

CONJUPRO BIOTHERAPEUTICS, INC.

v.

Ascletis Pharma China Co Ltd.

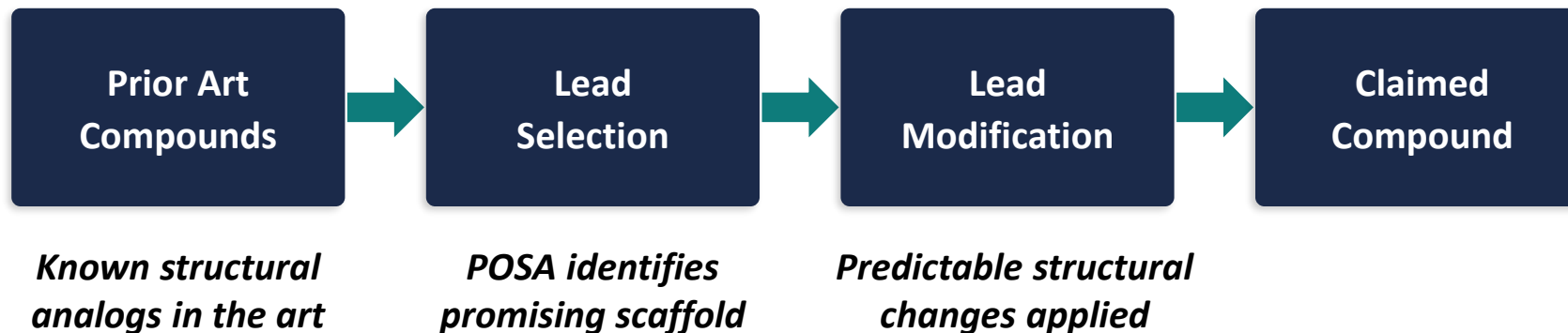
PGR2025-00057

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

Petitioners' Oral Argument Demonstratives

August 31, 2026

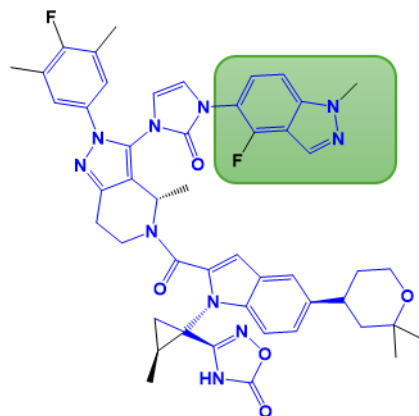
Legal Framework: Lead Selection and Lead Modification



- 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).
- To determine whether a new chemical was obvious, courts determine (1) whether a POSA would have selected the asserted prior art compound(s) as lead compound(s), or starting points for further development efforts, and (2) whether the prior art supplied a POSA with a reason or motivation to modify the lead compound. See *Otsuka Pharma. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012).

Petitioner Response to Patent Owner Request for Discretionary Denial (Paper 13) at 7-8; Petitioner’s Reply (Paper 34) at 16.

Background: Orforglipron and Later GLP1R Agonists

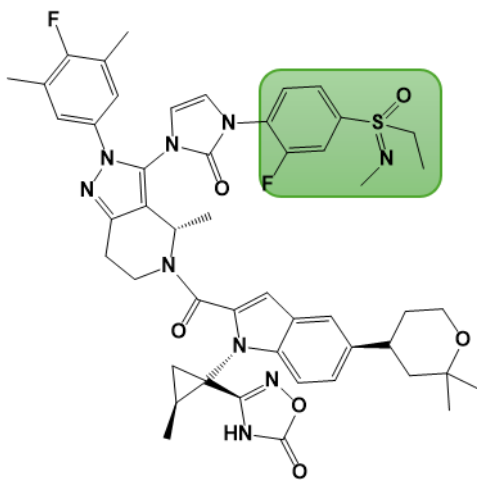


orforglipron

- **Orforglipron is the only compound that advanced to Phase 3 clinical trial**
- **Multiple compounds with different scaffolds failed in clinical development**

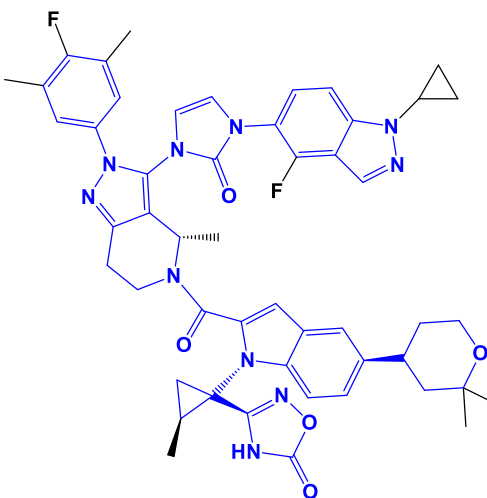
Petition (Paper 1) at 10, 53; Petitioner's Reply (Paper 34) at 3.

EX1008 (Yoshino) at 99.



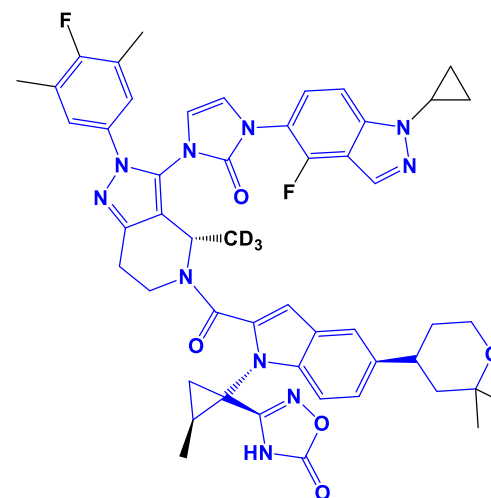
compound 164

EX2019 (Huang) at 407.



compound 175

EX1007 (Su) at 328.



compound 176

EX1007 (Su) at 328.

Lead Selection Under Ground 1: Su Compounds

Lead Selection Framework: Ground 1

Orforglipron

Clinically validated Phase 3 compound



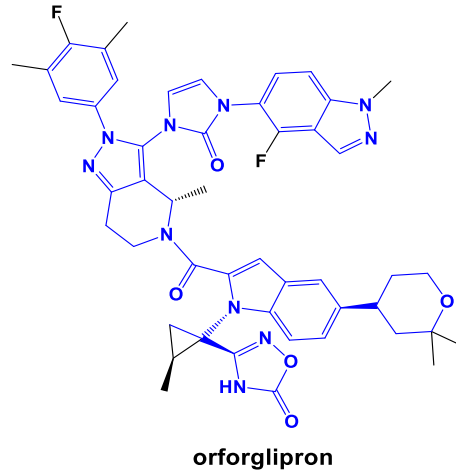
**Compounds Sharing Orforglipron's
Core Scaffold**

e.g. Su Compounds 44, 175, 176 — peripheral modifications only



**Deuteration Identified as Indicator of
Priority Status**

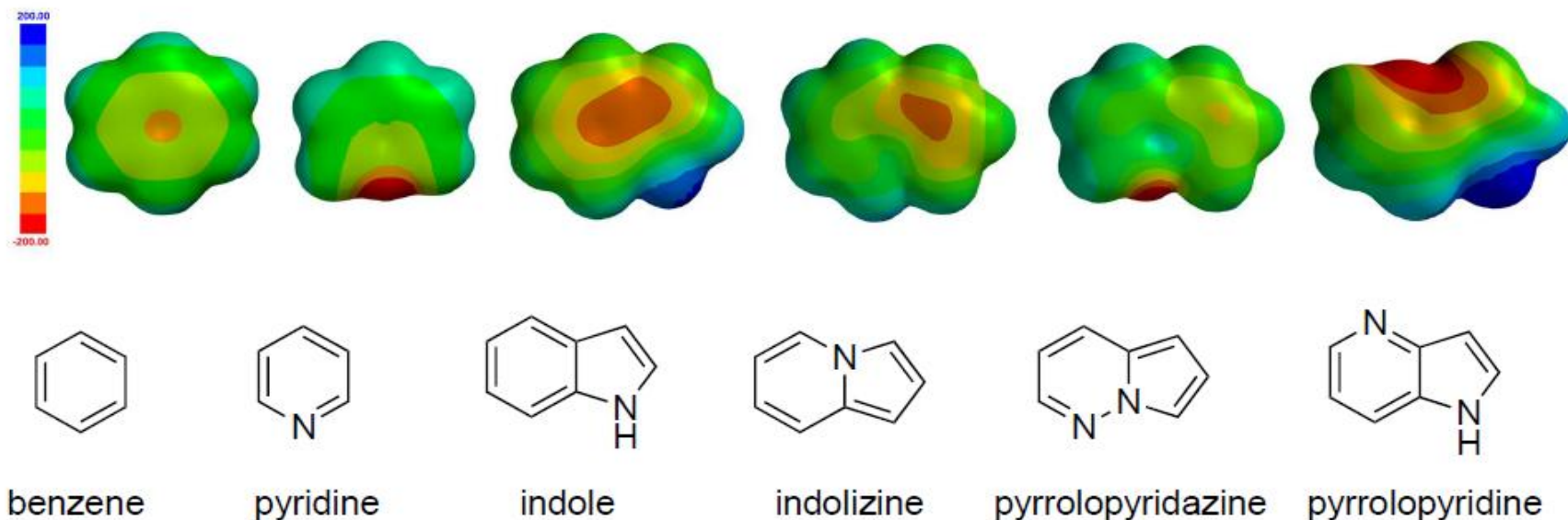
Clinical Success + Competitor Failures + Expert Opinions All Point to Compounds with Orforglipron's Core Scaffold for Lead Selection



- **A POSA would first make only peripheral modifications while preserving the core scaffold. EX1002, ¶152.**
- **PO Expert: “even subtle changes in molecular structure and stereochemical orientation can result in profound differences in biological activity.” EX2079, ¶ 56.**

PO's Own Expert Confirms the Core Scaffold Rationale

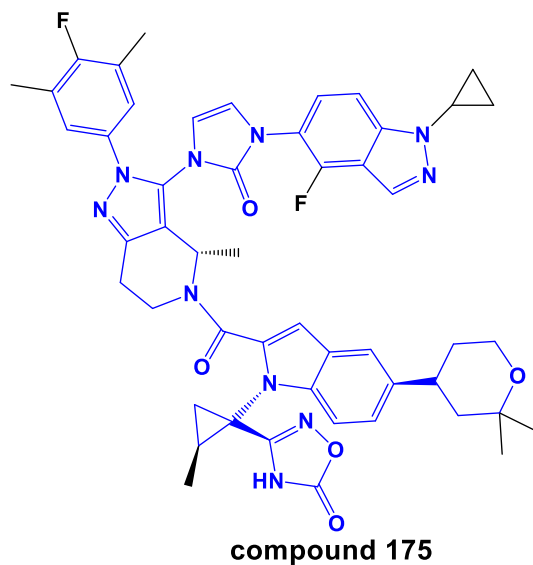
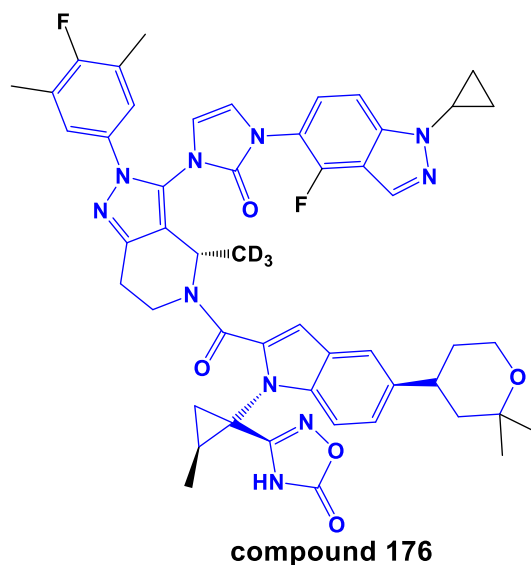
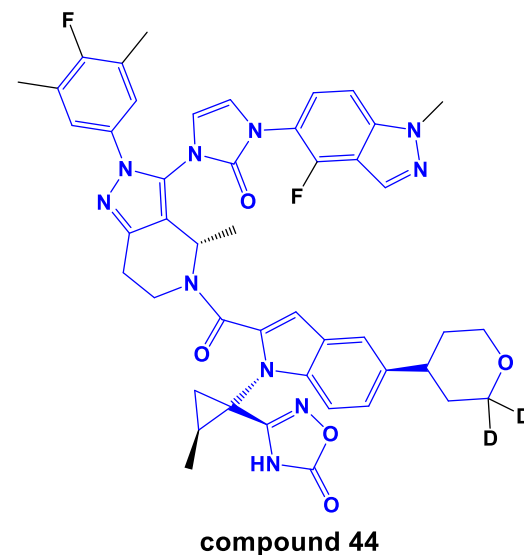
- “In particular, **[e]lectrostatic interactions play a key role in molecular recognition, and their characterization and modulation are at the heart of structure-based drug design** (“SBDD”). In SBDD, maximizing shape and electrostatic complementarity between ligand and protein is a well-established strategy to improve binding affinity and **selectivity** against **antitargets**.” EX2079, ¶ 294 (emphasis added).
- “As a result, a skilled artisan would not have an expectation that a change to the ring structure of orforglipron would result in desirable properties.” EX2079, ¶ 295.



EX2079, ¶ 294

Lead Selection Rationale: Preserve Orforglipron's Clinically Validated Core Scaffold

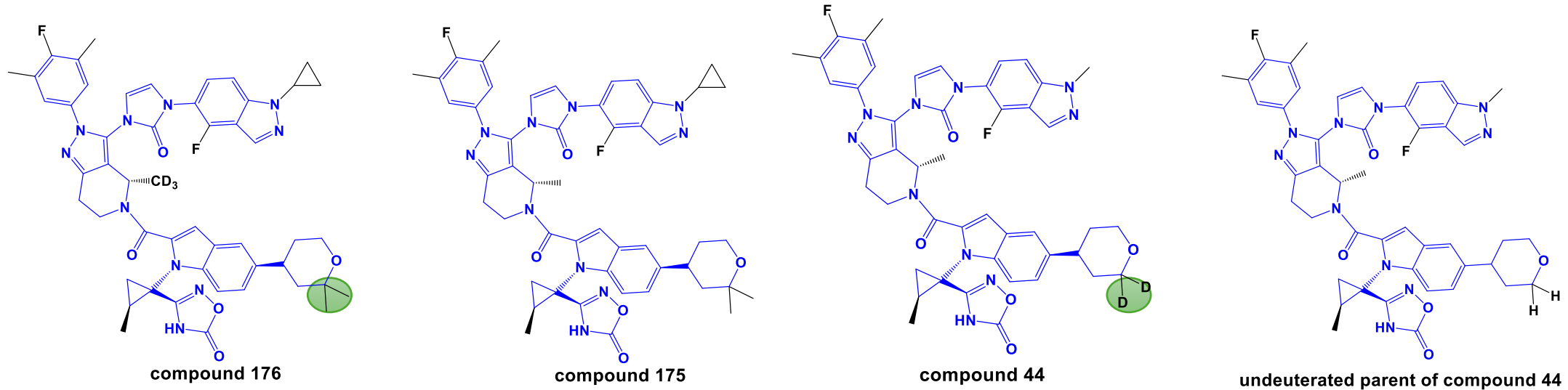
Representative compounds in Su sharing Orforglipron's core scaffold:



EX1002, ¶ 61, 63; EX1007 at 327, 328, claim 12.

EX1007 (Su) at 328.

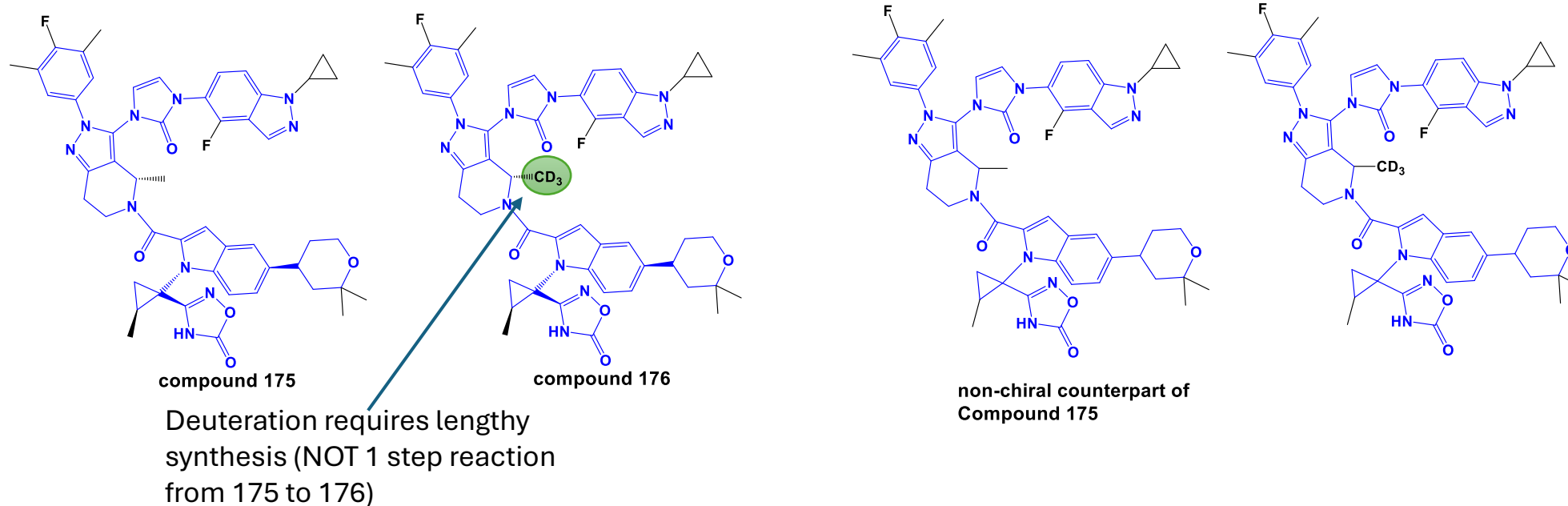
Deuteration = Priority Status: Promising Compounds Get Deuterated



- Of Su's 452 compounds, only seven stereoisomerically pure compounds and their non-stereoisomerically pure counterparts (including compounds 44, 176 and 35) were deuterated. Petitioner's Reply (Paper 34) at 7; EX1007, ¶ 327-328.
- The fact that only a few selected compounds are deuterated and recited in the claims indicates their priority significance. Petitioner's Reply (Paper 34) at 7; EX1002, ¶ 62.

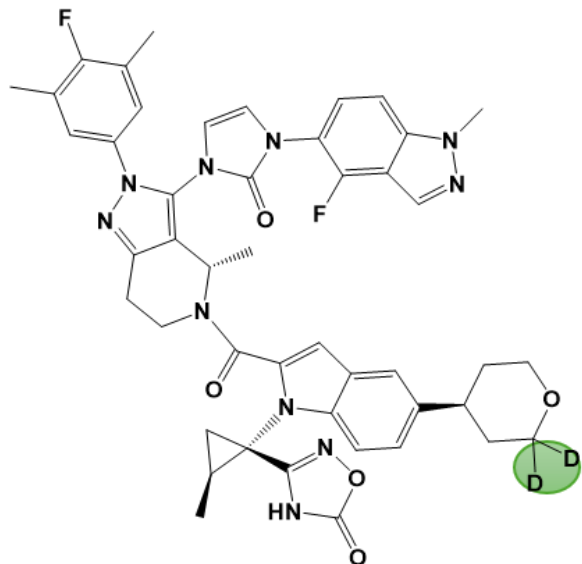
Deuteration Expands IP Around High-Value Parent Compounds

Deuteration Requires Significant Investment

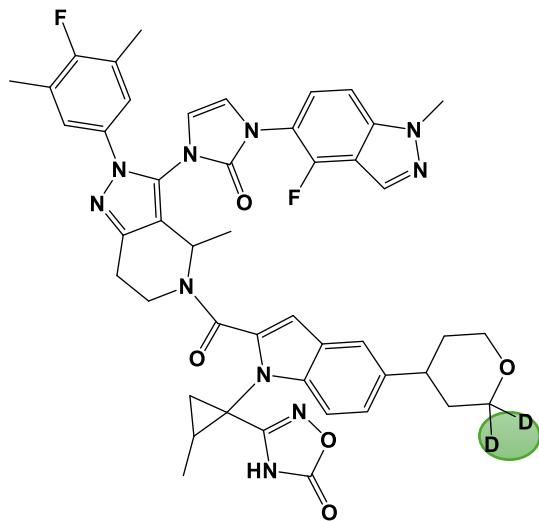
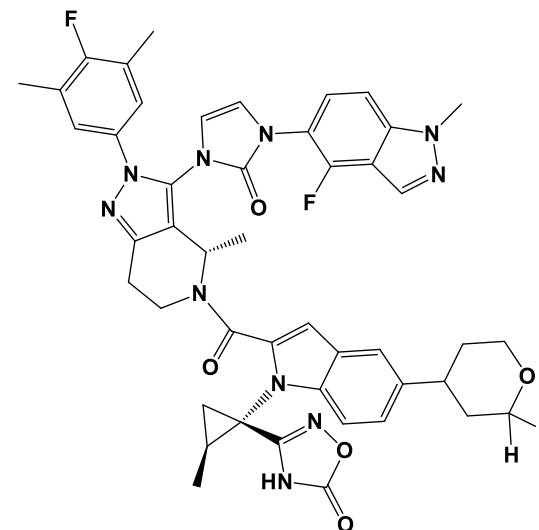


- Deuterated compounds expand IP space around parent compounds with favorable activity → investment signals value. Petitioner's Reply (Paper 34) at 7; EX1036 at 19; EX1034 at 182:20–183:8.
- The non-stereoisomerically pure counterpart is also deuterated and recited in the claim. Paper 34 at 7; EX1007, 329.

Deuteration for IP expansion



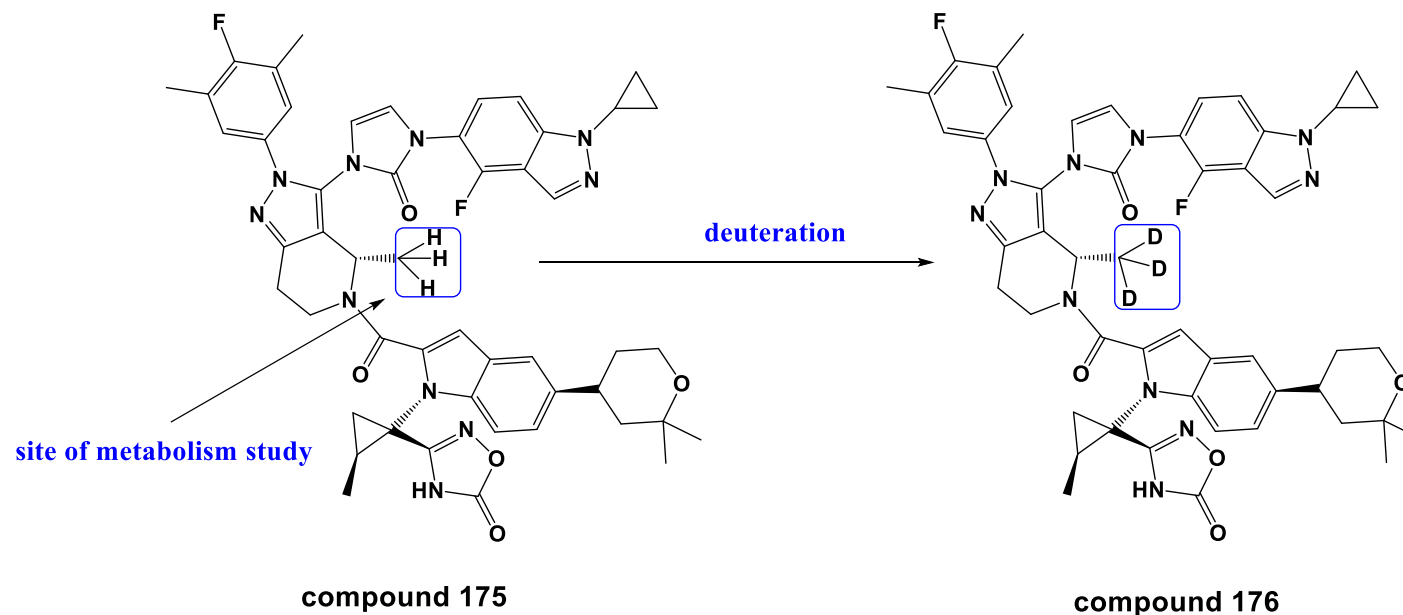
Compound 44



non-deuterated parent of compound 44

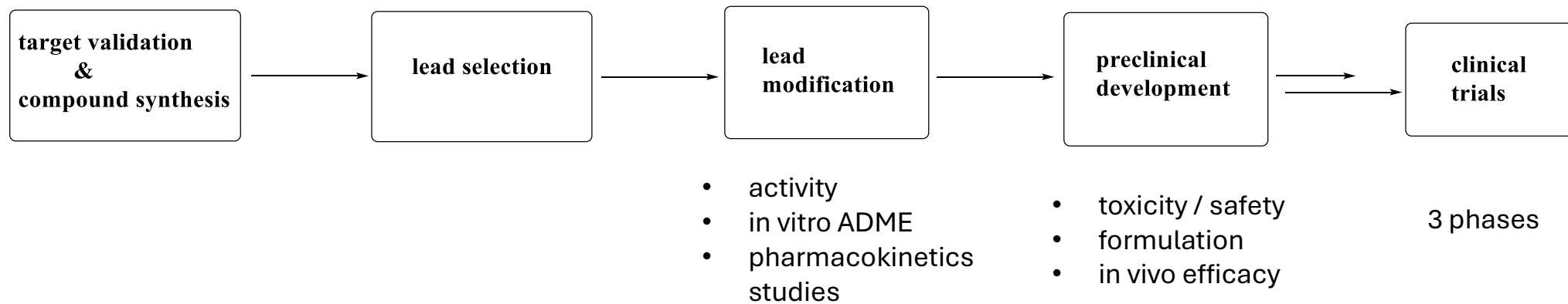
- The deuterated Compound 44 is a stereoisomerically pure structure with defined stereochemistry on each carbon. Its counterpart non-chiral structure is also deuterated and recited in the claim. Petition (Paper 1) at 26-27, 51, 55; EX1007 at 327-328.

Deuteration on Active Compounds for PK Study



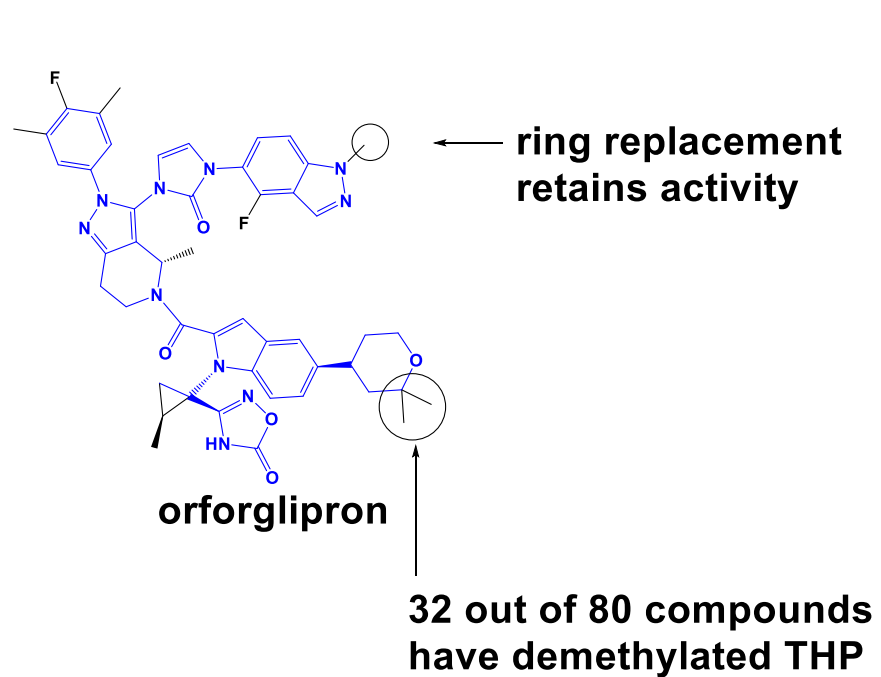
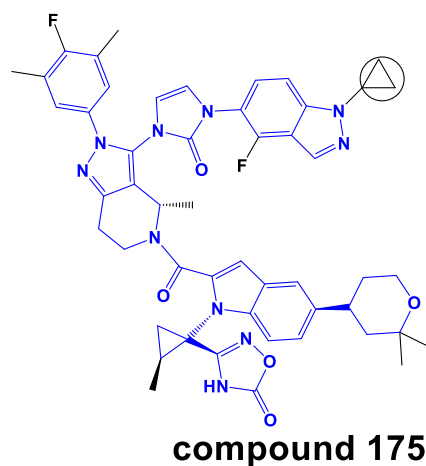
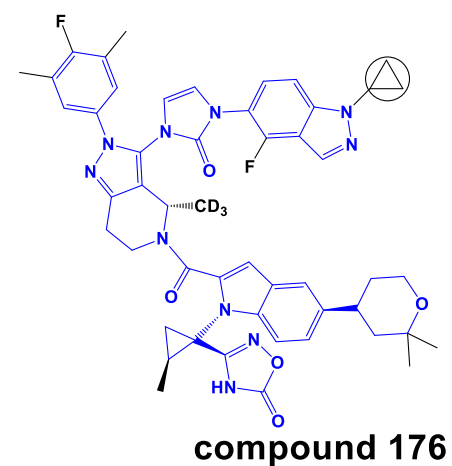
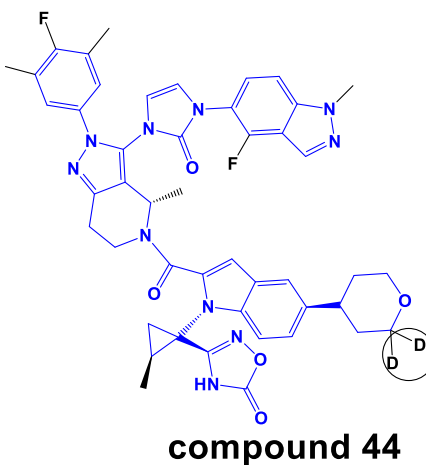
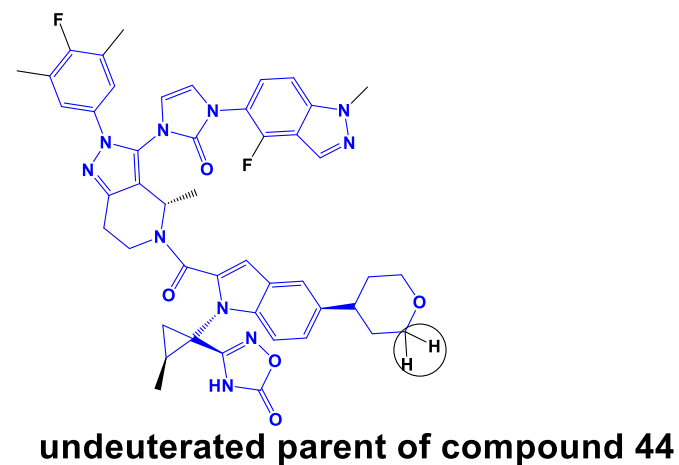
- A POSA would not have deuterated a compound for pharmacokinetics study unless it exhibited good activity and development potential. EX1002, ¶¶150–154.
- Deuteration determines or improves pharmacokinetic properties by suppressing metabolism at the deuteration site (the D-C bond being stronger than the H-C bond). EX1036, 2–3. Ex2033, 84.

Deuteration is an indicator of active compounds with known pharmacokinetics data

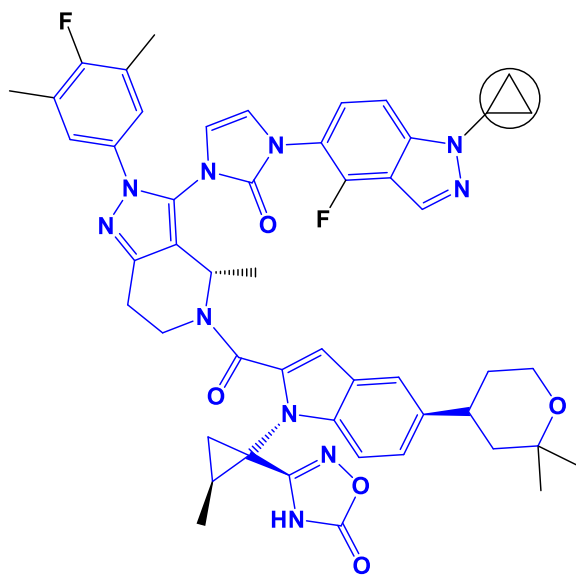


- Metabolic stability and pharmacokinetic properties are determined after active compounds have been identified.
- A POSA would not have deuterated a compound for pharmacokinetics study unless it exhibited good activity and development potential.
- A POSA would understand that the PK profile of a compound must be determined before deuteration is pursued.

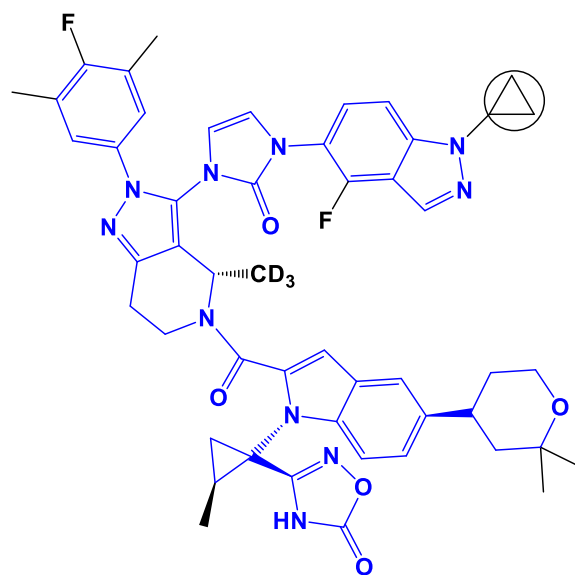
Yoshino SAR Data Support the Deuterated Compounds and Their Parents as Leads



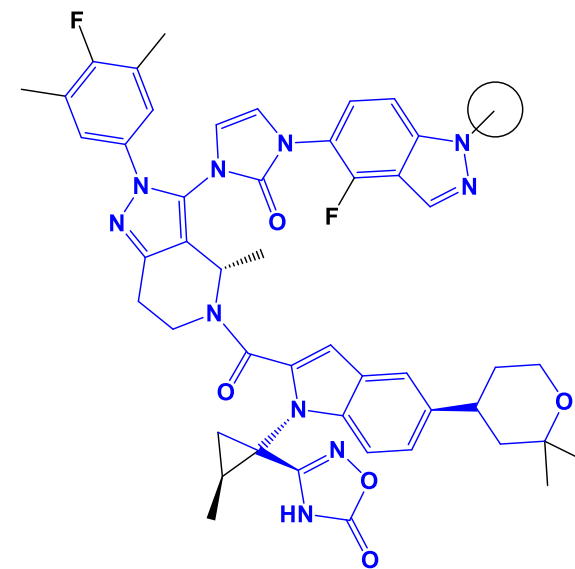
Lead Compounds 175 and 176 Also Contain Cyclopropyl Known to Provide PK Benefits



compound 175

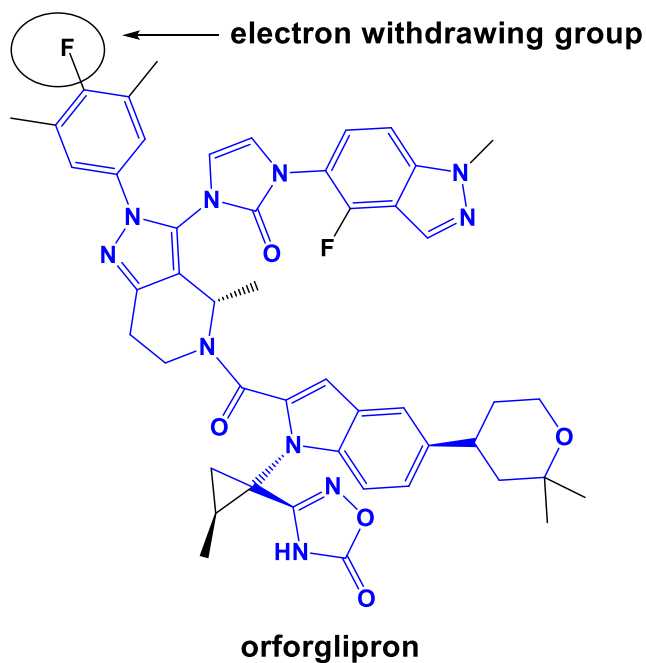
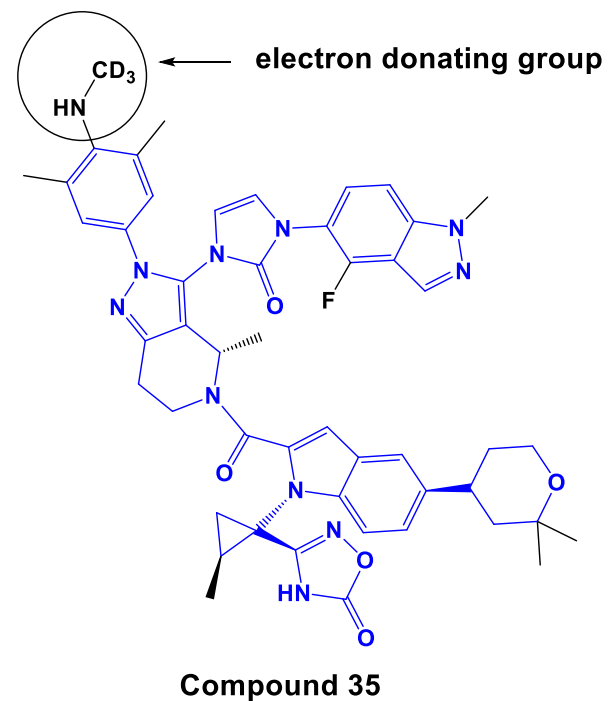


compound 176

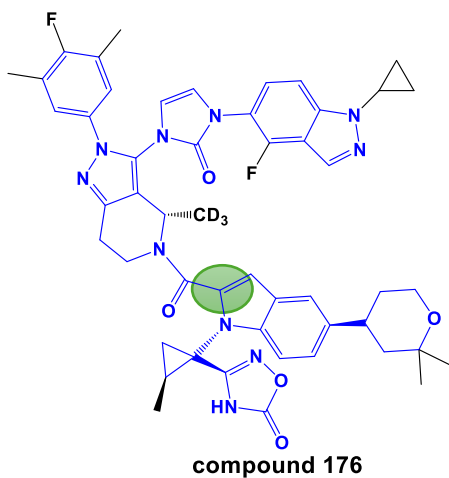
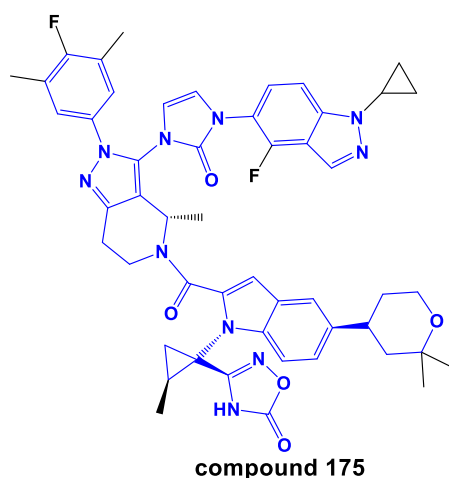
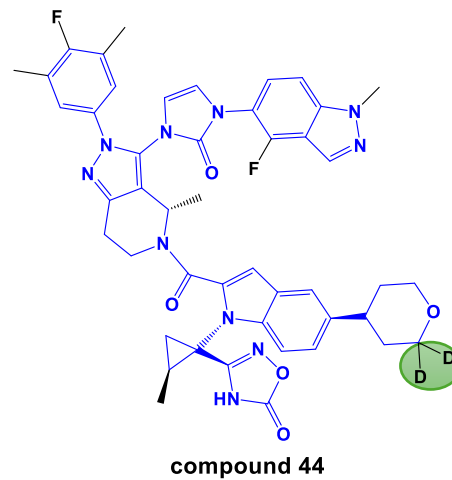
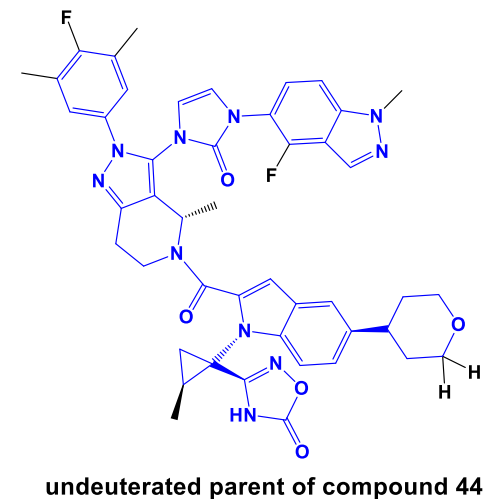


orforglipron

Why Compound 35 Is Not a Preferred Lead: Electron-Donating Group



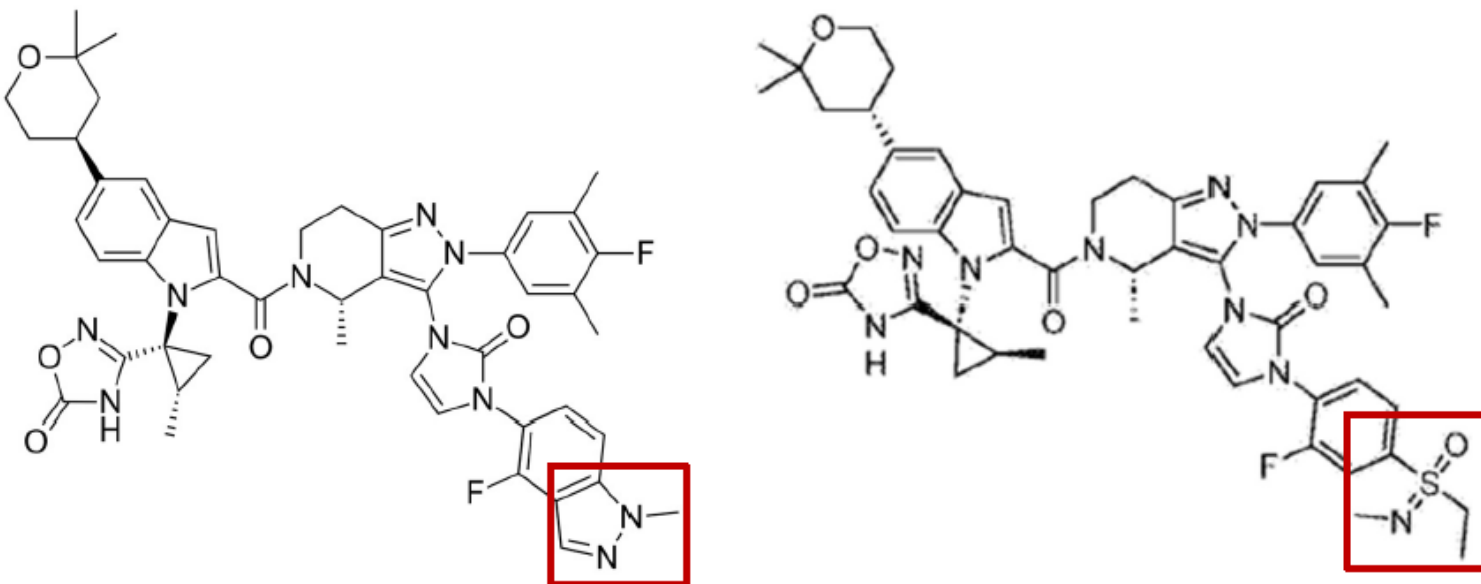
Lead Selection Summary



Selection of compounds 176, 44 and their nondeuterated parent compounds are therefore supported by:

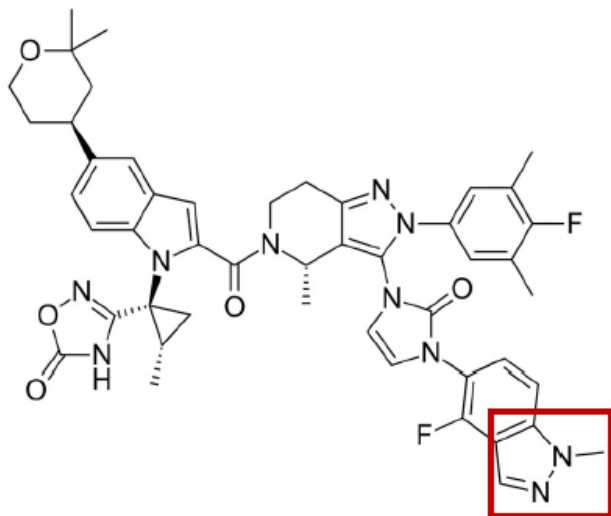
- Common core scaffold with Orforglipron
- IP expansion via deuteration
- Deuteration as indicator for active compounds advanced to pharmacokinetics properties
- Structure-activity relationship established in Yoshino
- Known benefit of cyclopropyl ring

PO's Preferred Compounds: Different Scaffold = Different (Unknown) Risk Profile

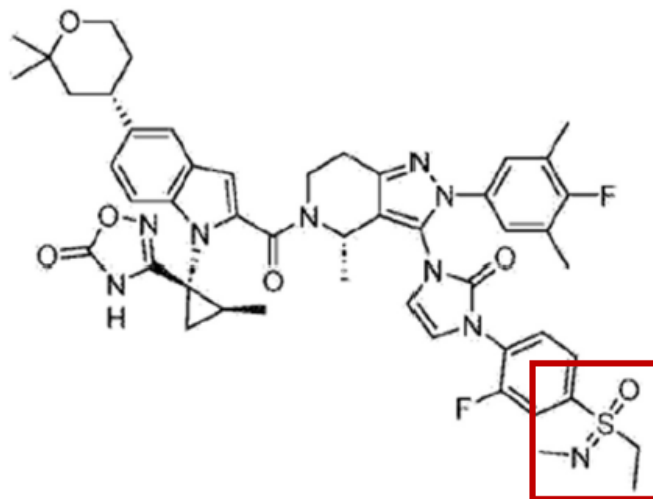


- Critical pharmaceutical properties, including toxicity, safety, and in vivo efficacy, are typically established during preclinical and clinical development, which are significantly more costly and time-consuming than lead discovery. EX2034 at 29; EX2032 at 2, 4.
- No evidence on safety, toxicity, and clinical efficacy for compounds of EX2019, therefore, no evidence of superiority over orforglipron which was at phase 3 trial at the time.

PO's "Superior Compounds" Could Not Match Orforglipron's PK Profile



Compound C-5 (Orforglipron)
 EC_{50} : 0.033nM
 AUC: 4398ng*h/mL (2mpk)
 C_{max} : 573ng/mL



Compound 164
 EC_{50} : 0.024nM
 AUC: 9545 ng*h/mL (5 mpk)
 C_{max} : 1793ng/mL

Table 5A

Compound No.	$t_{1/2}$ (hr)
C-5	8.1
164	2.4
180	3.0
195	4.3
238	4.78

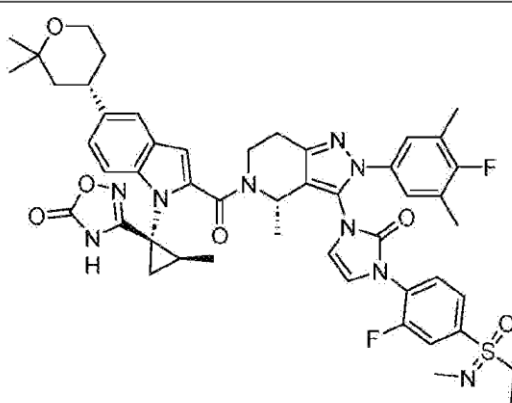
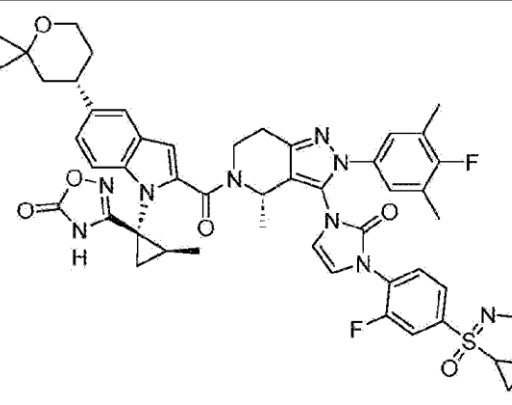
PO's "Superior Compounds" Could Not Match Orforglipron's PK Profile

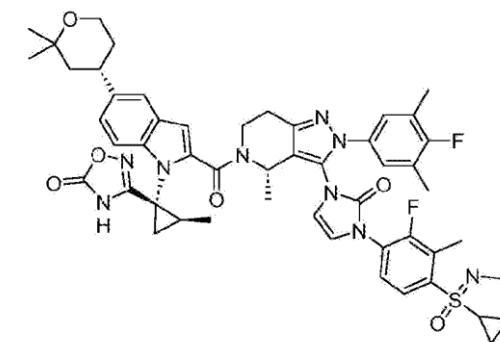
Table 5A

Orforglipron

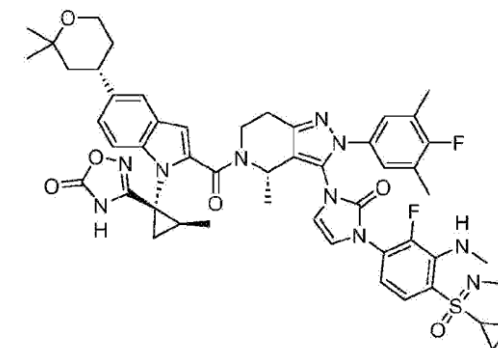
Compound No.	Bioavailability (%F)
C-5	36%
164	29.4%
180	28%
195	14%
238	25.5%

Table 4

164	 <p>Single unknown enantiomer</p>	<p>EC₅₀: 24 pM</p> <p>Caco-2 Perm (nm/s): 6.2</p> <p>Efflux: 5.5</p> <p>Solubility (FaSSIF, μM): 8.9</p>
180	 <p>Single unknown enantiomer</p>	<p>EC₅₀: 30 pM</p> <p>Caco-2 Perm (nm/s): 6.1</p> <p>Efflux: 5.4</p> <p>Solubility (FaSSIF, μM): 30</p>



195

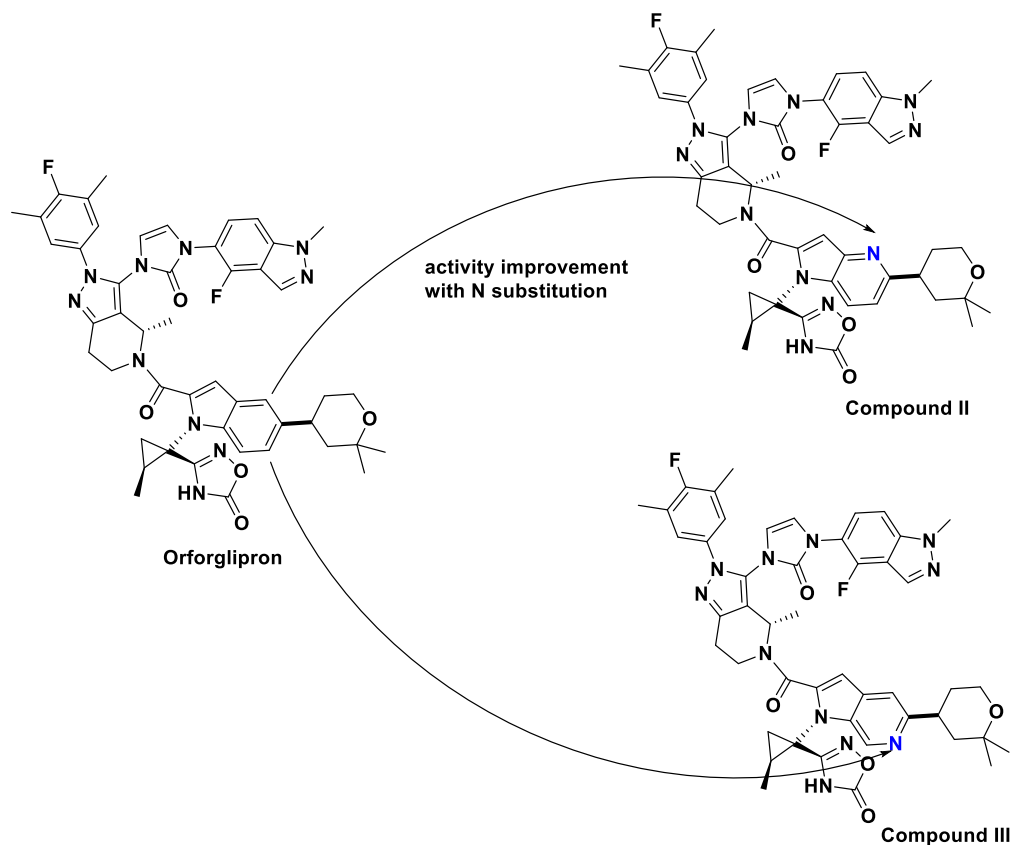


238

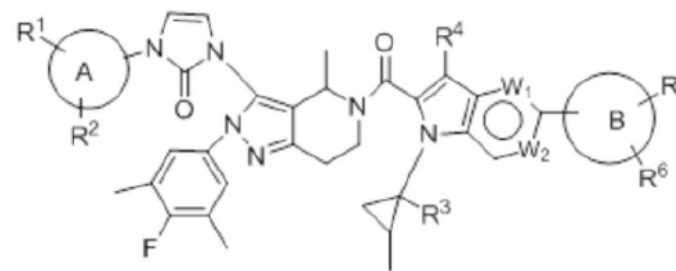
PO Mischaracterizes Dr. Pirrung's Statement on Compound Comparison

PO asserts: "As Petitioner's expert conceded, compounds "functionally characterized" with data are more likely leads for further development. (EX2033, 53:20-54:7, 61:1-63:6.)"

Meng discloses only two specific options to modify orforglipron



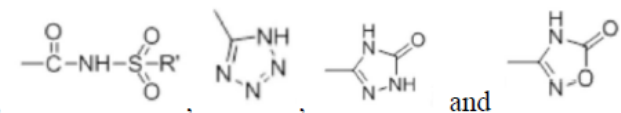
1. A GLP-1 receptor agonist or a pharmaceutically acceptable salt thereof, the agonist having the following structure:



(I)

wherein A is selected from one of an aromatic group, heteroaryl, a heteroaromatic ring-fused aromatic group, an aromatic ring-fused heteroaryl group, a heteroaromatic ring-fused heteroaryl group, an alicyclic ring-fused aromatic ring group, and an alicyclic ring-fused heteroaromatic ring group;

R¹ and R² are each independently selected from -H, -F or -CH₃;



R³ is selected from one of -CN,

R' is selected from isopropyl, methyl or cyclopropyl;

R⁴ is selected from -H, -CH₃ or -F;

W₁ and W₂ are each independently selected from -CH- or -N-, and at least one of W₁ and W₂ is -N-;

B is selected from a 5- to 7-membered saturated alicyclic ring or heteroalicyclic ring on which H atoms on one or more carbons are capable of being substituted by R⁵ and R⁶; the heteroalicyclic ring is an alicyclic ring on which one or two C atoms are substituted by N or O;

R⁵ and R⁶ are each independently selected from -H, -F or -CH₃, or R⁵ and R⁶ together with the carbon atom to which they are attached form cyclopropane.

PO Mischaracterizes Dr. Pirrung's Statement on Orforglipron

Dr. Pirrung's comments on Orforglipron (EX2033, 62: 2-25)

A. Well, Kawai does do further development beyond pharmacokinetics, and Kawai chooses Orforglipron to determine the structure because that is the compound that they are taking into clinical study.

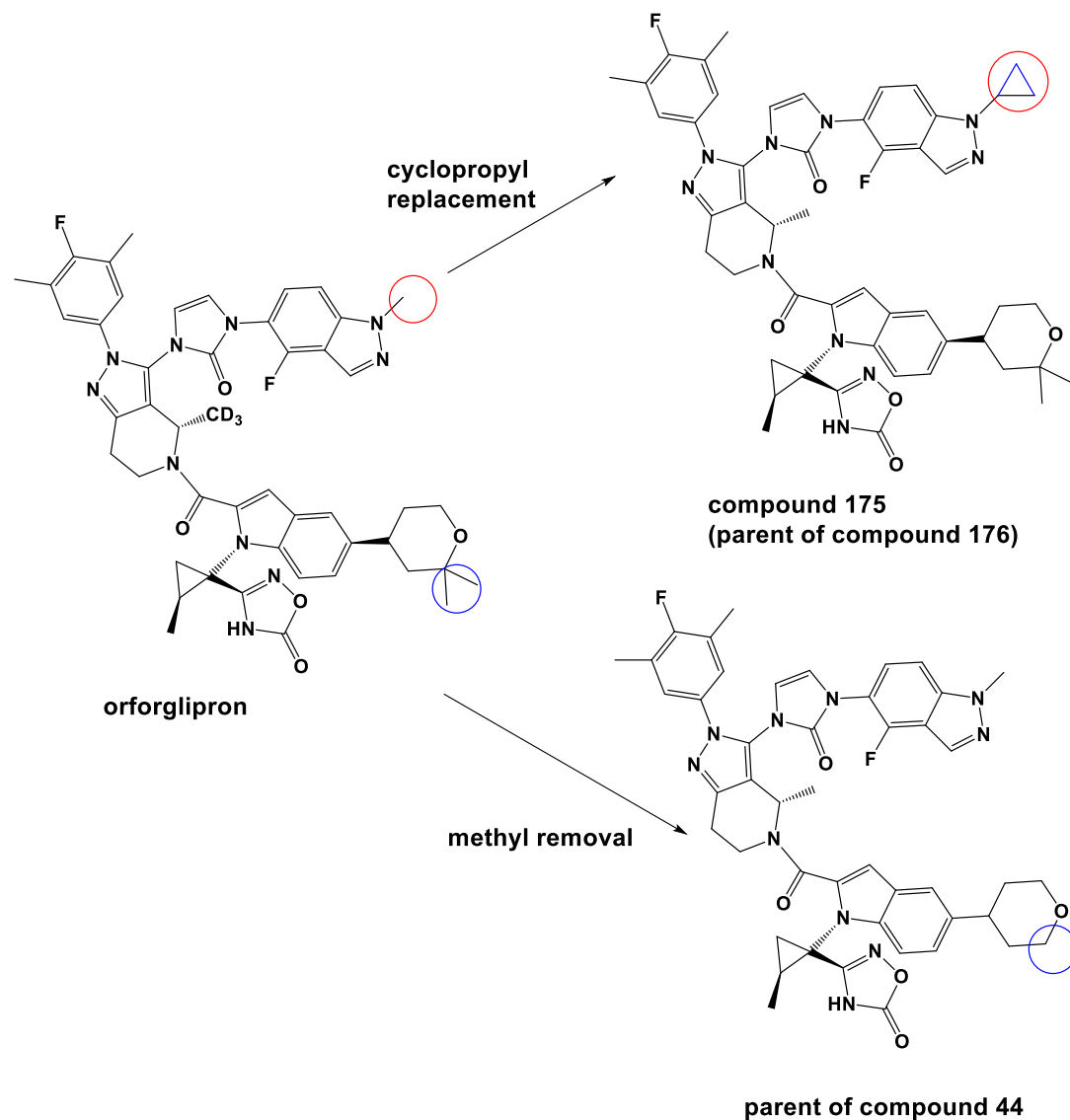
Nowhere did the Petitioner or Dr. Pirrung suggest that compounds “functionally characterized” with data are more likely lead compounds for further development.

Lead modification

Where a skilled artisan pursues “***known options***” from a “***finite number*** of identified, predictable solutions,” obviousness is appropriate.

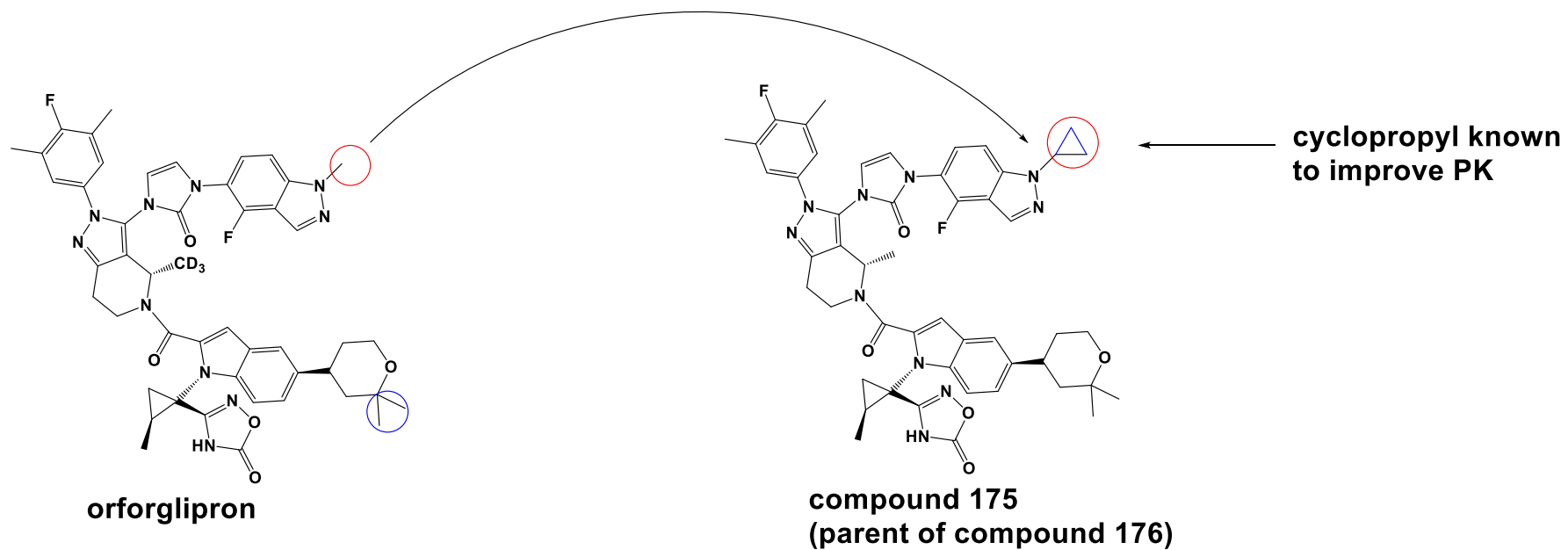
KSR Int’l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)

Priority Compounds of Su Show Only Two Structural Changes to Orforglipron

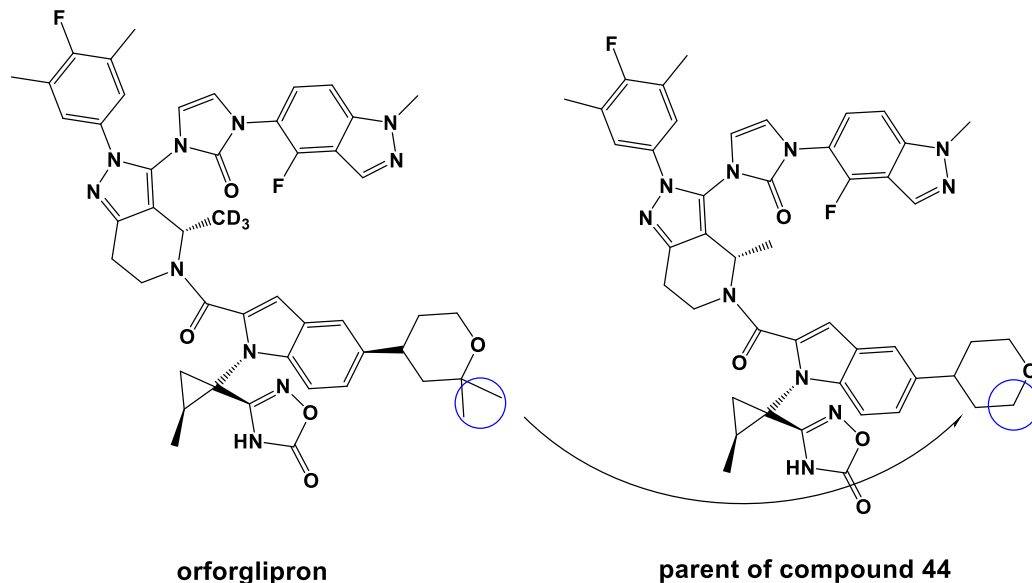


Limited known modification options in comparison with Orforglipron

Cyclopropyl Replacement Provides Predictable Outcome

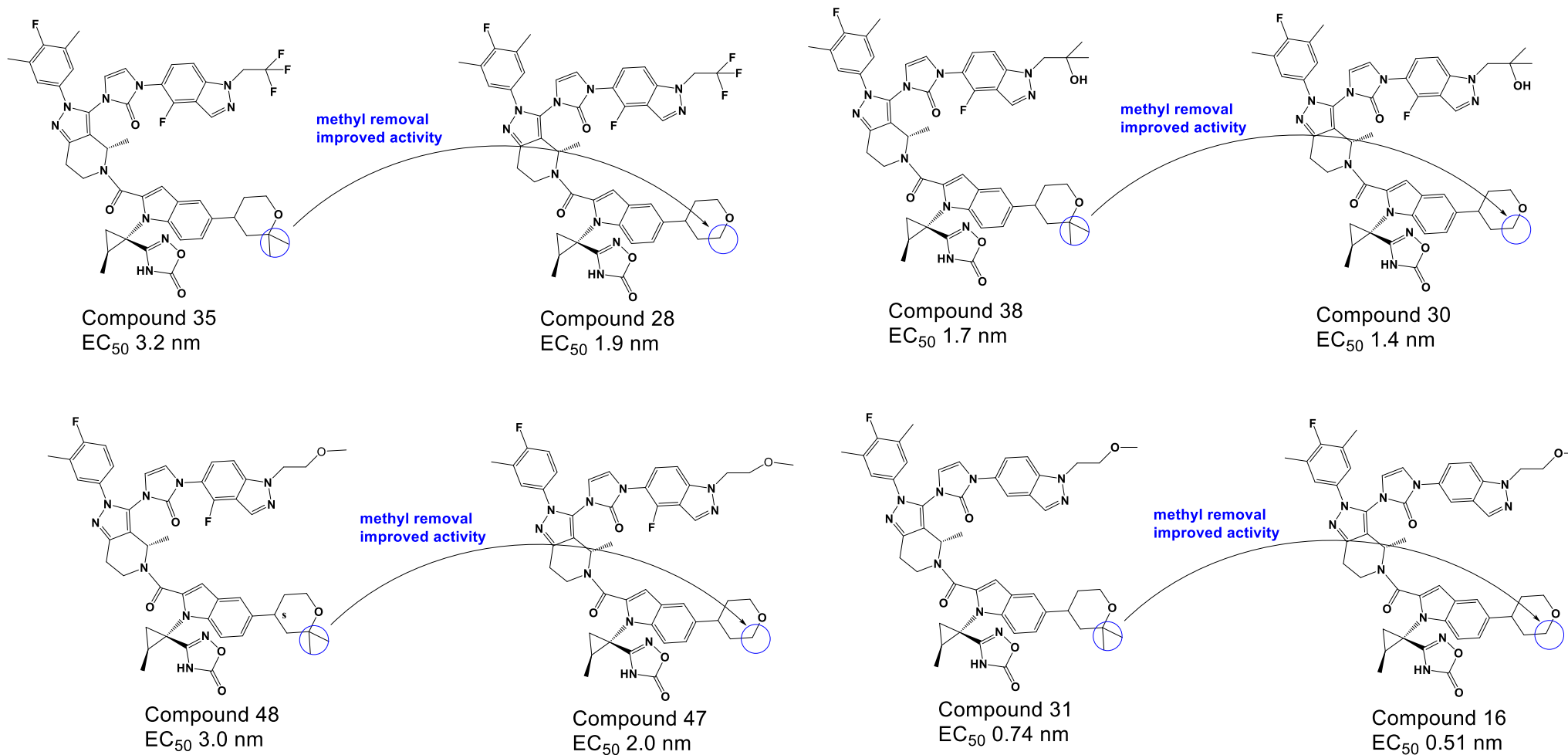


Methyl Removal Provides Predictable Outcome



- 32 out of 80 compounds in Yoshino have demethylated THP
- All 32 compounds exhibit single-digit nanomolar activity
- After demethylation, **6 out of 10 compounds exhibit improved** activity; 1 compound remain comparable. EX1008, ¶162-163.
- Removal of dimethyl groups renders the THP ring symmetrical (no chiral center) and simplifies synthesis. EX1002f the, ¶166.

Methyl Removal Provides Predictable Outcome



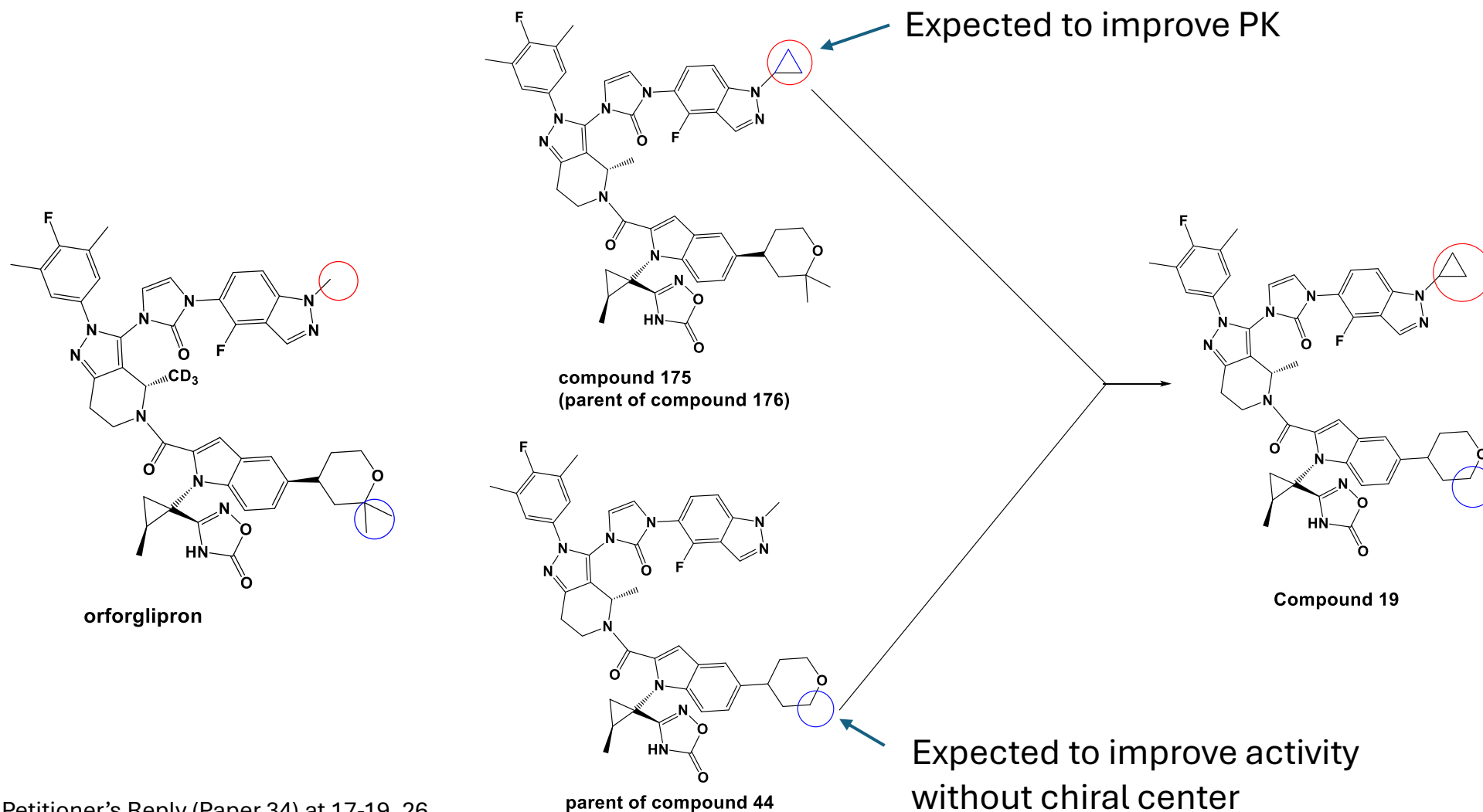
Petition (Paper 1) at 24, 97; EX.1008, Table 3; Petitioner's Reply (Paper 34) at 10-11, 18.

Yoshino SAR Supports Methyl Removal for Improved Activity

Pair for comparison	Group A:Compound with dimethyl in THP	Group A compound activity EC50 (nM)	Group B: Compound without dimethyl in THP	Group B compound activity EC50 (nM)
1	35	3.2	28	1.9 ↑
2	38	1.7	30	1.4 ↑
3	31	0.74	16	0.51 ↑
4	37	2.5	29	1.4 ↑
5	42	1.9	44	1.5 ↑
6	48	3.0	47	2.0 ↑
7	68	1.8	72	2.3
8	67	1.2	23	1.8
9	70	1.5	27	2.3
10	59	1.5	54	3.9
11	43	1.5	45	1.6 —

6 out of 10 compounds exhibit improved activity after demethylation in THP,
1 compound remain comparable (1.5 nM v 1.6 nM)

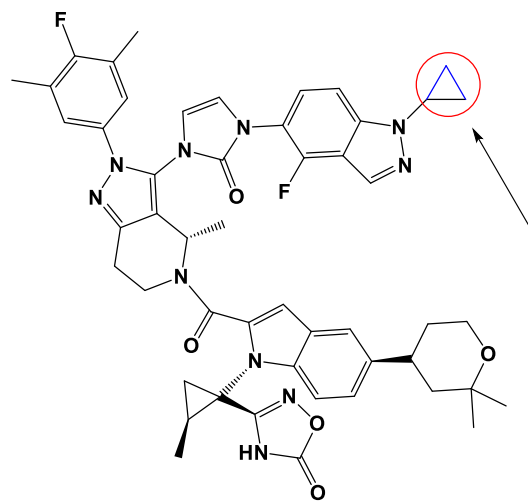
Motivation: Combining Cyclopropyl Replacement and Methyl Removal to Achieve Predictable & Combined Benefits



Secondary Considerations Do Not Overcome the Strong Prima Facie Case of Obviousness

- *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371-72 (Fed. Cir. 2007): Although objective indicia such as unexpected results, commercial success, and long-felt need must be considered, such evidence does not necessarily overcome a strong prima facie case of obviousness.
- *Bristol-Myers Squibb v. Teva*, 752 F.3d 967, 977 (Fed. Cir. 2014): Unexpected improvements in a known property do not overcome a strong prima facie case of obviousness where the alleged benefits reflect only enhanced performance of an expected characteristic.
- *Purdue Pharma v. Accord Healthcare*, 669 F. Supp. 3d 286, 303–04 (D. Del. 2023), aff'd (Fed. Cir. 2024): Quantitative improvements represent merely differences in degree rather than differences in kind carry limited weight in rebutting obviousness.

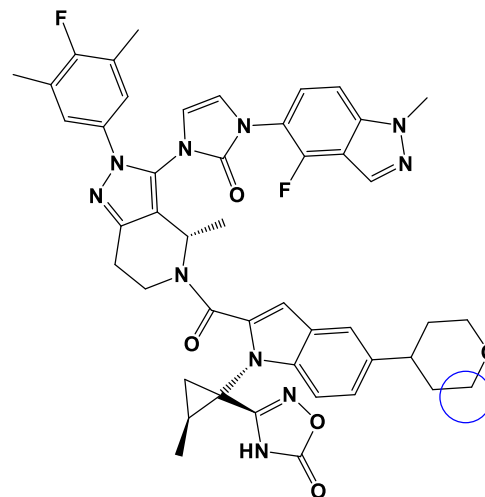
A Strong Prima Facie Case of Obviousness is Supported by the Prior Art



compound 175
(parent of compound 176)

Known benefits to improve PK

strong motivation for combine the two well-known
beneficial features to achieve the predictable advantages of both



parent of compound 44

Consistent single-digit nanomolar
activity in all 32 compounds without
chiral center in THP ring

PO's "Failure of Others" Argument: Different Scaffolds Leads to Different (Unknown) Risks

Different scaffold = different failure mode

- Failed oral GLP-1 drugs (e.g., danuglipron) have “core scaffolds substantially different from orforglipron” → these failures do not predict outcomes for orforglipron-based modifications
- These structurally distinct compounds do not implicate the same risks or provide relevant teaching

Challenged compounds

- direct derivatives of orforglipron with only peripheral modifications → risk profile different from the failed compounds with different scaffolds
- *“There is no evidence the challenged compounds, as derivatives of the clinically successful orforglipron, address any additional hepatotoxicity concerns”*

Ground 2: Orforglipron (Yoshino 67) — The Only Oral GLP-1R Agonist to Reach Phase 3

Orforglipron (Yoshino 67) as Lead Compound

- Only compound specifically recited in Yoshino's claims. EX1008, 166.
- Only Yoshino compound advanced to clinical trials before priority date → provides both activity and safety data
- Claim specificity + clinical advancement = lead compound under Takeda and Otsuka

Proposed Modifications

- Modifications flow from Yoshino SAR, Kawai structural data, Talele and established benefits of cyclopropyl group

Legal Standard: No “Deficiency” Required — Only a Reason to Modify

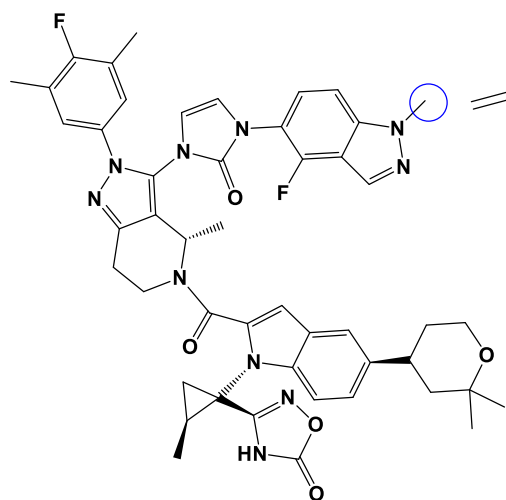
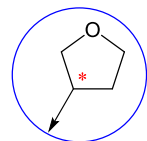
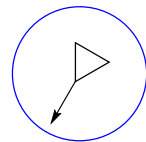
- *Takeda v. Alphapharm* (Fed. Cir. 2007): Lead compound = one a POSA would “reasonably select as a starting point for further development”
- *Otsuka v. Sandoz* (Fed. Cir. 2012): Selection guided by “evidence of the compound's pertinent properties”
- *Daiichi Sankyo v. Matrix Lab’ys* (Fed. Cir. 2010): Shared core scaffold + available SAR is sufficient, motivation need not be explicit.

NO requirement of “identified deficiency”

- Standard is “most promising to modify” — not “has identified deficiency requiring modification”
- Orforglipron's clinical success as the only Phase 3 compound motivates modification, not avoidance

Yoshino SAR and Talele Support Cycloalkyl Replacement with Predictable Outcome

- Ring retains activity
- Reduces entropic penalties
- Improves affinity



Why Cyclopropyl

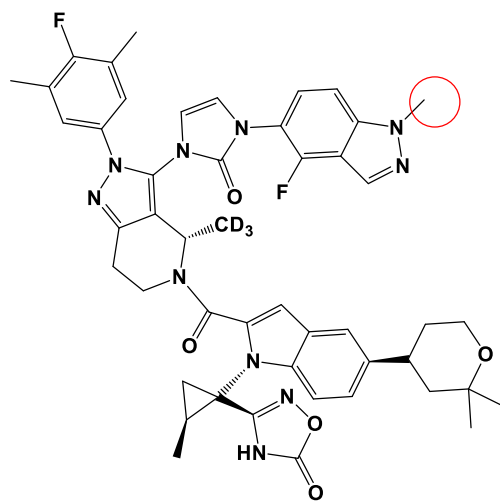
- cycloalkyl preferred over heterocyclic ring due to absence of chirality
- cyclopropyl is most comparable to a methyl group at the indazole nitrogen in size and lipophilicity
- PK benefits of cyclopropyl is well-known

- **Talele:** 4 out of 5 cases, cyclopropyl improved metabolic stability and PK properties.

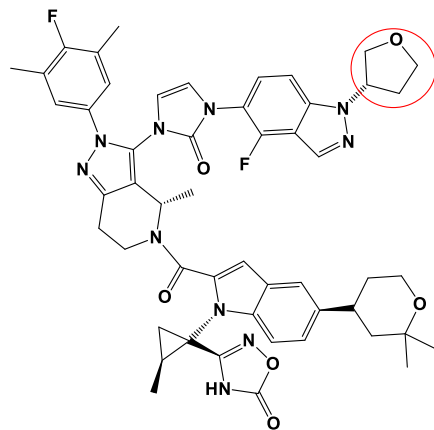
Yoshino Does Not Teach Away From Cyclopropyl

- 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).
- Yoshino does not criticize cyclopropyl — it simply does not exemplify it. Silence ≠ teaching away under *In re Fulton*.
- *Eli Lilly* case cited by PO: 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).

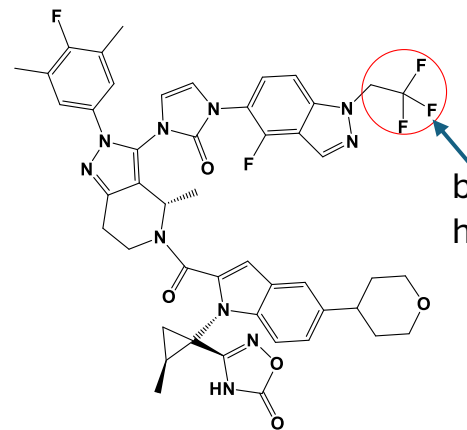
PO's SAR Analysis is Flawed



orforglipron

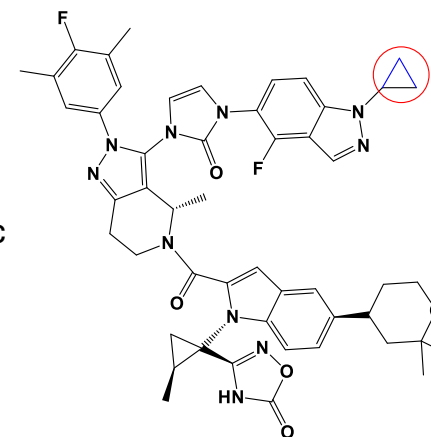


compound 40



compound 28

bulky &
hydrophobic

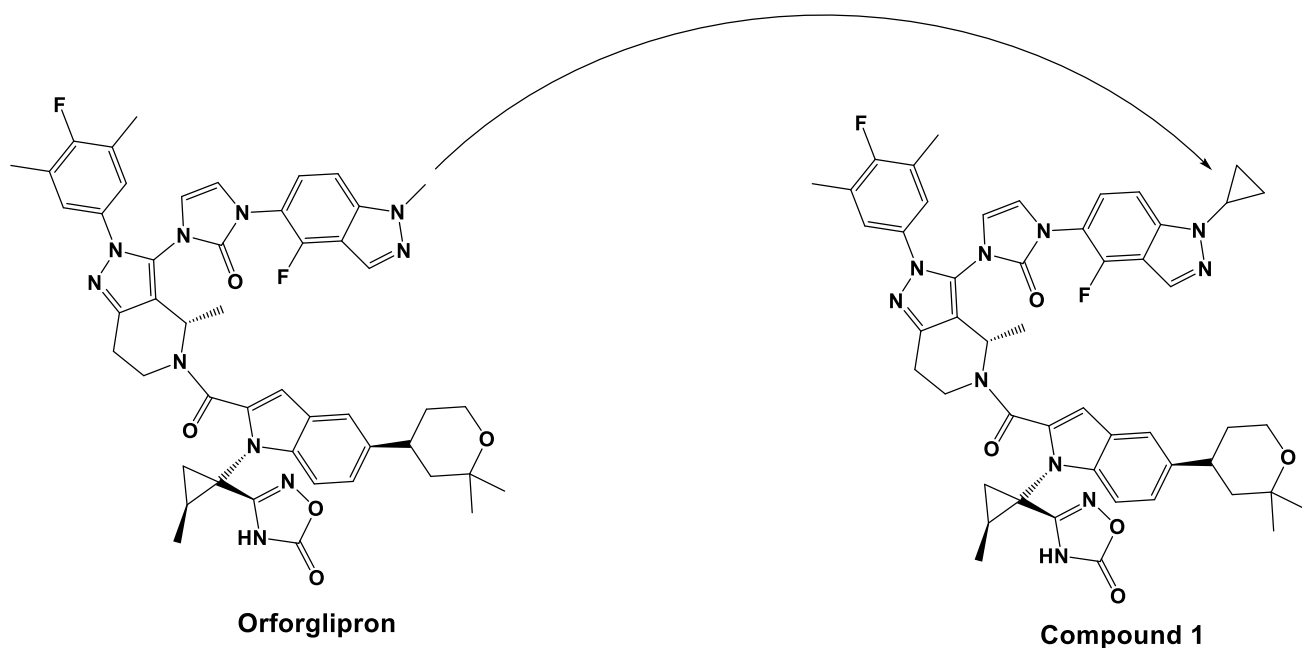


compound 175
(parent of compound 176)

- PO: binding pocket surrounding the indazole methyl is “mainly hydrophilic” with little room for a bulkier substituent. POR, 33–37; EX2079, ¶¶93, 176–181. However, compound 28 has a much bulkier and hydrophobic group on the indazole nitrogen. EX1008; EX1002, ¶77; EX1035, ¶28.
- Dr. Wipf conflates polarity with hydrophilicity. EX2079, ¶¶44, 166, 177, 178.

Motivation for cyclopropyl replacement in view of Yoshino SAR and PK benefits

Modification per Yoshino & Talele

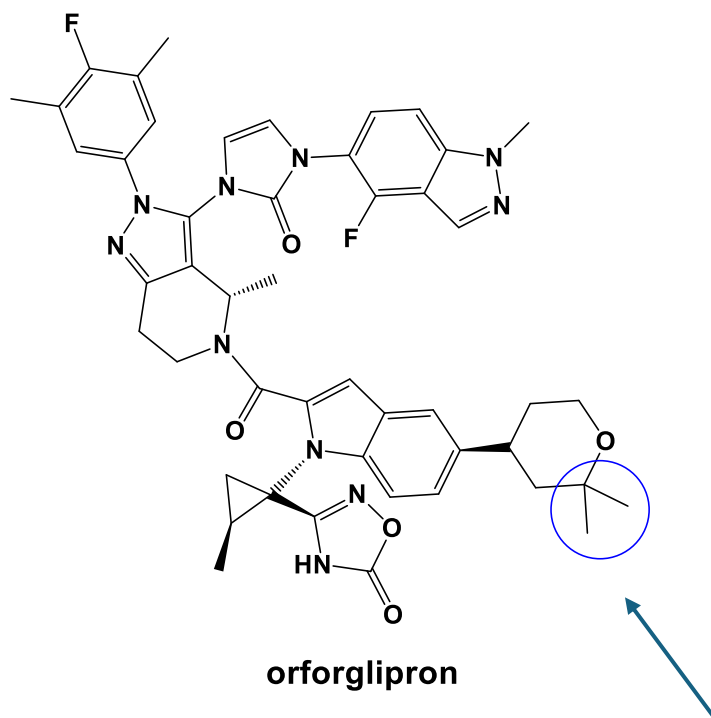


Why Cyclopropyl

- Ring retains activity
- Provides benefits in entropy and affinity
- most comparable to methyl at the indazole nitrogen in size and lipophilicity
- PK benefits well known

Petition (Paper 1) at 83-86; Petitioner's Reply (Paper 34) at 22-24.
EX1002, ¶¶163, 213, 225; EX1008, 162-163; EX2034, 99, 116; EX1009 (Talele), 24.

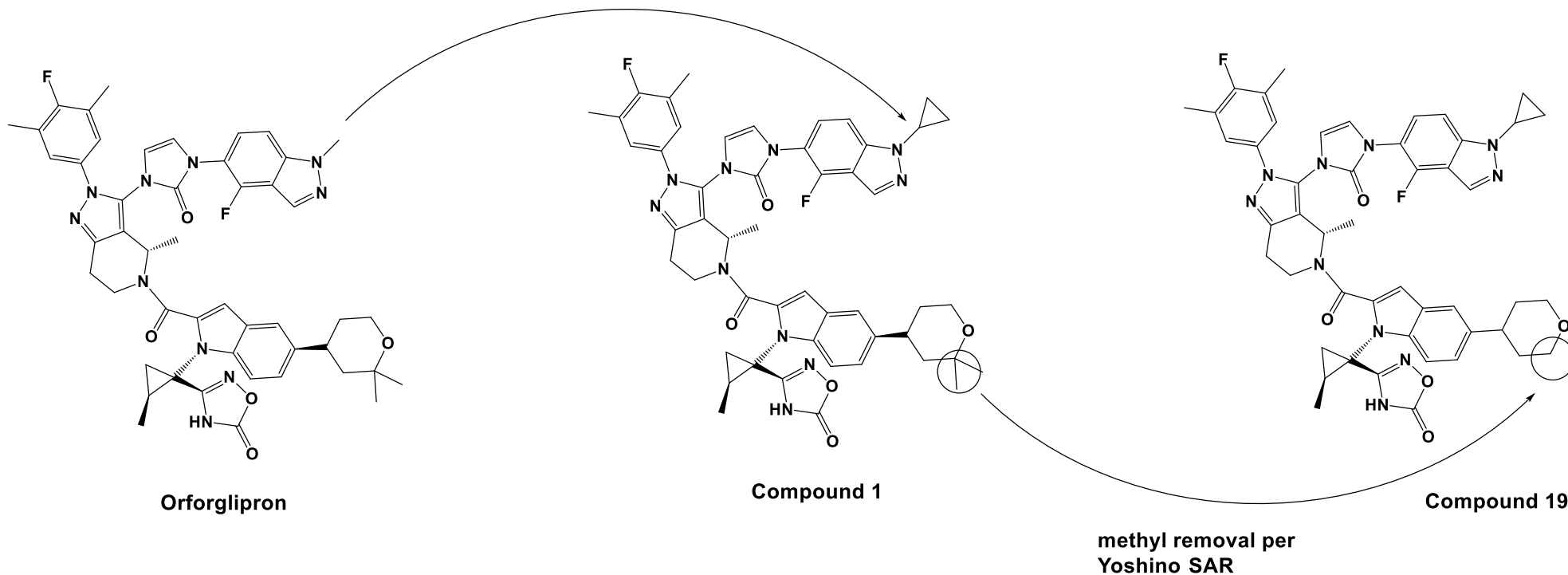
Yoshino SAR Teaches Methyl Removal



**SAR teaches
removal of methyl
from THP**

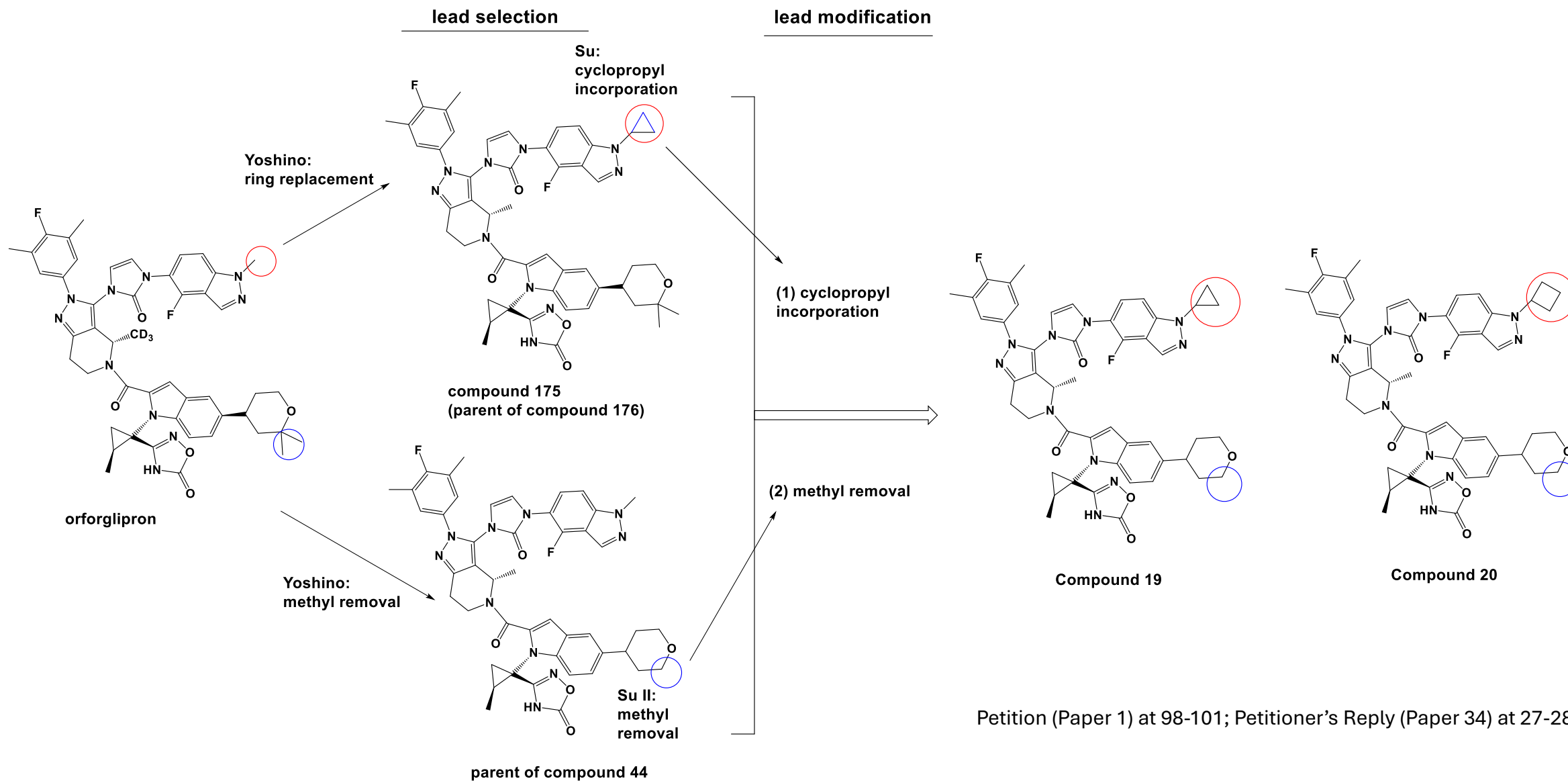
- 32 out of 80 compounds with activity data contains demethylated THP. EX1008 at 28-130.
- All 32 compounds with demethylated-THP exhibit single digit nanomolar level activities. EX1008 at 162-163. Removal of the dimethyl groups renders the THP ring symmetrical (no chiral center) and simplifies synthesis. EX1002, ¶66.
- 6 out of 10 compounds exhibit improved activity after demethylation in THP. EX1008 at 162-163

Motivation for cyclopropyl replacement and methyl removal in view of Yoshino SAR and PK benefits



Compound 19 is expected to have improved PK and activity in view of Yoshino and Talele. EX1009, 24; EX1002, ¶¶ 169–170.

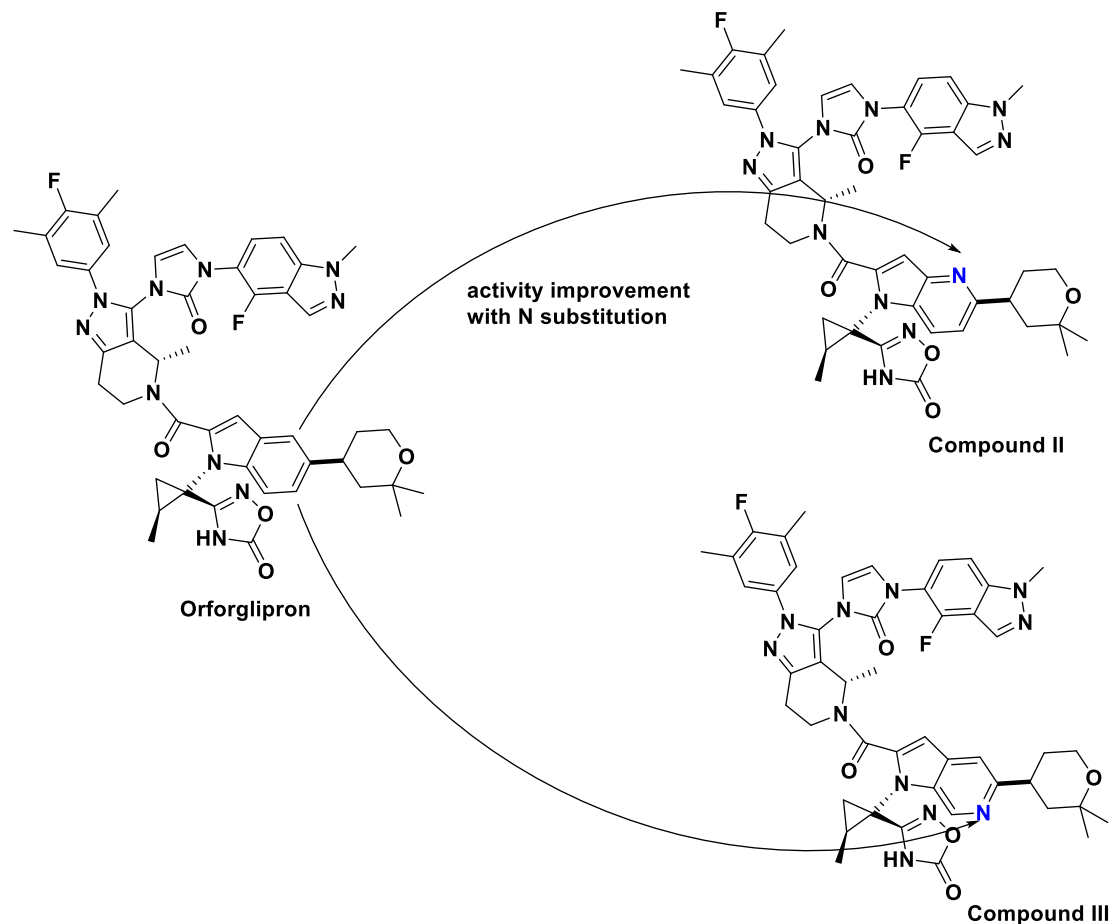
Compound 20: Obvious Over Su and Yoshino (Cyclobutyl Variant)



Petition (Paper 1) at 98-101; Petitioner's Reply (Paper 34) at 27-28.

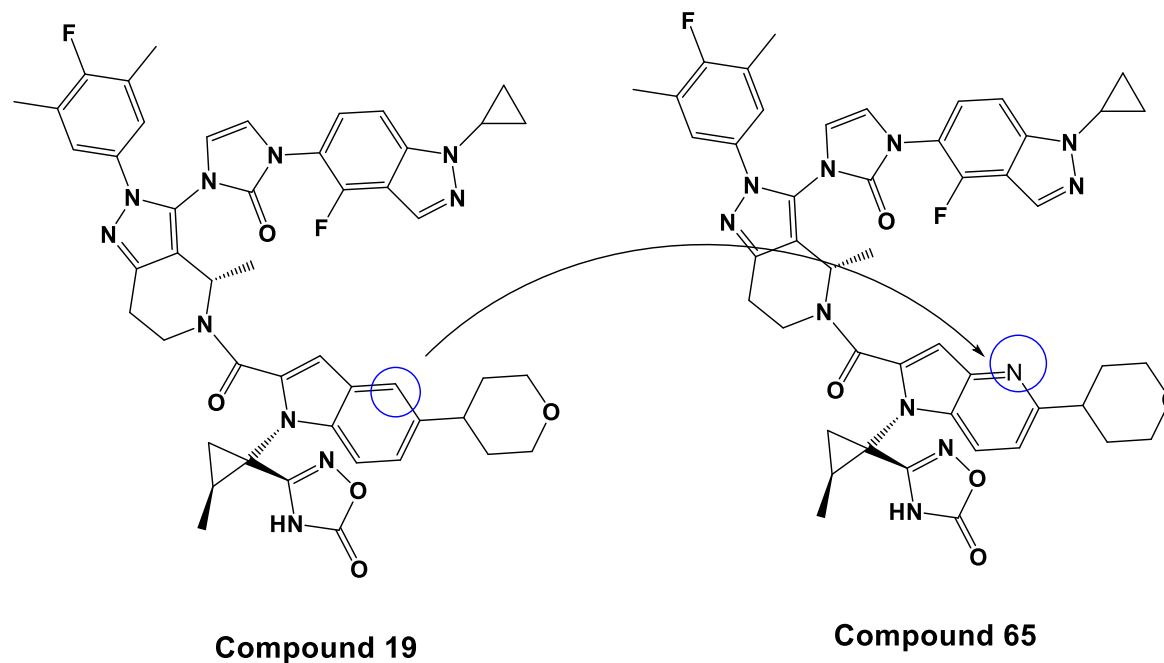
Compound 65: Meng Teaches Nitrogen Introduction to Indole Ring

Meng discloses only two specific options to modify orforglipron



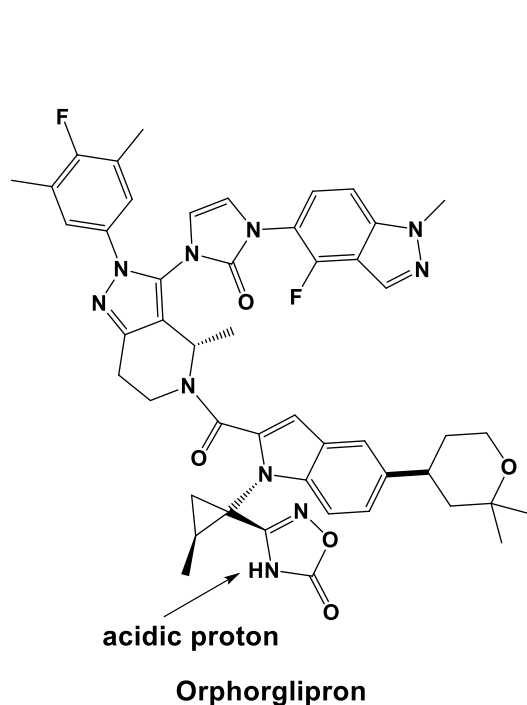
Meng teaches replacing a ring carbon with nitrogen.

Compound 65: Obvious Over Meng (Nitrogen Substitution)

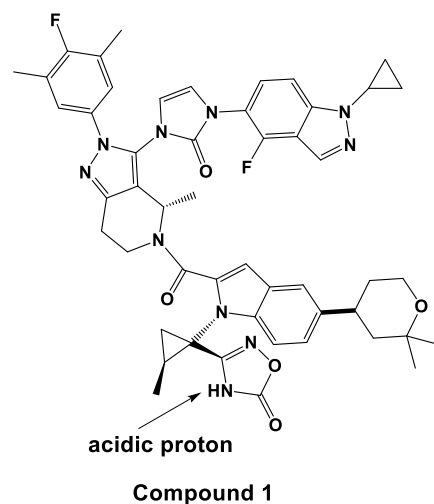
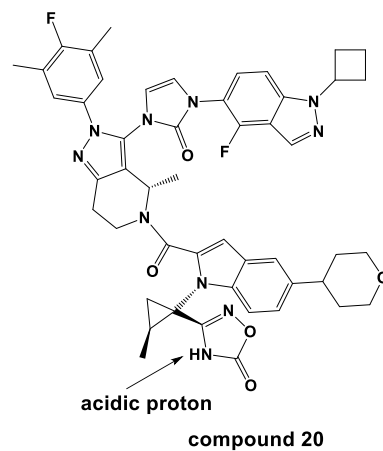
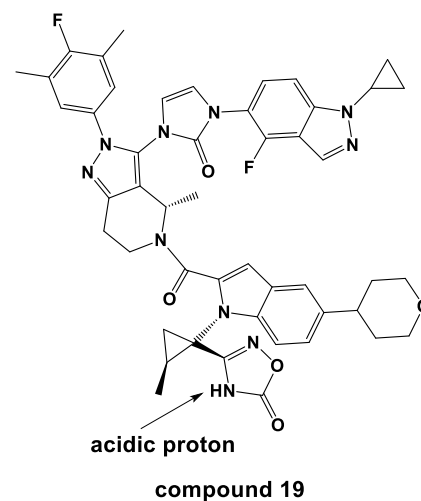
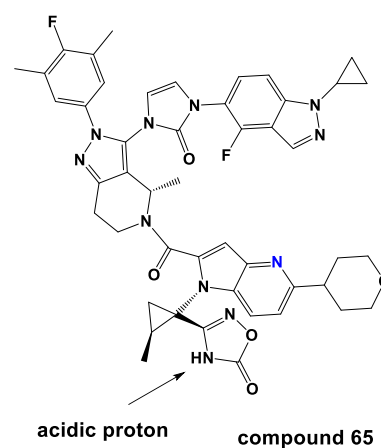


The introduction of a nitrogen atom is also known to improve solubility. EX1026, 1-6.

Hemicalcium Salt is Obvious Over Su + Bethel



Bethel expressly discloses a hemicalcium salt form of orforglipron. EX1032, 19-22, 46-82.

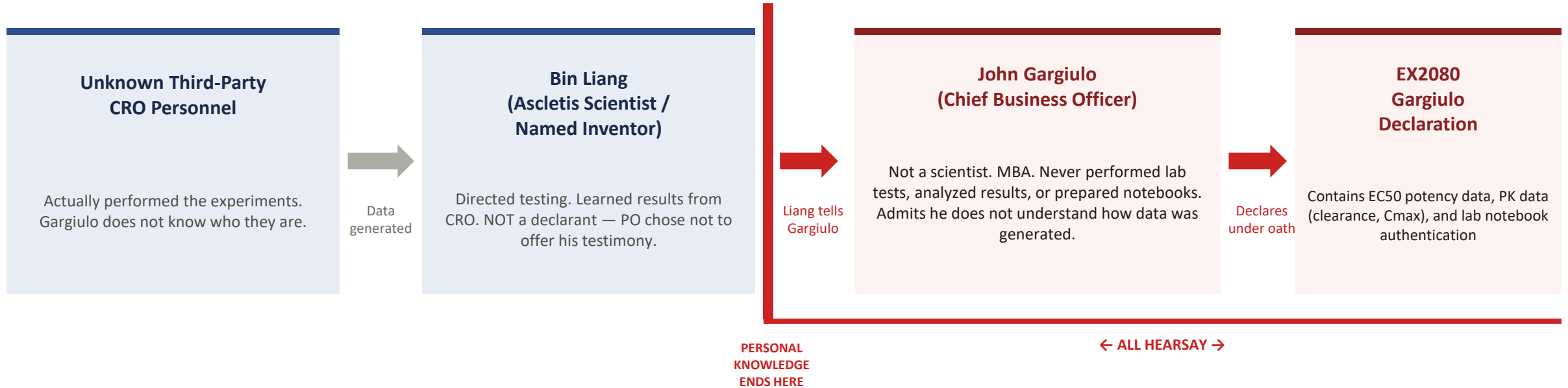


- Compounds 1, 19, 20, and 65 each contain the same acidic proton, which Dr. Wipf confirmed is the most acidic site in each molecule. EX1034, 185:2–186:16.
- Sodium salts are similarly obvious over Yoshino. EX1008, 2:45-56, 8:5-60, 34:7-15, FIGS. 1, 2, and 5-8.

Conclusion: All Challenged Compounds Are Obvious

- Ground 1: Compound 19 (claims 1-4, 6, 12-14, 24, 25) is obvious over Su, Yoshino, Kawai and Talele
- Ground 2: Compounds 1, 19, 20 (claims 1-9, 12-17, 24, 25) are obvious over Yoshino, Kawai and Talele.
- Ground 3: Compound 65 (claims 1-4, 21-25) is obvious over Meng in view of Ground 1 or Ground 2.
- Ground 4: Compound Hemicalcium salt form (claims 4, 9) is obvious over Bethel in view of Ground 1, Ground 2 or Ground 3.

The Gargiulo Declaration Is Built on a Chain of Hearsay, Not Personal Knowledge



- Gargiulo did not conduct, supervise, or direct any testing
- Gargiulo did not review any source documentation
- Gargiulo did not independently verify data accuracy — believes it only because “Mr. Liang told him so”
- **PO chose NOT to present testimony from Bin Liang — a named inventor who oversaw the testing – or anyone else with personal knowledge**

No Business Record Documents Were Reviewed — And the Lab Notebook Does Not Qualify

A. The Declaration (EX2080)

- NO documents reviewed beyond those cited in the declaration itself
- Unaware of any documents containing PK data he presents
- Has “not verified” any data; has not reviewed “source documentation”
- **A properly founded declaration would come from the scientist who directed experiments (Bin Liang) or the CRO personnel — not a CBO repeating what he was told**

What PO Should Have Done:

Present testimony from Bin Liang (a named inventor who oversaw testing) with proper foundation for experimental data and protocols.

B. The Lab Notebook (EX2081)

- **Created March 4, 2026 — ONE DAY before Response deadline**
- “-3” version (GLNB007230-3) — no other versions or audit trail provided
- Gargiulo did not know who decided to conduct testing
- Has no understanding of software, did not access database nor know who did
- NOT a business record under FRE 803(6) — created in anticipation of litigation.
- Tested at pH 11 — not physiologically relevant

What PO Actually Did:

Presented a secondhand account from a CBO who cannot perform, analyze, or verify any of the data he presents.

The Gargiulo Declaration Fails Every Applicable Evidentiary Standard

Evidentiary Standard	Result	Why It Fails
Personal Knowledge (FRE 602)	FAIL	Gargiulo did not conduct, supervise, or direct any testing. Does not know who performed experiments.
Lay Opinion (FRE 701)	FAIL	Gargiulo presents and contextualizes experimental results beyond mere attestation — exceeds scope of lay testimony.
Expert Testimony (FRE 702)	FAIL	Gargiulo is not a scientist, chemist, or pharmacologist — has an MBA, is the CBO.
Hearsay (FRE 801–805)	FAIL	Multi-layered: CRO → Liang → Gargiulo → Dec. FRE 803(6) fails (litigation). FRE 807 fails (no trustworthiness).
Authentication (FRE 901)	FAIL	Cannot authenticate lab notebook — lacks knowledge of who performed testing, where stored, whether other versions exist.
Business Records (FRE 803(6))	FAIL	Declaration created for litigation. Notebook created one day before deadline. Gargiulo is not a custodian or qualified witness.
Prejudice (FRE 403) / 37 C.F.R. § 42.65	FAIL	Non-physiological testing (pH 11). No cross-exam of data creators. Unexplained version history. Inadequate protocol details.

These exhibits are inadmissible under every applicable standard. To the extent Dr. Wipf's opinions rely on this inadmissible data, the Board should exclude or give those portions no weight. FRE 703 does not make inadmissible evidence admissible — it merely permits an expert to rely on such data, subject to the balancing test.