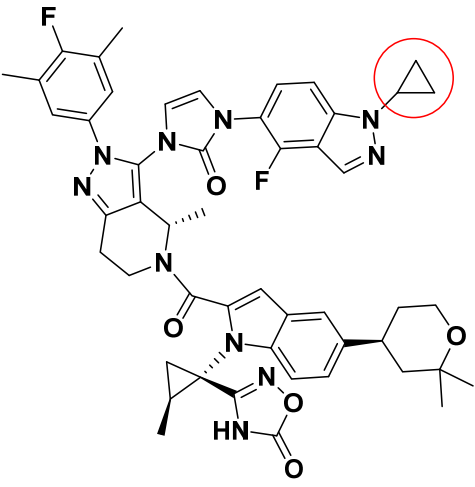
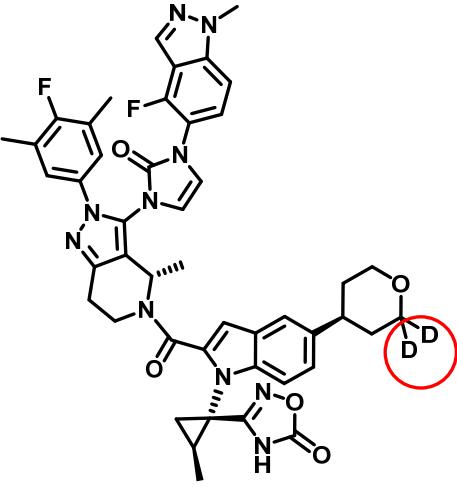
XIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. GROUND 1: CLAIMS 1-4, 6, 12-14, 24, AND 25 ARE OBVIOUS OVER SU, YOSHINO, AND KAWAI IN VIEW OF TALELE

As discussed in Section VII.B, claims 1–4, 6, 12–14, 24, and 25, at least insofar as they encompass Compound 19, are not entitled to a priority date earlier than October 23, 2023. (EX1002, ¶¶134-138; *supra* Section VII.B.) Accordingly, Su, Yoshino, Kawai, and Talele each qualify as prior art for purposes of assessing the patentability of these claims. (*Id.*) For the reasons discussed below, claims 1-4, 6, 12-14, 24, and 25 would have been obvious based on the relevant teachings of Su, Yoshino, Kawai, and Talele, at least with respect to Compound 19. (*Id.*, ¶¶146-199; *supra* Section VIII.)

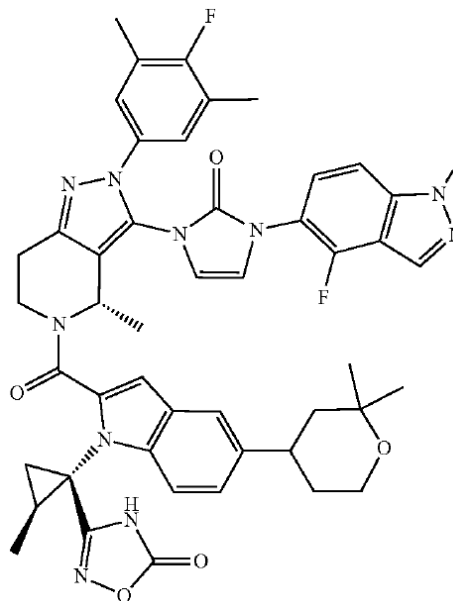
Claim 1:

The combination of Su, Yoshino, and Kawai in view of Talele renders at least Compound 19 of Claim 1 obvious.

Compound 19 of the '236 Patent	Prior Art
<p data-bbox="695 304 714 325">19</p>  <p data-bbox="203 703 430 745">Compound 19</p>	<p data-bbox="743 304 941 346">Su discloses:</p> <p data-bbox="743 357 1412 735">Deuterated Compound 176, its non-deuterated parent Compound 175, and Compound 44, as illustrated below, maintain the scaffold of orforglipron (see Compound 67 as disclosed in Yoshino) and contain only peripheral modifications (as depicted with red circles) with respect to orforglipron. (EX1002, ¶148; EX1006, 327, 328 and claim 12; EX1007, 327, 328, and claim 12.)</p>  <p data-bbox="836 1228 1209 1270">non-deuterated compound 175</p>  <p data-bbox="836 1816 990 1858">Compound 44</p>

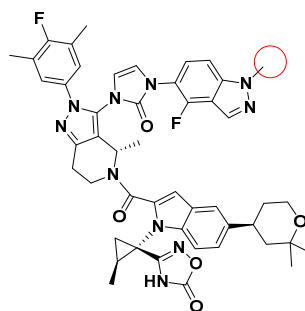
(EX1007, 327, 328, and claim 12.)

Yoshino discloses:



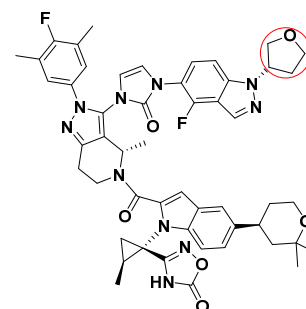
(Compound 67, also known as orforglipron)

Yoshino also teaches that replacement of methyl with a ring and removal of di-methyl results in improved or comparable activities as measured by EC_{50} values. (EX1002, ¶148; EX1008, claims 13 and 14, 183:1-65, Tables 2-5.)



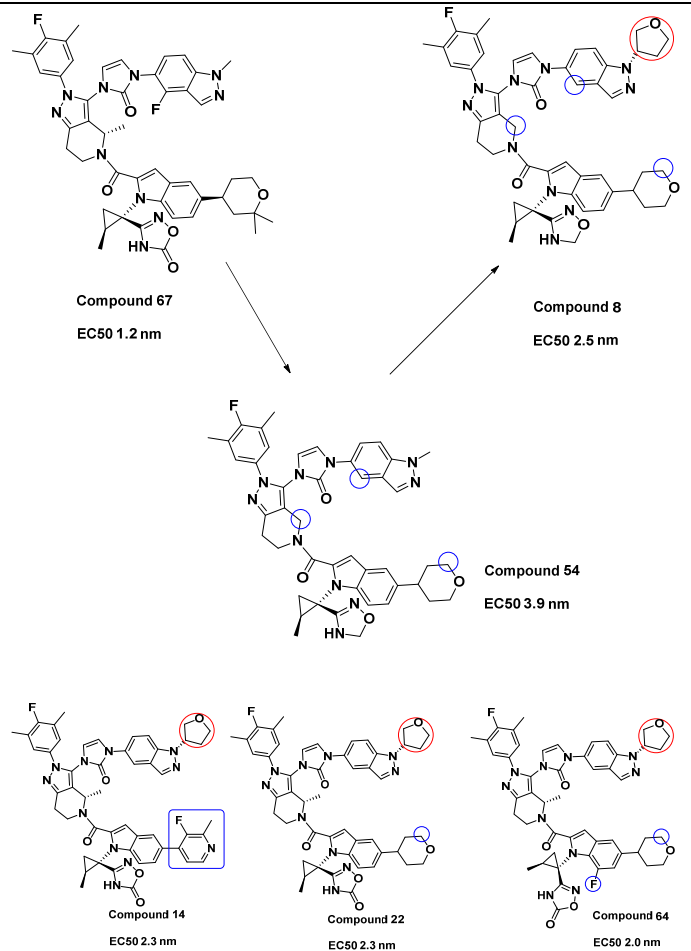
Compound 67

EC_{50} 1.2 nm



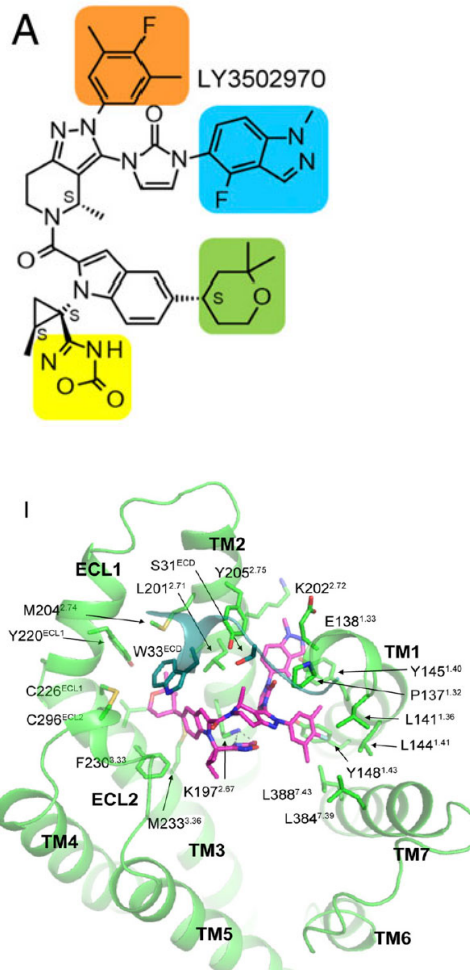
Compound 40

EC_{50} 2.2 nm



Kawai discloses:

structural basis for GLP-1 receptor activation by orforglipron. (EX1004, 1; EX1002, ¶148.) In particular, Kawai discloses a high resolution cryo-EM structure of orforglipron in complex with the GLP-1 receptor, along with a detailed protein-ligand interaction model illustrating the ligand-binding pocket surrounding orforglipron, as shown below:



(EX1004, 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. (EX1004, 4; EX1002, ¶148.) 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

	<p>ligand-binding pocket, and thus would likely maintain binding potency. (<i>Id.</i>)</p> <p>In addition, the binding pocket adjacent to the methyl group of the 4-fluoro-1-methyl-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. (<i>Id.</i>)</p> <p>Talele teaches: Cyclopropyl is known to enhance metabolic stability and decrease plasma clearance and substitution of a methyl group with cyclopropyl will enhance metabolic stability. (EX1009, 1-2; EX1002, ¶148.)</p>
--	---

As illustrated above and further discussed below, a POSA would have been motivated to combine the teachings of Su, Yoshino, and Kawai in view of Talele. Such a combination teaches each and every feature of Compound 19 recited in claim 1 of the '236 Patent, and combined with the knowledge of a POSA provides a motivation to do so.

In Su II, Su discloses that out of the 218 working examples, only seven stereoisomerically pure compounds—Compounds 35, 44, 123, 139, 176, 188, and 212—were deuterated. (EX1002, ¶149; EX1006, 303, 309, 327, 328, 365, and claim 12; EX1007, 303, 309, 327, 328, 365, and claims 12 and 27.) Su also discloses the deuteration of the non-stereoisomerically pure counterpart compounds of

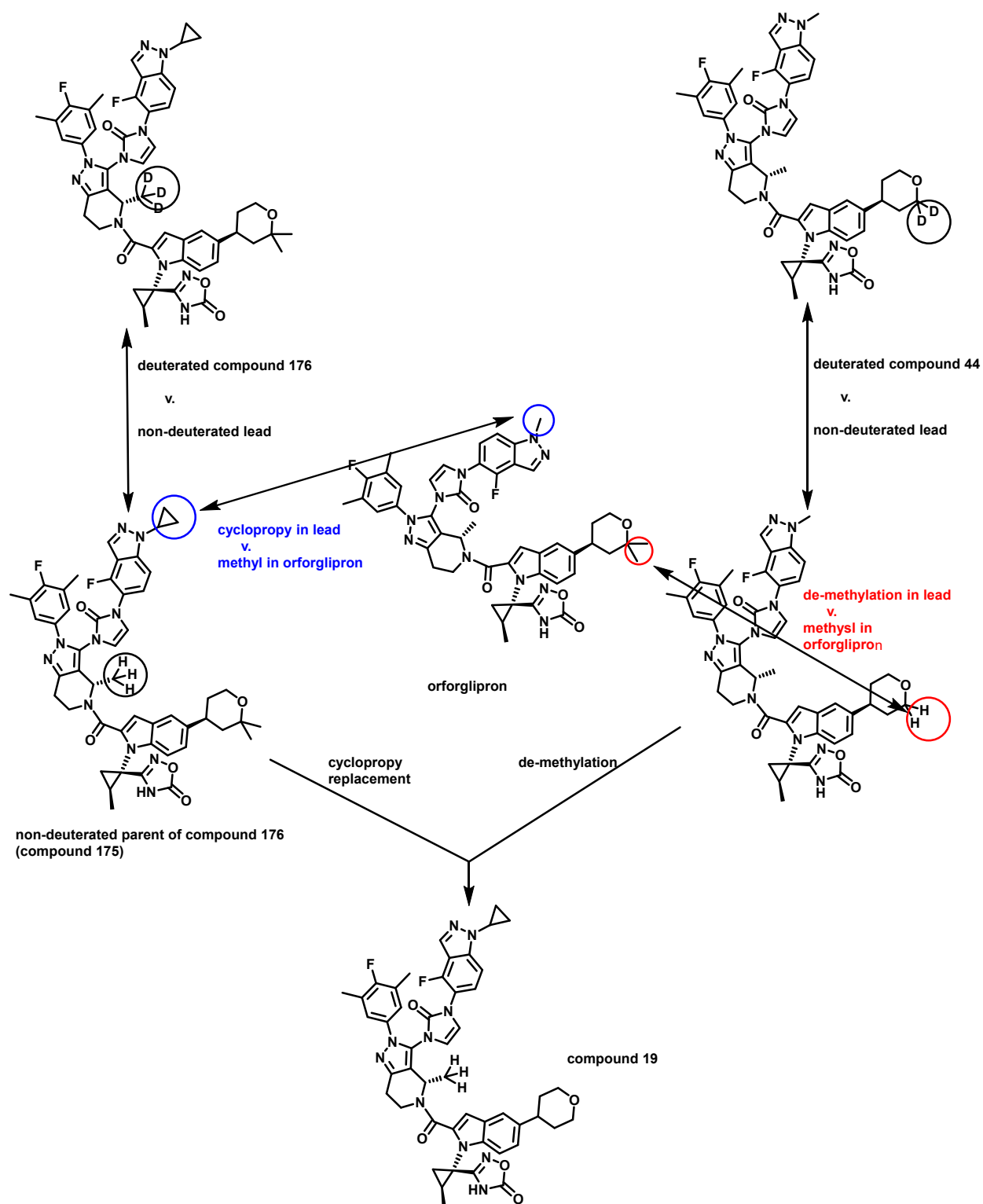
Compounds 35, 44, and 176 (EX1002, ¶149; EX1006, 326-329, and claim 12; EX1007, 327, 328, and claim 12).

A POSA would have understood that the selective deuteration of particular compounds within a chemical series is indicative of their perceived potential for lead optimization. (EX1002, ¶150.) Due to practical constraints, such as time, synthetic complexity, and resource limitations—it is generally not feasible to deuterate every compound in a given series. (*Id.*) For example, the synthesis of deuterated Compound 176 involves a lengthier and more synthetically demanding route than that required for its non-deuterated counterpart, Compound 175. (*Id.*) This further underscores the deliberate nature of its selection. (*Id.*)

As such, a POSA would have reasonably inferred that those structures associated with the small number of deuterated compounds, namely, Compounds 35, 44, 123, 139, 176, 188, and 212, represent a subset of particular interest and are likely to have been considered promising candidates for further development. (*Id.*, ¶¶61, 149) Notably, Compound 176 is among the limited group of disclosed deuterated stereoisomerically pure compounds and is the deuterated analog of stereoisomerically pure Compound 175. (*Id.*; *see* EX1006, 328, claim 12; EX1007, 328, claim 12.) Su II also discloses the non-stereoisomerically pure counterpart of Compound 175 and its corresponding deuterated analog. (EX1002, ¶151; *see* EX1006, 329, claim 12; EX1007, 329, claim 12.) The disclosure of both

stereoisomerically pure and non-stereoisomerically pure analogs, non-deuterated and deuterated, of Compound 175 further emphasizes to a POSA the structural and developmental relevance of this chemotype within the broader series. (EX1002, ¶151.)

As discussed above, orforglipron is a known small-molecule GLP-1 receptor agonist that was undergoing Phase 3 clinical trials at the time of the '236 Patent filing. (*See supra* Section VI.) As discussed *supra* Section VIII and below, a POSA would have been aware of various modifications to drug molecules that could improve metabolic stability, modulate biological activity of drug molecules, and/or improve molecular, physicochemical, and pharmacokinetic properties. A POSA seeking to modify orforglipron would have therefore been motivated to introduce peripheral modifications to improve or optimize certain properties, while maintaining the core scaffold of the molecule to preserve activity. (EX1002, ¶152.) A POSA would have appreciated this could be achieved in multiple ways.



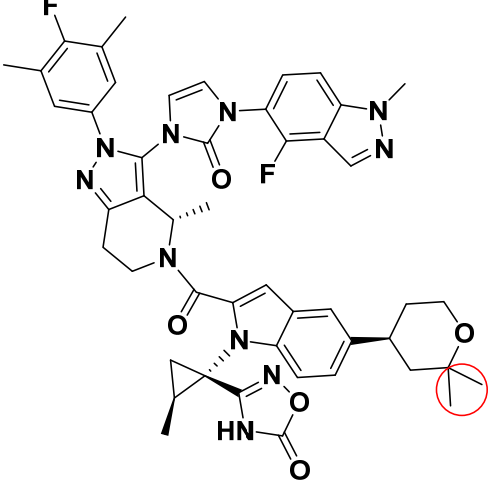
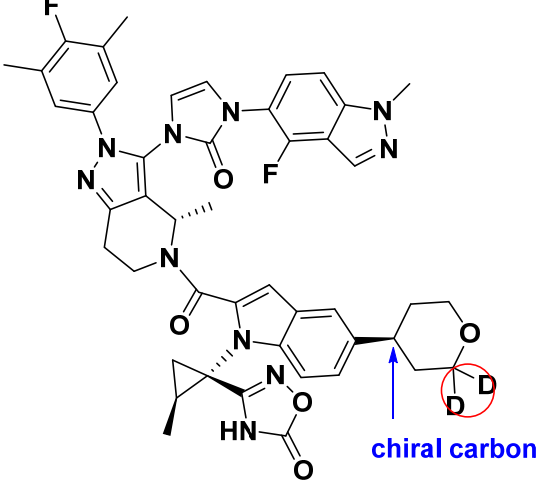
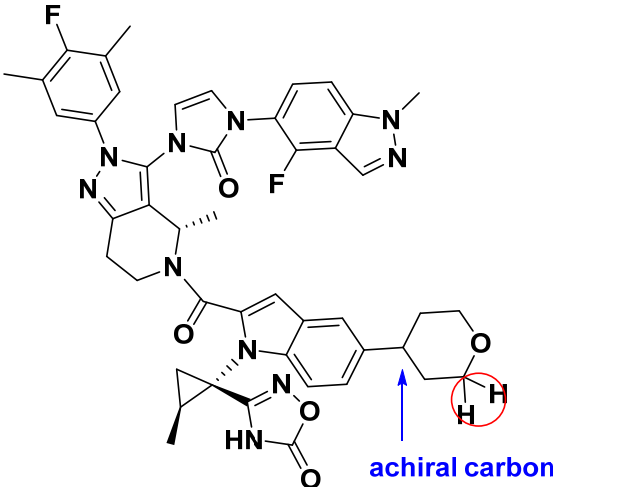
First, Su's Compound 175, which shares the same core scaffold as orforglipron and differs only by a peripheral cyclopropyl substitution, was selected

for deuteration, further reinforcing its structural significance. (*Id.*) The presence of the cyclopropyl group in place of a methyl group suggests, to a POSA, that such a substitution was viewed as pharmacologically meaningful, and that Compound 175 represents a logical scaffold for further optimization. (*Id.*) The selection of this compound for deuteration, despite the more challenging synthetic route, supports its relevance to a POSA as a lead structure. (*Id.*)

Similarly, Su's deuterated Compound 44 and its non-stereoisomerically pure analog also retain the same core scaffold as orforglipron, except that they lack the two methyl groups on the tetrahydropyran ring. (*Id.*, ¶154; EX1006, 327; EX1007, 327.) This structural change indicates to a POSA that the dimethyl substitution is not critical for pharmacological activity. (EX1002, ¶154.) Moreover, a POSA would have readily understood that a non-deuterated analog of Compound 44 is its closest structural relative, presenting additional practical benefits, including greater synthetic simplicity and the absence of a chiral center within the tetrahydropyran ring. (*Id.*)

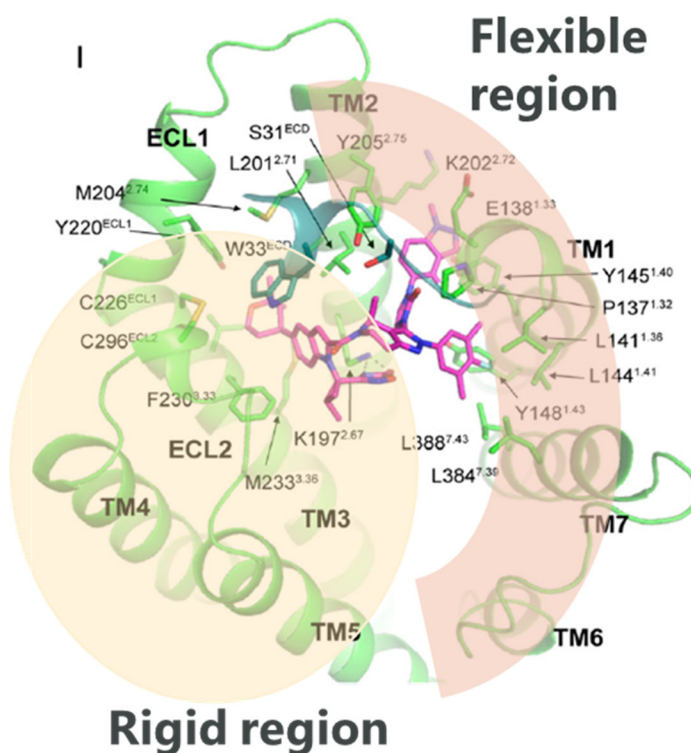
Accordingly, the collective teachings of Su support a clear rationale for making the specific modifications embodied in Compounds 175 and 44, including replacing a methyl group on the indazole moiety with a cyclopropyl ring, and substituting a dimethyl-substituted tetrahydropyran ring with a non-substituted, achiral tetrahydropyran ring. (*Id.*, ¶¶152-154.) These teachings would have provided

a POSA with both the motivation and a reasonable expectation of success in arriving at the claimed compounds, including Compound 19 of the '236 Patent, through routine structural optimization. (*Id.*)

Orforglipron	Compound 44
	<div data-bbox="792 520 1328 1003">  <p>chiral carbon</p> </div> <hr/> <div data-bbox="792 1134 1421 1785"> <p>Non-deuterated counterpart of Compound 44</p>  <p>achiral carbon</p> </div>

Second, or alternatively, as Dr. Pirrung explains, Compound 175 would have been reasonably considered by a POSA as a promising lead compound for further structural modification, particularly in view of the fact that it was among a limited subset of compounds expressly selected for deuteration. (*Id.* ¶153.) In light of the teaching provided by Compound 44, also one of the very few deuterated stereoisomerically pure compounds disclosed, which demonstrates the removal of the dimethyl group relative to orforglipron, a POSA would have been motivated to implement the same modification to Compound 175. (*Id.*, ¶154.) Such a modification would have resulted in Compound 19, as claimed in the '236 Patent. (*Id.*)

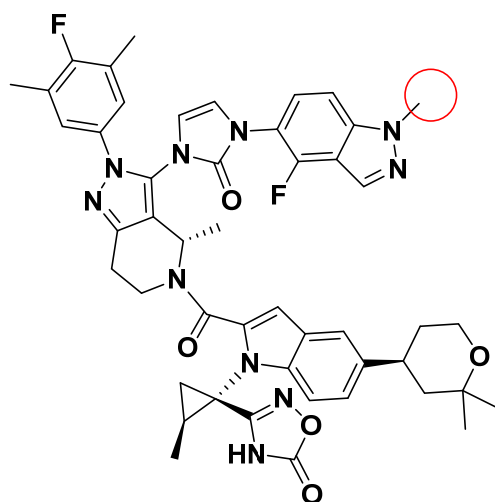
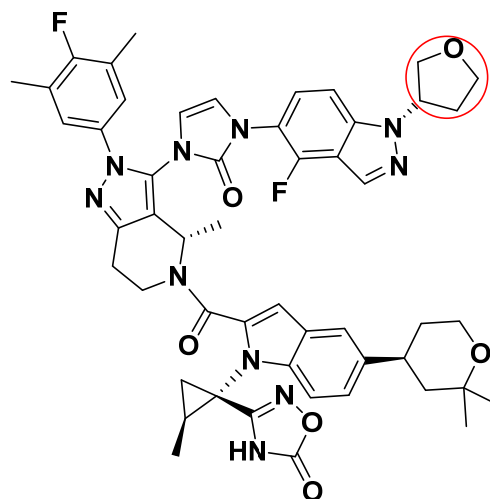
As Dr. Pirrung explains, Yoshino and Kawai further support the above conclusion that a POSA would have been motivated to pursue the peripheral modifications as taught by Su. (*Id.*, ¶155.) Kawai discloses the high-resolution three-dimensional structure of orforglipron bound to the N-terminal extracellular domain of the GLP-1 receptor, revealing the ligand-binding pocket and key interactions. (EX1004, FIG. 1, 1-9.) According to Dr. Pirrung, this structural data provides a valuable framework for structure-based drug design. (EX1002, ¶157.) Kawai also identifies the region formed by TM1, TM2, TM6, and TM7, adjacent to 4-fluoro-1-methyl-indazole moiety, as flexible (*Id.*, ¶158; EX1004, 4.), while the TM3–TM5 region is described as rigid, as shown below. (*Id.*)

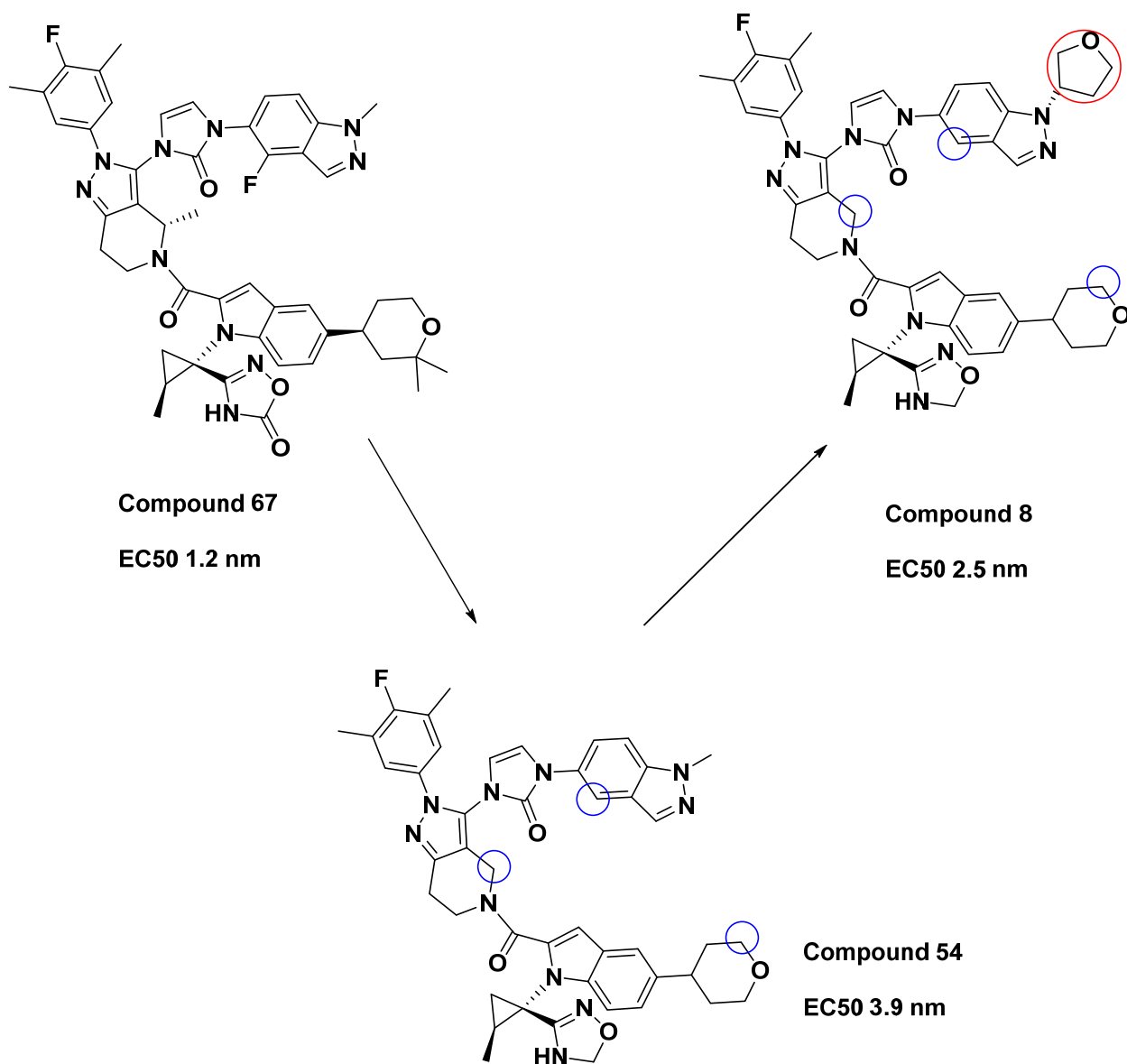


(EX1004, FIG. 1, 1-9 (emphases added to indicate the flexible and rigid regions).)

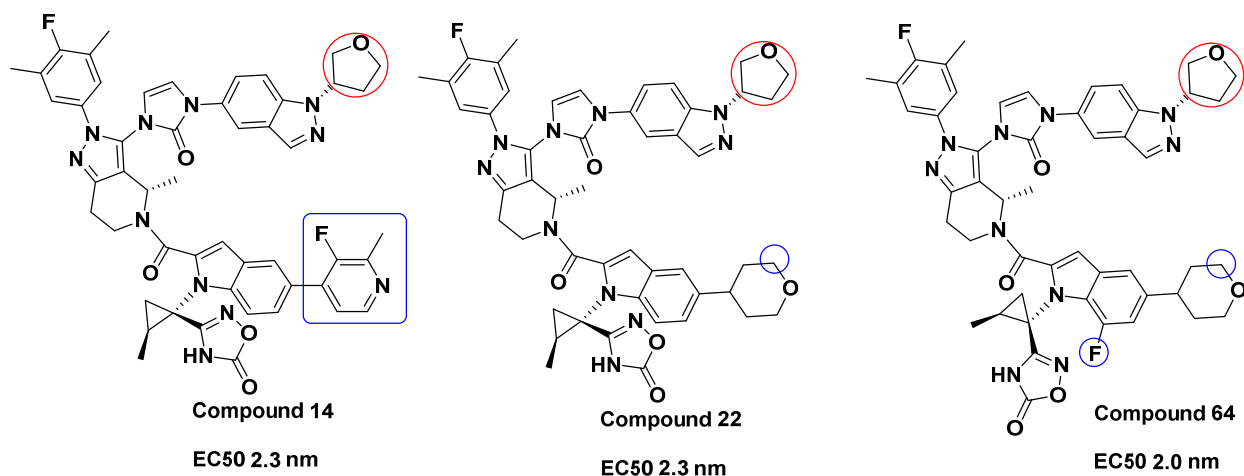
Thus, a POSA would have understood that modifications to the indazole moiety would likely preserve receptor binding affinity. (EX1002, ¶158.) In particular, a POSA would observe that the methyl group of the indazole moiety is located in a hydrophobic pocket formed by carbon atoms of the side chains of Y205, K202, and E318, and a POSA would have recognized this environment as suitable for substitution with larger hydrophobic groups, such as three- to five-membered rings. (*Id.*, ¶159.)

Yoshino further corroborates this understanding because it shows that substitution of the methyl group with a tetrahydrofuran ring yields compounds retaining biological activity (*e.g.*, Compound 40 relative to Compound 67). (*Id.*, ¶160; EX1008, 50, 99, Table 3.) Even when removal of multiple substituents reduced activity (*e.g.*, Compound 54), substitution with a tetrahydrofuran moiety partially restored it. (EX1002, ¶161; EX1008, 34, 92, 99, Table 3.) Yoshino also discloses additional analogs with tetrahydrofuran rings that maintained activity. (EX1002, ¶162; EX1008, 37, 41, 97, Table 3.)

**Compound 67****EC50 1.2 nm****Compound 40****EC50 2.2 nm**



Consistent with these observations, a POSA would have understood that replacement of the methyl group with a carbocyclic ring could maintain or improve binding. (EX1002, ¶162; EX1008, 37, 41, 97, Table 3.)



This rationale is further supported by Talele, which describes the widespread use and therapeutic relevance of cyclopropyl groups (a type of carbocyclic ring) in medicinal chemistry. (*Id.*, ¶¶164-166; EX1009, 1.) Talele reports that cyclopropyl moieties are present in eight of the top 200 FDA-approved drugs and that over 100 compounds containing cyclopropyl rings are currently in preclinical or clinical development. (EX1009, 1-2.)

Talele states that

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.*, 1, 2 (emphases added).)

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.

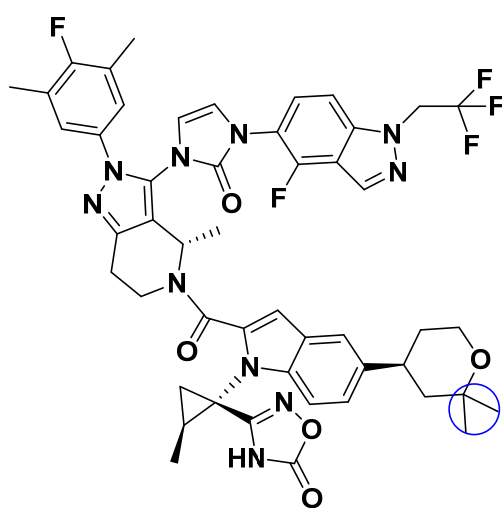
(*Id.* (emphasis added))

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. (EX1002, ¶167.)

In light of these teachings, 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 19 of the '236 Patent. (*Id.*) Indeed, among potential carbocycles, a POSA would understand that 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. (EX1002, ¶163.) Carbocycles are preferred to simple alkyl groups because they have fewer rotational degrees of

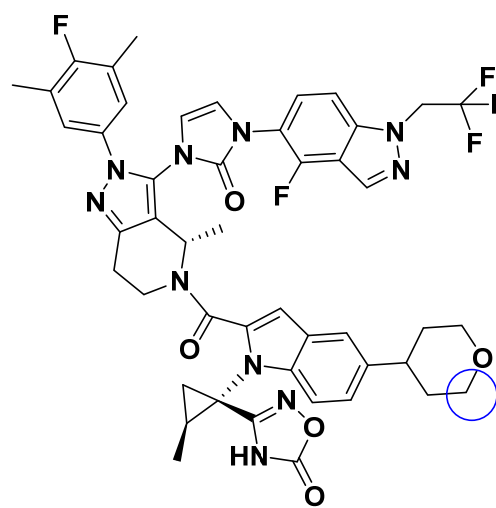
freedom, meaning they pay smaller entropic penalties when they achieve their bound confirmations, which restricts their rotation. (*Id.*) Moreover, cyclopropyl substitution offers practical synthetic and pharmacological advantages. (*Id.*) Unlike heterocyclic alternatives, the cyclopropyl group lacks a chiral center, thereby simplifying synthesis, reducing the potential for undesirable stereoisomer formation, and improving the overall drug development profile. (*Id.*)

Further, Yoshino teaches that removal of the dimethyl groups from the 2,2-dimethyl-tetrahydropyran moiety can maintain biological activity. (*Id.*, ¶168.) For instance, removal of the dimethyl groups from Compound 35 yields Compound 28 with comparable activity, and similar trends are observed between Compounds 30 and 38. (*Id.*; EX1008, 44, 45, 48, 49, Table 3.) Notably, more than 30 of the 80 active compounds listed in Table 3 of Yoshino feature a non-substituted, achiral tetrahydropyran ring. (EX1002, ¶169.)



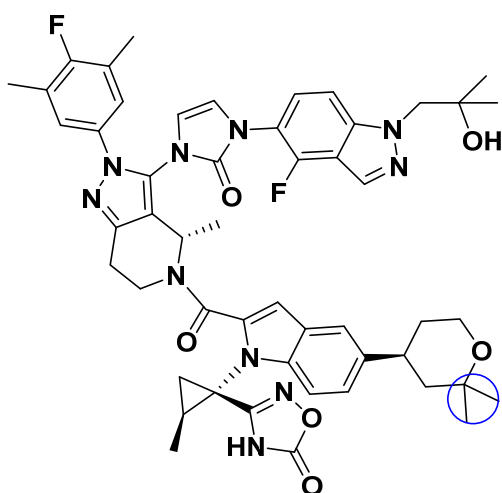
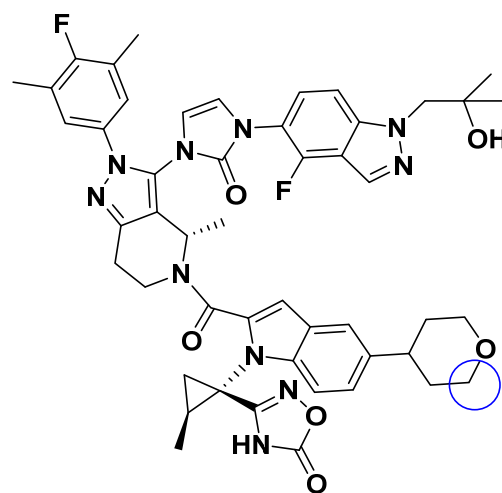
Compound 35

EC50 3.2 nm



Compound 28

EC50 1.9 nm

**Compound 38****EC50 1.7 nm****Compound 30****EC50 1.4 nm**

Accordingly, a POSA would have been motivated to incorporate the modifications exemplified by Compounds 175 and 44: substitution of the methyl group with a cyclopropyl group, and removal of the dimethyl substituents to generate an achiral tetrahydropyran ring. (*Id.*, ¶170.) These modifications would have been reasonably expected to preserve or improve activity, and in combination, would have led a POSA to arrive at Compound 19 as claimed in the '236 Patent. (*Id.*)

With respect to the claim limitation “a pharmaceutically acceptable salt thereof” recited in claim 1, Yoshino expressly discloses GLP-1 receptor agonists or salts thereof, including, for example, sodium and calcium salts. (*Id.*, ¶171; EX1008, 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Specifically, Yoshino teaches various forms of such compounds, including “a hydrate of the free form, a salt of the free form, and a hydrate of salt,” and 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.” (EX1002, ¶171; EX1008, 34:7-15.) Similarly, Su discloses GLP-1 receptor agonists and their pharmaceutically acceptable salts across multiple sections of the specification. (EX1002, ¶171; EX. 1007, 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.)

Therefore, claim 1 of the '236 Patent would have been obvious over the prior art.

Claim 2:

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.”

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.” (EX1002, ¶174; EX1008, 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. (EX1002, ¶¶173-175.)

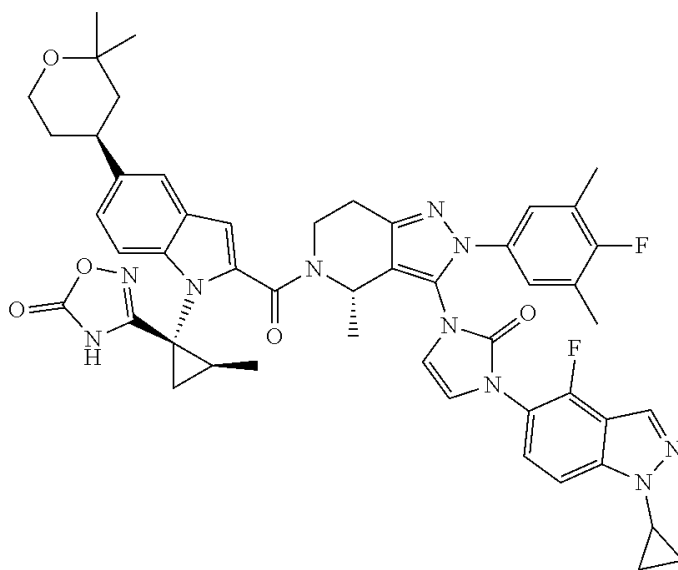
Accordingly, claim 2 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 3:

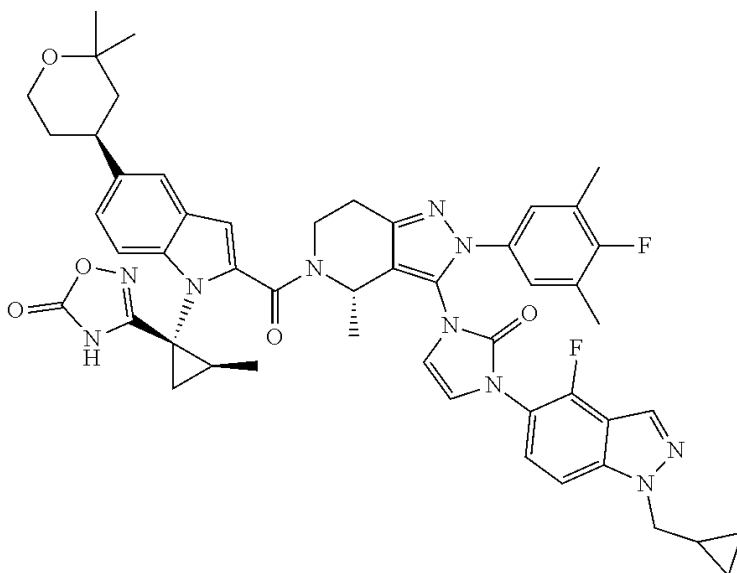
Claim 3 depends from claim 1 and recites:

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

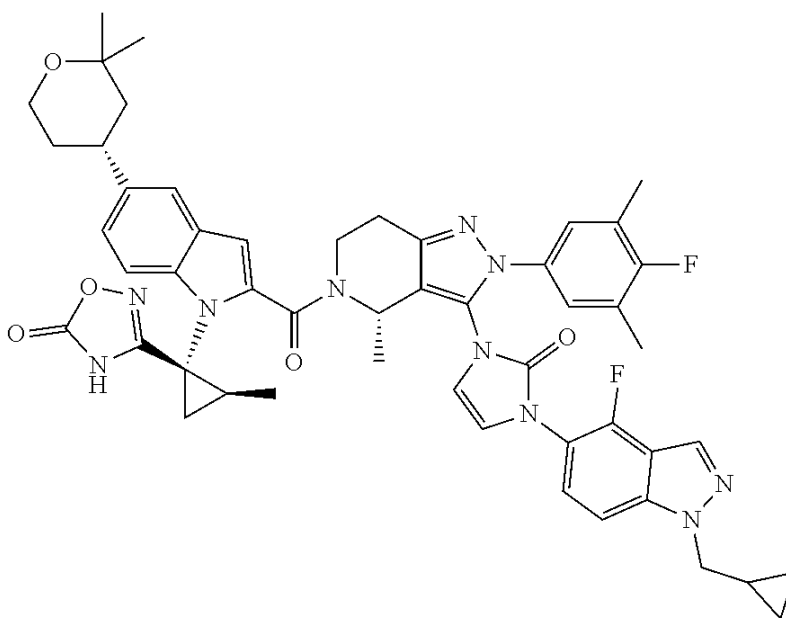
*Na



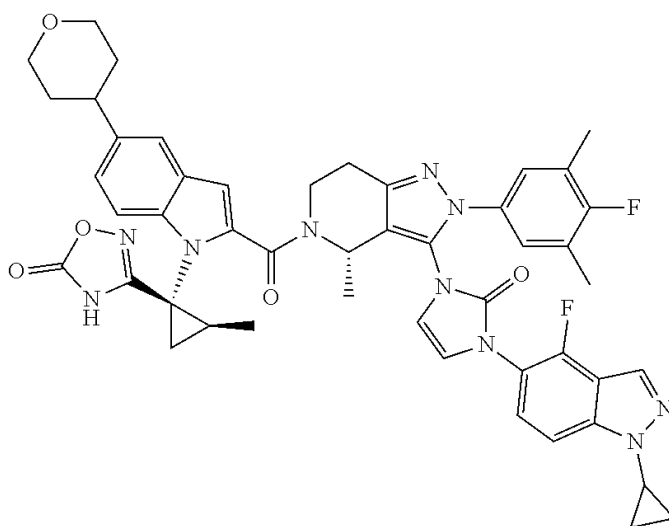
*Na



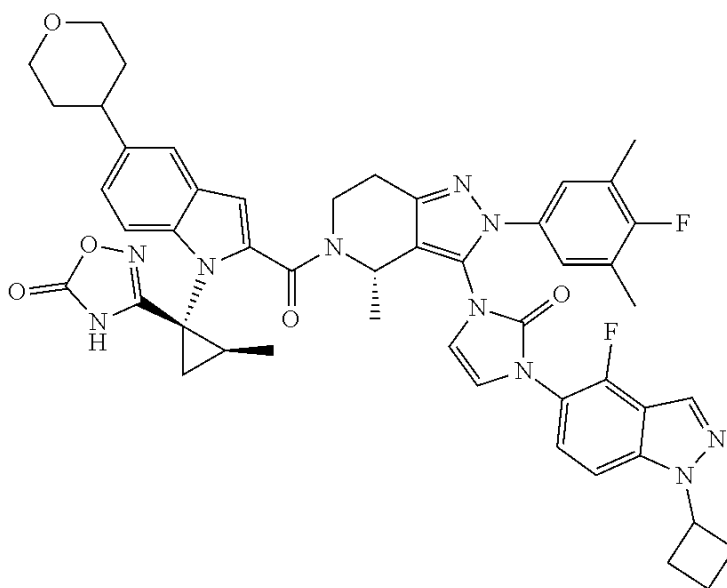
*Na



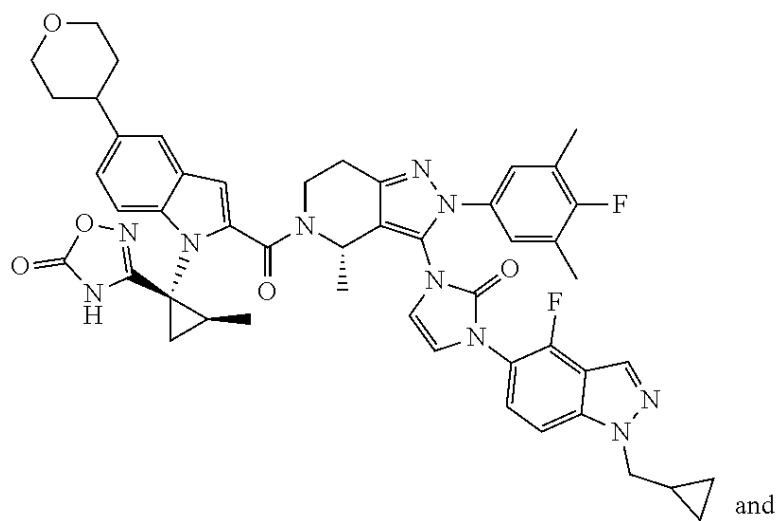
*Na



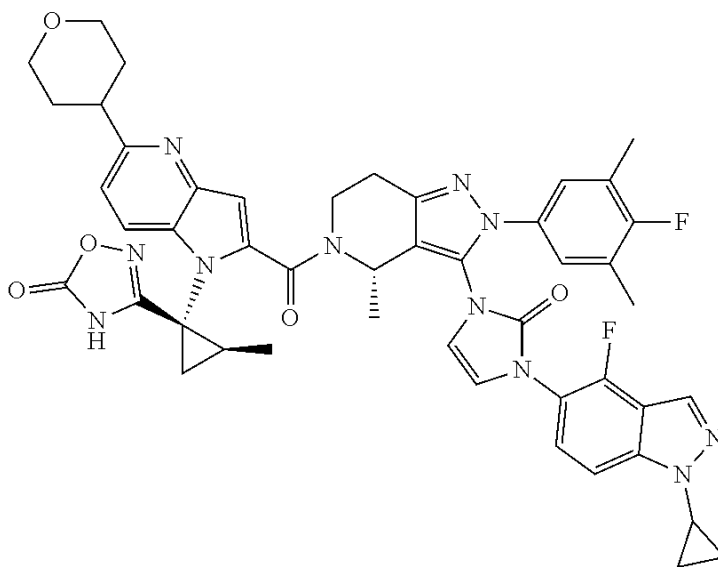
*Na



*Na



*Na



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.” (EX1002, ¶177; EX1008, 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. (EX1002, ¶¶176-178.)

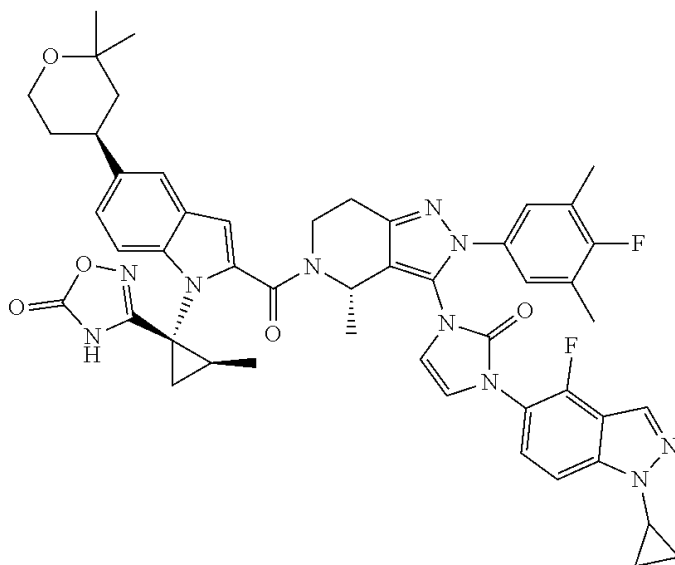
Thus, claim 3 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 2.

Claim 4:

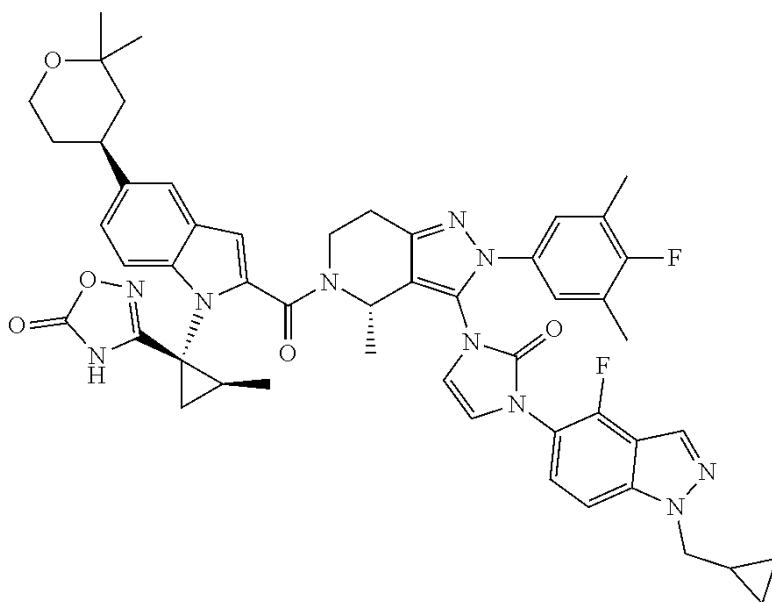
Claim 4 depends from claim 1 and recites:

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

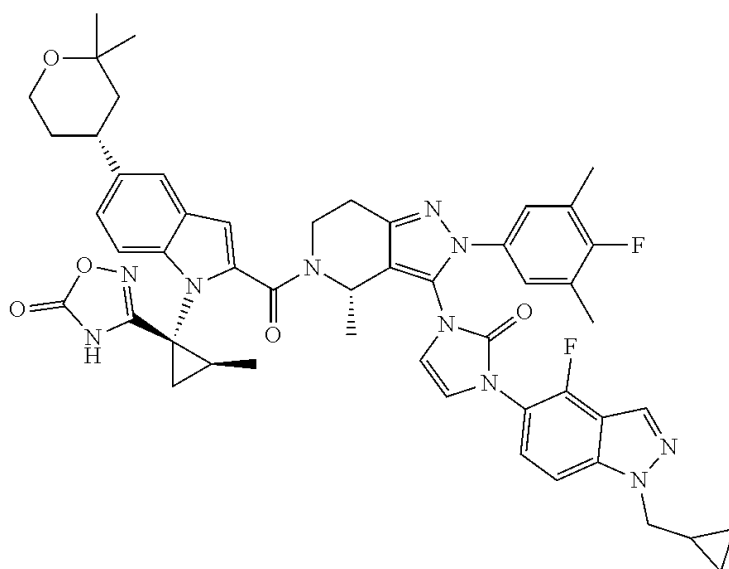
*1/2 Ca



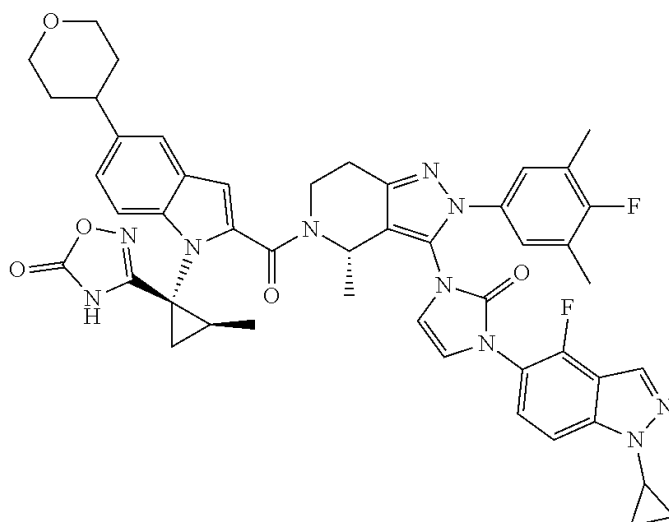
*1/2 Ca



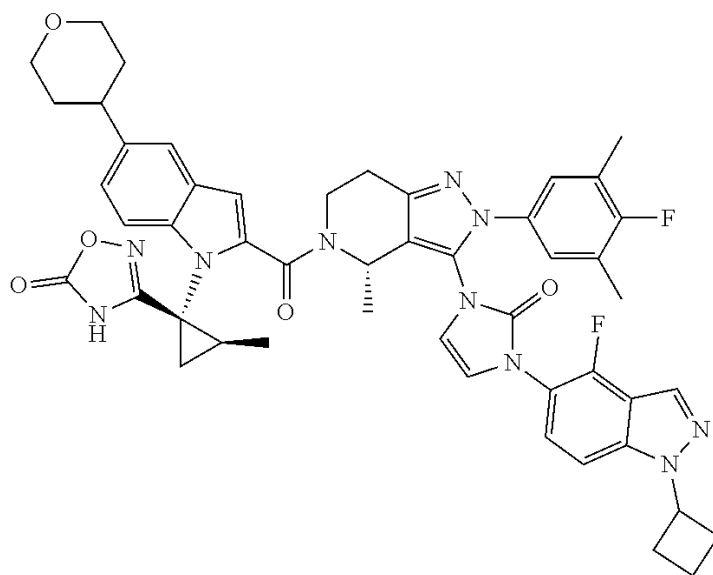
*1/2 Ca



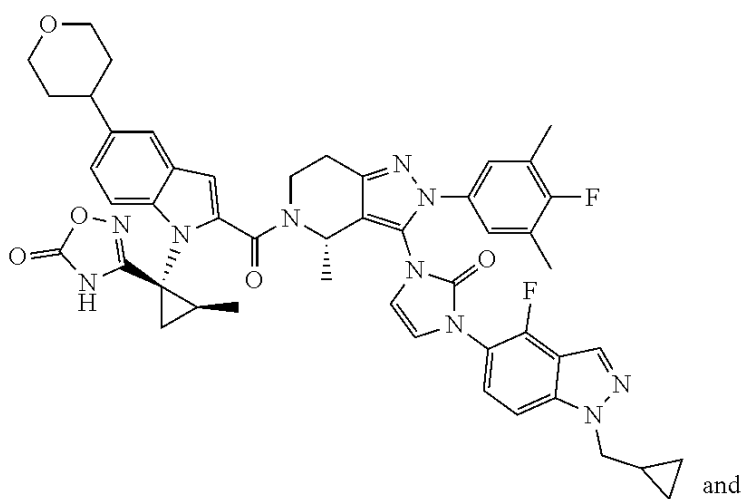
*1/2 Ca



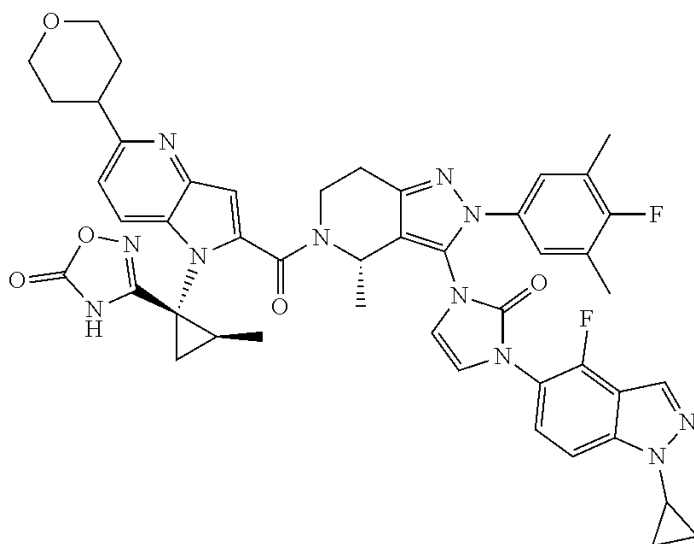
*1/2 Ca



*1/2 Ca



*1/2 Ca



As discussed above with respect to claims 1 and 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. (EX1002, ¶180; EX1008, 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 calcium salt of Compound 19 as recited in claim 4 of the '236 Patent. (EX1002, ¶¶179-181.)

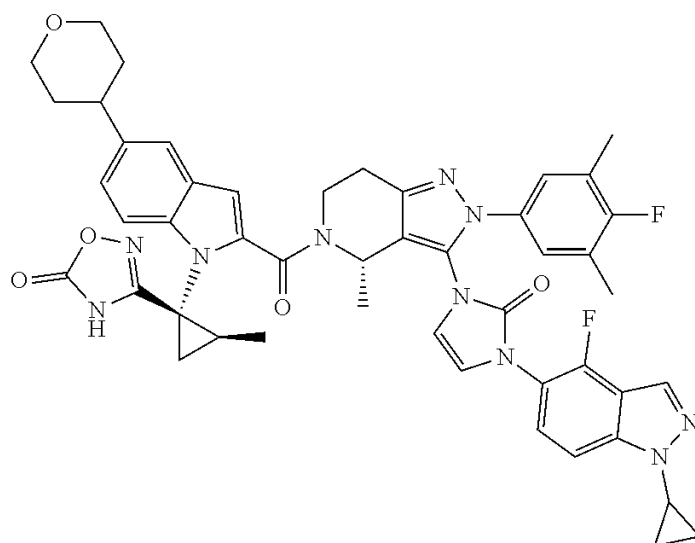
Thus, claim 4 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 2.

Claim 6:

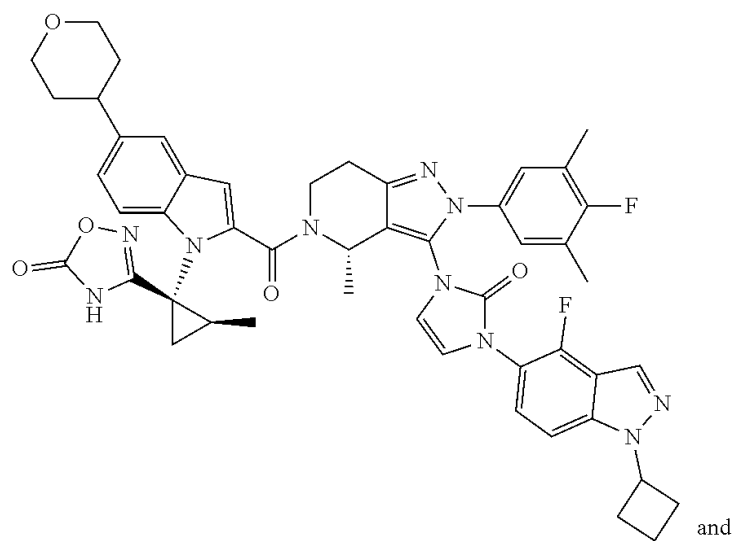
Claim 6 depends from claim 1 and recites:

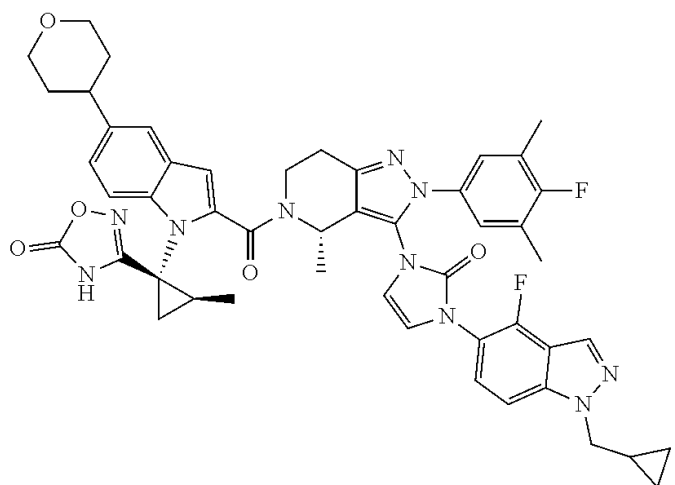
the compound is selected from the group consisting of:

19



20





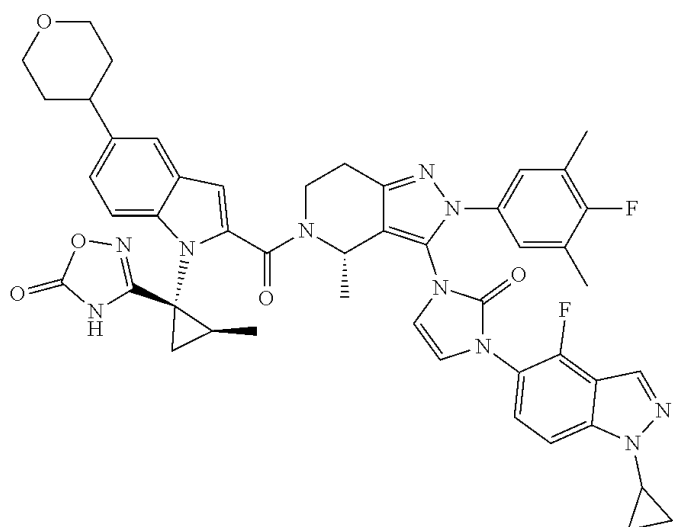
As discussed above with respect to claim 1, it would have been obvious for a POSA to arrive at Compound 19 as recited in claim 6 of the '236 Patent in view of the teachings of Su and Yoshino. (EX1002, ¶¶182-184.)

Thus, claim 6 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 12:

Claim 12 depends from claim 1 and recites:

the compound is



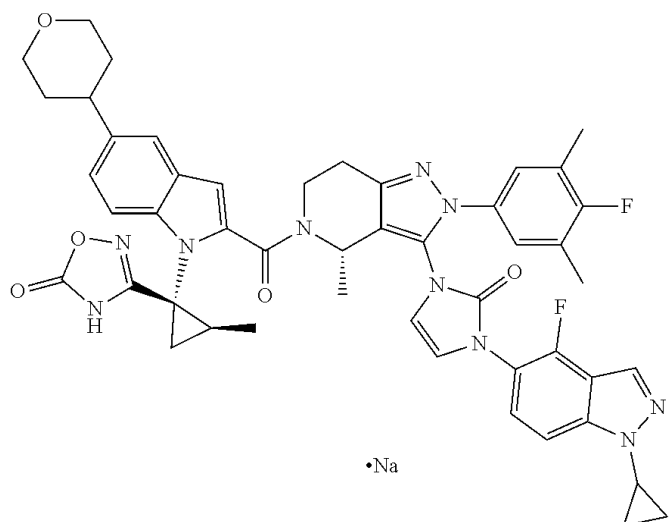
As discussed above with respect to claim 1, it would have been obvious for a POSA to arrive at Compound 19 as recited in claim 6 of the '236 Patent in view of the teachings of Su and Yoshino. (EX1002, ¶¶185-187.)

Thus, claim 12 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 13:

Claim 13 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



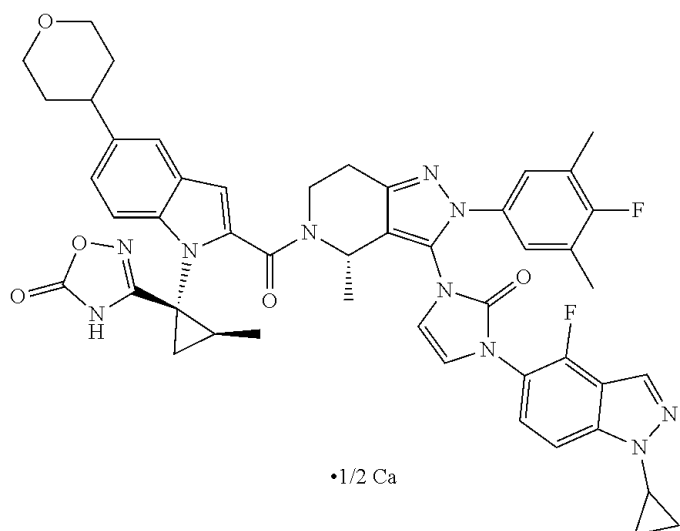
As discussed above with respect to claims 1-3, Yoshino discloses a compound which is a GLP-1 receptor agonist or a salt thereof, such as a sodium salt thereof, including a sodium salt of the free form and a hydrate of the sodium salt. (EX1002, ¶189; EX1008, 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Therefore, it would have been obvious for a POSA to prepare sodium salt of Compound 19 as recited in claim 13 of the '236 Patent. (EX1002, ¶¶188-190.)

As a result, claim 13 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1- 3.

Claim 14:

Claim 14 depends from claim 1 and recites:

the pharmaceutically acceptable salt is



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. (EX1002, ¶192; EX1008, 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 calcium salt of Compound 19 as recited in claim 14 of the '236 Patent. (EX1002, ¶¶191-193.)

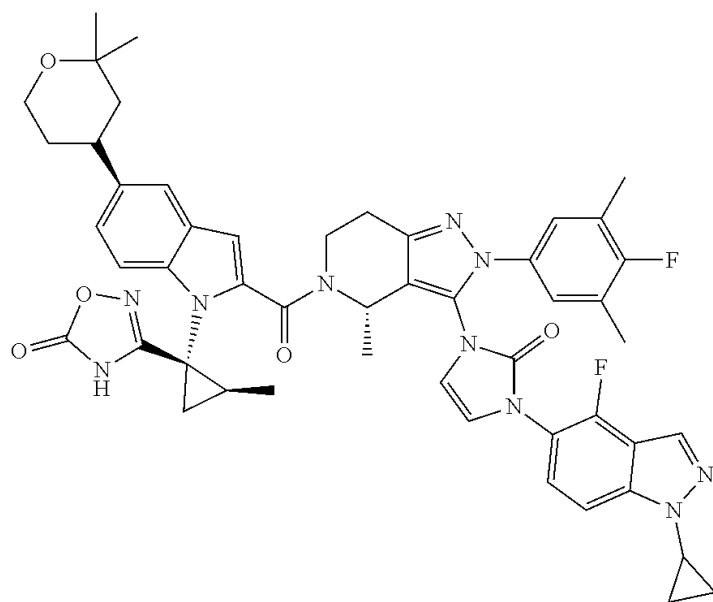
Thus, claim 14 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1, 2, and 4.

Claim 24:

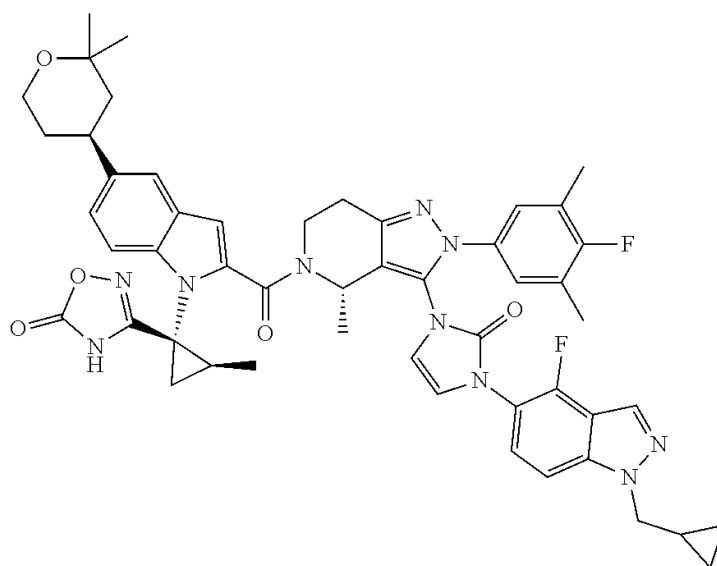
Claim 24 recites:

A compound, selected from the group consisting of:

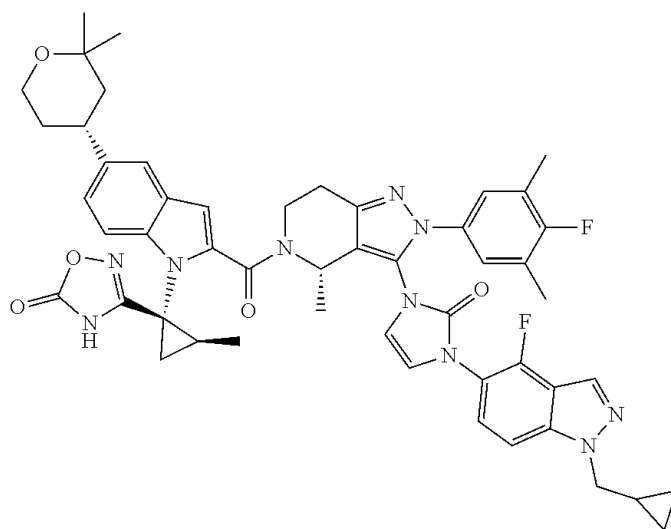
1



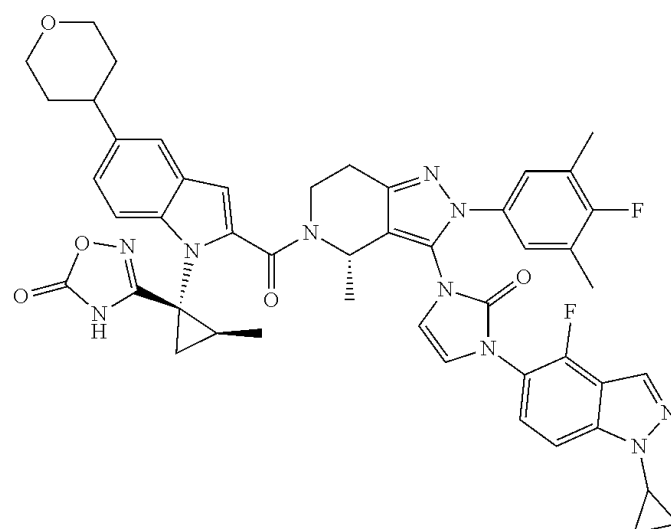
13



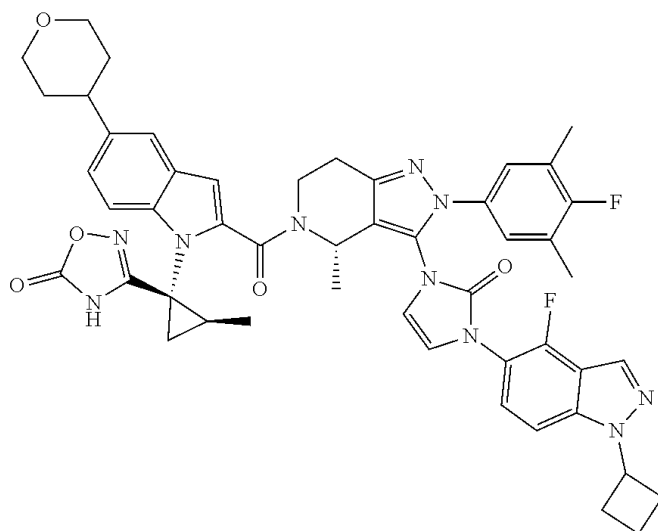
18



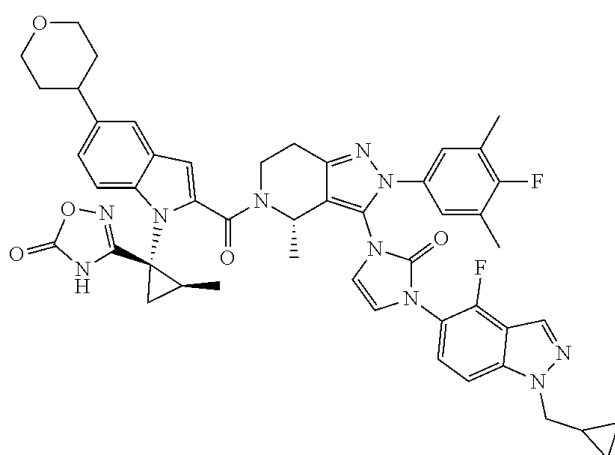
19



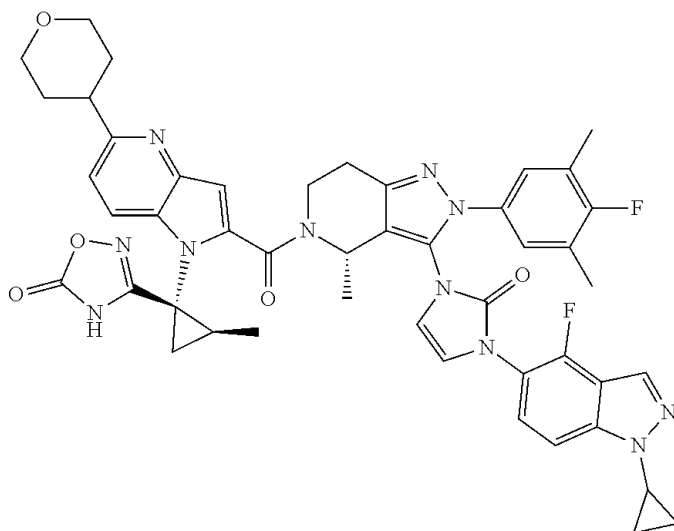
20



21



and



As discussed above with respect to claims 1, 6, and 12, it would have been obvious for a POSA to arrive at Compound 19 in view of the teachings of Su and Yoshino. (EX1002, ¶¶194-196.)

Thus, claim 24 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1, 6, and 12.

Claim 25:

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.”

Yoshino discloses various pharmaceutical formulations and a pharmaceutically acceptable additive that includes an excipient. (EX1002, ¶198; EX1008, 35:45-67.) Su also discloses pharmaceutical formulations and a

pharmaceutically acceptable additive that includes an excipient. (EX1002, ¶¶197-199; EX1006, 77:12-14; EX1007, 77:12-14.)

Thus, claim 25 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

B. GROUND 2: CLAIMS 1-9, 12-17, 24, AND 25 ARE OBVIOUS OVER YOSHINO AND KAWAI IN VIEW OF TALELE

For the reasons discussed below, claims 1-9, 12-17, and 24-25 would have been obvious based on the relevant teachings of Yoshino, Kawai, and Talele. (EX1002, ¶¶200-267; *supra* Section VIII.)

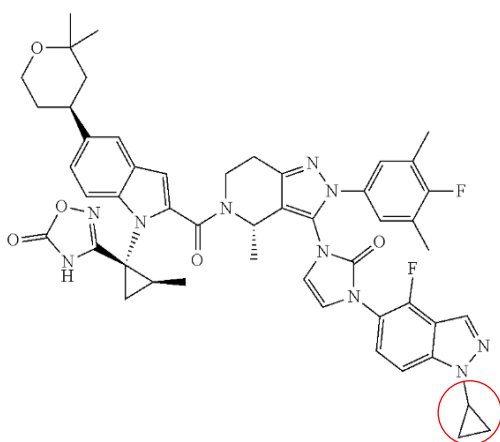
Claim 1:

Yoshino and Kawai in view of Talele render at least Compounds 1, 19, and 20 as obvious, as shown below.

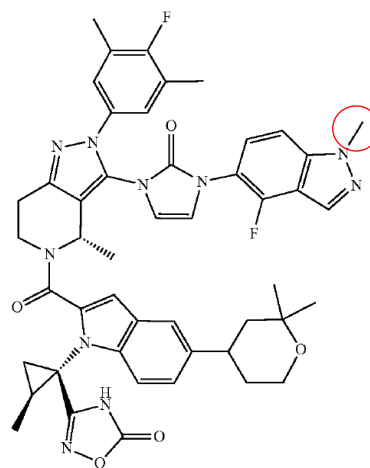
(i) Compound 1

As shown in the chart below, claimed Compound 1 differs from orforglipron (Compound 67) in one respect (circled in red): the substitution of a cyclopropyl group in place of the methyl group on the indazole moiety.

Compound 1 of the '236 Patent	Prior Art
-------------------------------	-----------

**Compound 1**

Yoshino discloses and claims:

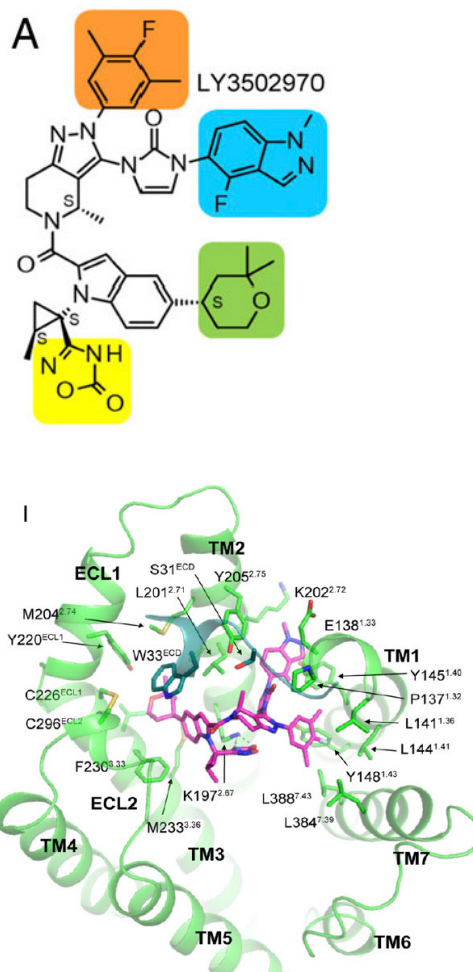


(Compound 67, also known as orforglipron; the sole difference between claimed Compound 1 and orforglipron is highlighted in the red circle) (EX1002 ¶203; EX1008, 99.)

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. (EX1002, ¶203; EX1008, Table 3.)

Kawai discloses:

structural basis for GLP-1 receptor activation by orforglipron. (EX1002, ¶203; EX1004, 1.) In particular, Kawai discloses a high resolution cryo-EM structure of orforglipron in complex with the GLP-1 receptor, along with a detailed protein-ligand interaction model illustrating the ligand-binding pocket surrounding orforglipron, as shown below:



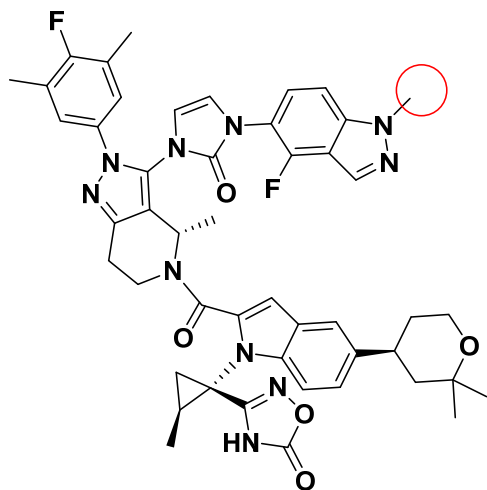
(EX1002, ¶203; EX1004, FIGS. 1A and 1I.)

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. (EX1002, ¶203; EX1004, 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,

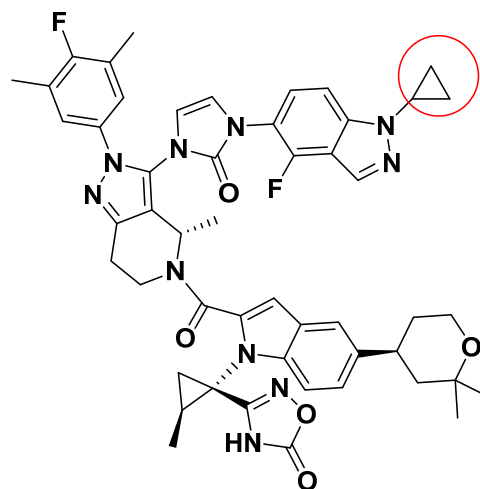
	<p>and thus would likely maintain binding potency. (EX1002 ¶203.)</p> <p>In addition, the binding pocket adjacent to the methyl group of the 4-fluoro-1-methyl-indazole moiety is shown as being surrounded by a spacious hydrophobic environment, suggesting that the pocket could reasonably accommodate a compound bearing a bulkier ring substituent in place of the methyl group. (<i>Id.</i>)</p> <p>Talele teaches: Cyclopropyl is known to enhance metabolic stability and decrease plasma clearance and substitution of a methyl group with cyclopropyl will enhance metabolic stability. (EX1002, ¶203; EX1009, 1.)</p>
--	--

As Dr. Pirrung explains, Yoshino in view of Kawai and Talele support the substitution of a cyclopropyl group on the indazole moiety. (EX1002, ¶¶203-217.)

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. (EX1002, ¶204.)

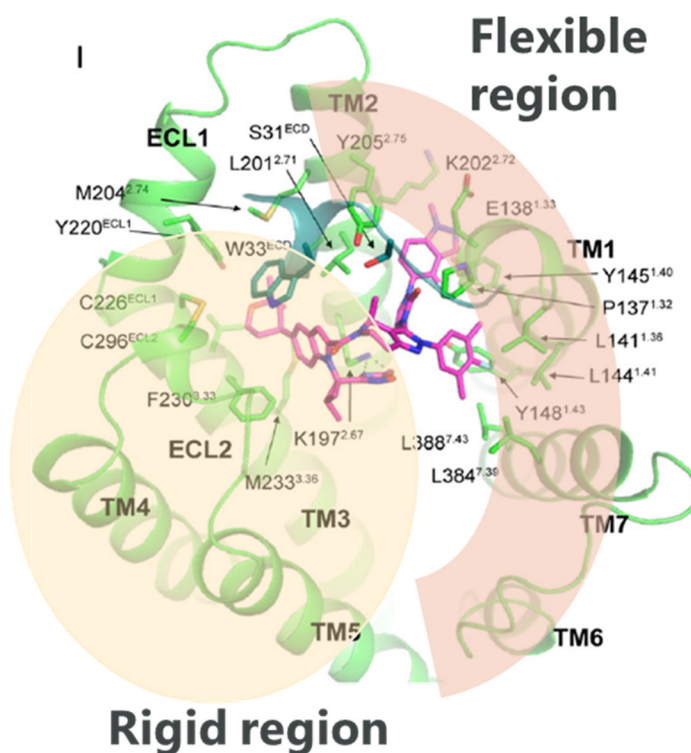


Compound 67 (Lilly prior art)



Compound 1

Kawai further elucidates the structural basis for GLP-1 receptor activation by orforglipron. (EX1002, ¶205.) Specifically, Kawai presents a high-resolution cryo-EM structure of orforglipron in complex with the N-terminal extracellular domain of the GLP-1 receptor. (*Id.*) This structure reveals the detailed ligand-binding pocket encompassing the compound and provides a comprehensive three-dimensional model of protein-ligand interactions, as shown below:



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

Accordingly, Kawai provides a robust framework for structure-based drug design. (EX1002, ¶206.) In particular, Kawai identifies regions of the GLP-1 receptor binding pocket that exhibit conformational flexibility, thereby permitting structural modifications of the ligand without compromising binding affinity. (*Id.*, ¶¶206-207.) The structural model demonstrates that the region formed by transmembrane helices TM1, TM2, TM6, and TM7, adjacent to 4-fluoro-1-methyl-indazole moiety, is characterized by conformational flexibility. (*Id.*, ¶207; EX1004,

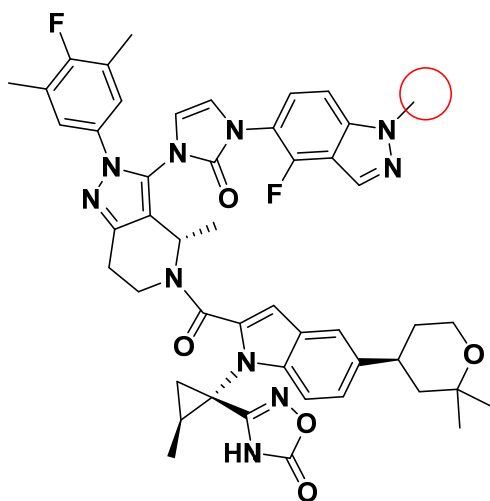
4.) In contrast, the region comprising TM3, TM4, and TM5 is described as relatively rigid. (*Id.*)

Accordingly, a POSA, applying the structure-activity insights disclosed in Kawai, would have reasonably expected that modifications to the flexible portions of the ligand, specifically the 4-fluoro-1-methyl-indazole moiety, could be made without inducing significant perturbation to the receptor's binding pocket. (EX1002, ¶208.) Accordingly, such modifications would have been expected to retain receptor binding and biological activity. (*Id.*)

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.*, ¶209; EX1004, FIG. 1I.) This environment is formed by the side chain of tyrosine at position 205 (Y205) and carbon atoms of the side chains of the lysine at position 202 (K202) and glutamate at position 318 (E318) residues. (*Id.*, ¶209; EX1004, FIG. 1I.) Thus, a POSA would have reasonably inferred that this hydrophobic pocket could accommodate a bulkier hydrophobic substituent, such as a three- to five-membered ring, in place of the methyl group. (EX1002, ¶209.)

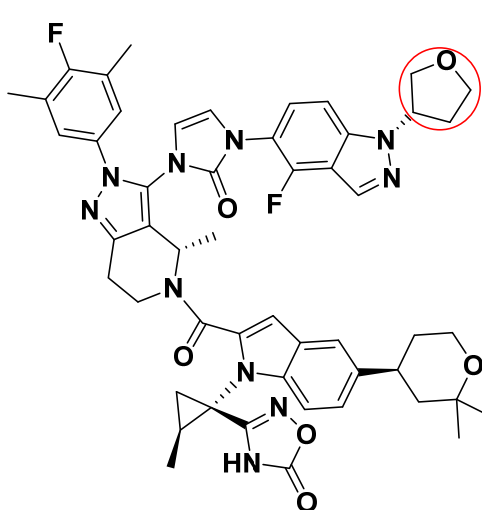
Yoshino supports this conclusion by disclosing several compounds wherein the methyl group of Compound 67 is replaced by a ring structure. Notably,

substitution with a tetrahydrofuran ring to yield Compound 40 results in biological activity comparable to that of Compound 67. (EX1002, ¶210; EX1008, 50, 99, Table 3.)



Compound 67

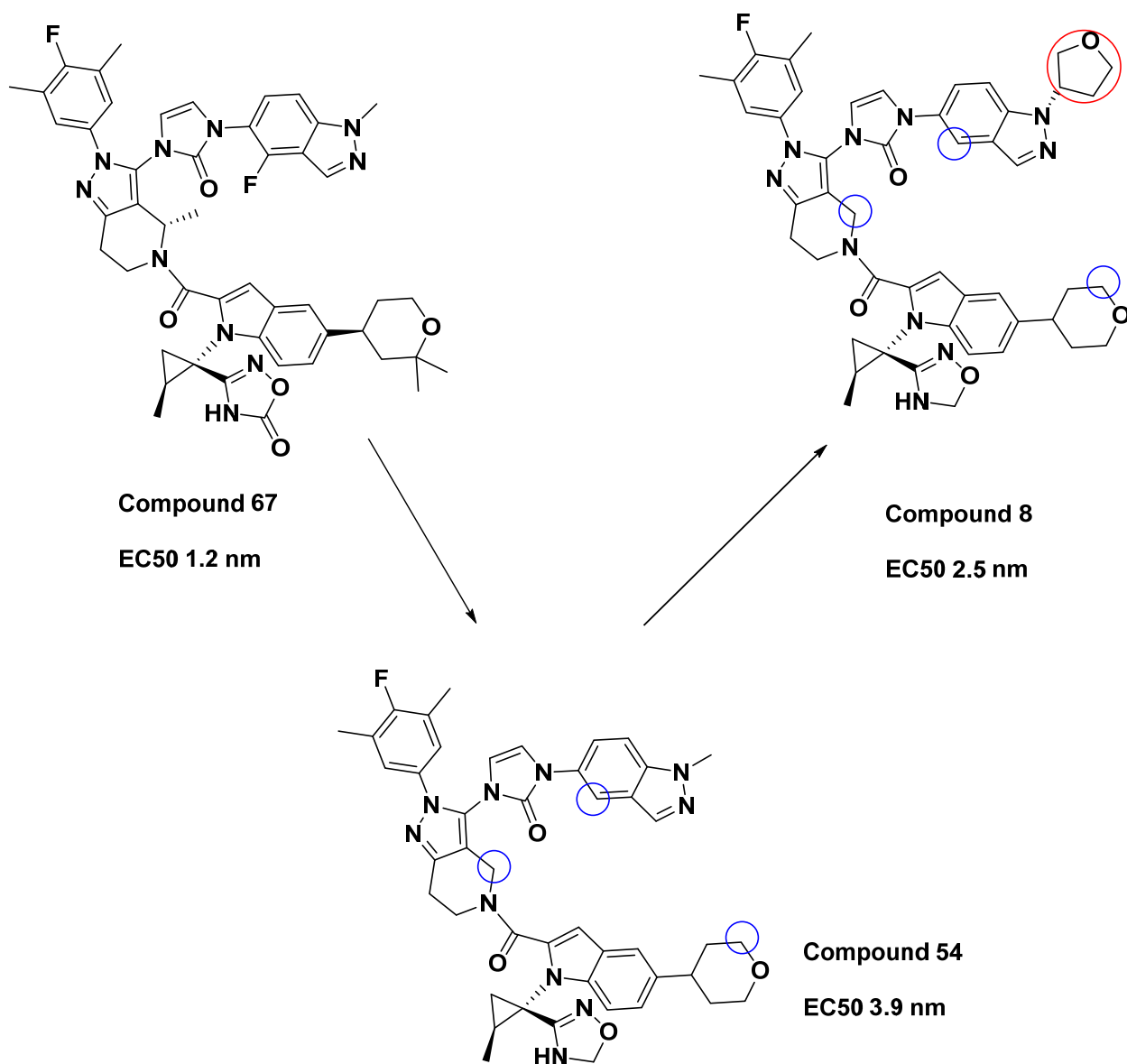
EC50 1.2 nm



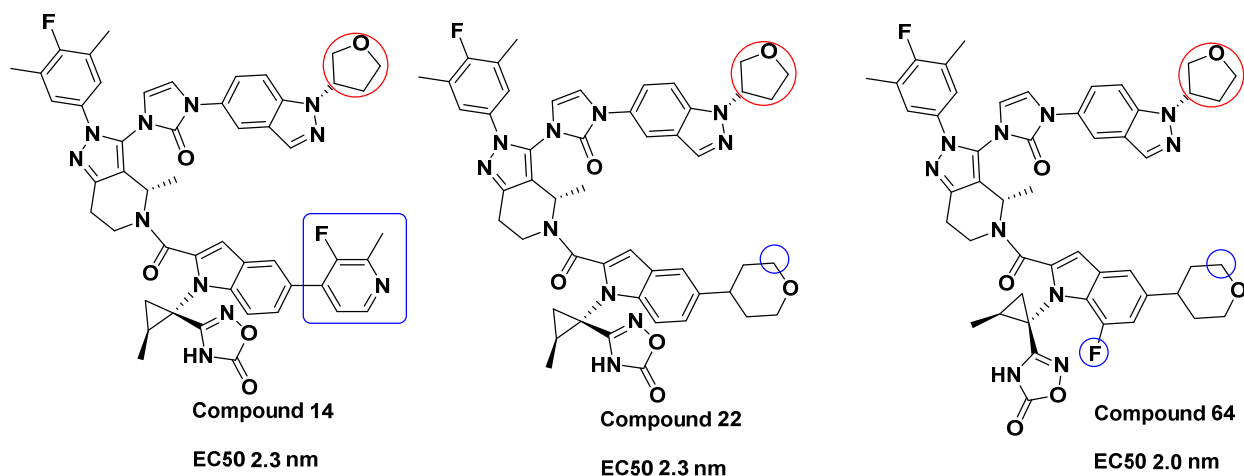
Compound 40

EC50 2.2 nm

Further, Yoshino reports that even when multiple substituents are removed, as in Compound 54, the tetrahydrofuran ring substitution restores or partially mitigates the loss of activity, highlighting the tolerability and contribution of ring substitutions at this position. (EX1002, ¶211; EX1008, 34, 92, 99, Table 3.)



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. (EX1002, ¶212; EX1008, 37, 41, 99, Table 3.)



Accordingly, when considered as a whole, Yoshino suggests that replacement of the methyl group with a ring structure can preserve or restore the biological activity of the lead compound. (EX1002, ¶213.) As discussed above, the hydrophobic character of the binding pocket favors the incorporation of a carbocyclic ring as a suitable replacement for the original methyl group. (*Id.*) 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 conformations, which restricts their rotation. (*Id.*)

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. (*Id.*)

This rationale is further supported by Talele, which describes the widespread use and therapeutic relevance of cyclopropyl groups in medicinal chemistry. (*Id.*,

¶¶214-216.) Talele reports that cyclopropyl moieties are present in eight of the top 200 FDA-approved drugs and that over 100 compounds containing cyclopropyl rings are currently in preclinical or clinical development. (*Id.*; EX1009, 1-2.) Talele concludes that the cyclopropyl ring is a “versatile player” in drug design and will likely continue to be employed in the development of new therapeutic agents. (*Id.*)

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 pK_a to reduce its P-glycoprotein efflux ratio.

(EX1009, 1, 2 (emphases added).)

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))

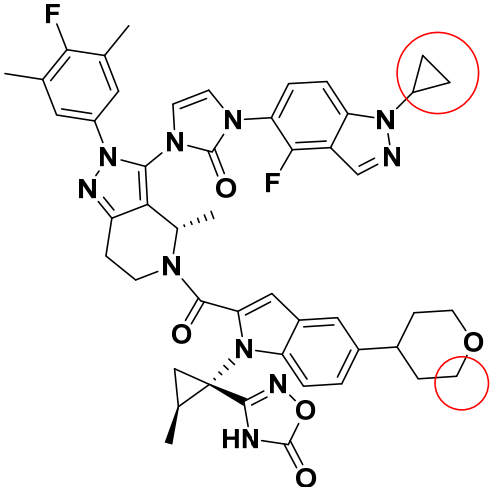
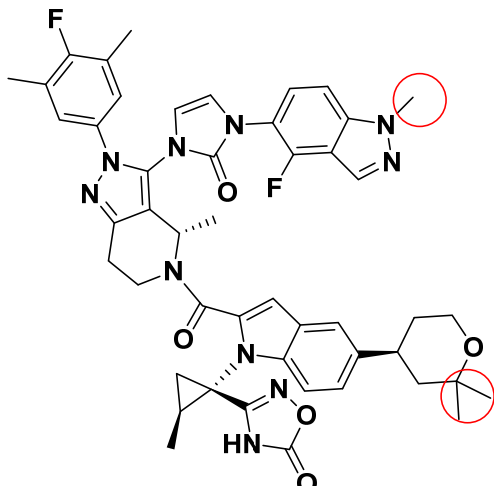
Thus, Talele teaches that substitution with a cyclopropyl ring is a well-established strategy in medicinal chemistry for enhancing metabolic stability, improving pharmacokinetic properties, or modulating the biological activity of a drug molecule. (EX1002, ¶¶213-216.)

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. (*Id.*) Moreover, as Dr. Pirrung explains, cyclopropyl substitution offers practical synthetic and pharmacological advantages. (*Id.*, ¶213.) Unlike heterocyclic alternatives, the cyclopropyl group lacks a chiral center, thereby simplifying synthesis, reducing the potential for undesirable stereoisomer formation, and improving the overall drug development profile. (*Id.*)

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.

(ii) Compound 19

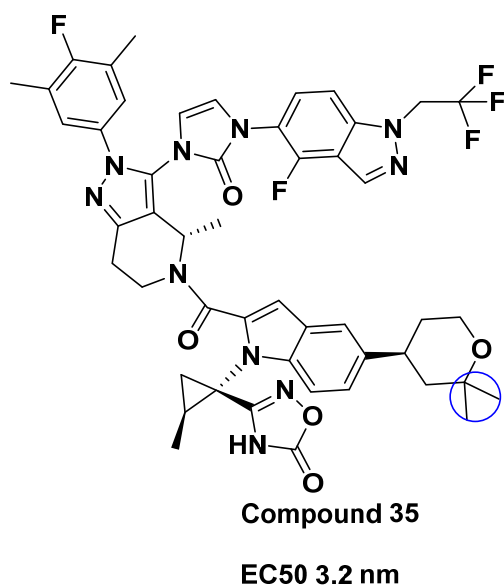
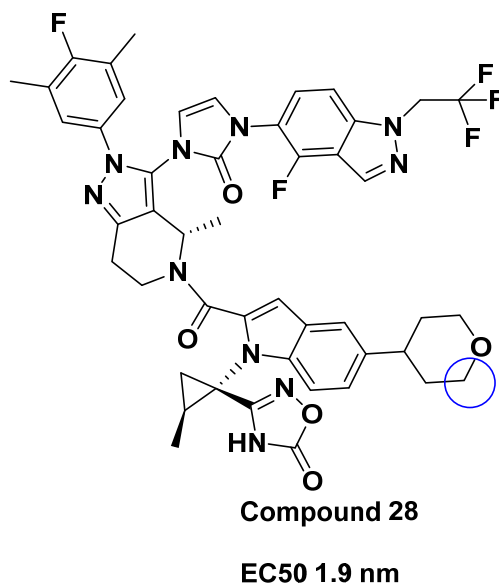
As shown in the chart below, claimed Compound 19 differs from orforglipron (Compound 67) disclosed in Yoshino in two respects (illustrated in red-circled regions): the substitution of a cyclopropyl group in place of the methyl group on the indazole moiety and the removal of the dimethyl groups from the tetrahydropyran moiety. (EX1002, ¶218.)

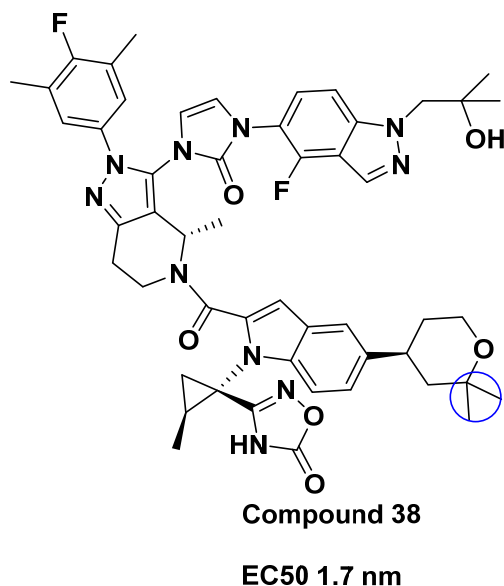
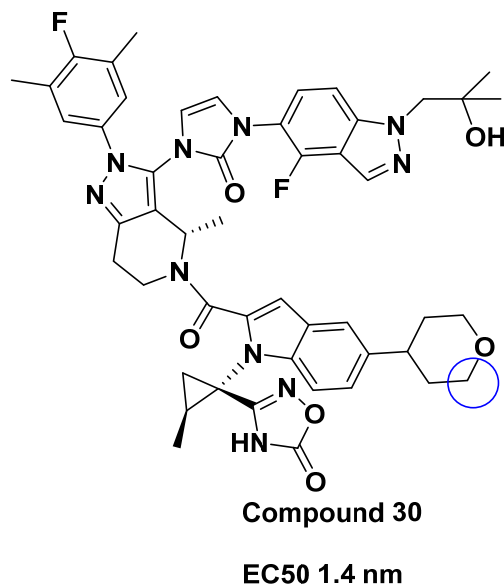
Compound 19 of the '236 Patent	Prior Art
 <p>Compound 19</p>	<p>Yoshino discloses and claims:</p>  <p>(Compound 67, also known as orforglipron; the differences between claimed Compound 19 and orforglipron are highlighted in the red circle) (EX1008, 99.)</p>

A POSA, having reviewed Yoshino and the teachings related to orforglipron, would have been motivated to implement both modifications, individually and in combination, in pursuit of improved or comparable biological activity. (*Id.*, ¶219.) As discussed above with respect to Compound 1, the substitution of a methyl group with a cyclopropyl group on the indazole moiety would have been a predictable

modification supported by the structure-activity relationships disclosed in the prior art. (*See Supra* Section XIII.B.i)

In addition, a POSA would understand that Yoshino expressly teaches that removal of the dimethyl groups from the tetrahydropyran moiety preserves, or even improves, biological activity. (EX1002, ¶220.) For instance, Yoshino reports that Compound 28, which lacks the dimethyl groups present in Compound 35, retains comparable potency. (*Id.*; EX1008, 44, 48, Table 3.) Likewise, Compound 30, which features a non-substituted tetrahydropyran ring, exhibits the same level of activity as Compound 38, which contains dimethyl substitution. (EX1002, ¶220; EX1008, 45, 49, Table 3.)





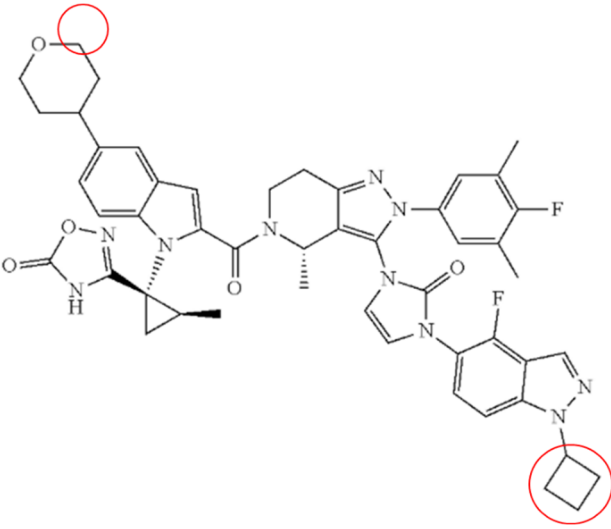
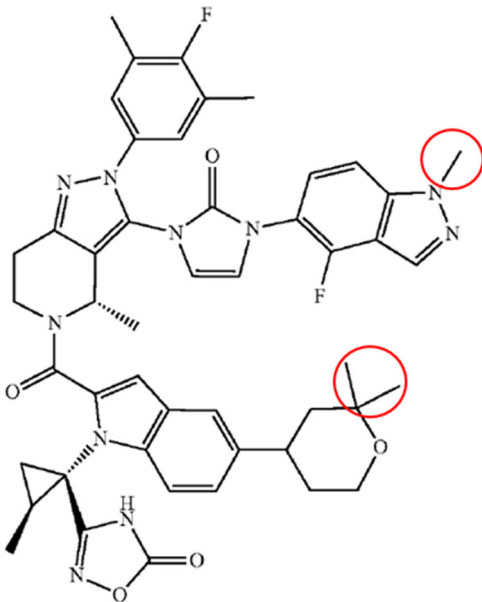
Notably, among the 80 compounds listed in Table 3 of Yoshino, over 30 possess a non-substituted, achiral tetrahydropyran ring, and many of these exhibit reported biological activity. (EX1002, ¶221; EX1008, Table 3.) This trend reinforces the teaching that removal of the dimethyl groups from the tetrahydropyran ring does not compromise, and may indeed enhance, pharmacological properties. (EX1002, ¶221.)

Accordingly, based on the disclosures of Yoshino and the structure-activity data therein, a POSA would have been motivated to remove the dimethyl groups from the 2,2-dimethyl-tetrahydropyran moiety of orforglipron. (*Id.*) When combined with the substitution of the cyclopropyl group on the indazole moiety, these two routine and predictable modifications would have resulted in claimed Compound 19. (*Id.*, ¶221-222.)

Therefore, for the reasons stated above, claim 1 of the '236 Patent would have been obvious to a POSA in view of Yoshino, at least with respect to Compound 19.

(iii) Compound 20

As shown in the chart below, claimed Compound 20 also differs from orforglipron (Compound 67), disclosed in Yoshino, in two respects (*Id.*, ¶223.):

Compound 20 of the '236 Patent	Prior Art
 <p>Compound 20</p>	<p>Yoshino discloses and claims:</p>  <p>(Compound 67, also known as orforglipron; the differences between claimed Compound 20 and orforglipron are highlighted in the red circle)</p>

As previously discussed with respect to claimed Compound 19, it would have been obvious to a POSA to remove the dimethyl group from the 2,2-dimethyl-

tetrahydropyran moiety of orforglipron, as such modification is supported by the structural and functional teachings in the prior art. (*Id.*, ¶¶224-226; *supra* Section XIII.B.ii.)

Furthermore, it would also have been obvious to a POSA to substitute the methyl group on the 4-fluoro-1-methyl-indazole moiety of orforglipron with a small carbocycle, such as a cyclopropyl or cyclobutyl ring, thereby arriving at the structure of claimed Compound 20. (*Id.*, ¶226.) This substitution is consistent with the principles of structure-activity relationship (SAR) analysis and conventional lead optimization practices, which aim to improve pharmacological or pharmacokinetic properties while retaining activity at the target receptor. (*Id.*, ¶¶225-226.)

As further discussed with respect to Compounds 1 and 19, the prior art provides a reasonable expectation of success in substituting the methyl group on the 4-fluoro-1-methyl-indazole moiety with a three- or four-membered cycloalkyl ring. (*Id.*, ¶225; *supra* Sections XIII.B.i-ii.) A POSA would appreciate that 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. (EX1002, ¶225.) 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. (*Id.*) This makes the four-membered ring cycloalkyl group similarly more resistant to metabolism than simple alkyl groups. (*Id.*)

As Dr. Pirrung explains, it is also well recognized in medicinal chemistry that simple structural modifications of alkane groups, such as the addition of CH₂ units, are considered obvious, as reflected in the commonly recited sequence of “methyl, ethyl, propyl, butyl” familiar even to novice medicinal chemists. (*Id.*) The four-membered cycloalkyl ring in Compound 20 can be formally produced by addition of a CH₂ group into a cyclopropane structure. (*Id.*)

Accordingly, a POSA would have found it obvious to substitute the methyl group with a three- or four-membered cycloalkyl ring on the 4-fluoro-1-methyl-indazole moiety of orforglipron. (*Id.*, ¶226.) Such modification would reasonably have led to the structure of claimed Compound 20. (*Id.*) Thus, in view of the prior art references discussed above, claim 1 would have been obvious to a POSA, at least with respect to Compound 20.

With respect to the limitation “a pharmaceutically acceptable salt thereof” recited in claim 1, Yoshino expressly discloses a compound that functions as a GLP-1 receptor agonist or a salt thereof, including pharmaceutically acceptable salts such as sodium and calcium salts. (*Id.*, ¶226; EX1008, 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.) Yoshino further specifies that suitable forms include “a hydrate of the free form, a salt of the free form, and a hydrate of salt,” with preferred embodiments comprising “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, 34:7-15.)

Therefore, claim 1 of the '236 Patent would have been obvious over Yoshino and Kawai in view of Talele.

Claim 2:

For the reasons discussed above with respect to claims 1 of Ground 2 and claim 2 of Ground 1, claim 2 is also obvious. (EX1002, ¶¶229-231.)

Claim 3:

As discussed above with for 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. (*Id.*, ¶¶232-234.) Thus, for the reasons discussed above with respect to claims 1 and 2 of Ground 2 and claim 3 of Ground 1, claim 3 is also obvious.

Claim 4:

As discussed above for claims 1 and 2, it would have been obvious for a POSA to prepare calcium salt of Compounds 1, 19, and 20 as recited in claim 4 of the '236 Patent. (*Id.*, ¶¶235-237.) For the reasons discussed above with respect to claims 1 and 2 of Ground 2 and claim 4 of Ground 1, claim 4 is also obvious.

Claim 5:

As discussed above for claim 1, it would have been obvious for a POSA to arrive at Compound 1 as recited in claim 5 of the '236 Patent. (*Id.*, ¶¶238-239.) Thus, for the reasons discussed above with respect to claim 1 of Ground 2 and claim 5 of Ground 1, claim 5 is also obvious.

Claim 6:

As discussed above for 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. (*Id.*, ¶¶240-241.) Thus, for the reasons discussed above with respect to claim 1 of Ground 2 and claim 6 of Ground 1, claim 6 is also obvious.

Claim 7:

As discussed above for claim 1, it would have been obvious for a POSA to arrive at Compound 1 as recited in claim 7 of the '236 Patent. (*Id.*, ¶¶242-243.) Thus, for the reasons discussed above with respect to claim 1 of Ground 2 and claim 7 of Ground 1, claim 7 is also obvious.

Claim 8:

As discussed above for claims 1-3, it would have been obvious for a POSA to prepare a sodium salt for Compound 1 as recited in claim 8 of the '236 Patent. (*Id.*, ¶¶244-245.) Thus, for the reasons discussed above with respect to claims 1-3 of Ground 2 and claim 8 of Ground 1, claim 8 is also obvious.

Claim 9:

As discussed above for claims 1, 2, and 4, it would have been obvious for a POSA to prepare a calcium salt for Compound 1 as recited in claim 9 of the '236 Patent. (*Id.*, ¶¶246-247.) Thus, for the reasons discussed above with respect to claims 1, 2, and 4 of Ground 2 and claim 9 of Ground 1, claim 9 is also obvious.

Claim 12:

As discussed above for claims 1 and 6, it would have been obvious for a POSA to arrive at Compound 19 as recited in claim 12 of the '236 Patent. Thus, for (*Id.*, ¶¶248-249.) the reasons discussed above with respect to claims 1 and 6 of Ground 2 and claim 12 of Ground 1, claim 12 is also obvious.

Claim 13:

As discussed above for claims 1-3, it would have been obvious for a POSA to prepare a sodium salt for Compound 19 as recited in claim 13 of the '236 Patent. (*Id.*, ¶¶250-252.) Thus, for the reasons discussed above with respect to claims 1-3 of Ground 2 and claim 13 of Ground 1, claim 13 is also obvious.

Claim 14:

As discussed above for claims 1, 2, and 4, it would have been obvious for a POSA to prepare a calcium salt for Compound 19 as recited in claim 14 of the '236 Patent. (*Id.*, ¶¶253-255.) Thus, for the reasons discussed above with respect to claims 1, 2, and 4 of Ground 2 and claim 14 of Ground 1, claim 14 is also obvious.

Claim 15:

As discussed above for claims 1 and 6, it would have been obvious for a POSA to arrive at Compound 20 as recited in claim 15 of the '236 Patent. (*Id.*, ¶¶256-257.) Thus, for the reasons discussed above with respect to claims 1 and 6 of Ground 2 and claim 15 of Ground 1, claim 15 is also obvious.

Claim 16:

As discussed above for claims 1-3 and 6, it would have been obvious for a POSA to prepare a sodium salt for Compound 20 as recited in claim 16 of the '236 Patent. (*Id.*, ¶¶258-259.) Thus, for the reasons discussed above with respect to claims 1-3 and 6 of Ground 2 and claim 16 of Ground 1, claim 16 is also obvious.

Claim 17:

As discussed above for claims 1, 2, 4, and 6, it would have been obvious for a POSA to prepare a calcium salt for Compound 20 as recited in claim 17 of the '236 Patent. (*Id.*, ¶¶260-261.) Thus, for the reasons discussed above with respect to claims 1, 2, 4, and 6 of Ground 2 and claim 17 of Ground 1, claim 17 is also obvious.

Claim 24:

For the reasons discussed above with respect to claims 1, 6, and 12 of Ground 2 and claim 24 of Ground 1, Claim 24 is obvious. (*Id.*, ¶¶262-264.)

Claim 25:

As discussed above for claims 1-4, 6-9, and 12-17, it is obvious for a POSA to arrive at a pharmaceutical composition comprising Compounds 1, 19, and 20 or

the pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. (*Id.*, ¶¶265-267.) Thus, for the reasons discussed above with respect to claims 1-4, 6-9, and 12-17 of Ground 2 and claim 25 of Ground 1, Claim 25 is also obvious.

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

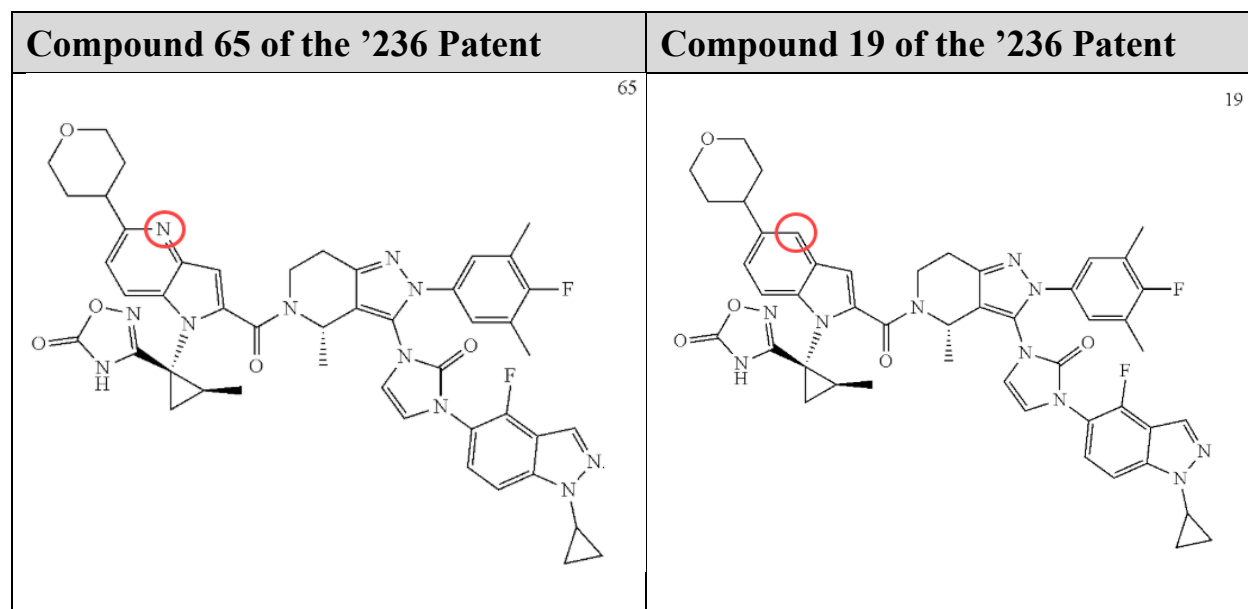
As discussed in Section VII.B, claims 1–4 and 24–25, at least with respect to Compound 65, are not entitled to a priority date earlier than January 31, 2024. Accordingly, Su, Yoshino, Kawai, Talele, Meng, Patel, and Ren each qualify as prior art for purposes of assessing the patentability of these claims. For the reasons discussed below, claims 1-4 and 21-25 would have been obvious based on the relevant teachings of Su, Yoshino, Kawai, Talele, and Meng, when further considered in view of Patel and Ren at least with respect to Compound 65. (EX1002, ¶¶268-306; *supra* Section VIII.)

Claim 1:

Claim 1 would have been obvious over the combination of Su, Yoshino, and Kawai, further in view of Talele, Patel, and Pennington, at least with respect to Compound 65. (*Id.*, ¶¶268-272.)

Compound 65 differs from Compound 19, addressed *supra* in Grounds 1 and 2, by the incorporation of a nitrogen atom into the aromatic ring to which the

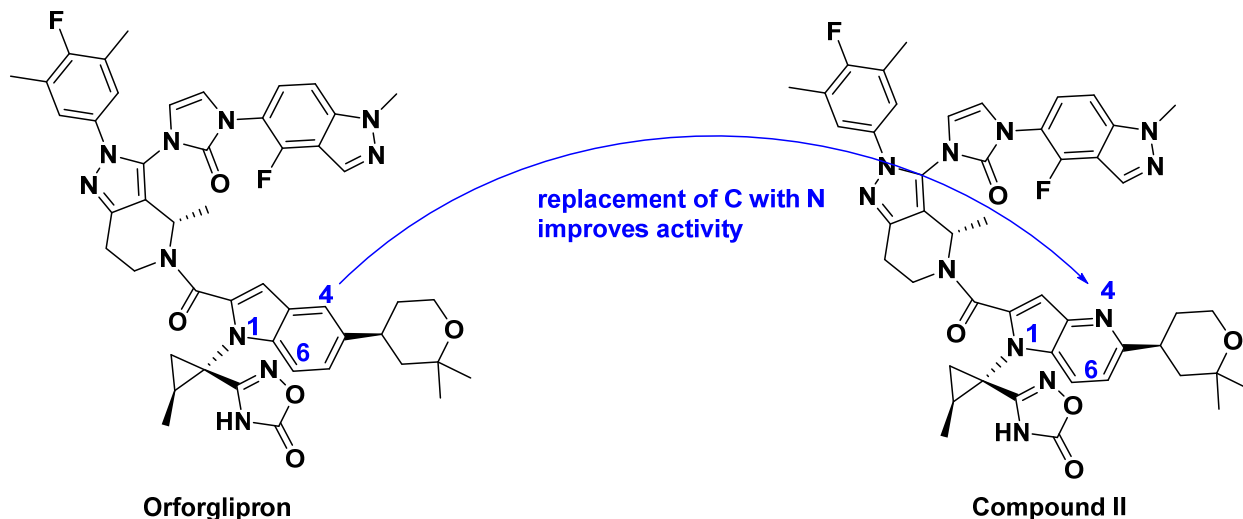
tetrahydropyran moiety is attached, as illustrated below. (*Id.*, ¶273; *see also supra* Sections XIII.A-B.)



As detailed in Grounds 1 and 2, a POSA would have found it obvious to arrive at Compound 19 based on the combined teachings of Su, Yoshino, Kawai, and Talele. (*Id.*, ¶274; Sections XIII.A-B.)

Meng builds upon the structure of Compound 19 by disclosing a rational modification to the aromatic core of orforglipron analogs—specifically, the incorporation of an additional nitrogen atom into the heteroaromatic ring. (*Id.*, ¶275.) In particular, Meng discloses and claims Compound (II), which includes an additional nitrogen atom in the core scaffold compared to orforglipron. (*Id.*, ¶¶86, 275.) Structurally, Compound (II) is nearly identical to orforglipron, with the sole distinction being the presence and position of the added nitrogen atom within the

aromatic ring. (*Id.*) This close structural similarity between Compound (II) and orforglipron is illustrated below.



(*Id.*)

Importantly, Compound (II) is one of only two compounds in Meng that are structurally and functionally characterized in detail. (*Id.*, ¶¶87, 276.) Meng describes a comparative study evaluating Compound (II) relative to a reference compound, identified as Compound 67 of TW201827426. (*Id.*) TW201827426 is the Taiwanese counterpart to Yoshino, and that Compound 67 disclosed therein is chemically identical to orforglipron. (*Id.*)

The comparative data in Meng show that introducing a nitrogen atom into the aromatic core of orforglipron analogs significantly enhances GLP-1 receptor potency. (*Id.*) Specifically, Compound (II) demonstrates a 1.6-fold improvement in potency compared to orforglipron, as evidenced by a lower EC₅₀ value in GLP-1 receptor activation assays. (*Id.*)

As Dr. Pirrung explains, a POSA, armed with the teachings of Meng and the known structure of Compound 19, would have been motivated to pursue structural modifications consistent with the medicinal chemistry strategies disclosed in Meng. (*Id.*, ¶277.) Specifically, Meng teaches that the introduction of a nitrogen atom into the aromatic ring, as exemplified by Compound (II), enhances potency. (*Id.*) Given this teaching, a POSA would have reasonably expected that incorporating a nitrogen atom into the corresponding position of Compound 19 would yield a compound with improved pharmacological properties. (*Id.*) This modification represents a routine and predictable design choice and leads directly to the structure of Compound 65 as claimed in the '236 patent. (*Id.*)

Moreover, as Dr. Pirrung explains, the incorporation of nitrogen atoms into aromatic systems is a well-established and routine strategy in medicinal chemistry. (*Id.*, ¶278.) As Patel explains, pyridine is the most frequently encountered aromatic heterocycle among FDA-approved pharmaceuticals and is commonly employed as an isosteric replacement for benzene. (*Id.* (citing EX1027 at 1).) This substitution is known to modulate key physicochemical and pharmacokinetic properties—including lipophilicity, aqueous solubility, metabolic stability, and hydrogen-bonding potential—while preserving favorable structural attributes such as molecular planarity and π - π stacking interactions. (*Id.*) As further noted by Patel:

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.

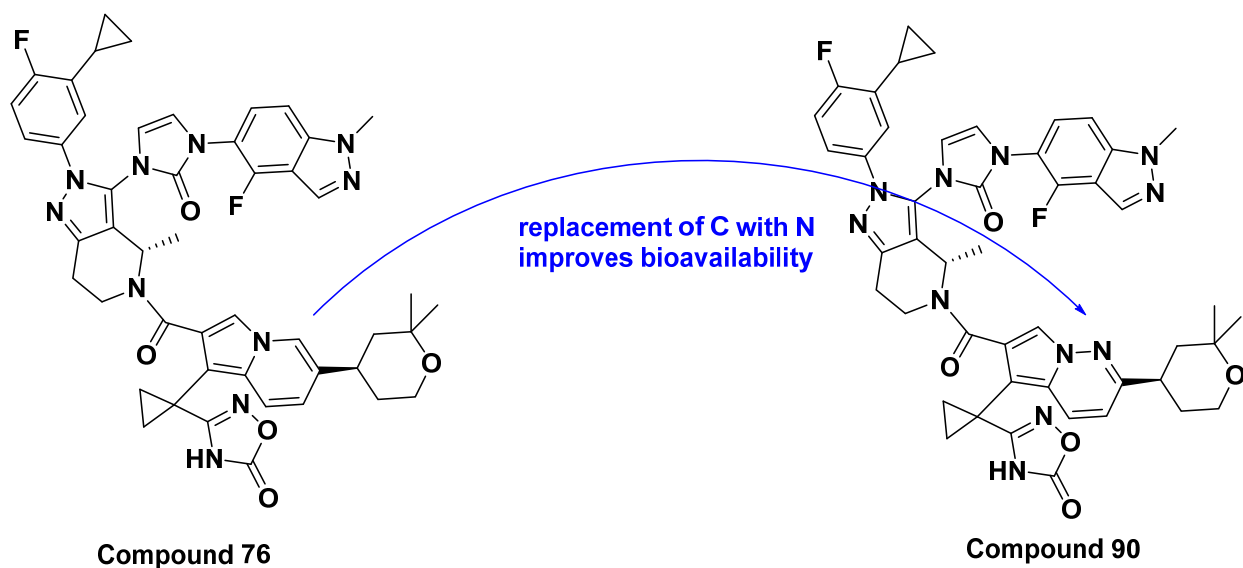
(*Id.* (emphases added; internal citations omitted).)

The concept of the “necessary nitrogen atom” was introduced by Pennington *et al.* in a 2017 review article as a high-impact structural motif in medicinal chemistry. (*Id.*, ¶279; EX1027.) As explained in the abstract, the “necessary nitrogen atom” serves as a “versatile high-impact design element for multiparameter optimization,” capable of conferring “ $\geq$ 10-, 100-, or 1000-fold improvement in a variety of key pharmacological parameters.” (*Id.*)

Accordingly, as Dr. Pirrung explains, a POSA seeking to further optimize the drug-like properties of Compound 19—which already represents a reasonable starting point as set forth in Grounds 1 and 2—would have been strongly motivated to introduce a nitrogen atom into the aromatic ring. (*Id.*, ¶280.) This modification represents a well-established and predictable medicinal chemistry strategy aimed at

improving physicochemical and pharmacokinetic properties such as aqueous solubility, receptor binding affinity, metabolic stability, and oral bioavailability. (*Id.*) Compound 65 is a direct and logical result of applying this widely accepted optimization approach. (*Id.*)

Further evidence supporting the advantageous effects of nitrogen substitution is provided in Ren, which describes Compounds 76 and 90, reproduced below. (*Id.*, ¶281; EX1030, 393:1-67, 445:1-67.) Ren discloses Compounds 76 and 90. (*Id.*) These two compounds are structurally identical except that Compound 90 incorporates an additional nitrogen atom into the core aromatic ring—a modification that distinguishes it from Compound 76. (*Id.*)



Ren further provides pharmacokinetic data for both compounds in Table 30. (*Id.*, ¶93 (citing EX1030, 459:46–460:30, Example 81).) This data reveals that Compound 90, which includes the additional nitrogen atom, exhibits significantly

improved oral bioavailability. (*Id.*) Specifically, Compound 90 demonstrates an oral bioavailability (F%) of 59%, compared to only 30% for Compound 76—an improvement of nearly two-fold. Ren attributes this enhancement in pharmacokinetic performance to the presence of the additional nitrogen atom in the aromatic ring. (*Id.*)

TABLE 30-continued

Cmpd No.	PO parameters			
	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

As Dr. Pirrung explains, these data would have further confirmed to a POSA 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. (*Id.*, ¶283.) Thus, Compound 65 constitutes a predictable variation of Compound 19, achieved through the application of well-established medicinal chemistry principles in view of explicit guidance in the prior art. (*Id.*)

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.*, ¶284; EX1008, 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. (EX1002, ¶284; EX. 1007, 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.)

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

Claim 2:

As discussed above with respect to claim 1, 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. (EX1002, ¶¶286-288.)

Accordingly, claim 2 of the '236 Patent would have been obvious to a POSA over the prior art.

Claim 3:

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. (*Id.*, ¶¶289-291.)

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

Claim 4:

As discussed above with respect to claims 1 and 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. (*Id.*, ¶293; EX1008, 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. (EX1002, ¶¶292-294.)

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

Claim 21:

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. (*Id.*, ¶¶295-296.) Accordingly, claim 21 of the '236 Patent would have been obvious to a POSA in view of the prior art.

Claim 22:

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. (*Id.*, ¶¶297-298.) Accordingly, claim 22 of the '236 Patent would have been obvious to a POSA in view of the prior art.

Claim 23:

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. (*Id.*, ¶¶299-300.) Accordingly, claim 23 of the '236 Patent would have been obvious to a POSA in view of the prior art.

Claim 24:

As discussed above with respect to claims 1 and 21, it is obvious for a POSA to arrive at Compound 65. (*Id.*, ¶¶301-303.) Accordingly, claim 24 of the '236 Patent would have been obvious to a POSA over the prior art.

Claim 25:

Yoshino discloses various pharmaceutical formulations and a pharmaceutically acceptable additive that includes an excipient. (*Id.*, ¶¶304-306; EX1008, 35:45-67.) Su also discloses GLP-1 receptor agonists and pharmaceutically acceptable salts thereof. (EX1002, ¶¶304-306; EX. 1007, 5, 14, 20, 24, 29, 36, 48, 52, 55, 59, 60, 68, 75.) 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 ARE OBVIOUS OVER SU AND BETHEL

As addressed in Section VII.B, claims 4 and 9 are not entitled to the benefit of a priority date earlier than 2024. (EX1002, ¶307.) Su discloses and claims Compound 175, which is chemically identical to Compound 1 of the '236 patent. (EX1002, ¶¶309-310; EX1006 at 328–29, claim 12; EX1007 at 328–29, claim 12.) As explained in Ground 1, a POSA would have identified Compound 175 as a promising lead compound for further development. This is supported by Su's selection of Compound 175 for deuteration, indicating its potential and suitability for optimization in drug discovery. (EX1002, ¶310.)

Bethel describes the treatment of subjects with type 2 diabetes (T2D), obesity, or overweight with at least one comorbidity using Compound 1a, that is chemically identical to orforglipron. (EX1032, 4; EX1002, ¶311.) Bethel discloses multiple formulations of the ½ calcium salt of orforglipron, including capsules (Examples 1 and 2), tablets (Example 3), and provides clinical data from Phase 2 studies (Examples 4A and 4B). (EX1032, 46–66; EX1002, ¶311.) These studies demonstrate favorable safety and efficacy profiles, with Compound 1a being well tolerated and achieving meaningful reductions in HbA1c and weight. (EX1032, 57, 59; EX1002, ¶311.) Bethel also discloses Phase 3 clinical trials using the same ½

calcium salt formulation. (EX1032, Examples 5, 7–12; *id.* at 66–74; EX1002 at ¶311.)

As Dr. Pirrung explains, in view of clinical data reported by Bethel showing successful use of the ½ calcium salt of orforglipron, a POSA would have been motivated to prepare a calcium salt of Compound 175, which is chemically identical to Compound 1 of the '236 patent. (EX1002, ¶312.) The combination of Su and Bethel provides both the rationale and supporting data for selecting a calcium salt form. (*Id.*) Bethel's disclosures would also give a POSA a reasonable expectation of success in preparing and using the ½ calcium salt formulation. Accordingly, it would have been obvious to a POSA to prepare a ½ calcium salt of Compound 175, thereby arriving at the subject matter recited in claims 4 and 9 of the '236 patent. (*Id.*)

Claim 9:

As discussed above for claim 4, based on the combined teachings of Su and Bethel, it would have been obvious to a POSA to prepare a calcium salt of Compound 175 that is chemically identical to Compound 1, thereby arriving at the ½ calcium salt of Compound 1 as claimed in Claim 9 of the '236 patent. (*Id.*, ¶¶313–314.)

XIV. DISCRETIONARY DENIAL UNDER 35 U.S.C. §325(d)

When evaluating whether to exercise its discretion to deny institution of an PGR under Section 325(d), the PTAB applies a two-part test: “(1) whether the same

or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 8 (PTAB Feb. 13, 2020) (precedential). In the first step, the PTAB considers the similarities and material differences between the asserted art and the prior art involved during prosecution. (*See Id.*, 9.) If the first step is satisfied, the PTAB then goes to the second step and considers the extent to which the prior art was the basis for rejection, whether Petitioner has pointed out sufficiently how the Office erred in its evaluation of the prior art, and the extent to which additional evidence and facts presented in the petition justify reconsideration of the prior art or argument. (*See Id.*, 10-11.)

Applied here, the PTAB should not exercise its discretion to deny institution for at least the following reasons.

First, the grounds presented here do not rely on the same or substantially same art or arguments considered by the Examiner. As discussed *supra* Section VII.A, the Examiner (1) received a report identifying hundreds of prior art compounds from dozens of references but otherwise not identifying disclosures within those references and (2) was inundated with hundreds of prior art references from the

Patent Owner mere days prior to issuing a Notice of Allowance. The only information expressly considered by the Examiner in the Notice of Allowance was a single compound from a single reference, Yoshino, which discloses at least 159 different compounds. (*Supra* Sections VII.A., VIII.A.) There is no evidence the Examiner otherwise considered the disclosures of Yoshino, at least because the image used in the Notice of Allowance was from the Examiner's report, and not from Yoshino's disclosures. (*See Id.*) There is also no evidence the Examiner expressly considered Yoshino's Compound 67, relied upon here, or any of the other prior art: Su, Kawai, Talele, or Patel. (*Id.*)

In addition, the Examiner's report did not even identify Su, Talele, Meng, Patel, or Ren. (*See* EX1003 at 176-703.) Moreover, it strains credibility to think that the Examiner would have reviewed the dozens, much less hundreds, of prior art references that each disclosed dozens or hundreds of prior art compounds and other teachings in the few days it had awareness of these references before the Notice of Allowance was issued. But, as explained above, each of these references—Yoshino, Su, Kawai, Talele, Meng, Patel, and Ren—not only disclose compounds materially distinct from the sole compound cited in the Notice of Allowance but also disclose motivations to combine or modify the references and other knowledge of a POSA that renders the claims of the '236 Patent obvious. Because these are new arguments that rely on new disclosures, the Board should not deny institution.

Even assuming *arguendo* that the art was considered by the Examiner, the Office erred in a manner material to the patentability. As explained above, the Examiner's Notice of Allowance relied upon disclosures not from the prior art reference(s) but from a third-party report. Thus, the Examiner failed to appreciate other compounds and disclosures in the prior art references including, *e.g.*, Compound 67 of Yoshino or the three-dimensional disclosures of Kawai that show the flexible and rigid regions of the compound.

In addition, the Examiner did not undertake any analysis to determine whether each of the claimed compounds are entitled to the earliest possible claimed priority date of the '236 Patent. As a result, the Examiner did not consider additional references, such as Su, that could qualify as prior art for rejecting specific claimed compounds. (*See supra* Section VIII.B; EX1003, 168-175.) As explained in detail in Section VII.B above, the application that issued as the '236 Patent claims priority to fourteen (14) earlier-filed applications. (EX1001, 1:10-45.) However, not all of the claimed compounds are disclosed in the earliest of these priority documents. Accordingly, several claimed compounds of the '236 Patent are not entitled to the earliest asserted priority date of September 14, 2023. Due to this oversight, the Examiner failed to identify additional material prior art references relevant to the patentability of the Challenged Claims, including the Su reference.

But for these material errors, the Challenged Claims would not have issued. Accordingly, the Patent Trial and Appeal Board should decline to exercise discretionary denial under 35 U.S.C. § 325(d).

XV. CONCLUSION

Based on the foregoing, Petitioner requests institution of PGR for claims 1-9, 12-17, and 21-25 of the '236 Patent based on the grounds specified in the Petition.

Dated: June 20, 2025

By: /Jin Zhu /

Jin Zhu, Ph.D.

Reg. No. 62,869

Counsel for Petitioners

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for Post Grant Review of Claims 1-9, 12-17, and 21-25 of U.S. Patent No. 12,234,236 contains, as measured by the word-processing system used to prepare this paper, 17,120 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: June 20, 2025

By: /Joe Chen/

Joe G. Chen, Ph.D.

Reg. No. 70,066

Counsel for Petitioners

CERTIFICATE OF SERVICE

I hereby certify that on June 20, 2025, I caused a true and correct copy of the foregoing Petition for Post Grant Review of Claims 1-9, 12-17, and 21-25 of U.S. Patent No. 12,234,236 to be served by Federal Express on the Patent Owner at the following correspondence address of record as listed on the USPTO's Patent Center website:

83682 - Nevriy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC
UNITED STATES

Dated: June 20, 2025

By: /Joe Chen/
Joe G. Chen, Ph.D.
Reg. No. 70,066
Counsel for Petitioners