

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

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

Patent Owner (“PO”) has failed to rebut Petitioner’s prima facie case of obviousness. The prior art provides clear motivation to select and modify lead compounds sharing orforglipron’s validated core scaffold, with a reasonable expectation of success.

First, a POSA would have selected compounds sharing orforglipron’s core scaffold for three reasons: (1) orforglipron’s clinical success, combined with competitors’ failures, demonstrates the importance of maintaining the validated scaffold; (2) selection of compounds 44 and 176 for deuteration signals heightened developmental interest; and (3) Yoshino’s structure-activity relationship (SAR) further supports their selection as leads.

Second, the combined teachings of Su, Yoshino, Kawai, and Talele provide a finite number of predictable modifications (cyclopropyl incorporation and methyl removal) that would have guided a POSA to the claimed compounds with a reasonable expectation of success.

Finally, PO’s objective indicia arguments merely show differences in degree, not kind, over prior art and would have been expected based on prior art teaching. PO’s expert Dr. Wipf’s analysis contradicts prior art data.

II. PATENT OWNER HAS NOT REBUTTED PETITIONER'S PRIMA FACIE CASE OF OBVIOUSNESS

A. GROUND 1: COMPOUND 19 IS OBVIOUS OVER SU, YOSHINO, KAWAI, AND TALELE

1. Lead Compound Selection

A lead compound is one that a POSA would reasonably select as a starting point for further development. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357–59 (Fed. Cir. 2007). Critically, the motivation to select and modify a lead need not be explicit. *Daiichi Sankyo Co. v. Matrix Lab'ys, Ltd.*, 619 F.3d 1346, 1352-54 (Fed. Cir. 2010) (where, as here, lead compound selection is based on a shared “backbone” or core scaffold with a known prior art drug candidate, together with available SAR information in the prior art as a whole). Compounds 44 and 176, along with their non-deuterated parents, are properly selected as leads for three reasons. First, they share orforglipron’s core scaffold. Second, their selection for deuteration signals heightened developmental interest. Third, the prior art SAR supports their selection.

(a) A POSA Would Select Compounds Sharing Orforglipron’s Core Scaffold as Leads

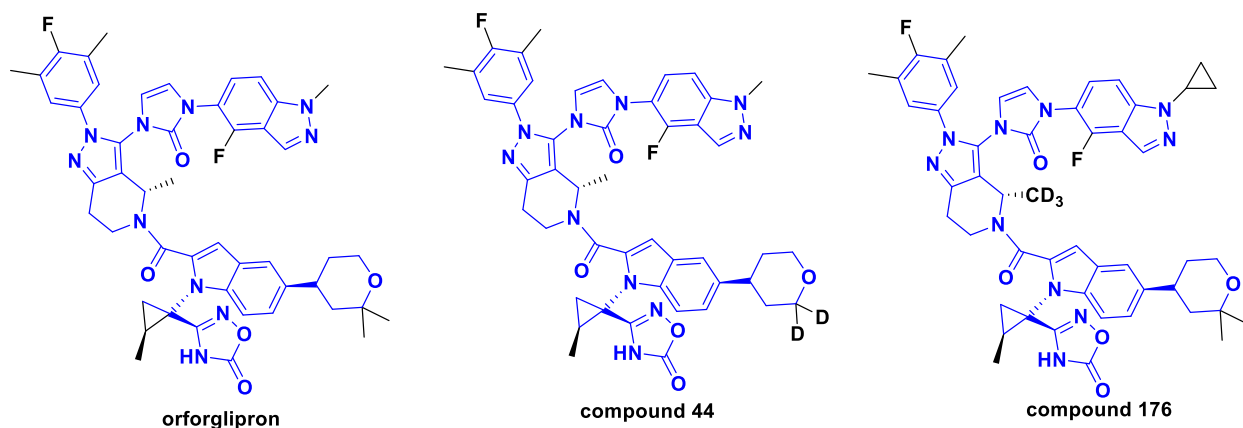
The continuing need to modify known drug candidates with good pharmaceutical profiles is well-recognized by a POSA. EX1007, 4; EX1002, ¶152. Orforglipron’s clinical success, combined with competitors’ failures, provides

strong motivation to select leads sharing orforglipron's core scaffold, especially when unguided small structural changes can lead to unpredictable outcomes. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359–60 (Fed. Cir. 2007) (where, in the absence of any teaching or guidance from prior art, small changes in molecular structure can have unpredictable effects on properties such as biological activity and toxicity). As of the priority date, orforglipron was in Phase 3 trials, having demonstrated significant HbA1c and body weight reductions with a favorable safety profile in Phase 2. EX1002, ¶¶48–51; EX1012, 1-2. By contrast, other small-molecule GLP-1 receptor agonists repeatedly failed due to insufficient potency and safety liabilities. EX2079, ¶230. This failure pattern for structurally distinct compounds weighs against selecting leads differing from orforglipron's core scaffold. As Dr. Pirrung explained, “a POSA, when contemplating modifications to orforglipron, would have been motivated to first make only peripheral modifications while maintaining the core scaffold.” EX1002, ¶152.

PO's expert, Dr. Wipf, reinforces this approach. He cautioned against core scaffold ring changes, warning that such modifications “could significantly change the properties of the compound” through electrostatic interactions. EX2079, ¶¶172, 294–295. Yoshino's SAR confirms this concern: core scaffold modifications are associated with decreased activity (e.g., compounds 4 and 57). EX1008, Table 3.

Although Su discloses pharmacokinetic data for compounds 1, 3, 64, 173, and 174, none share orforglipron's core scaffold. EX1007, 294, 326–365. PO's expert acknowledged "the five compounds for which data is disclosed in Su have significant structural differences compared to orforglipron." EX2079, ¶80. A POSA seeking to maintain a favorable pharmaceutical profile (including safety and selectivity) would not select compounds with a different core scaffold, particularly where small structural changes cause significant and unpredictable functional changes. EX1002, ¶152. However, Compounds 44, 175, and 176—all sharing orforglipron's core scaffold—would therefore be among a POSA's candidates for lead selection.

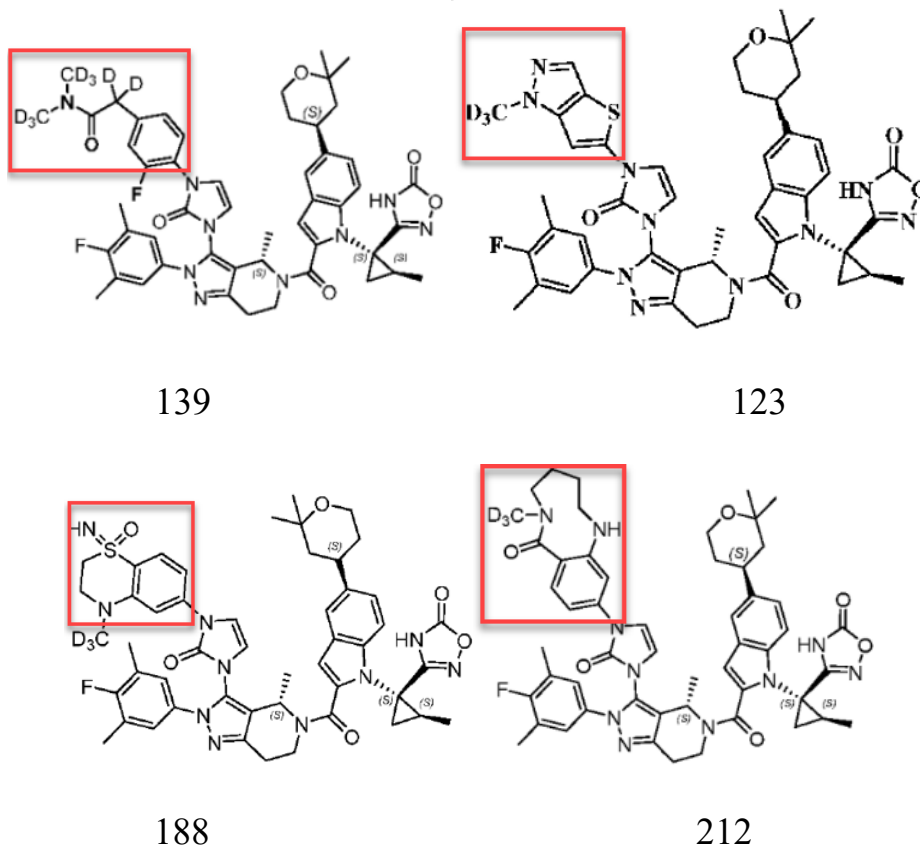
Orforglipron and deuterated compounds 44 and 176 share the same core scaffold (highlighted in blue)



While deuterated, discussed *infra*, other Su compounds (123, 139, 188, and 212) as shown below would also be excluded from lead consideration because they too lack orforglipron's core scaffold. EX2033, 91:23-92:1. Each compound features

a different terminal ring (shown below), resulting in differences in size and electrostatic interaction that would prevent them from sharing orforglipron's favorable pharmaceutical profile. EX2079, ¶294.

Compounds with core scaffolds different from orforglipron



PO's argument relies on a mischaracterization of Dr. Pirrung's testimony. (See POR, 21; EX2033, 61:1–63:6; EX2079, ¶280.) Dr. Pirrung did not “agree[] that compounds in a patent application that are ‘functionally characterized’ with pharmacokinetic data, such as Su Compounds 1, 3, 64, 173, and 174, are more likely to be ‘lead candidates’ for further development.” Rather, he explained that orforglipron's selection as a lead in Ground 2 rests on multiple factors, including its

advanced clinical stage, Kawai's structural analysis, and its unique status as the only individual compound recited in Yoshino's claims. EX2033, 61:1–63:6. At no point did he suggest that pharmacokinetic characterization alone, absent contextual considerations, makes a compound more likely to be a lead.

Meanwhile, PO's assertion that Dr. Pirrung relied on pharmacokinetic data of Meng for lead selection is also inaccurate and misleading, because Meng did not disclose any such data and Dr. Pirrung cited only Meng's activity data. POR, 21; EX2079, ¶280; EX1002, ¶¶87-88.

(b) Deuteration of Compounds Sharing Orforglipron's Core Scaffold Signals Heightened Developmental Interest

Deuteration further motivates lead selection. Active compound identification necessarily precedes investigation of metabolic stability and pharmacokinetic properties. EX2034, 29–30; EX1002, ¶62; EX1036, 18. Deuteration determines or improves pharmacokinetic properties by suppressing metabolism at the deuteration site (the D-C bond being stronger than the H-C bond). EX1036, 2–3. A POSA would understand that the PK profile of a compound must be determined before deuteration is pursued (EX1034, 276:15–278:11), and would not deuterate or advance a compound to pharmacokinetic study unless it exhibited good activity and development potential. EX1002, ¶¶150–154. Thus, even where a reference does not expressly disclose activity or pharmacokinetic data for deuterated compounds, a

POSA would have recognized that the underlying undeuterated parent compounds had already been characterized for both activity and pharmacokinetic properties.

Deuterated compounds also expand intellectual property space surrounding parent compounds with favorable activity profiles. EX1036, 19; EX1034, 182:20–183:8. The fact that only a few selected compounds are deuterated and recited in the claims indicates their priority significance. EX1002, ¶62.

Further, deuteration is a deliberate, knowledge-intensive optimization strategy rather than a preliminary screening tool, noting significant “synthetic and analytical challenges in controlling site and extent of D enrichment” and “high manufacturing costs.” EX1036, 18. These challenges underscore that deuteration is reserved for compounds demonstrating sufficient promise to justify the investment.

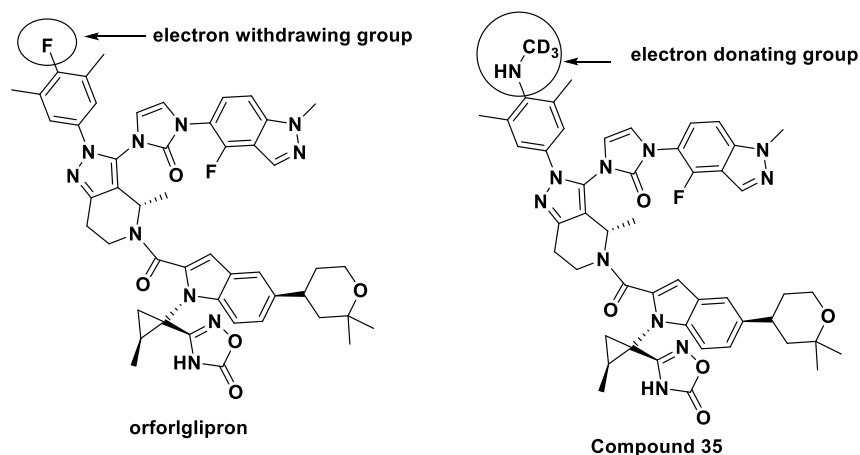
Of Su’s 452 compounds, only seven stereoisomerically pure compounds (and their non-stereoisomerically pure counterparts) were deuterated. EX1007, claims 3–30. Of these seven, only three (including compounds 44 and 176) share orforglipron’s core scaffold. EX1007, claim 12. Further, the non-deuterated parent of compound 44 is compound 23¹ of Yoshino, which exhibits activity similar to

¹ The chemical structure of Compound 23 depicted in Yoshino (EX1008) appears to contain a typographic error (missing the fluorine atom); however, the chemical name provided in Yoshino is correct and consistent with the correct chemical structure and chemical name described in Yoshino’s Japanese priority document (JP2019099571A) (EX1038, 51), whose counterpart EP Application No. EP3517538 is in English. (EX1037, 36)

orforglipron. EX1008, Table 3. The selection of only compound 23 from over 130 compounds in Yoshino for deuteration underscores heightened interest in this compound. Accordingly, the narrow selection of compounds for deuteration to evaluate pharmacokinetic properties and to expand IP space reflects elevated interest in these compounds as lead candidates.

Deuterated compound 35, though sharing orforglipron's core scaffold, is not a strong lead candidate because it contains an electron-donating group that contrasts with orforglipron's electron-withdrawing fluorine. Dr. Pirrung testified this modification constitutes a more pronounced and less favorable electronic change compared to cyclopropyl incorporation (Compound 175) or dimethyl removal (Compound 44). EX1002, ¶¶67. Dr. Wipf similarly cautioned that ring changes could significantly alter compound properties through electrostatic interactions. EX2079, ¶¶294–295. A POSA would therefore remove Compound 35 from lead consideration.

Electronic withdrawing group v electron donating group

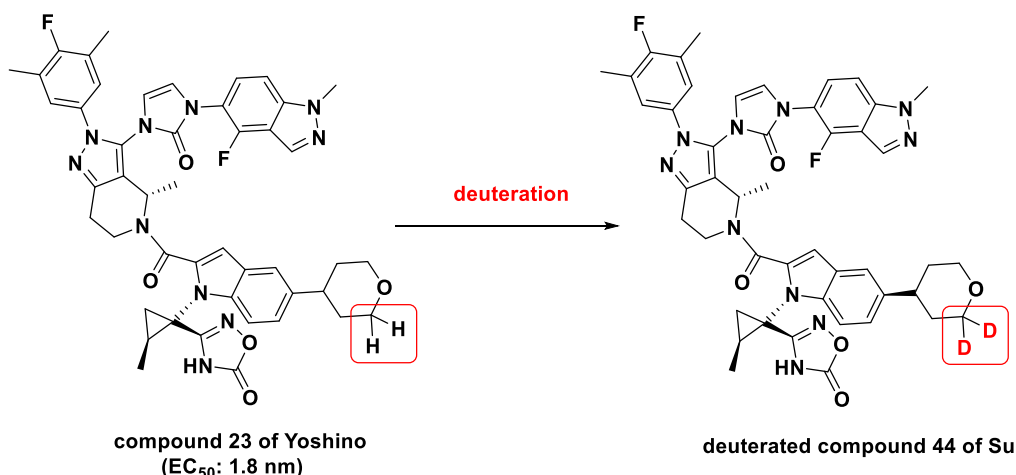


(c) SAR and Structural Data in the Prior Art Further Support Selection of Compounds 44, 176, and Their Parent Compounds as Leads

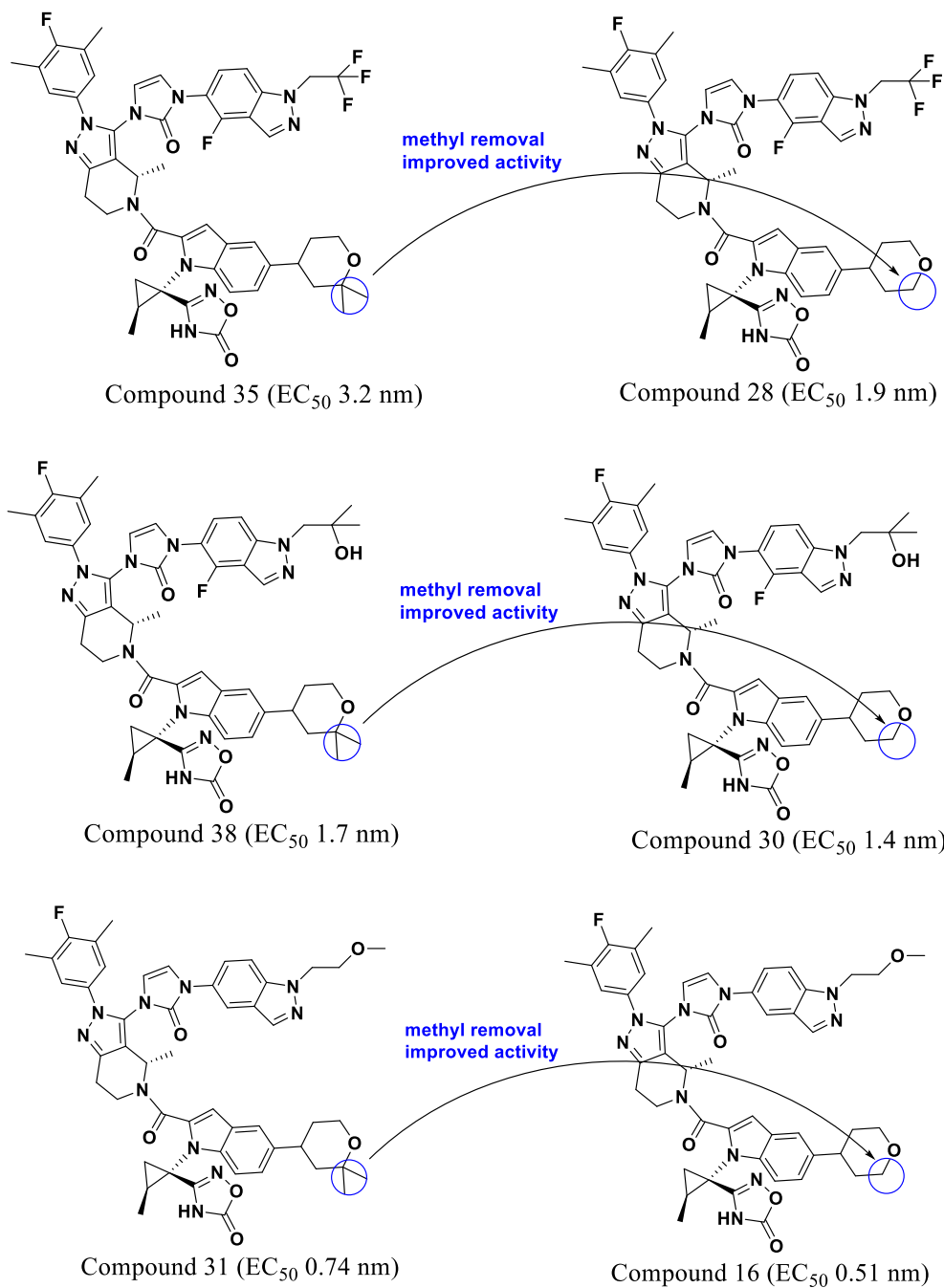
SAR Supports Compound 44 and Its Non-Deuterated Parent (Compound 23 of Yoshino) as Leads

The activity of compound 44 finds direct support from compound 23 of Yoshino. EX1008, Table 3. Both compounds 23 and 44 bear an unsubstituted THP.

Deuteration of compound 23 to provide compound 44



SAR from direct comparisons between multiple compound pairs in Su (comparing dimethyl-substituted tetrahydropyran (THP) with unsubstituted THP) also supports the role of unsubstituted THP in improving activity. EX1008, Table 3. For example, compound 28, bearing an unsubstituted THP, exhibits improved potency over compound 35. EX1008, Table 3. Likewise, compounds 30 and 16 exhibit enhanced activity relative to their counterparts (compounds 38 and 31) with dimethyl-substituted THP. EX1008, Table 3.

Methyl removal improved compound activity

The selection of compound 44 as a lead is therefore supported not only by deuteration, which indicates promising activity, but also by Yoshino's SAR identifying unsubstituted THP as beneficial for activity. Further, removing the

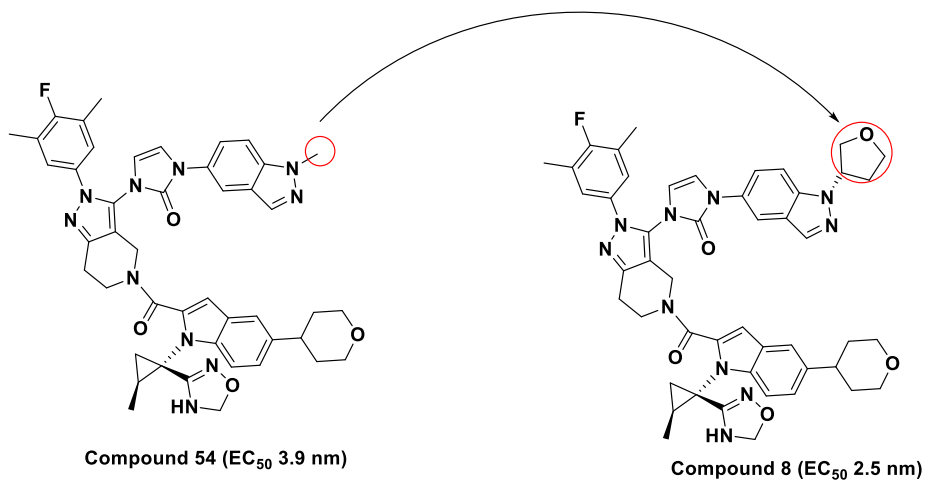
dimethyl groups renders the THP ring symmetrical and simplifies synthesis. EX1002, ¶66.

Structural Data and SAR Support Compound 175 as a Lead

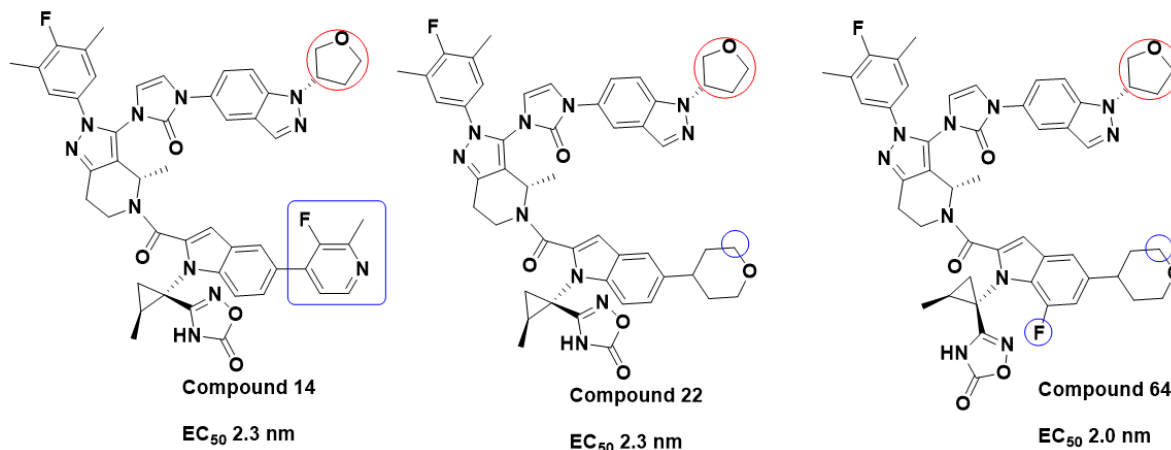
Compound 175 differs from orforglipron only by a cyclopropyl ring on the indazole nitrogen. Consistent with Dr. Pirrung's view on the flexible region around the indazole, Petitioner's expert Dr. Fan opines that Kawai's structure reveals the region adjacent to the indazole moiety, where peripheral modifications occur, exhibits conformational flexibility and accommodates the ring. EX1004, 4; EX1002, ¶¶157–159, 208; EX1035, ¶¶21–37. Dr. Fan's docking analysis confirms that the cyclopropyl ring can be accommodated through a small side-chain adjustment of E138. *Id.*

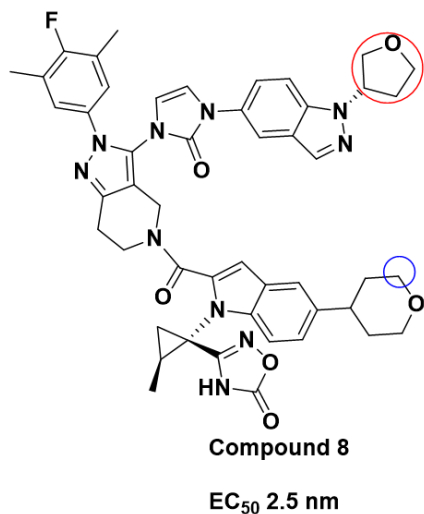
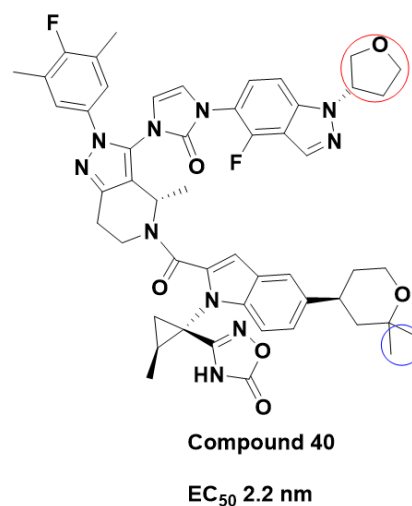
Yoshino's SAR is consistent with this structural analysis. In a direct comparison, compound 8 (featuring a THF ring) improved activity relative to compound 54 (bearing a methyl substituent on the indazole nitrogen). EX1002, ¶74. Additional compounds (14, 22, and 64) incorporating a THF ring on the indazole maintain largely consistent activity notwithstanding variations in other substituents (circled in blue), further supporting ring tolerance in this region. EX1002, ¶75; EX1008, Table 3.

Ring replacement for methyl maintains activity



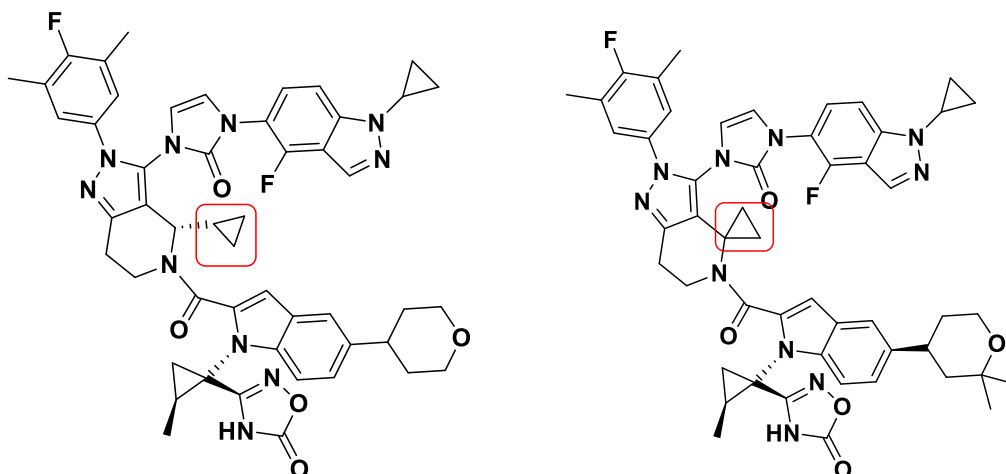
Ring (in red) on indazole preserves activity





The two compounds cited by PO as evidence of unpredictability are inapposite. In those compounds, ring substitution in the central moiety resulted in approximately 45-fold decreased activity or complete activity loss (POR, 39, 53; EX2080, ¶8; EX2079, ¶¶185–186). This acknowledged unpredictability actually underscores the importance for a POSA of adhering to Yoshino's established SAR when selecting leads, supporting both cyclopropyl-containing compound 175 and compound 176 as appropriate leads.

Activity loss due to ring incorporation at other positions of core scaffold



*Known Pharmacokinetic Benefits of Cyclopropyl Support Compound
175 as a Lead*

The well-established advantages of cyclopropyl substitution further support compound 175 as a lead. These advantages include reductions in lipophilicity, metabolic liability, off-target pharmacology, and entropic penalties upon binding, all increasing the likelihood of therapeutic viability. EX1002, ¶¶83–84; EX1009, 24. Talele reports that in four of five cases, cyclopropyl ring incorporation improved metabolic stability and pharmacokinetic profiles. EX1009, 24. A reasonable expectation of success does not require certainty. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). A POSA would have recognized that the cyclopropyl substituent in compound 175 presents a strong opportunity to enhance pharmacokinetic properties.

In sum, the shared core scaffold with orforglipron, the selection for deuteration to evaluate pharmacokinetic properties and to expand IP space,

Yoshino's SAR, Kawai's structural insights, and the known pharmacokinetic benefits of cyclopropyl substitution collectively support identification of compound 175 as a lead.

(d) Dr. Wipf's Analysis Is Flawed

PO contends that Su does not explain the purpose of deuteration and that the effects of deuteration are unknown. POR, 23; EX2079, ¶145. This argument ignores the well-understood principle that selection of compounds for deuteration itself reflects favorable activity and development potential, irrespective of deuteration's ultimate outcome. EX1002, ¶62. The motivation to select and modify a lead need not be expressly articulated in the prior art. *Eisai Co. v. Dr. Reddy's Labs., Inc.*, 533 F.3d 1353, 1356–57 (Fed. Cir. 2008). A POSA would have understood that the non-deuterated parent compounds corresponding to deuterated compounds 44 and 176 were of particular interest, having been selected for deuteration from among hundreds of compounds disclosed in Su and Yoshino.

PO's reliance on the "magic methyl effect" is unavailing. POR, 29; EX2079, ¶52. The magic methyl effect is not a law of chemistry; it is a phenomenon observed in some cases for specific biological targets other than GLP-1 receptors. As PO's own reference recognizes, "the addition of a methyl group is just as likely to decrease potency as it is to increase it." EX2034, 110.

PO's teaching-away argument on the cyclopropyl ring is also unfounded. Teaching away requires that a reference clearly indicate to a POSA that the reference's preferred embodiments do not work or cannot be combined; mere silence on a particular substituent is insufficient. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). The *Eli Lilly* decision on which PO relies underscores this point: the court found teaching away only because the prior art identified specific drawbacks of disfavored substituents through direct comparison. *Eli Lilly v. Zenith Goldline*, 471 F.3d 1369, 1378 (Fed. Cir. 2006). Yoshino provides no such comparison; it is entirely silent on cyclopropyl and does not address any effect, positive or negative, from any cycloalkyl ring. PO's theory that anything not expressly disclosed constitutes a teaching away finds no support in the law; under that rationale, a POSA would be confined to the precise chemical groups in each reference. The absence of cyclopropyl from Yoshino's generic formula at most reflects the scope of a claim, not a teaching-away.

2. Lead Compound Modification

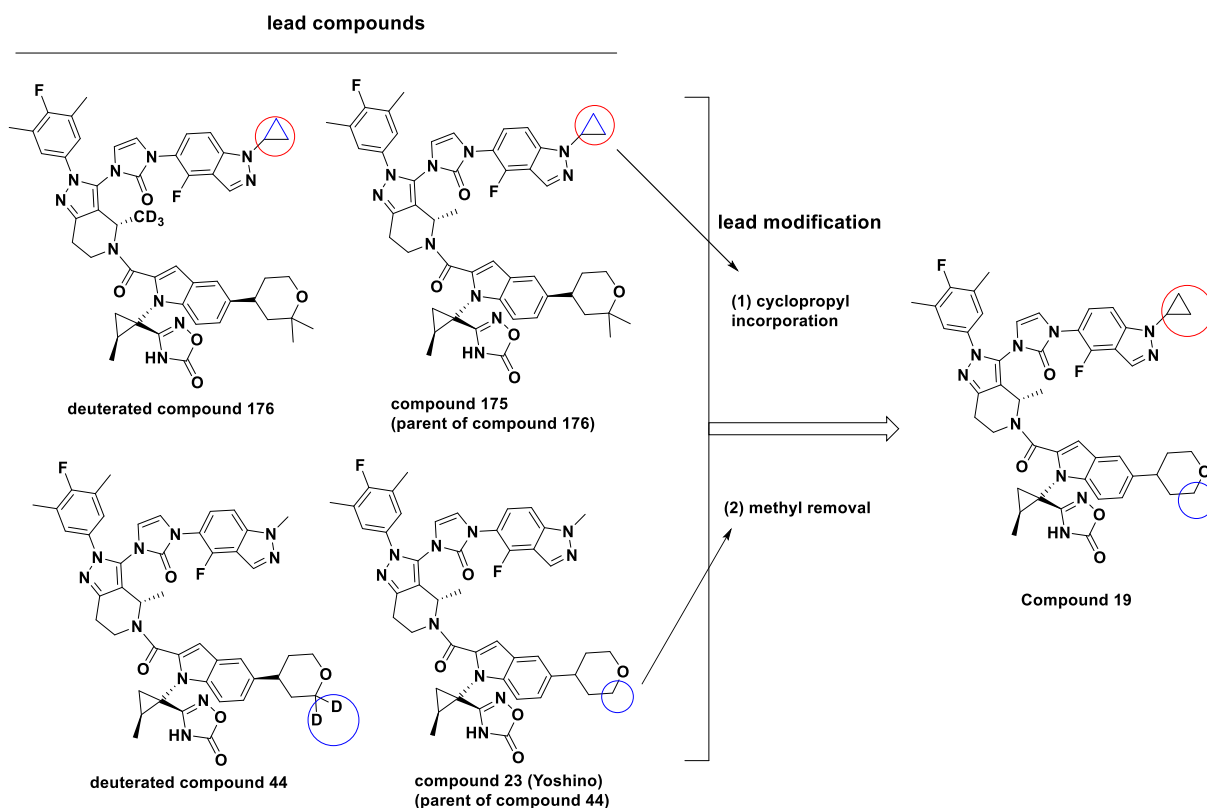
Where a skilled artisan pursues "known options" from a "finite number of identified, predictable solutions," obviousness is appropriate. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Given the specific disclosures relating to compounds 23, 44, 175, and 176 as compared to orforglipron, a POSA would have

been motivated to combine features of these lead compounds in a particular manner to arrive at compound 19.

(a) Modification of Lead Compounds in a Particular Manner to Arrive at Compound 19

The improvements in the lead compounds relative to orforglipron are clear and specific: (1) incorporation of a cyclopropyl group, as demonstrated in compounds 175 and 176; and (2) removal of methyl groups from the THP ring, as shown in compounds 44 and 23.

A limited number of modifications to the lead compounds



In view of these limited and specific structural improvements relative to orforglipron, the logical next step would be combining the changes (cyclopropyl incorporation and methyl removal) to arrive at compound 19.

(b) Predictable Outcome in Lead Modifications

Identifying an active compound is a critical step in developing a viable drug candidate. EX2034, 28–29. The combined effects of cyclopropyl incorporation and methyl removal would have been reasonably expected to provide an active compound in view of Yoshino's SAR and structural data.

First, Yoshino's SAR and structural data show that a ring substituent on the indazole nitrogen is tolerated. EX1008, Table 3; EX1035, ¶¶21–22, 41–44. It can thus be reasonably expected that cyclopropyl incorporation would retain or improve activity.

Second, Yoshino shows that removing a methyl substituent from the THP ring leads to improved activity in three of four direct comparisons discussed above. EX1008, Table 3. Combining cyclopropyl incorporation and methyl removal would have been expected to produce a more active compound compared to the parent compound with a dimethyl-substituted THP ring. Su and Yoshino thus provide a finite number of predictable solutions for modifying the lead compounds.

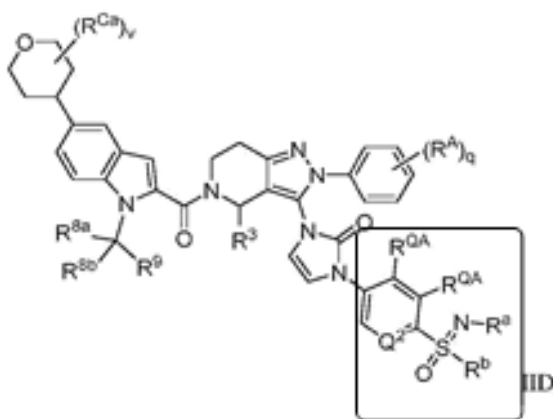
Further, a POSA would have reasonably expected these modifications to improve pharmacokinetic properties relative to orforglipron. As Talele explains,

replacing a methyl group with a cyclopropyl ring is a common practice to enhance metabolic stability and pharmacokinetic profile. EX1009, 1–2, 24.

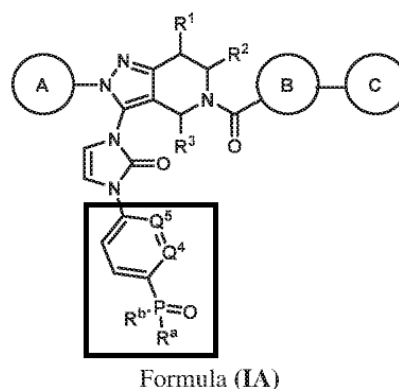
(c) Patent Owner and Dr. Wipf's Analysis Is Flawed

PO cites several references arguing that a POSA would have had multiple potential modification sites on orforglipron without any direction to particular modifications. POR, 49. A closer examination confirms that PO's cited references either (i) describe compounds or genera with core scaffolds substantially different from orforglipron, or (ii) encompass broad genera without any guidance on lead selection or modifications as conceded by PO. These references would have actually directed a POSA to Yoshino and Su, which identify priority compounds and demonstrate a clear SAR for lead selection and modification.

PO's references disclose genera with core scaffolds significantly different from orforglipron



EX2019 page 64



Formula (IA)

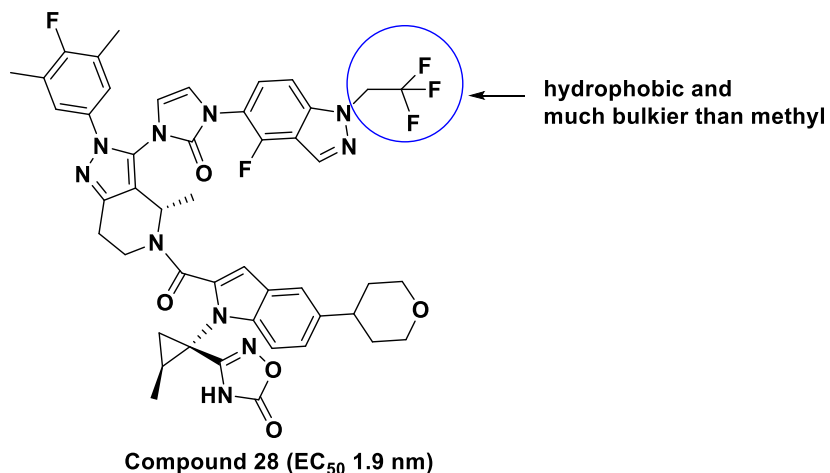
EX2020 page 231

Further, PO's argument ignores that compounds lacking orforglipron's core scaffold would not qualify as appropriate lead candidates, given orforglipron's clinical success and the failure of structurally distinct compounds. EX1002, ¶¶48–51; EX2046, 4; EX2048; EX2051.

(d) PO Mischaracterizes the Structural Data and Contradicts Yoshino

PO and its expert Dr. Wipf contend that the binding pocket surrounding the indazole methyl group is “mainly hydrophilic” and that little room exists for a bulkier substituent. POR, 33–37; EX2079, ¶¶93, 176–181. However, his position contradicts Yoshino's activity data. For example, compound 28, bearing a much bulkier hydrophobic trifluoroethyl group on the indazole nitrogen, exhibits single-digit nanomolar activity. EX1008; EX1002, ¶¶77; EX1035, ¶28.

Hydrophobic and bulky group is tolerated on indazole nitrogen



Dr. Wipf also conflates polarity with hydrophilicity, asserting that hydrophilic substituents are favored at this position. EX2079, ¶¶44, 166, 177, 178. But

compound 28's polar trifluoroethyl is actually a hydrophobic group, which performs well in this region, directly contradicting his conclusion. EX1035, ¶28.

Further, Dr. Wipf did not account for the conformational flexibility of TM1 and TM2. EX1034, 118:7–120:14, 96:9–97:1; EX1035, ¶¶23–25. He relied solely on residue-level coloring that does not distinguish which atoms face the pocket interior. EX2079, ¶¶91, 177; EX1035, ¶¶38–40.

Dr. Fan's quantitative analysis refutes Dr. Wipf's conclusions and confirms a POSA's understanding of the art. She performed electrostatic potential mapping and structural overlays of TM1 and TM2 from multiple cryo-EM structures. EX1035, ¶¶21–22, 41–44. Her analysis shows the pocket surrounding the indazole methyl position exhibits a **largely hydrophobic** interior, with K202 and E138 polar side chains oriented toward solvent, not “mainly hydrophilic” as Dr. Wipf asserts. *Id.* Dr. Wipf failed to consider side-chain orientation and admitted he did not account for solvent or rotamer conformations. EX1034, 92:11–22, 93:17–94:5. Dr. Fan's docking studies further show cyclopropyl can be accommodated through local conformational adaptation of E138 and K202. EX1035, ¶¶34–37.

Kawai's cryo-EM structure further supports ring incorporation at the indazole moiety. The pocket region formed by TM1, TM2, TM6, and TM7 (adjacent to the 4-fluoro-1-methyl-indazole moiety) exhibits *conformational flexibility*, whereas the region formed by TM3, TM4, and TM5 (interacting with the core scaffold) is

relatively rigid. EX1004, 4; EX1002, ¶¶157-158. This flexibility would motivate a POSA to incorporate a ring at the peripheral indazole moiety, which would not be expected to cause significant structural perturbation and would likely preserve binding potency. EX1002, ¶¶208–209.

B. GROUND 2: COMPOUNDS 1, 19, AND 20 ARE OBVIOUS OVER YOSHINO, KAWAI, AND TALELE

1. Lead Selection

Orforglipron (compound 67) is the only compound specifically recited in Yoshino’s claims. EX1008, 166. It was also the only Yoshino compound advanced into clinical trials before the ’236 patent’s priority date. This combination of claim specificity and clinical advancement establishes orforglipron as a lead.

2. Lead Modification

Yoshino’s SAR indicates that ring substitution at the indazole nitrogen is well tolerated and improves or preserves activity. In a direct comparison as explained above, compound 8 (bearing a THF substituent) improves activity relative to compound 54 (with a methyl group at the indazole nitrogen). EX1002, ¶74. Other compounds bearing a THF ring maintain activity despite variations of other substituents. EX1002, ¶75; EX1008.

Kawai’s structural data reinforces this conclusion. The region surrounding the indazole moiety is conformationally flexible, in contrast to the relatively rigid core scaffold. EX1002, ¶¶157–159; EX1004, 4. Dr. Fan’s structural overlays of TM1 and

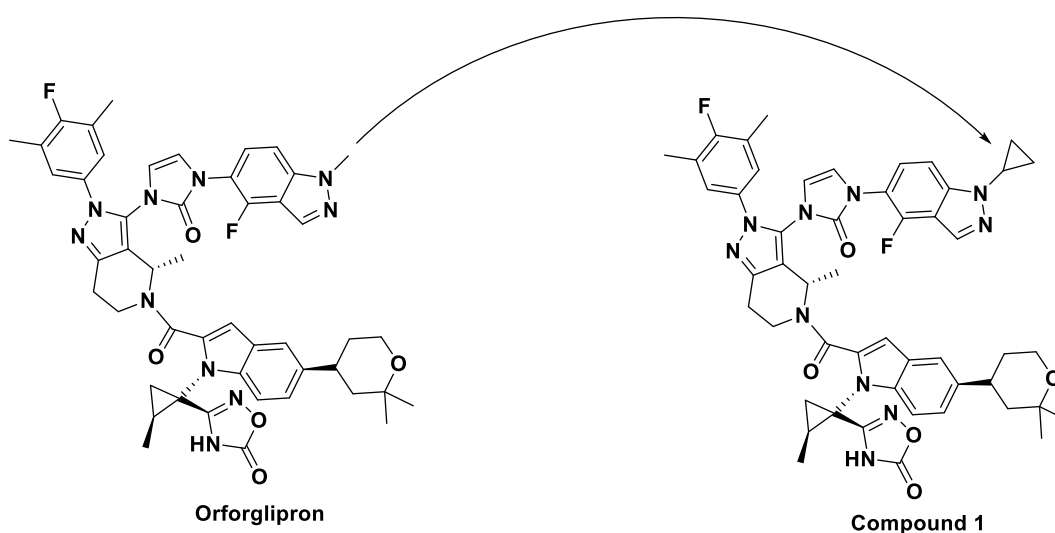
TM2 regions from six cryo-EM structures confirm this flexibility is an intrinsic property of GLP-1R, not merely a consequence of binding to a particular ligand type. EX1035, ¶¶21–28. Ring incorporation at the peripheral indazole position would therefore not significantly perturb the binding pocket and would likely preserve binding affinity and potency. EX1002, ¶208.

(a) Compound 1

Among common rings, cyclopropyl is most comparable to a methyl group at the indazole nitrogen in size and lipophilicity. EX1002, ¶163. A POSA would therefore have been motivated to replace the methyl with cyclopropyl, yielding compound 1.

Modification to lead compound orforglipron

incorporation of ring per teaching of Yoshino and Kawai



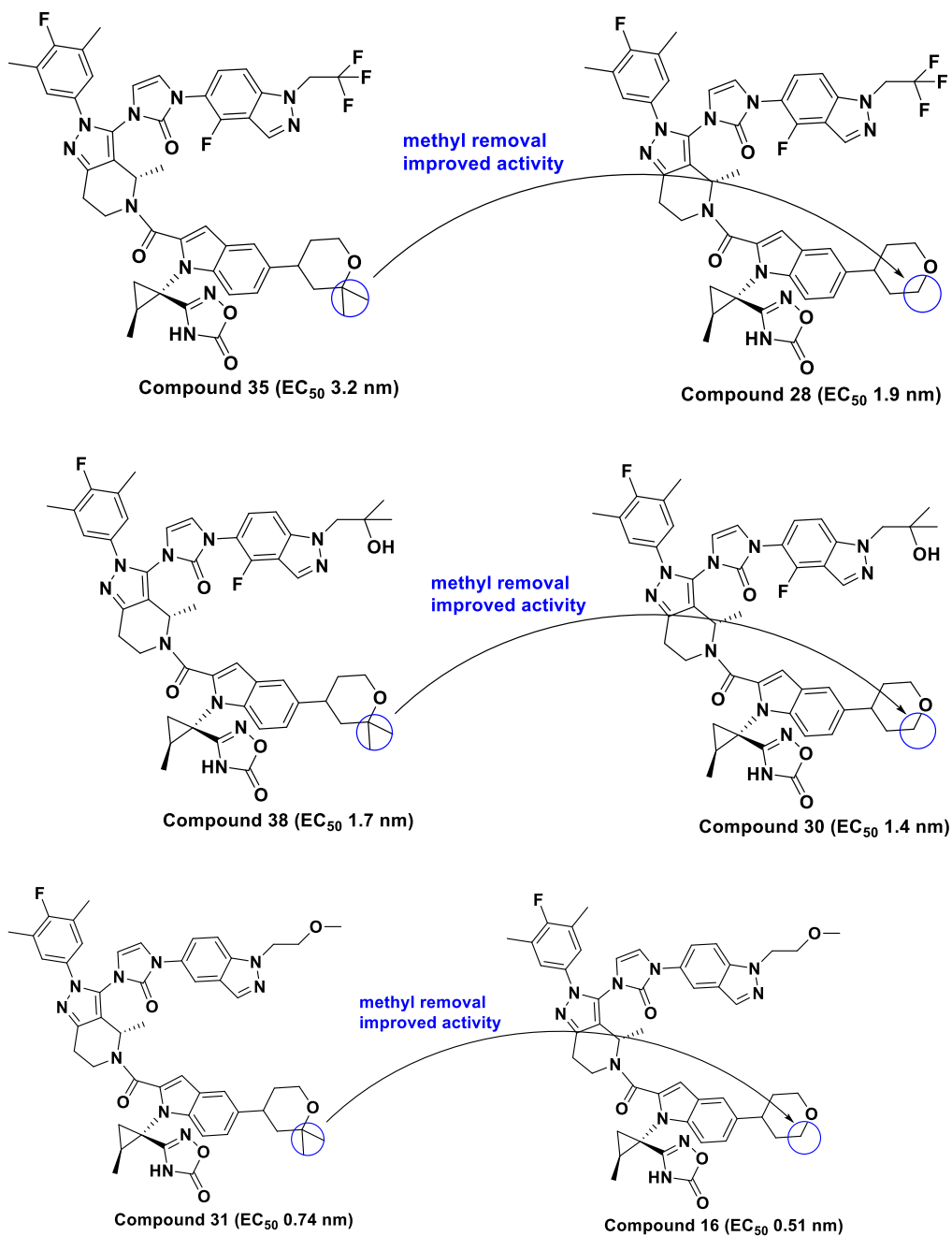
Further, identifying an active compound is a critical prerequisite in drug development and a central objective, especially in view of the unpredictability in

drug discovery. EX2034, 28–29; EX1002, ¶152. Here, a POSA would have had a reasonable expectation of success in obtaining an active compound bearing a cyclopropyl substituent. Specifically, cyclopropyl lies intermediate between methyl and THF substituents, both of which Yoshino discloses as yielding active compounds. This SAR would have reinforced the expectation that substituting the methyl group of orforglipron with cyclopropyl would likewise afford an active compound, namely compound 1. EX1002, ¶¶73–76.

Cyclopropyl substitution in place of a methyl group is also expected to improve the pharmacokinetic profile of compound 1. EX1002, ¶¶81–84. As Talele recognizes, “one can expect to achieve a metabolically stable derivative upon replacement of the methyl group with a cyclopropane ring.” EX1009, 2, 24.

(b) Compound 19

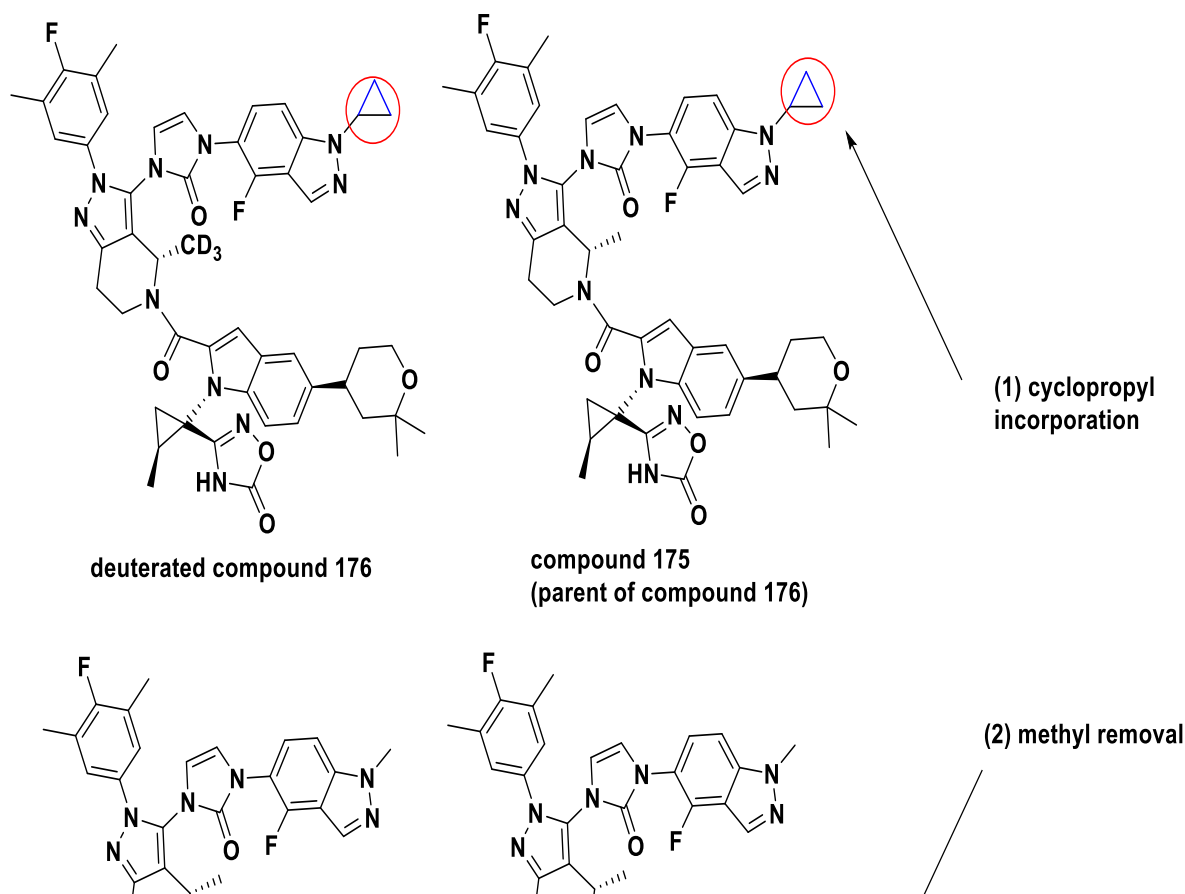
As explained above and in Ground 1, Yoshino’s SAR demonstrates that substituting a ring for a methyl group at the indazole moiety improves or preserves activity, while demethylation of the THP moiety can improve activity. EX1008, 162–163.

Methyl removal from THP improved compound activity

Compounds 23 and 175, which share the core structure of orforglipron and were selected for deuteration from among hundreds disclosed by Yoshino and Su, and supported by SAR analysis as discussed in Ground 1, further underscore the

strong potential of cyclopropyl incorporation and methyl removal to improve activity and pharmacokinetic properties. EX1007, claim 12; EX1008, 162–163; EX1009, 24.

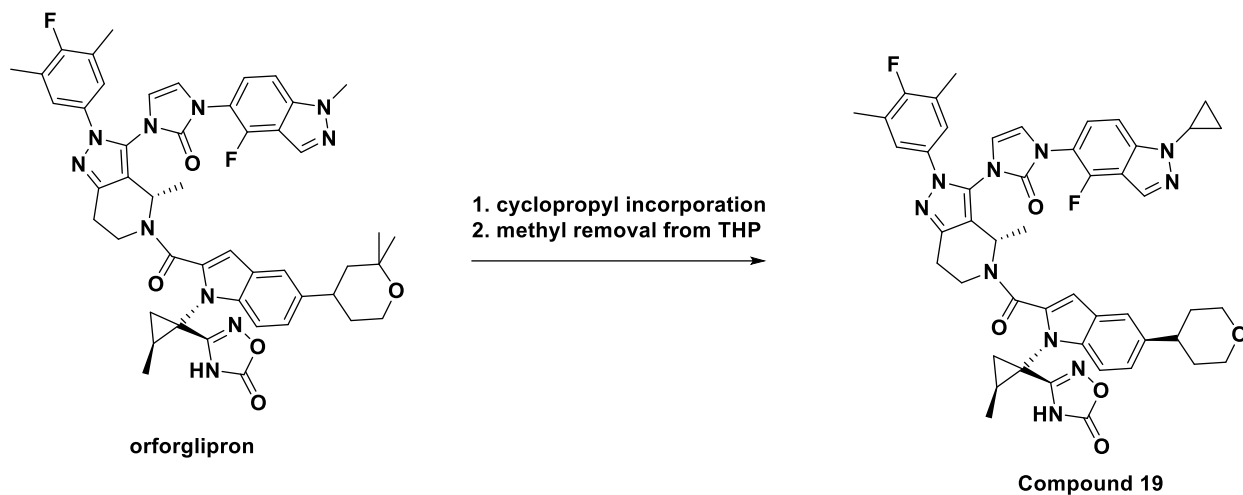
Cyclopropyl incorporation and methyl removal for improvements in activity and pharmacological properties pe Yoshino and Su



Under the combined teachings of Yoshino, Su, and Talele, a POSA would have been motivated to modify orforglipron in a particular manner: (1) replacing the methyl with cyclopropyl and (2) removing the methyl groups from THP to arrive at compound 19. These modifications would have been reasonably expected to yield

improved activity and pharmacokinetic properties relative to orforglipron. EX1002, ¶¶219–222.

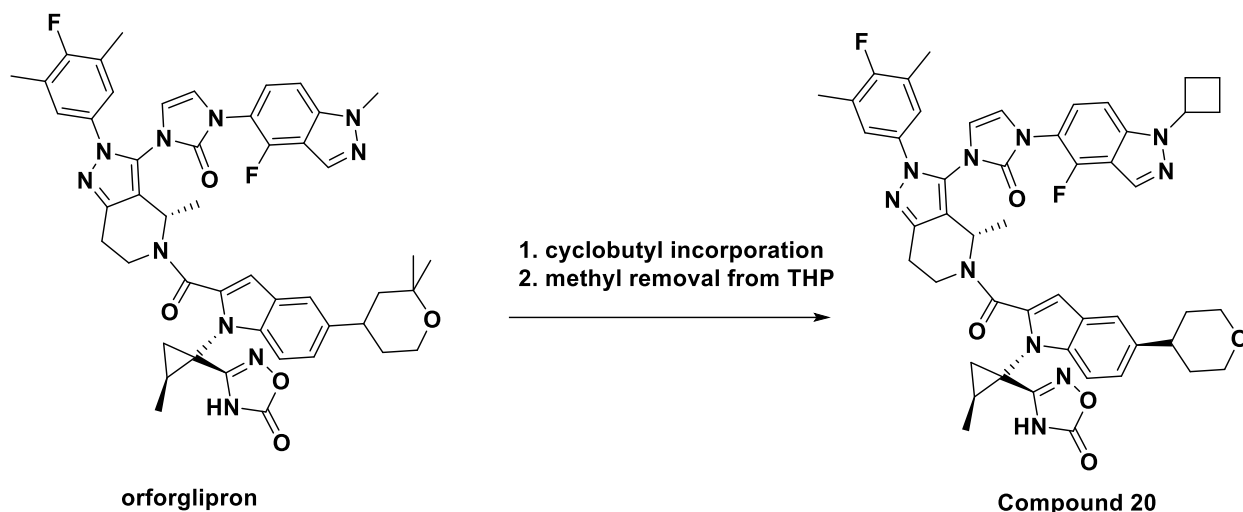
modification of orforglipron to provide compound 19



(c) Compound 20

Based on Yoshino's SAR for methyl removal and ring substitution at the indazole nitrogen as explained above, it would have been obvious to remove the methyls from THP in orforglipron and replace the indazole methyl with a cyclopropyl or cyclobutyl. EX1002, ¶224. Deuterated compound 176 and its parent compound 175 provide additional guidance to incorporate a carbocyclic ring on the indazole nitrogen, and compound 20 is reasonably expected to exhibit improved metabolic stability. EX1002, ¶¶225–226.

modification of orforglipron to provide compound 20



(d) PO Mischaracterizes Yoshino's Teaching

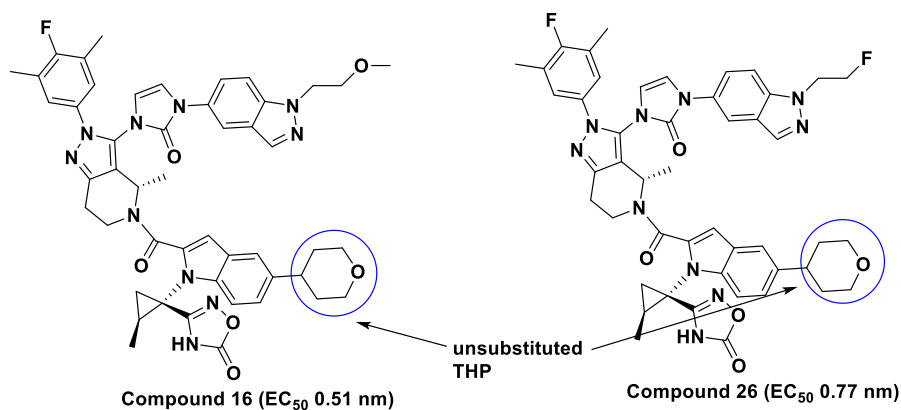
PO mischaracterizes Yoshino to incorrectly claim a lack of benefit from ring substitution at the indazole nitrogen. POR, 30. THF-substituted compounds consistently exhibit single-digit nanomolar activity across structural variations. EX1002, ¶75; EX1008, Table 3. In a direct comparison, THF-substituted compound 8 demonstrates improved activity over methyl-substituted compound 54. EX1002, ¶74. THF also preserves activities of other compounds regardless of substituent variations. EX1008, Table 3.

Given the inherent unpredictability of drug discovery, illustrated by substantial activity loss in PO's two cited compounds (POR, 39, 53; EX2080, ¶8), the consistent favorable impact of THF ring substitution (yielding single-digit nanomolar activity) would have encouraged a POSA to explore other ring substitutions at this position.

A POSA would not have limited Yoshino's teaching to THF. EX1002, ¶¶163–164. Given the binding pocket's hydrophobic nature, a POSA would have recognized that carbocyclic rings could be similarly accommodated. *Id.* Cyclopropyl's pharmacokinetic advantages and reduced entropic penalties upon binding further support its suitability as a THF alternative. *Id.*

PO's assertion that Yoshino prefers other substituents over THP similarly disregards the SAR. POR, 31. For example, methoxyethyl-substituted compound 16 and fluoroethyl-substituted compound 26 both require an unsubstituted THP moiety, which plays the key role in maintaining potency. EX1008, Table 3.

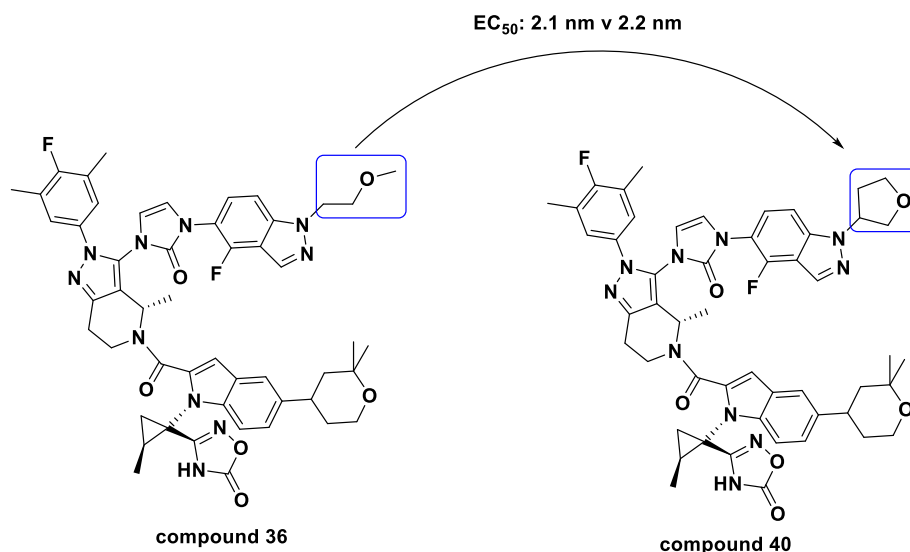
Unsubstituted THP contributes to compound activity



Although methoxyethyl-substituted compound 31 exhibits good activity, that activity is more likely attributable to the absence of a fluoro substituent on the indazole in comparison with compound 36, rather than any intrinsic benefit of the methoxyethyl group. No direct comparison establishes that methoxyethyl substitution alone enhances activity.

A direct comparison between compounds 36 and 40 shows no appreciable advantage of methoxyethyl over a THF ring, as reflected by nearly identical EC_{50} values (2.1 nM vs. 2.2 nM). EX1008, Table 3. Yoshino thus provides no clear SAR support for substituents other than THF at the indazole nitrogen.

*No advantage for methoxyethyl (compound 36)
over THF ring (compound 40)*



Further, ring systems are generally preferred over flexible alkyl chains because they possess fewer rotational degrees of freedom and incur lower entropic penalties upon binding. EX1002, ¶213. Yoshino's SAR based on THF-containing compounds would have directed a POSA toward incorporating a ring substituent at the indazole position. *Id.*

PO asserts that other ring systems could serve as alternatives to THF at the indazole position. POR, 37. But cyclopropyl uniquely balances the key attributes for

lead optimization: it most closely approximates THF's ring character while maintaining lipophilicity similar to methyl. EX1002, ¶¶73–76.

PO's cited references address substituents that differ materially from both methyl and THF in size, lipophilicity, aromaticity, or overall structural complexity, including oxetanes (EX2008), oxadiazoles (EX2009), thiadiazoles (EX2010), bicyclopentanes (EX2011), nitrogen-containing heterocycles (EX2012), aromatic rings (EX2013), medium-sized rings (EX2014), and bicyclic systems (EX2015). None of these alternatives provides the same combination of minimal steric perturbation, favorable lipophilicity, and enhanced metabolic stability that cyclopropyl offers as a methyl substitute. A POSA would have been preferentially motivated to select cyclopropyl over these structurally and functionally divergent alternatives cited by PO.

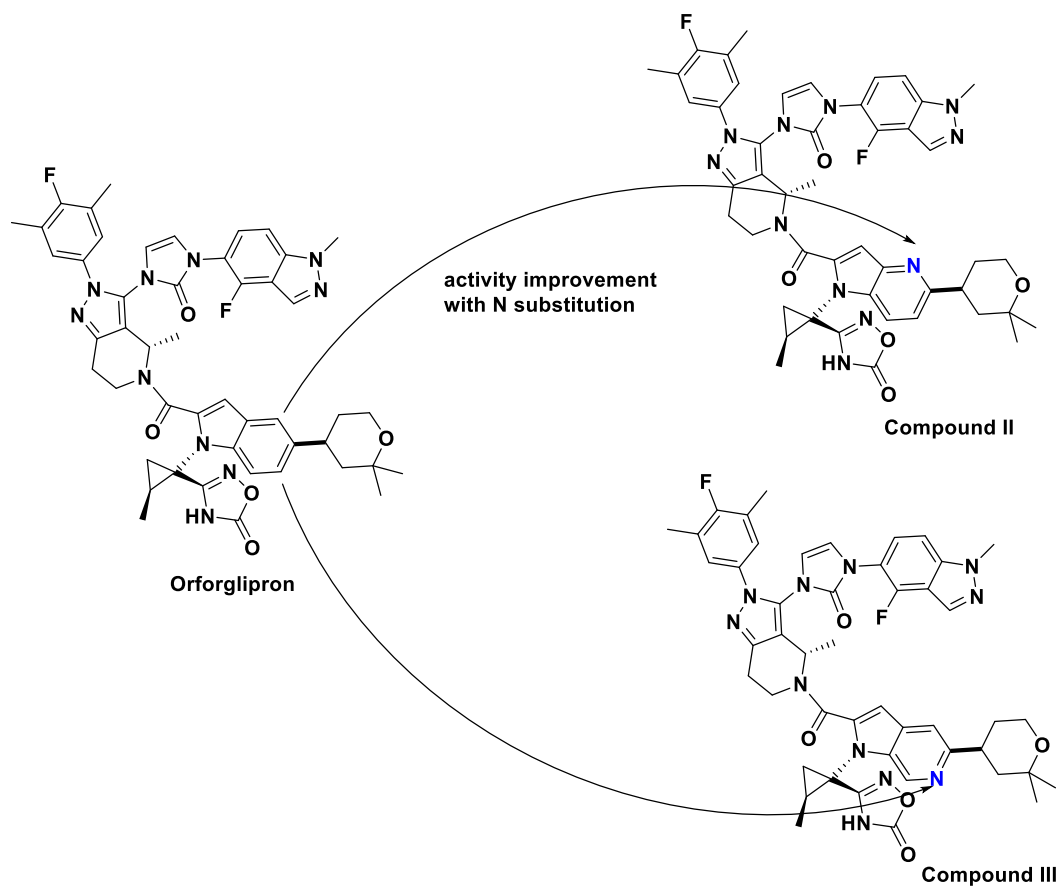
C. GROUND 3: COMPOUND 65 IS OBVIOUS OVER SU, YOSHINO, KAWAI, TALELE, MENG, PATEL, AND REN

Claims 1–4 and 21–25 would have been obvious to a POSA, at least with respect to compound 65. The same prior art motivations supporting cyclopropyl substitution and THP modification (Grounds 1 and 2) apply here and would have guided a POSA to compound 19.

Meng synthesized and evaluated only two compounds, each differing from orforglipron by incorporation of a nitrogen atom within a particular ring and each demonstrating improved activity. EX1029, 9-23. The introduction of a nitrogen atom

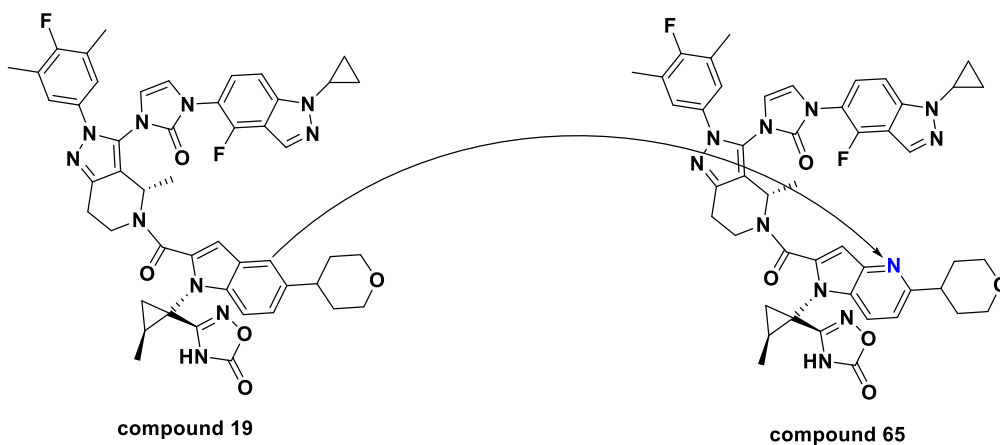
is also known to improve solubility. EX1026, 1-6. A finite number of identified, predictable solutions was therefore available in prior art.

Meng discloses only two specific options to modify orforglipron



In view of Meng's specific teaching on orforglipron modification, a POSA would have been motivated to apply the same modification to compound 19, which shares orforglipron's core scaffold. This modification would have been reasonably expected to yield compound 65 with improved activity and pharmacokinetic properties.

Nitrogen introduction per Meng to provide compound 65



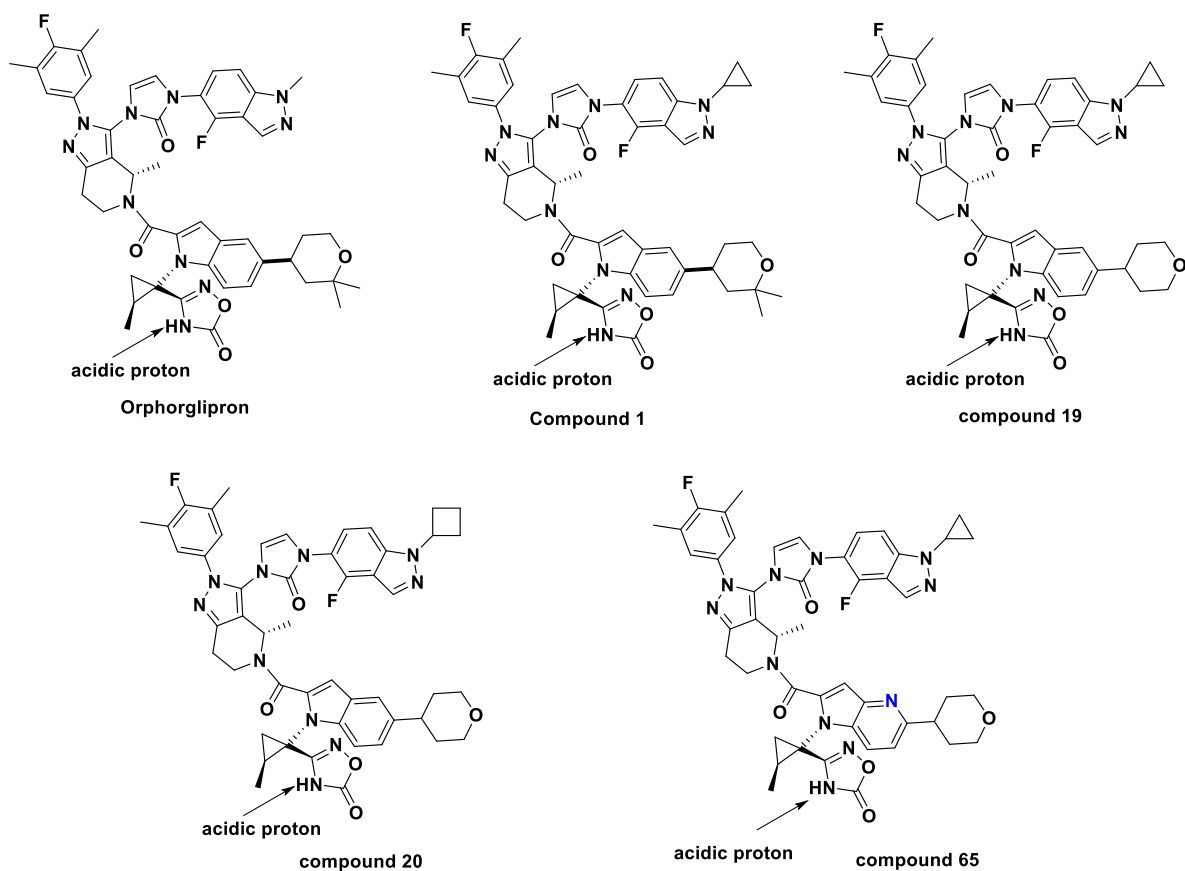
D. GROUND 4: HEMICALCIUM SALT OF COMPOUND 1 (CLAIMS 4 AND 9) IS OBVIOUS OVER SU AND BETHEL

Bethel expressly discloses a hemicalcium salt form of orforglipron. EX1032, 19-22, 46-82. Formation of this salt involves deprotonation of the acidic proton. Compounds 1, 19, 20, and 65 each contain the same acidic proton, which Dr. Wipf confirmed is the most acidic site in each molecule. EX1034, 185:2–186:16. Because this proton is positioned distal from other substituents (such as cyclopropyl, THP, and N-substituted heteroaryl groups), a POSA would have had a reasonable expectation that these compounds would undergo the same hemicalcium salt formation process as orforglipron. EX1002, ¶¶307–312.

The law is clear that “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Courts have consistently found salt forms of known active ingredients

obvious where the prior art teaches acid-addition salt formation generally. *Id.* Bethel discloses the hemicalcium salt formation process for orforglipron, and the structural similarity of Compound 1 to orforglipron provides a POSA with a reasonable expectation of achieving the same salt form.

Compounds 1, 19, 20 and 65 share the same acidic proton with orforglipron



III. THE ALLEGED IMPROVEMENT IS NOT UNEXPECTED

The alleged improvements for the claimed compounds 1, 19, 20, and 65 are not unexpected in view of prior art, which provides a strong prima facie showing of

obviousness.² Even assuming any improvement is “significant,” this does not equate to “unexpected.” Once a compound is obvious, subsequently identified advantageous properties cannot establish patentability unless they are unexpected *in kind*, not merely *in degree*. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (improvements in potency insufficient to outweigh obviousness); *Purdue Pharma L.P. v. Accord Healthcare Inc.*, 669 F. Supp. 3d 286, 303–04 (D. Del. 2023), *aff’d*, No. 2023-1953, 2024 WL 5244764 (Fed. Cir. Dec. 30, 2024) (“[E]vidence of unexpected results and other secondary considerations will not necessarily overcome a strong *prima facie* showing of obviousness.”).

The alleged improved activity of compounds 19 and 20 (incorporating an unsubstituted THP moiety) relative to orforglipron and compound 175 in Su would have been expected based on Yoshino’s SAR demonstrating the beneficial effects of unsubstituted THP. POR, 8; EX1008, Table 3; EX1002, ¶77.

Here, PO points to no different mechanism of action from the prior art GLP-1R agonists. The alleged improvements in activity amount only to differences in

² PO’s unexpected results arguments also rely on unverified, hearsay, which should be excluded and accorded no weight. (See POR at 9, 38-39, 52-55, 65-66, 80-81 (citing Exs. 2080-2081); Ex. 1039 at 27-28, 60, 80, 85, 91-92, 97, 127 (confirming declarant did not perform, collect, or verify data).)

degree and would have been expected in view of the SAR established in Yoshino. Therefore, they are insufficient to overcome obviousness.

Similarly, the alleged improved drug exposure for compounds 1, 19, 20, and 65 relative to orforglipron would have been reasonably expected given the well-known effects of cyclopropyl substitution in enhancing metabolic stability and extending half-life. EX1009, 24; EX1002, ¶¶83–84. Moreover, in Ground 1, the pharmacokinetic properties of compound 175 (same as compound 1 bearing a cyclopropyl) and compound 23 (bearing an unsubstituted THP) would have been known due to deuteration. EX1034, 277:8–278:11. Any further improvement in exposure for compounds 19, 20, and 65 merely represents differences in degree and is insufficient to overcome obviousness.

Finally, PO's asserted solubility improvement for compound 65 lacks probative value. A POSA would have recognized that compound 65, obtained by modifying compound 19 in accordance with Meng, would also be expected to exhibit improved solubility due to introducing a nitrogen atom into the aromatic ring. EX1002, ¶278; EX1026, 1-6. In addition, PO's solubility testing was conducted only at pH 11, far outside the physiological pH range of the human gastrointestinal tract (approximately pH 1–8), and thus does not inform pharmaceutical utility as an oral drug. No solubility data at physiologically relevant pH has been provided. Moreover,

the testing occurred on March 4, 2026, one day before PO's Response was filed, suggesting litigation-driven results rather than genuine, unexpected properties.

IV. FAILURE OF OTHERS DOES NOT SUPPORT NON-OBVIOUSNESS

PO's reliance on alleged failures of others is misplaced, because the nexus requirement is not satisfied. POR, 58. Unlike the challenged compounds, the Pfizer compounds (lotiglipron, danuglipron, and PF-06954522) are benzimidazole-based compounds sharing no meaningful structural similarity with the orforglipron scaffold. EX2048; EX2050; EX2051. More importantly, these compounds failed due to hepatotoxicity, a safety issue unrelated to potency or pharmacokinetics. *Id.* There is no evidence the challenged compounds, as derivatives of the clinically successful orforglipron, address any additional hepatotoxicity concerns.

V. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that the Board find claims 1-9, 12-17, and 21-25 of the '236 Patent unpatentable as obvious under 35 U.S.C. § 103.

Dated: May 28, 2026

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(c), the undersigned certifies that the foregoing Petitioner's Reply to Patent Owner's Response in Post Grant Review of claims 1-9, 12-17, and 21-25 of the 12,234,236 Patent contains, as measured by the word-processing system used to prepare this paper, 5,317 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting toward the word limit.

Dated: May 28, 2026

By: /Jin Zhu/

Jin Zhu, Ph.D.

Reg. No. 62,869

Counsel for Petitioners

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on May 27, 2026, I caused a true and correct copy of the foregoing Petitioner's Reply to Patent Owner's Response in Post Grant Review of claims 1-9, 12-17, and 21-25 of the 12,234,236 Patent to be served by electronic mail, as authorized by Patent Owner, at the following email addresses:

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