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

DECLARATION OF DR. PETER WIPF IN SUPPORT OF PATENT OWNER'S RESPONSE

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TABLE OF EXHIBITS

Exhibit No.	Description of Document
2001	Declaration of Geoffrey D. Biegler ("Biegler")
2002	Excerpts of File History of U.S. Patent No. 12,234,236
2003	Excerpts of File History of U.S. Patent Application No. 18/885,065
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I, Peter Wipf, Ph.D., declare as follows:

1. I have been retained by Ascletis Pharma China Co. Ltd. ("Ascletis" or "Patent Owner") to provide opinions regarding U.S. Patent No. 12,234,236 (the "'236 patent"). Specifically, I have been asked to respond to the Petition for Post Grant Review ("PGR") No. 2025-00057 filed by Conjupro Biotherapeutics, Inc. ("Conjupro" or "Petitioner"), which challenges the patentability of claims 1-9, 12-17, and 21-25 of the '236 patent (the "Challenged Claims") and the accompanying Expert Declaration of Michael C. Pirrung, Ph.D.

2. I have personal knowledge of the facts and opinions set forth in this declaration and believe them to be true. If called upon to do so, I would testify competently thereto.

I. INTRODUCTION AND QUALIFICATIONS

A. Qualifications and Experience

3. My curriculum vitae is attached hereto as Appendix A. Below, I highlight my educational background, career history, publications, and other relevant qualifications.

4. I am currently a Distinguished Professor in the Department of Chemistry at the University of Pittsburgh in Pittsburgh, Pennsylvania, a position I have held since 2004. I am also a Professor in the Department of Pharmaceutical Sciences, a position I have held since 2001, and a Professor in the Department of

Bioengineering, a position I have held since 2014. I also serve as the Director of the Combinatorial Chemistry Center and the Director of the Center for Chemical Methodologies and Library Development, positions I have held since 1997 and 2002, respectively.

5. I received a Diploma in Chemistry from the University of Zurich in 1984 and a Ph.D. in Chemistry from the University of Zurich in 1987. My Ph.D. thesis title was "Synthesis and Conformational Analysis of Peptides with α,α-Disubstituted α-Amino Acids." After receiving my Ph.D., I was a Swiss National Science Foundation Postdoctoral Fellow in the Department of Chemistry at the University of Virginia from 1988 to 1990. My research topics included the total synthesis of FK-506 and stereoselectivity in the silyl ester enolate Claisen rearrangement.

6. After completing my Postdoctoral Fellowship, I joined the faculty at the University of Pittsburgh in 1990 as an Assistant Professor in the Department of Chemistry. I was promoted to Associate Professor in 1995, Professor in 1997, and Distinguished Professor in 2004. In 2001 and 2014, respectively, I was additionally appointed as a Professor in the Department of Pharmaceutical Sciences and a Professor in the Department of Bioengineering.

7. My teaching responsibilities throughout my years as a professor have included graduate and undergraduate level courses in medicinal chemistry, synthetic

organic chemistry, molecular pharmacology, and small molecule drug discovery and development. I have consistently taught graduate courses on synthetic organic chemistry at the University of Pittsburgh since 1991 and courses on medicinal chemistry and drug development since at least 2001.

8. I supervise undergraduate and graduate student researchers, postdoctoral associates and research staff in my research laboratory at the University of Pittsburgh Department of Chemistry, within the Dietrich School of Arts and Sciences. My research focuses on synthetic organic and medicinal chemistry, computational analysis of small molecule properties, discovery of innovative methods in heterocyclic and strain-release chemistry, and the total synthesis of natural products. My research includes the discovery of new drugs by making modifications to existing compounds using structure-activity relationship ("SAR") analysis. I have published over 640 papers in peer-reviewed journals, including papers related to the discovery and development of potential small molecule GLP-1 agonists, medicinal chemistry structure-activity relationships, synthetic organic concepts and strategies, and chemical biology.

9. Aside from my academic experience, I have collaborated and consulted with more than 30 companies on medicinal chemistry and process research and development problems over the last 30 years. As one example, I collaborated with

Eli Lilly and Co. as part of the Open Innovation Drug Discovery ("OIDD") Program in evaluating small molecule GLP-1R agonist candidates. (EX20XX.)

10. I also have over 125 issued patents, including filings in the United States and internationally, that mostly relate to the synthesis and characterization of organic compounds, small molecule drug design, and new compositions of matter.

11. I have received numerous awards and honors for my research, including the National Academy of Inventors Fellow (2024), the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (2023), the Humboldt Research Award of the Alexander von Humboldt Foundation (2014), and the Ernest Guenther Award in the Chemistry of Natural Products (2009), among others. I was elected Chair of the Division of Pharmaceutical Sciences of the American Association for the Advancement of Science (2016) and ranked in the Top 0.04% of all Scientists globally in the Stanford/Elsevier List (2020-2025).

12. In addition, I have served on numerous professional boards and scientific review panels, including as an Associate Editor of *ACS Medicinal Chemistry Letters* from 2009 to 2020 and a Member of the Editorial Advisory Board of *ACS Medicinal Chemistry Letters* since 2021, as Associate Editor for North America of *Organic & Biomolecular Chemistry* (2002-2006) and a Member of the International Advisory Editorial Board for *Organic and Biomolecular Chemistry*

since 2007, on the Board of Directors for *Organic Syntheses*, Inc., since 2013, and as the Series Editor of the *Chemistry of Heterocyclic Chemistry* from 1997 to 2015.

B. Compensation

13. I am being compensated at my standard consulting rate of $1000 per hour for my work in this matter. My compensation is in no way based on the outcome of this matter and has not influenced my views in this matter.

C. Materials Considered

14. In writing this Declaration, I have considered all of the papers and exhibits filed in this proceeding as of December 22, 2025. I have also considered the exhibits listed above in the Table of Exhibits

I. LEGAL STANDARDS

15. In expressing opinions on legal issues, I have applied the following legal standards conveyed to me by counsel for Ascletis.

16. I understand that for a post grant review, invalidity must be shown under a preponderance of the evidence standard. I understand that to establish something by a preponderance of the evidence it must be proven that it is more likely true than not.

A. Claim Construction

17. I understand that claim language should be interpreted to have the plain and ordinary meaning it would have had to a person of ordinary skill in the art

("skilled artisan") at the time of the invention. I understand that the construction should be based on the claim language itself, the specification of the patent, and the prosecution history pertaining to the patent.

18. In his declaration, Dr. Pirrung did not propose constructions for any of the Challenged Claims. For purposes of this declaration, I applied the plain and ordinary meaning of each term as it would have been understood by a skilled artisan at the time of the invention. I reserve the right to supplement my opinions if Petitioner and/or Dr. Pirrung are allowed to advance any other construction of the Challenged Claims.

B. Obviousness

19. I understand that a patent claim is invalid as obvious if the differences between the claimed subject matter and what is taught by the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art at the time that the invention was made. I understand that four factual inquiries guide this determination: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) relevant objective considerations, such as unexpected results, commercial success, long-felt but unsolved needs, failure of others, copying by others, licensing, acclaim and awards, teaching away or skepticism in the art, and contemporaneous invention by others.

20. I understand that, for a claim to have been obvious, the challenger must prove that there was (1) a reason or motivation for a skilled artisan to modify or combine the teachings of the prior art references to achieve the claimed invention, and (2) a reasonable expectation of success achieving the claimed invention in view of the prior art.

21. I understand that one way a challenger can prove obviousness of a new chemical compound is under the lead compound theory. Under this theory, first, the challenger must show that a skilled artisan would have selected a particular prior art compound as a lead compound. The skilled artisan's choice of lead compounds should be guided by the compound's properties and not solely based on structural similarity. Then, the challenger must show that the prior art would have motivated the skilled artisan to modify a lead compound to make the claimed compound and expect to succeed.

22. I understand that a claim may be found obvious based on a single prior art reference or a combination of two or more prior art references. However, if they rely on multiple embodiments in a single reference, the challenger must set forth sufficiently articulated reasoning, with rational underpinnings, explaining why a skilled artisan would have been motivated to combine those embodiments to arrive at the claimed subject matter.

23. I further understand that a hindsight approach to the obviousness analysis, i.e., using the challenged patent as a guide through the prior art references, combining the references in a particular way to achieve the claims at issue, is not permitted. Instead, one must put oneself in the place of a skilled artisan at the time of the invention and consider only what was known at the time of the invention without the guidance of the challenged patent in hand. For that reason, a patent challenger must identify a record-supported reason to combine the references to avoid the impermissible use of hindsight.

24. I understand that obviousness should be considered in light of the problems known to a skilled artisan in the field and the complexity of the alternatives for solving the problems. Simply because individual elements of the claimed invention are disclosed in the prior art is not sufficient, by itself, to reach a conclusion of obviousness.

25. Further, I understand that while certain combinations of the prior art might be "obvious to try," any obvious to try analysis will not render a patent invalid unless it is shown that the possible combinations are (1) sufficiently small in number so as to be reasonable to conclude that the combination would have been selected; and (2) such that the combination would have been believed to be one that would produce predictable and well understood results.

26. I understand that a prior art reference must be evaluated in its entirety, including portions that suggest an invention would not be obvious and must be considered for everything that it teaches. I understand that it is impermissible to pick and choose from any one reference to the exclusion of other portions of the reference for support of a given position, or to ignore portions of the reference that contradict obviousness. I also understand that the prior art references must be evaluated for what they teach in the proposed combinations together, as well as separately.

27. I also understand that a reference may teach away from a claimed invention when a skilled artisan, upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent from the path taken by the patent applicant.

28. I further understand that the obviousness inquiry requires that the prior art provide a skilled artisan with a reasonable expectation of success in carrying out the claimed invention. In the context of developing a new compound, a reasonable expectation of success in making a modification can be precluded because of the complicated and unpredictable nature of drug discovery, which is generally conducted through trial and error, even if the challenger can show that the prior art teaches the modification. Further, I understand that proof of obviousness based on the structural similarity between the claimed compounds and the prior art requires that the skilled artisan would have a reasonable expectation of success that the new,

claimed compound would have desired properties compared to the old, prior art compound. A skilled artisan's expectation of success must also match the highly desired improvement, and cannot switch to a different, less challenging goal.

29. Finally, I understand that courts must consider objective evidence before determining obviousness. I understand that objective evidence can be the most probative evidence of the patent's nonobviousness and can help avoid the improper use of hindsight.

30. One form of objective evidence is unexpected results. I understand that unexpected results include superior properties or advantages of the claimed invention that a skilled artisan does not expect from the closest prior art. I further understand that unexpected results can include entirely new properties or improvement of understood properties so long as the advantage is unexpected.

31. I understand another form of objective evidence is the failure of others. I understand that actual reports that others tried and failed to develop the claimed inventions can negate an expectation of success.

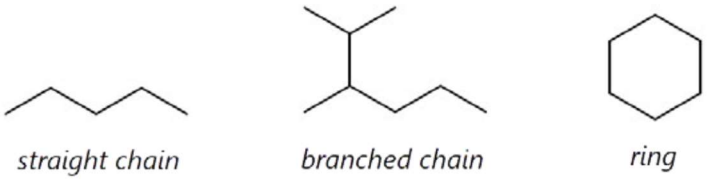
II. TECHNOLOGY BACKGROUND

32. In the following section, I provide a brief summary of the relevant principles of chemistry, medicinal chemistry, and GLP-1R agonists.

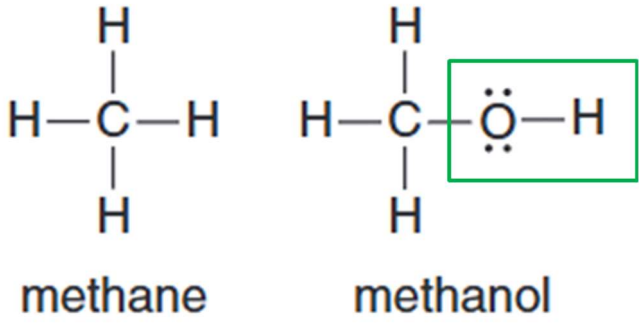
A. Relevant Principles of Chemistry

33. The compounds at issue in this proceeding are drug compounds that bind to the glucagon-like peptide-1 receptor ("GLP-1R"). Specifically, the compounds at issue are small molecule organic drug compounds.

34. Organic compounds are chemical molecules that contain carbon atoms, typically forming carbon-carbon and carbon-hydrogen bonds. Such compounds are the primary constituents of living organisms. In organic compounds, the carbon atoms can form chains, rings, and other complex structures. These structures can be represented like the images below, where each corner point is a carbon atom and the hydrogen atoms and carbon-hydrogen bonds are not shown.



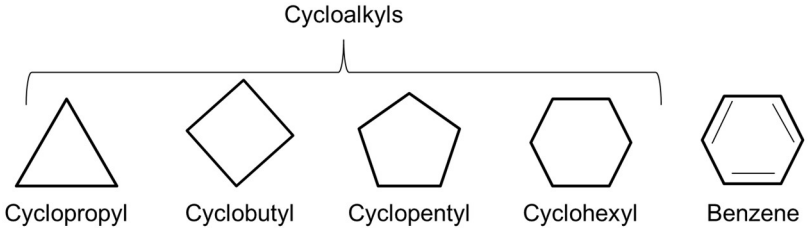
35. In organic compounds, a hydrogen bonded to a carbon can be substituted for another atom, or group of atoms. The atom or group of atoms replacing the hydrogen is called a "substituent." An example of a substituent is highlighted in the green box below, where the hydrogen atom on a methane molecule is substituted for a hydroxyl group:



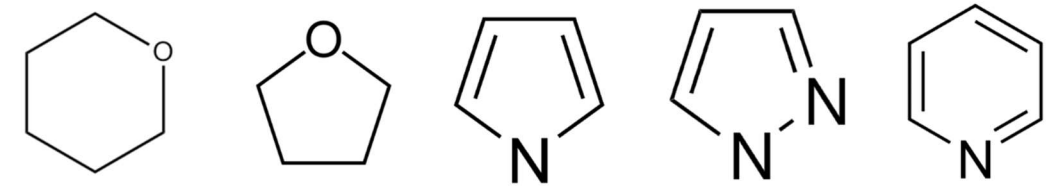
36. Organic compounds can also have "functional groups," which are specific groupings of atoms that are responsible for chemical reactions of the compound. These functional groups can be part of the backbone of an organic compound, or act as a substituent by replacing a hydrogen like the hydroxyl group above.

37. Below, I discuss some of the functional groups and substituents relevant to this proceeding.

38. Ring moieties are one broad category of functional groups and substituents. The ring structures can be composed completely of carbon and hydrogen atoms, such as cycloalkyls and benzene rings.

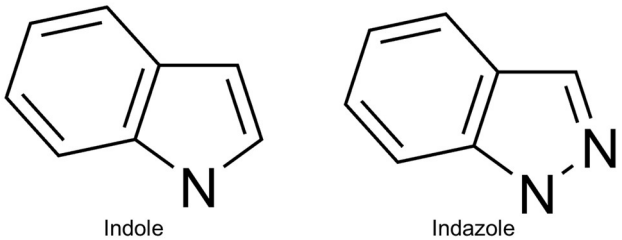


39. Carbon atoms can also form ring structures with atoms other than carbon, such as nitrogen and oxygen, which are called heterocycles. Below are some heterocycles relevant to orforglipron and the compounds claimed in the ’236 Patent.



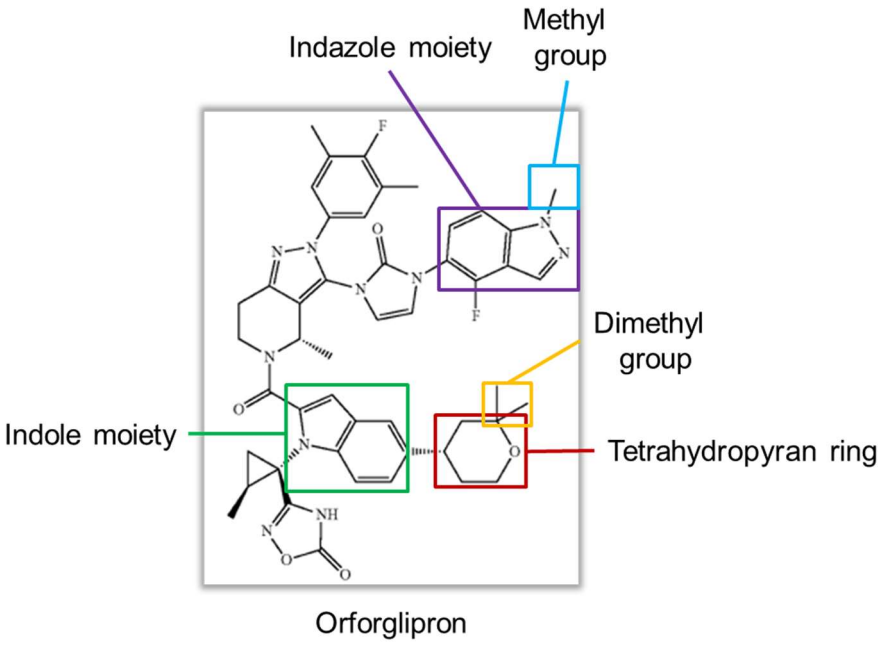
Tetrahydropyran Tetrahydrofuran Pyrrole Pyrazole Pyridine

40. The ring moieties can also be fused together. For example, a benzene ring and pyrrole ring together form an indole. As another example, a benzene ring and pyrazole ring form an indazole.



Indole Indazole

41. The moieties in orforglipron addressed in the Petition and Dr. Pirrung’s declaration are shown in the colored boxes below. The indazole moiety is highlighted in the purple box, the indole moiety is highlighted in the green box, and the tetrahydropyran ring is highlighted in the red box. The indazole moiety is substituted with a methyl group, shown in the blue box (in addition to a fluorine), and the tetrahydropyran is substituted with a dimethyl group, shown in the orange box.



42. Different ring structures have different properties, whether as an individual ring or a fused ring. Further, rings with non-carbon atoms can have an outsized effect on compounds because of their polarity and electron configuration.

43. Polarity refers to the unequal sharing of electrons in a molecule, creating a positive charge on one end of the molecule and a negative charge on the other end. Functional groups and substituents may be polar or non-polar. A polar molecule has an unequal distribution of electron density among the atoms in the molecule that results in the molecule having distinct positive and negative zones. Carbon-oxygen ("C-O") bonds and oxygen-hydrogen ("O-H") bonds are well-known examples of polarized bonds. In contrast, non-polar molecules generally lack

this unequal distribution of electron density. Carbon–carbon ("C–C") bonds and, in many contexts, carbon–hydrogen ("C–H") bonds are non-polar. (EX2037, 30-33.)

44. The polar zones of a molecule, such as a functional group or an electron-withdrawing substituent on a small molecule organic compound, influences the compound's solubility, molecular interactions, and other physical and chemical properties of the compound. In particular, polar molecules readily interact and mix with water, which itself is polar, and are considered hydrophilic. Non-polar molecules, by contrast, are hydrophobic and avoid interactions with water.

B. Medicinal Chemistry

45. Medicinal chemistry concerns the discovery, development, identification and interpretation of the mode of action of biologically active compounds, including the study, identification, and synthesis of drugs and related compounds. Medicinal chemistry focuses on the interactions of drug compounds with the complex chemical systems in the body, particularly the organic and biochemical reactions of the drug compounds with their targets, as well as the synthesis and analysis of the drug compounds. (EX2034, 27-28.) Medicinal chemists effectively act as the "engineers" of drug discovery, not just making molecules, but attempting to refine them into drugs by balancing potency, selectivity, pharmacokinetics, and safety—a theme that underpins concepts such as the target compound profile, discussed below. (EX2034, 28.)

46. There is no linear path in medicinal chemistry to arrive at a candidate drug or to modify an existing drug to obtain new properties. Identification of new drug candidates generally involves iterative, time consuming, and unpredictable experimentation, including screening compounds for activity against a particular target, analyzing the properties of various compounds that result from those screens, and attempting to modify the properties of candidate molecules through structural changes, such as by use of SAR analyses.

47. A skilled artisan seeking to modify a molecule typically seeks to achieve a target compound profile ("TCP"). A TCP, along with a related target product profile ("TPP"), describes the desired preclinical and clinical profiles for safe and effective drug candidates. (*See* EX2032, Abstract.) The TCP is a set of criteria that lists all the necessary features and properties a compound should have for lead optimization, including potency, selectivity, and ADME (absorption, distribution, metabolism, and excretion) parameters. Medicinal chemists use the TCP to decide on the direction of experimentation, including the compounds to modify and the modifications to attempt. The TPP complements the TCP and is focused on the patient and the market. Among other factors, it defines clinical efficacy, dosage forms (e.g., pill or injection), patient populations, as well as mission-critical and desirable clinical outcomes.

48. Generally, a skilled artisan would not modify an existing compound with the aim of synthesizing new molecules that had the same properties or "maintained" activity. Rather, the goal is to try to improve one or more properties in the existing molecule that could lead to a safer or more effective drug. If warranted, properties that a medicinal chemist may look to improve include potency, selectivity, and pharmacokinetic parameters. This, however, depends on the properties of the existing compound and the defined TCP. If the existing compound meets the desired criteria for a particular property or feature, a skilled artisan typically would not be focused on modifying the compound to change that property.

49. Achieving a TCP or improving a property of a known molecule is highly complicated. In the field of medicinal chemistry, small structural changes can result in big differences in potency, target selectivity, and/or ADME. The differences may be caused by a multitude of factors, including the arrangement of atoms in the molecule, or conformational changes, influencing binding affinity to a target, bioavailability, metabolic degradation, or any combination thereof.

50. For instance, adding, removing, or relocating even the smallest organic substituent, the methyl group, can lead to dramatic changes in a molecule's chemical properties. As one example, Wermuth illustrates the effect of adding or removing a methyl group on various positions on a class of targeted therapy drugs, known as PI3K inhibitors, that inhibit tumor growth in various cancers. The image below

shows the varying potencies of a PI3K inhibitor where there is no methyl group substituent, a methyl group is added at the C-7 position, or a methyl group is positioned at the C-6 position:

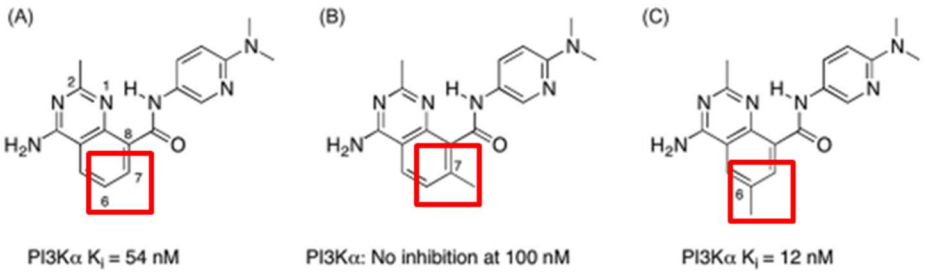


FIGURE 11.14 Structures of putative PI3K/mTOR inhibitors. The methyl group placement proved to be important for activity. (A) Absence of a methyl group at C-7 led to a fairly potent inhibitor with an IC_{50} of 54 nM, while (B) with a 7-methyl was inactive and (C) with a 6-methyl was the most potent inhibitor with an IC_{50} value of 12 nM [82].

(EX2034, 111, Fig. 11.14 (annotated).)

51. Wermuth indicates that "[t]he methyl group placement proved to be important for activity." (EX2034, 111, Fig. 11.14.) As shown in the image, the molecule without the methyl group had fairly good potency (54 nM). When a methyl group was added at the C-7 position, however, the result was an inactive compound (no inhibition at 100 nM). Even more surprising, though, was that moving the methyl group to the adjacent C-6 position resulted in the most potent inhibitor. Wermuth demonstrates that the mere act of adding or moving a methyl group can drastically change the properties of a potential drug candidate.

52. The well-known outsized impact a single methyl group can have on a molecule's properties, including potency, target selectivity, and pharmacokinetics, is often referred to as the "magic methyl effect." (*See* EX2028, Abstract ("The

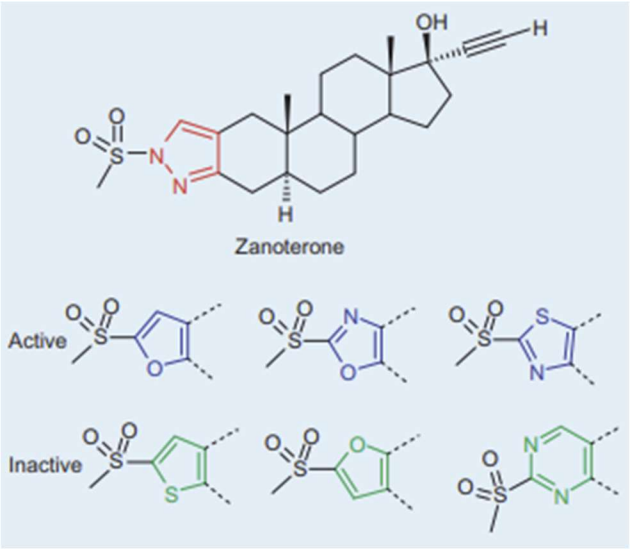
'methylation effect', or the 'magic methyl' effect, is a factor that stands out due to the number of examples that demonstrate profound changes in either pharmacodynamic or pharmacokinetic properties.").) The role of a methyl group in drug design includes a number of different factors, including facilitating hydrophobic interactions, solubility, lipophilicity or bioavailability, conformational properties, and metabolic reactions. (EX2028, 1.)

53. Pinheiro discloses a review of the "magic methyl effect," highlighting its use in the field of medicinal chemistry. (EX2028.) One example Pinheiro discloses relates to the anticancer drug tazemetostat. (EX2028, 2-3.) During drug discovery and development of tazemetostat, researchers discovered that the sole addition of a single methyl group unexpectedly increased potency. (EX2028, 2.) Further studies to find analogs of tazemetostat attempted changes to the position where the methyl group was added, including a cyclic substitution instead of the methyl group, which significantly diminished activity. (EX2028, 3.) As Pinheiro reports, "[t]he authors suggest that the cyclization abolished the 'magic methyl' effect previously reported to be key to the FDA-approved drug [tazemetostat]." (EX2028, 3.)

54. Pinheiro describes another example of the magic methyl effect, where researchers incorporated a single methyl group on an imidazole ring to design new analogs of benznidazole. (EX2028, 14-15.) The researchers added the methyl group

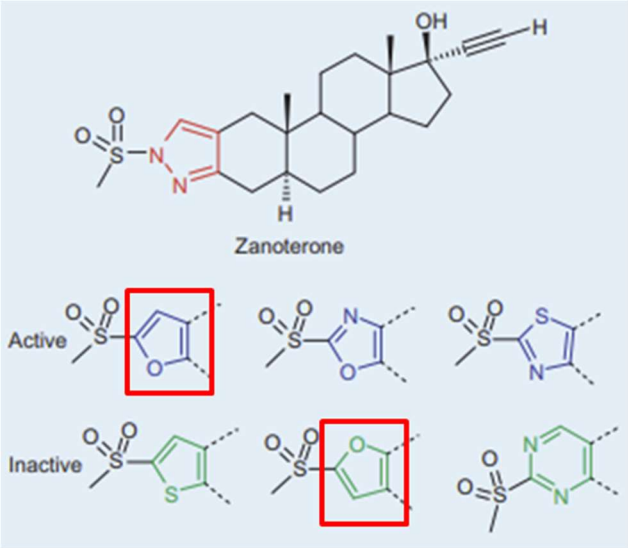
based on studies showing that it would improve potency and solubility. (EX2028, 14-15.) The resulting compound, with the methyl group added, resulted in improved drug activity. (EX2028, 15.) The methylation effect in this example underscores that a skilled artisan is generally more motivated to add methyl groups, not remove them.

55. Other small changes in a compound can also significantly change its properties. For example, heterocycles are carbon ring structures where a carbon atom has been replaced with a non-carbon atom, such as nitrogen or oxygen. Small changes in heterocycle composition and orientation can result in dramatic changes in activity. As shown below, the first image is the drug zanoterone, which was developed to treat prostate enlargement, and includes a five-membered heterocycle with two nitrogen atoms, depicted in orange:



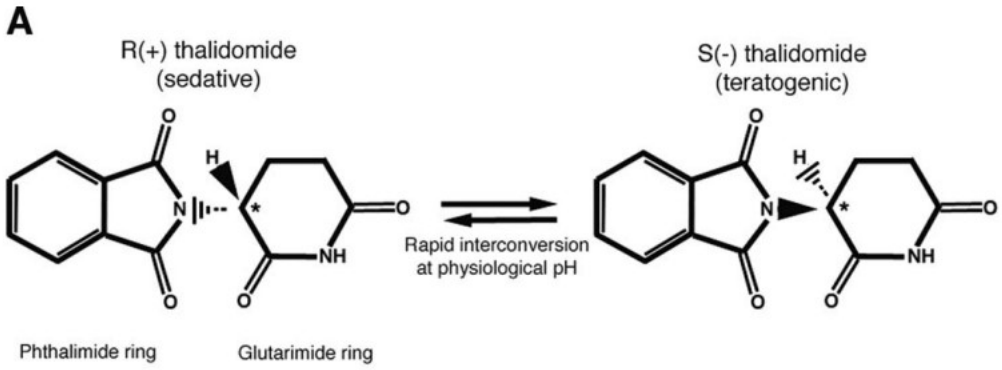
(EX2034, 56, Fig. 8.20.) Below the image of zanoterone are two rows depicting modifications to the five-membered heterocycle ring. Certain modifications (shown

in blue) maintained the activity of the compound, while other modifications (shown in green) rendered the compound inactive. Even where the only difference in the compound was the location of an oxygen atom in the ring, the compounds showed drastically different properties (activity v. no activity), as annotated in the red boxes below:



(EX2034, 56, Fig. 8.20 (annotated).)

56. Even molecules with the exact same chemical formula, but different arrangement of those atoms in space, can have markedly different properties. The history of thalidomide serves as a cautionary illustration of this principle. Introduced in the late 1950s as a sedative, thalidomide was largely marketed in Europe and other countries as over-the-counter as a drug for treating morning sickness in pregnant women. Thalidomide contains a single stereocenter and, therefore, exists as two mirror-image enantiomers, known as the (R)-enantiomer and the (S)-enantiomer:



(EX2038, Fig. 1.) When administered to a patient, thalidomide results in an equilibrium mixture of both forms and was thus marketed and administered as a "racemic" mixture. However, while the (R)-enantiomer acts as a sedative and treats morning sickness, the (S)-enantiomer is teratogenic, meaning that it causes birth defects in a developing fetus. In 1961, clinicians conclusively linked thalidomide exposure to severe congenital malformations in approximately 10,000 infants worldwide, leading to its withdrawal from the market. This historical example illustrates that even subtle changes in molecular structure and stereochemical orientation can result in profound differences in biological activity, a principle well understood by practitioners skilled in the art of medicinal chemistry.

C. Salt Formation

57. Once a drug compound is discovered and identified for a particular target, it can be formulated into a drug product, or pharmaceutical compound, that is ultimately administered to patients. However, the drug compound itself may not be suitable for formulation into a drug product without some modification to the

form of the drug compound itself. Researchers may therefore attempt to make different forms of the drug compound that have more favorable characteristics for administration to patients and/or large-scale manufacturing and commercialization.

58. To achieve this, researchers will sometimes attempt to make multi-component forms of the drug compound. Multi-component forms can have different performance characteristics, such as for bioavailability, manufacturing, and stability. Multi-component forms include solvates, hydrates, salts, and/or co-crystals comprising neutral molecular components. (EX2069, 1.)

59. To discover new multi-component forms of a drug compound, researchers will conduct a salt screen. Salt screens involve dissolving the drug compound with different counterions in one or more solvents under a variety of conditions. To do this, a skilled artisan must carry out a number of steps. First, the drug compound's physiochemical properties are measured, such as pH, pKa of each ionizable group in the molecule, and the log P value of the compound. (EX2070, 3, 5-6.) A skilled artisan will also select the particular counterions to use in the salt screen, of which there would be many options for any particular molecule. Further, a skilled artisan will also select solvents or solvent mixtures, which are also chosen amongst hundreds of options. Then, the skilled artisan will select the conditions, such as temperature, concentration, agitation, and pH, taking into account the potential dosage forms and targeted properties of the drug compound, as well as

considering the toxicological and safety implications of a particular counterion. (EX2070, 2.) After making each of these selections, only a small fraction of the experiments in the salt screen lead to any multi-component forms, including salt forms, which may or may not have the desired properties for the pharmaceutical drug product. (EX2043, 4.)

60. A skilled artisan would not know prior to conducting a salt screen whether a particular salt that forms a stable solid, has suitable polymorphism or hydration, and produces acceptable pharmaceutical properties exists or, if it did exist, how to make that form. A salt form may or may not appear regardless of the properties of the drug compound and counterion. (EX2044, 18.) Even very structurally similar compounds may not form salts with the same counterions. (EX2044, 18.) A skilled artisan would also not know before conducting a salt screen what characteristics a new salt form may have. There are no salt screening techniques that can facilitate the efficient selection of a salt that is most likely to exhibit the desired properties of a salt form of a drug compound. (EX2045, 1.) A skilled artisan also cannot reliably predict how a salt formation will affect the properties of the drug compound. (EX2043, 4.)

D. Obesity and GLP-1R Agonists

61. Globally, more than 800 million people are affected by obesity. (EX2016, 1.) Obesity is a chronic disease that affects an individual's weight, as well

as carrying an increased risk of type 2 diabetes, cardiovascular disease, fatty liver disease, cancer, and many others. (EX2016, 1.) Approximately 42% of adults have obesity in the United States, and obesity-related costs are estimated at $173 billion annually. (EX2016, 1.)

62. Glucagon-like peptide-1 ("GLP-1") is an endogenous incretin hormone that is secreted primarily in the intestine in response to a meal. (EX2016, 2-3.) The hormone signals fullness to the brain and reduces appetite. (EX2016, 2-3.) To achieve this effect, GLP-1 binds to the GLP-1 receptor ("GLP-1R"), which is a protein generally found in the pancreas and brain. (EX2016, 2.) GLP-1R plays an important role in stimulating glucose-dependent insulin secretion and suppressing glucagon, which in aggregate raises blood sugar, delays gastric emptying, and suppresses appetite. (EX2016, 2-3.)

63. GLP-1R agonists are a significant breakthrough in the treatment of obesity. (EX2016, 2.) GLP-1R agonist drugs mimic the GLP-1 hormone to bind to GLP-1R and thereby delay gastric emptying and reduce hunger. (EX2017, 2.) Some GLP-1R agonist drugs show a significant and sustainable weight loss of at least 15% for many patients, due to increased feelings of fullness and delayed stomach emptying. (EX2017, 4-5.)

64. Two GLP-1R agonists (liraglutide (Saxenda®) and semaglutide (Wegovy®)) were approved for chronic weight management in obese patients at the

time of the invention. (EX2017, 2; EX1001, 2:6-11.) Both of these drugs, however, are peptides, which are composed of short chains of amino acids and, at that time, required a weekly subcutaneous injection. (EX2017, 2.) While these drugs are effective, the injection can be a significant barrier to patient uptake and acceptability of the treatment. (EX2017, 2.)

65. By 2023, scientists were also studying several small-molecule GLP-1R agonists for oral administration, but none were approved. (EX2017, 2; EX1001, 2:11-12.) In contrast to peptides, small molecules are frequently lower in molecular weight than peptides and can offer better oral bioavailability and stability. One promising small molecule candidate was orforglipron. (EX2017, 2.) Orforglipron is a small molecule GLP-1 receptor agonist being developed by Eli Lilly for weight management and the treatment of type 2 diabetes. (EX2017, 2.) Orforglipron is administered orally, as a pill, once per day, compared to the once-weekly subcutaneous injections then required for peptide GLP-1R agonists. (EX2017, 2.)

66. By 2023, it was known that orforglipron has "GLP-1 receptor agonistic activity comparable or even stronger than GLP-1 derivatives." (EX1010, 4 (referring to GLP-1 peptide drugs as GLP-1 derivatives); EX1002, ¶49 ("Orforglipron demonstrates full agonist efficacy, promoting cAMP accumulation comparable to native GLP-1. It exhibits an EC_{50} of 1.1 nM for both human and cynomolgus monkey GLP-1 receptors.").) By 2023, it was also known that orforglipron has a favorable

pharmacokinetic profile that supports once-daily oral administration. (EX2017, 2.) As Dr. Pirrung admits, orforglipron is "structurally optimized for once-daily oral administration." (EX1002, ¶49.)

67. Phase 2 clinical trials showed that daily oral orforglipron causes weight reduction and related benefits similar to that observed with the peptide GLP-1 receptor agonists already approved for weight management. (EX2017, 7.) These Phase 2 clinical trials demonstrated that orforglipron had good efficacy and did not suggest that orforglipron had any glaring pharmacokinetic or safety issues. (EX2017, 2; EX2071.) Prior to 2023, Eli Lilly announced that it planned to begin Phase 3 clinical trials for orforglipron, further suggesting that it was a promising candidate. (EX2018; EX2065.) In his declaration, Dr. Pirrung does not point to any known issues with orforglipron or any reason a skilled artisan would seek to modify its properties.

68. In contrast to Lilly, other companies have struggled to develop small-molecule GLP-1R agonists. Before the current generation of GLP-1 receptor agonists, others failed to develop non-peptide GLP-1 receptor agonists. In 2007, scientists at the Institute of Materia Medica in Shanghai discovered a non-peptidic GLP-1R agonist, titled Boc5. Boc5 never moved to clinical development due to low bioavailability and poor pharmacokinetics. (EX2046, 4.) After performing SAR

studies, the researchers found a much more potent drug based on Boc5; however, the new drug's properties still did not prompt development. (EX2046, 4.)

69. Several Pfizer programs studying small-molecule GLP-1R agonists were discontinued due to safety concerns. (EX2047, 2.) For example, Pfizer's lotiglipron was discontinued after discovering concerning "transaminase elevations" in Phase 1 and Phase 2 studies. (EX2048, 1-2.) Transaminases are enzymes created by damaged liver cells. Elevated transaminase levels are an early sign of liver stress. In the Phase 2 study, elevated transaminase levels were observed in "6.6% and 6.0% of participants on lotiglipron in the T2D and obesity cohorts, respectively, compared with 1.6% on placebo in the obesity cohort." (EX2049, 2.) Pfizer also discontinued danuglipron after it caused a "potential drug-induced liver injury" in a patient during Phase 2 trials. (EX2050, 1.) Finally, Pfizer discontinued its third GLP-1R agonist, PF-06954522, after reviewing data from their Phase 1 study. (EX2051.)

III. THE PRIOR ART

A. The Asserted Prior Art Discloses Innumerable Potential Modifications to the Orforglipron Backbone

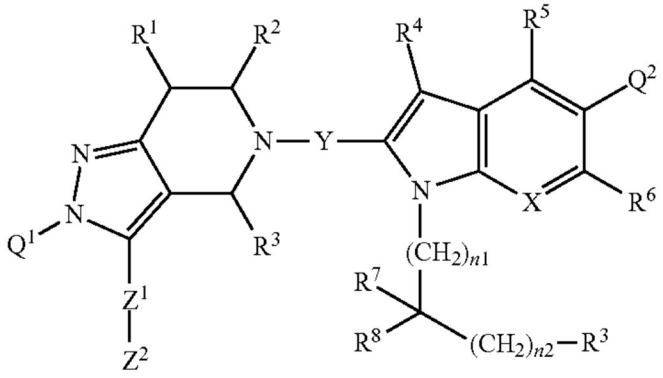
70. By 2023, orforglipron was well-known in the art and exhibited promising results in clinical trials. (EX2017.) As evidenced by the asserted prior art, many in the art had attempted to develop an analog of orforglipron, likely for commercial reasons. The prior art therefore discloses numerous references that

disclose derivatives of orforglipron and many possible modifications to it, resulting in millions of potential derivative compounds of orforglipron. I address each of Petitioner's asserted prior art references disclosing orforglipron or its derivatives below.

1. Yoshino (EX1008)

71. U.S. Patent No. 10,858,356 ("Yoshino") issued on December 8, 2020. (EX1008, cover.) Yoshino was the first patent to disclose orforglipron, as Compound 67, among many other GLP-1R agonist compounds. (EX1008, 3:1-6:2.)

72. Yoshino includes a single generic chemical formula of the invention, Formula (I):



(EX1008, 3:1-6:2.) As shown in the structure above, Yoshino's Formula (I) allows for modifications of at least 14 different positions. At each of those positions, Yoshino allows for numerous potential substitutions, resulting in millions of potential compounds.

73. Yoshino discloses that Z^2, the position of the indazole moiety in orforglipron, can be selected from five possible classes of substituents, including "C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl and 5 to 10 membered heteroaryl." (EX1008, 5:21-26.) Thus, Yoshino allows for an "indazole" moiety at Z^2, as indazole is a type of 5 to 10 membered heteroaryl. Yoshino goes on to teach that the "C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl and 5 to 10 membered heteroaryl are optionally substituted with one to five substituents" selected from eleven broad categories. (EX1008, 5:21-6:2.) These broad categories for substituents include C_{1-6} alkyl and 3 to 12 membered heterocyclyl but does not list cycloalkyl groups. (EX1008, 5:21-6:2.) These substituents can also be optionally further substituted. (EX1008, 5:21-6:2 ("C_{1-6} alkyl: wherein C_{1-6} alkyl is optionally substituted with one or more substituent . . . 3 to 12 membered heterocyclyl; wherein 3 to 12 membered heterocyclyl is optionally substituted with one or more substituents . . . ").) Thus, where an indazole moiety is selected for position Z^2, there could be between 10,000 to 1,000,000 different substituents just on the indazole.

74. Despite the vast number of substitutions allowed on the indazole moiety, Yoshino ***does not allow for a cycloalkyl***. As noted above, Yoshino does not include "cycloalkyl" as an option and the definition of "C_{1-6} alkyl" does not allow for ring structures. (EX1008, 5:21-67; *see also* EX1008, 9:57-62, 10:53-64 (defining "C_{1-6} alkyl" as a "straight chain or branched chain alkyl group" and separately from

"$C_{3\text{-}15}$ cycloalkyl," which is defined as "a cycloalkyl of 3 to 6 carbons" and includes cyclopropyl and cyclobutyl as examples).)

75. Yoshino discloses at least 159 exemplary compounds, one of which is orforglipron (compound 67). The other compounds include various modifications to the core structure of orforglipron, including various substituents on the indazole moiety. (*E.g.*, EX1008, Example Compounds 16, 126, 28, 26, 17, 120, 119, and 30.) Similar to Formula (I), despite the broad array of substituents, Yoshino does not include a single exemplary compound with a cycloalkyl substitution on the indazole moiety. (EX1008, pgs. 31-55, 89-90, 92-101, 120-121, 133-161.)

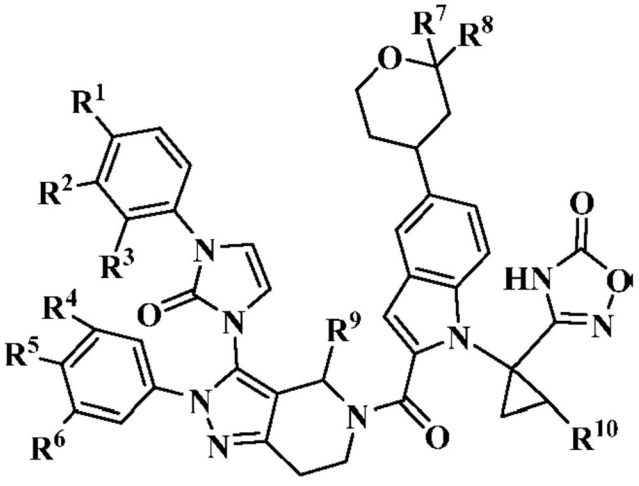
76. Yoshino discloses data for only Compounds 1-80 of the 159 exemplified compounds. (EX1008, 310:40-311:51, Table 3.) Specifically, Yoshino discloses the results of an assay measuring the activity of each exemplary compound. (EX1008, 310:1-40.) The EC_{50} values range from 12 nM (compound 4) to 0.51 nM (compound 16), with lower values indicating higher levels of activity. (EX1008, 310:40-311:51, Table 3.) Of the exemplary compounds that include substitutions on the indazole moiety, structures with a tetrahydrofuran ("THF") ring on the indazole moiety have less activity than orforglipron. (EX1008, Table 3 (*compare* Compounds 8 (2.5 nM), 14 (2.3 nM), 22 (2.3 nM), 40 (2.2 nM), 64 (2.0 nM), *with* Compound 67 (1.2 nM)).)

77. Of the at least thousands of compounds encompassed by Formula (I) and the 159 specific compounds, Yoshino provides pharmacokinetic data for only a single compound, orforglipron. (EX1008, 312:30-313:35.)

2. Su (EX1005)

78. PCT Application No. PCT/CN2024/108192 ("Su"), filed on July 29, 2024, also discloses a large number of small molecule oral GLP-1R agonists. (EX1005.) Su claims priority to thirteen Chinese patent applications, including CN 202311372605.9 ("Su II"), which was filed on October 20, 2023. (EX1007, 1.) I understand that only the disclosures of Su II are prior art to some of the Challenged Claims. For ease of reference, I cite to the relevant disclosures in Su II, but refer to it as Su.

79. Su discloses a generic structure, Formula (I):



(I)

(EX1007, 5:1-7:4.) Formula (I) allows for modifications at ten or more different positions, as well as upwards of nine distinct additional positions that allow for substitution at each of those positions, yielding millions of potential compounds. Su discloses that R^1 and R^2 can together attach with other atoms to form, among other substituents, a 5- to 12-membered heteroaryl, which includes forming the indazole moiety in orforglipron. (EX1007, 11:10-11.) Su further allows for additional substituents to the indazole moiety, chosen from at least 25 different substituent types. (EX1007, 11:14-22.)

80. Su also discloses 218 working examples with various modifications to the core structure of orforglipron. (EX1007, 97:7-289:23.) The majority of the exemplary compounds in Su are not focused on the modification of the indazole moiety at all. (EX1007, 97:7-289:23.) Su does not provide activity data for a single one of those 218 compounds. (*See*, *e.g.,* EX1007, 291:1-2, 292:11-14, 293:17-19 (disclosing only general statements on qualitative activity data).) Indeed, the only compound-specific data disclosed in Su is pharmacokinetic data for five of its 218 working examples, including Compounds 1, 3, 64, 173, and 174. (EX1007, 294:29-295:1.) Because Su only discloses data for these five compounds, a skilled person would have focused on those compounds. (EX2033, 62:14-63:6 (admitting that pharmacokinetic data disclosed in Yoshino is an important indicator of which compounds are of interest and advanced for further development).) Further, none of

those five compounds have any of the substitutions reflected in the compounds claimed in the ’236 Patent. In fact, the five compounds for which data is disclosed in Su have significant structural differences compared to orforglipron. (EX1007, Compounds 1, 3, 64, 173, and 174.)

81. Su also discloses a group of seven stereoisomerically pure compounds which are “deuterated.” (EX1007, Examples 176, 44, 35, 123, 139, 188, and 212; EX1002, ¶61.) Deuteration is the chemical process of substituting hydrogen atoms with deuterium. This substitution can create a stronger bond between the carbon and the hydrogen isotope. (EX2041, 5.) Deuteration is commonly used as a tool to probe metabolic pathways, investigate potential metabolic hotspots, or modulate pharmacokinetics. (EX2041, 5-6.) In other words, deuteration is one tool used by medicinal chemists to try to slow drug metabolism and increase stability and efficacy. (EX2041, 5-6.) Su does not give any explanation or analysis as to why the seven compounds in particular were deuterated.

82. Despite Su including no data whatsoever for them, Dr. Pirrung opines that a skilled artisan would look to two of the seven deuterated compounds, Compounds 44 and 176, to modify the core structure of orforglipron. (EX1002, ¶¶61-70.) As explained in more detail below, Dr. Pirrung’s opinion is based on impermissible hindsight as there is nothing in Su to cause a skilled artisan to focus on Compounds 44 and 176.

3. Kawai (EX1004)

83. Kawai was published on November 11, 2020. (EX1004.) Kawai discloses "the discovery and mechanism of action of [orforglipron], a nonpeptide GLP-R agonist." (EX1004, Abstract.) In particular, Kawai provides a "high resolution structure" of orforglipron "in complex" with the GLP-1 receptor. (EX1004, Fig. 1I, 8.) This high-resolution structure was obtained using cryoelectron microscopy ("cryo-EM") and illustrates the receptor-binding mechanism of orforglipron. (EX1004, 1-2.) Cryo-EM structures are three-dimensional, high-resolution images that are routinely used to determine biological structures and elucidate the binding of a compound to a receptor. (EX1004, 8.)

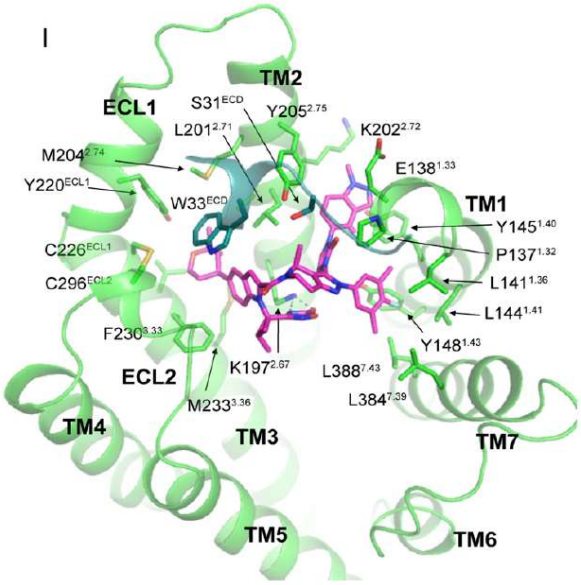
84. Kawai does not suggest any issues or shortcomings with orforglipron in binding to the GLP-1 receptor or suggest making any modifications to orforglipron. Instead, Kawai praises orforglipron (LY3502970), noting that it "displays a preclinical pharmacodynamic profile similar to marketed peptide-based GLP-1R agonists and possesses pharmacokinetic properties compatible with oral dosing in humans." (EX1004, 7.) Kawai also does not provide data for any compound other than orforglipron.

85. Dr. Pirrung opines that the Kawai shows "the binding pocket adjacent to the methyl group of the indazole moiety is shown as being surrounded by a ***spacious*** hydrophobic environment . . . suggesting that the pocket could ***reasonably***

accommodate a compound bearing a ***bulkier substituent*** in place of the methyl group." (EX1002, ¶58.) I disagree.

86. Kawai merely states that "there is enough space for the binding of both the 2,2-dimethyl-tetrahydropyran and the 4-fluoro-1-methyl-indazole moieties of LY3502970 between TM2-TM3 and TM1-TM2, respectively." (EX1004, 4.) It does not say that there is additional space to accommodate a "bulkier substituent." (EX1002, ¶209.) Kawai also discusses "the conformational flexibility of GLP-1R and GPCRs in general." (EX1004, 4.) But that passage refers to the conformational flexibility of the GLP-1 receptor in general not the binding pocket for the indazole moiety. (EX1002, ¶¶56-57.) Thus, the text of Kawai does not suggest that "the pocket could reasonably accommodate a compound bearing a bulkier substituent in place of the methyl group." (EX1002, ¶58.)

87. Kawai also includes several two-dimensional images of the cryo-EM structure. (EX1004, 3, 5-6.) Dr. Pirrung relies solely on the two-dimensional image shown below to reach his conclusions on Kawai's teachings:

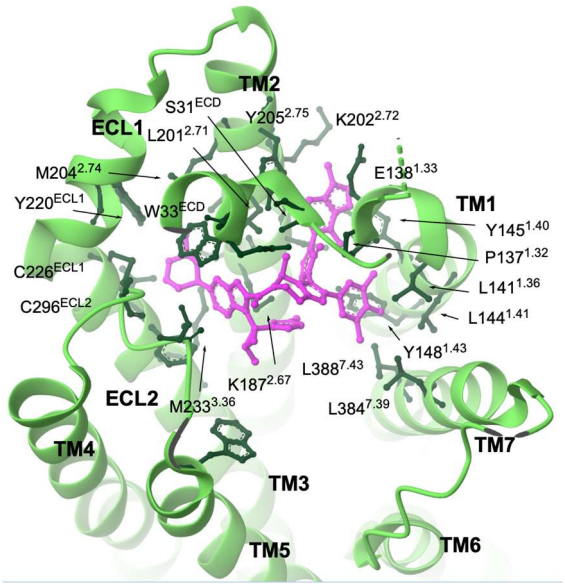


(EX1004, Fig. 1I, 8.)

88. In assessing Kawai, a skilled artisan would not just look at the two-dimensional images available in the paper but would also look for three-dimensional cryo-EM structures often deposited in the Protein Data Bank. Kawai discloses that the three-dimensional cryo-EM structure, showing orforglipron bound to the GLP-1 receptor, was deposited in the Protein Data Bank under code 6XOX prior to Kawai's publication. (EX1004, 8-9.) Protein Data Bank indicates that the full cryo-EM structure was deposited on July 7, 2020 and released on November 18, 2020, and was therefore available before the time of the invention. (EX2035, 10.)

89. I analyzed Kawai's three-dimensional cryo-EM structure in the Protein Data Bank and generated a similar image as depicted in Kawai, as shown below. Orforglipron is depicted in the center, in pink, and the portion of the GLP-1 receptor

to which orforglipron binds is depicted in green. I further annotated the image in black to indicate the same side chains and residues that Kawai labels in its image.

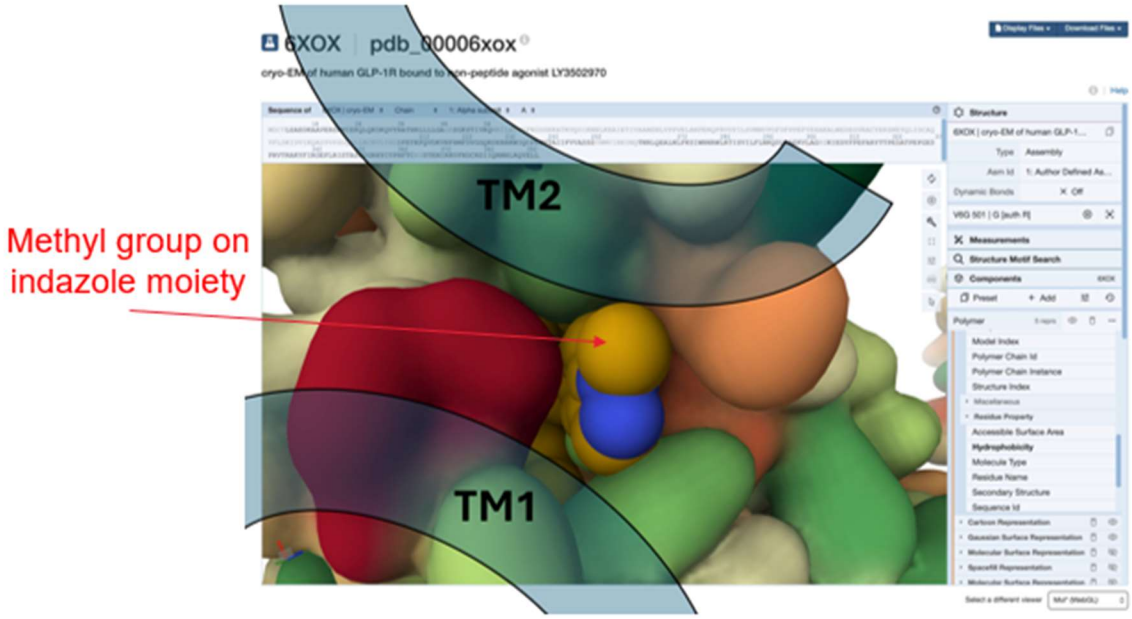


(EX2035, 1 (annotated labeling the side chains and residues).)

90. A skilled artisan would also be able to use the cryo-EM structure in the Protein Data Bank to analyze the interactions of the binding regions of the GLP-1 receptor and orforglipron. The cryo-EM structure in the Protein Data Bank is three-dimensional and can be readily rotated to show different viewing angles. In addition, the user can choose settings that color-code the regions of the receptor based on hydrophobicity and also show the different atoms in orforglipron in different colors.

91. Using this approach, I was able to focus on the interactions of the indazole moiety on orforglipron with the GLP1-R. In the annotated image below from the Protein Data Bank, green indicates the hydrophobic regions of the receptor

and red and orange indicate hydrophilic regions. The nitrogen atoms on the indazole moiety of orforglipron are depicted as blue spheres, and the methyl group is represented in yellow. I further annotated the image to illustrate where the TM1 and TM2 side chains are located in relation to the indazole moiety of orforglipron when it is bound to the receptor.



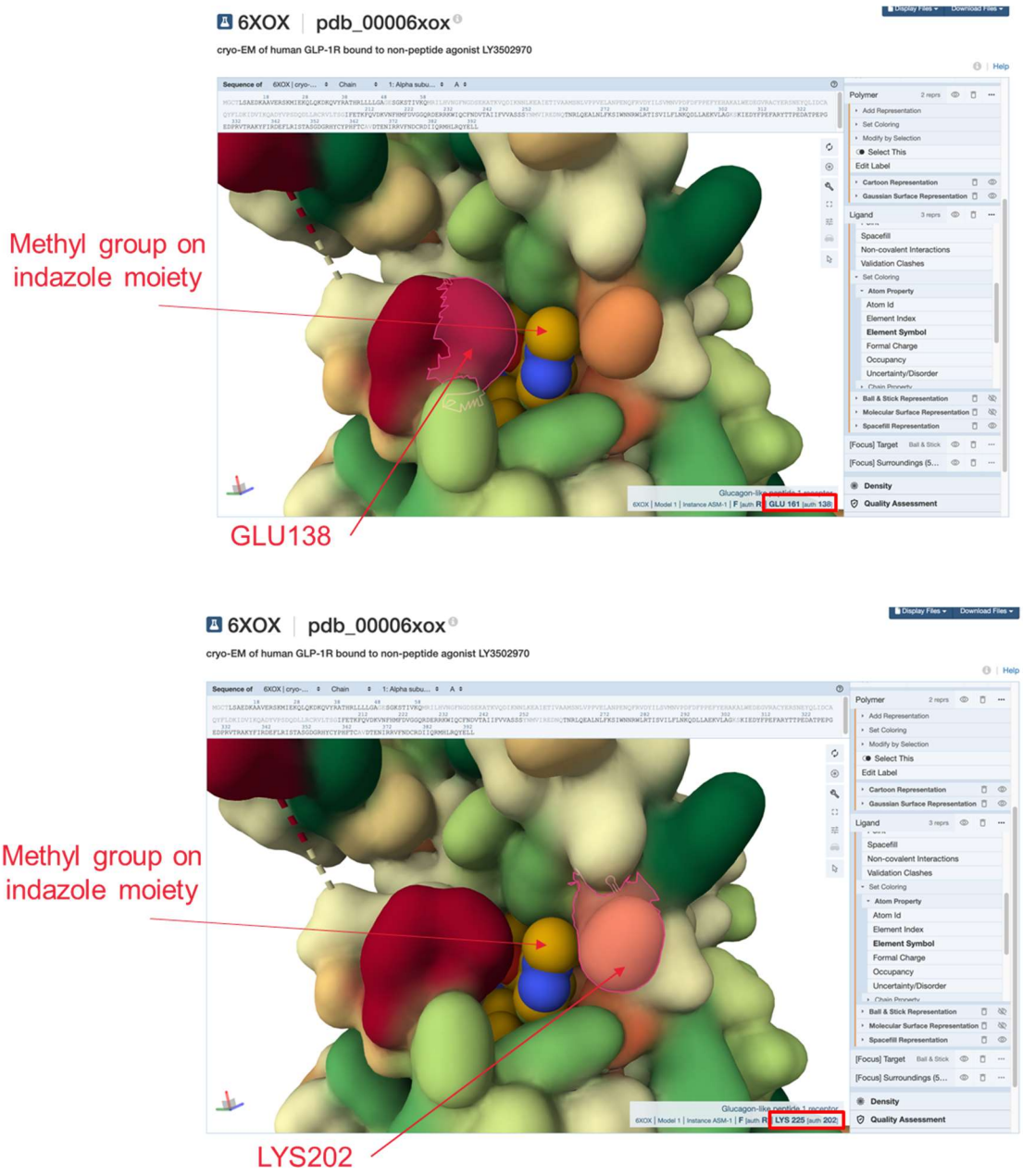
(EX2035, 2 (annotated indicating the TM1 and TM2 side chains and pointing to the methyl).)

92. As shown in the cryo-EM structure, the methyl group on the indazole moiety fits in this binding region of the GLP-1 receptor. As described in Kawai, the cryo-EM structure demonstrates that "there is enough space for the binding" of the indazole moiety with the methyl substituent and that this "unique conformation . . .

would be difficult to . . . predict." (EX1004, 4.) A skilled artisan reading Kawai and analyzing the cryo-EM structure described in Kawai would not understand that the binding region for the indazole moiety on the GLP-1 receptor would accommodate a bulkier substituent, like a cycloalkyl.

93. The cryo-EM structure also shows that the region surrounding the indazole moiety is mainly hydrophilic, and polar, contrary to Dr. Pirrung's statement that this region is hydrophobic. (EX1002, ¶58.) As can be seen in the image above, the methyl group on the indazole moiety (shown in yellow) is flanked by hydrophilic surfaces (orange and red).

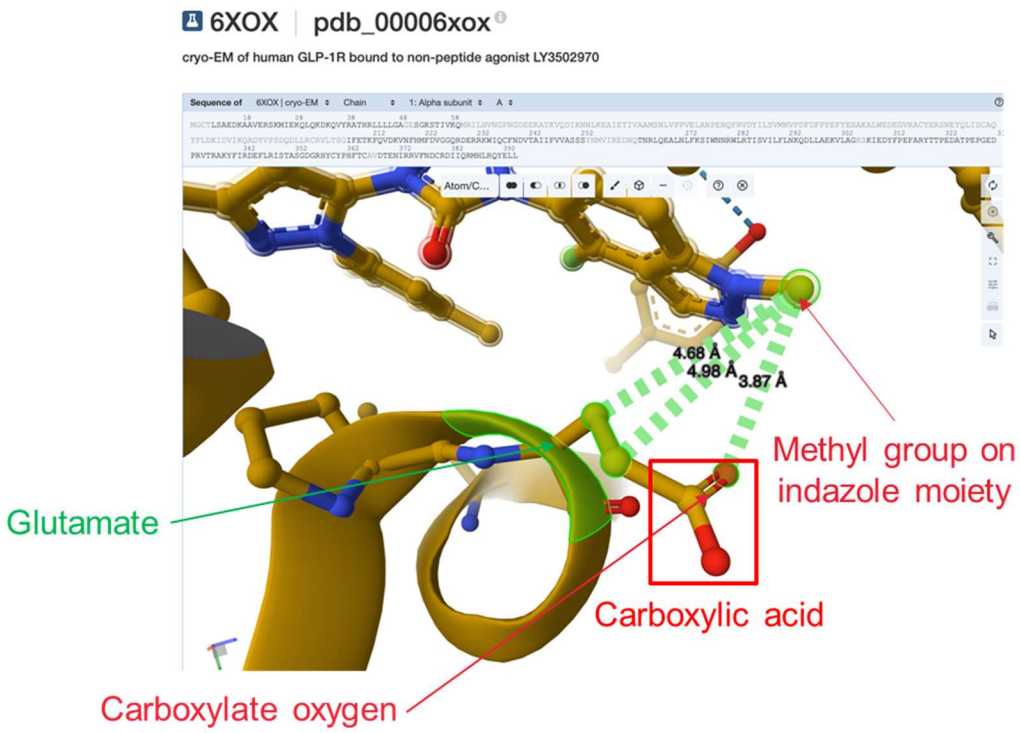
94. A skilled artisan would further be able to determine the exact amino acid residues surrounding the methyl group on the indazole moiety using the cryo-EM structure in the Protein Data Bank. In this Data Bank, a user can select an individual amino acid on the GLP-1R. In the first image below, I selected the amino acid in red adjacent the indazole methyl group and, in the second image below, I selected the amino acid in orange adjacent to the indazole methyl group.



(EX2035, 3-4 (annotated with arrows indicating the amino acid selected and the methyl group on the indazole moiety).) As shown in the cryo-EM structure, the methyl group is flanked by a glutamate (GLU138) and lysine (LYS202) residue,

both of which are characterized as polar amino acids, and is also exposed to water, which is also polar. (EX2036.)

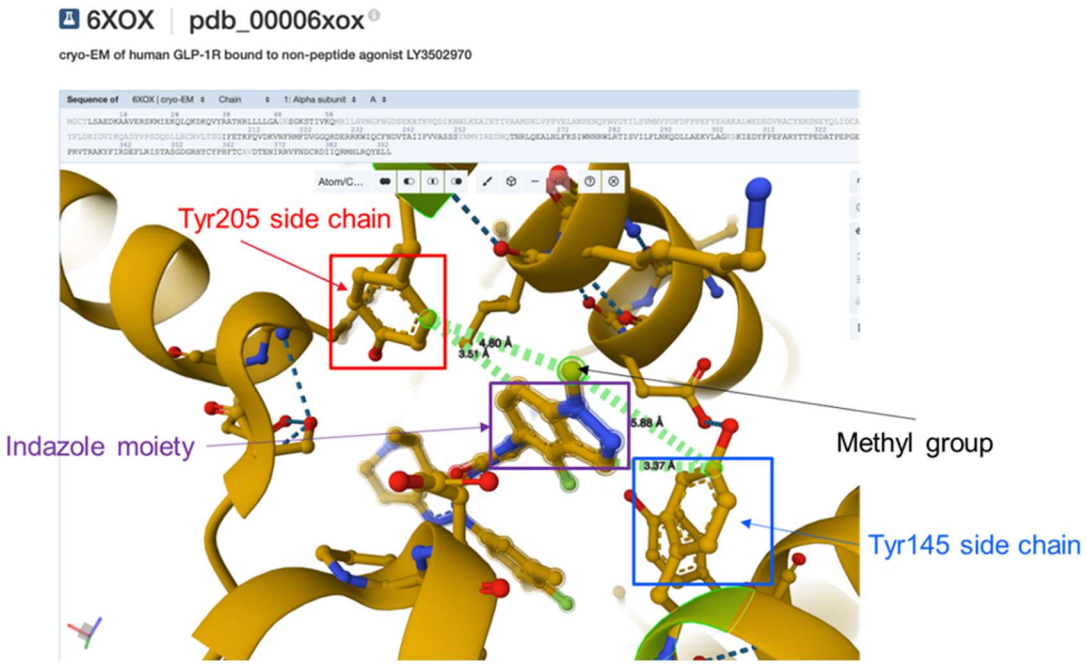
95. The cryo-EM structure in the Data Bank also allows a skilled artisan to measure the distance between groups on the drug compound and side chains of the amino acids in the receptor. I measured the distance between the methyl group on the indazole moiety and the side chain of the glutamate (GLU138), which includes a carboxylate that has a negative charge, and defines glutamate's polar properties. As shown in the image below, the methyl group is closer to the carboxylate oxygen on the glutamate side chain than it is to the carbon atoms of the glutamate side chain.



(EX2035, 7 (annotated).) Thus, the cryo-EM structure shows that, if anything, the region around the methyl group on the indazole moiety would reasonably be expected to favor more ***polar substituents*** rather than ***non-polar substituents***, like cycloalkyls.

96. Kawai also discloses that "the 4-fluoro-1-methyl-indazole moiety (Fig. 1A, blue shading) of [orforglipron] has aromatic interactions with Tyr205 and Tyr145." (EX1004, 4.) Aromatic interactions affect stability and are an important consideration in drug development, such as when considering SAR studies. Kawai therefore teaches that the aromatic ring on the indazole moiety has a stabilizing effect. Bulkier substituents, such as cycloalkyls, on the indazole moiety might disrupt this interaction by introducing another, non-aromatic ring structure as a substituent on the indazole moiety.

97. This is confirmed by the cryo-EM structure in the Protein Data Bank, which shows that the aromatic rings of Tyr205 and Tyr145 are closer to the aromatic ring on the indazole moiety than the methyl substituent. I measured the distance between the indazole moiety and methyl group to the side chains of Tyr205 and Tyr145.

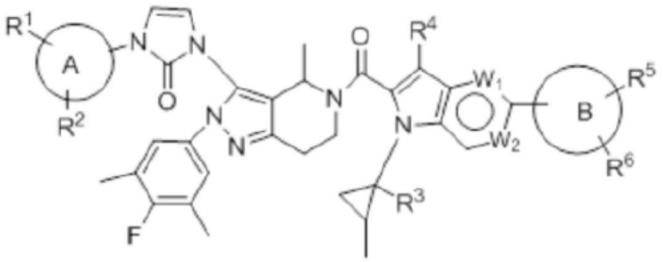


(EX2035, 9 (annotated).)

98. Thus, nothing in Kawai teaches or suggests trying to improve orforglipron and, particularly, Kawai does not teach that the GLP-1R binding pocket could accommodate a bulkier substituent on the indazole moiety or would favor a non-polar substituent.

4. Meng (EX1028)

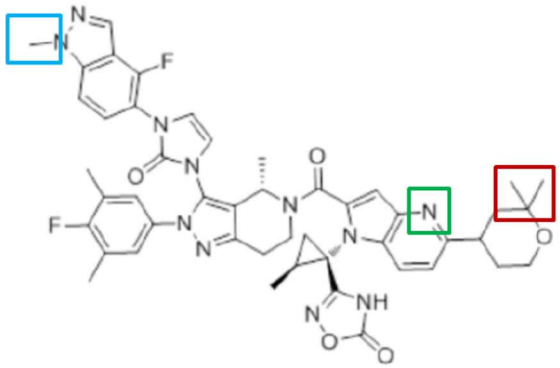
99. CN117069743A ("Meng") was published on November 17, 2023. Meng is yet another reference that discloses a large genus of GLP-1 agonist inhibitors that encompasses thousands to millions of potential compounds. (EX1029.) For example, claim 1 in Meng recites the following general structure for a GLP-1 receptor agonist, Formula I:



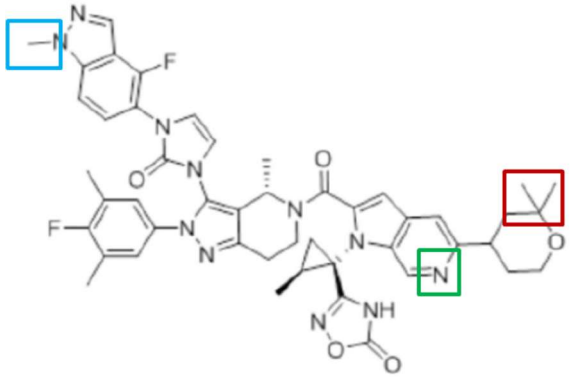
(EX1029, [0007].) There are at least 10 positions in Formula I that can be modified independently to include any of between three and 10 possible classes of molecules. (EX1029, [0009]-[0019].) Each functional group can also have substituents, selected from at least three different options, leading to millions or more structural variants. (EX1029, [0009]-[0019].)

100. The substituent group A is the location of the indazole moiety in orforglipron. At that one position, Meng allows 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." (EX1029, [0009].) The indazole group can include additional substituents, R^1 and R^2, which are selected each from a group of H, F, or CH_3. (EX1029, [0010].) Ming thus allows for thousands of possible options just at position A. Notably, despite the breadth of options at position A, Meng ***does not allow*** for a cycloalkyl group on the indazole moiety, as in the Challenged Compounds. (EX1029, [0010].)

101. Meng discloses Compounds II and III, which, have a single variation from orforglipron wherein a nitrogen atom is incorporated into the aromatic ring of a core structure. (EX1029, [0020]-[0021]; EX1002, ¶86.) The structures of Compounds II and III, however, are otherwise identical to orforglipron and contain the methyl group on the indazole moiety and the dimethyl group on the THP ring. (EX1029, [0020]-[0021], Example 1-3.)



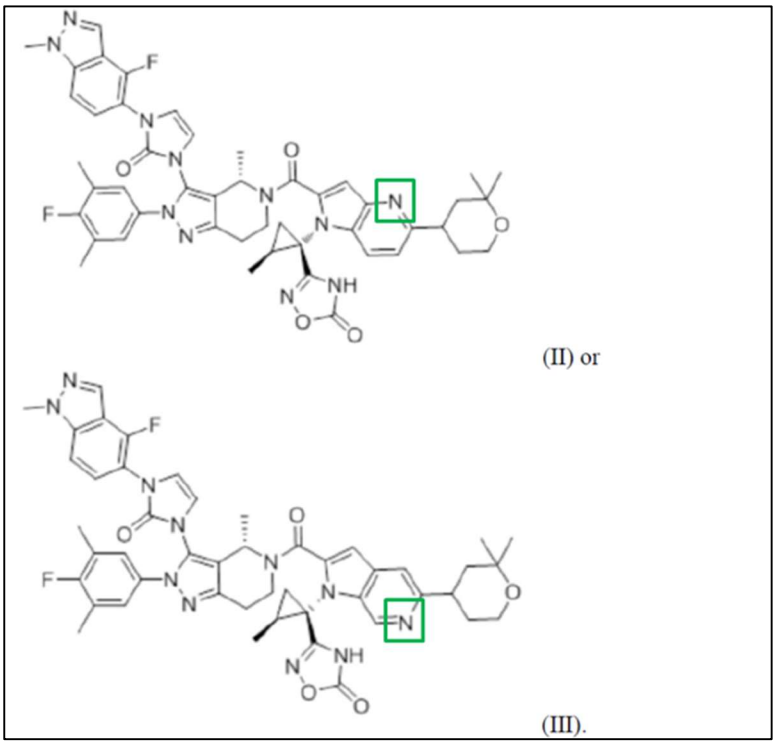
(II) or



(III).

(EX1029, [0020]-[0021] (annotated in colored boxes highlighting the additional nitrogen atom in green, the unchanged methyl group on the indazole moiety in blue, and the unchanged dimethyl group on the THP ring in red), Example 1-3.)

102. Dr. Pirrung relies solely on Compound II in Meng, which substitutes a nitrogen atom into the core structure of orforglipron at the same position as claimed Compound 65. (EX1002, ¶86.) But Dr. Pirrung ignores Compound III in Meng, which substitutes a nitrogen atom in a different position in the core structure of orforglipron:



(EX1029, [0020]-[0021] (depicting Compounds II and III) (annotated to show the substituted nitrogen atoms in green boxes); *see also* EX1029, [0014] ("W1 and W2 are each independently selected from -CH- or -N-, and at least one of W1 and W2 is -N-").)

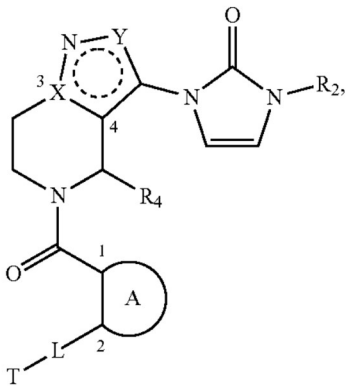
103. Meng provides data comparing the potency of both Compound II and III to orforglipron. (EX1029, [0186]-[0192] (comparing with Compound 67 of

Yoshino).) The data from the comparison study reported in Meng demonstrates that Compound III is more potent than orforglipron and also more potent than Compound II. (EX1029, [0186]-[0192].) Dr. Pirrung provides no reason why a skilled artisan, if they were to look to Meng in the first place, would focus on Compound II rather than the more potent Compound III. In my opinion, the only explanation is hindsight.

104. Further, Meng only discloses potency data for Compounds II, III and orforglipron. (EX1029, [0186]-[0192].) Meng does not conduct or report any data on the compounds' pharmacokinetic properties or indicate which compound out of the three has the most favorable pharmacokinetic properties. Therefore, Meng does not inform a skilled artisan of the effects of the nitrogen atom substitution on the pharmacokinetics of orforglipron.

5. Ren (EX1030)

105. U.S. Patent No. 12,037,339 ("Ren") was issued on July 16, 2024 from U.S. Patent Application No. 17/380,084, filed on July 20, 2021. (EX1030.) Ren discloses yet another generic structure of GLP-1R agonists. (EX1030.) Ren includes a single generic formula, referred to as Formula (I):

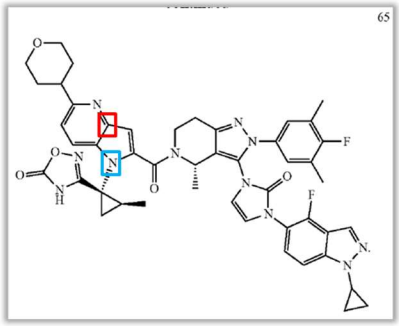


(EX1030, 3:51-67.) There are at least seven positions on Formula (I) at which modifications are allowed as disclosed in Ren.

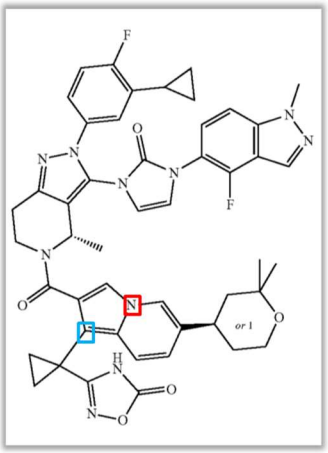
106. Position A is the position of the indole moiety in orforglipron. Ren teaches that A is a bicyclic heteroaryl, selected from 13 different functional groups, which includes an indole. (EX1030, 24:57-46:58.) The functional groups at position A can be further substituted with one or more substituents, and the substituent can also be further substituted with additional substituents. resulting in thousands of possible combinations for position A. (EX1030, 5:51-64; 46:59-54:2.)

107. Ren also discloses at least 103 exemplary compounds. (EX1030, 55-104.) Ren discloses activity data on all 103 exemplary compounds, as well as pharmacokinetic data on Compounds 19, 73, 76, 90, and 91 compared to orforglipron. (EX1030, 457:53-460:30, Tables 29-30.)

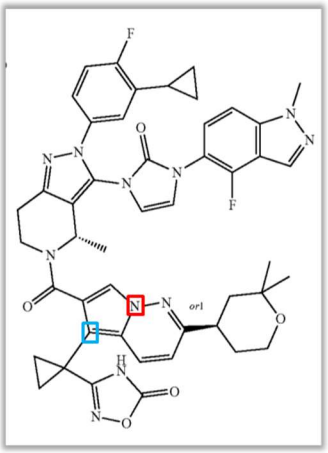
108. Dr. Pirrung opines that it would be a "rational strategy" to incorporate a nitrogen into the indole moiety of orforglipron based on Compounds 76 and 90. (EX1002, ¶¶93-94.) Both Compounds 76 and 90, however, also include a nitrogen in the ring structure (annotated in the red boxes below) that leads to a different functional group than the pyrrolopyridine in Compound 65. Further, Compounds 76 and 90 also have different heterocycles in this position, containing a carbon-linked cyclopropane substituent, compared to Compound 65 which has a nitrogen-linked cyclopropane substituent (annotated in blue boxes below).



Compound 65



Compound 76
(Ren)



Compound 90
(Ren)

109. The pharmacokinetic data disclosed in Ren demonstrates that, among Compounds 19, 73, 76, 90, and orforglipron, Compound 73 has the best bioavailability. (EX1030, 459:60-460:10.) As shown in the table below, Compound 73 has a higher C_{max} and AUC than Compound 90, and its bioavailability is 90% compared to 59% for Compound 90.

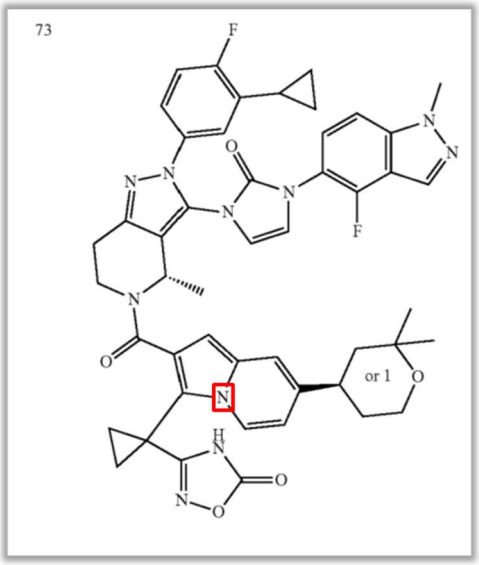
TABLE 30

	PO parameters			
Cmpd No.	Dose (mg/kg)	C_{max} (ng/mL)	AUC (ng hr/mL)	F (%)
Ref. Cmpd 1	10	571	4528	10
19	5	572	2998	26

TABLE 30-continued

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

(EX1030, Table 30.) Compound 73 substitutes the nitrogen atom in a different position than Challenged Compound 65:



Dr. Pirrung provides no reason that a skilled artisan would look to Compounds 76 and 90, instead of Compound 73, in attempting to modify orforglipron. Again, the only reason is hindsight.

6. Bethel (EX1032)

110. International Patent Application No. PCT/US2023/083545 ("Bethel") was filed on December 12, 2023 and was published on June 20, 2024 as WO2024/129676A1. (EX1032, 1.) Bethel discloses a hemicalcium salt of orforglipron. (EX1032.) Bethel is specific to the process of preparing orforglipron for oral administration. (EX1032, 45-53.) Bethel does not disclose any other salts of orforglipron or any other GLP-1R agonist structures or their salts. Nor does Bethel provide any data on the properties of the hemicalcium salt of orforglipron.

B. Dr. Pirrung Relies on Additional Prior Art Unrelated to Orforglipron or GLP-1R Agonists

1. Talele (EX1009)

111. Talele is a general review article on cyclopropyl substituents unrelated to GLP-1R agonists. (EX1009.) Instead, Talele reviews the use of the cyclopropyl ring in a number of different compounds and drugs, none of which are related to GLP-1R agonists.

112. Talele also discloses that cyclopropyl substituents do not always lead to the same outcomes and can in fact have undesirable effects. (EX1009, 24.) As one example, Talele describes replacing an isopropyl moiety in a Histamine H3 receptor antagonist with a cyclopropyl ring. (EX1009, 24.) While cyclopropyl leads to increased half-life in other compounds, this change in the Histamine H3 receptor antagonist reduced the half-life of the drug significantly. Because the cyclopropyl

substituent had the opposite effect in the Histamine H3 receptor antagonist compared to other compounds, Talele cautions that modulating pharmacokinetic properties with a cyclopropyl group "is context dependent and one strategy does not work in all cases." (EX1009, 24; *see also id.*, 20.)

113. Talele also does not provide any teaching or suggestion as to where a skilled artisan might introduce a cyclopropyl substitution on a GLP-1R agonist. It only provides a review for different compounds where that substitution was already made. As discussed below, cyclopropyl substitutions in other positions on the core structure of orforglipron have led to significantly worse properties.

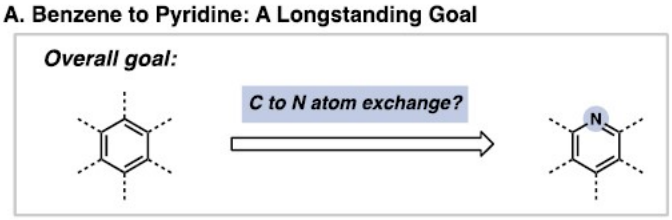
114. Talele is just one of numerous review articles on substituents that can be used in medicinal chemistry. Other articles similarly tout the potential benefits of substituents as diverse as oxetanes and thiadiazoles. (EX2007, EX2008 (oxetanes); EX2009 (oxadiazoles); EX2010 (thiadiazoles); EX2011 (bicyclopentanes); EX2012 (nitrogen heterocycles); EX2013 (aromatic rings); EX2014 (8-11-membered rings); EX2015 (bicyclic rings).) While a skilled artisan would generally be aware of all of these different substituents, there is no way to know what effect they will have at a given position on a given molecule without synthesis and testing.

2. Patel (EX1026)

115. Patel is yet another general review article that has no particular relevance to GLP-1 agonists. Patel discloses a protocol to convert benzenes into pyridines by substituting a carbon in the benzene ring for a nitrogen. (EX1026.)

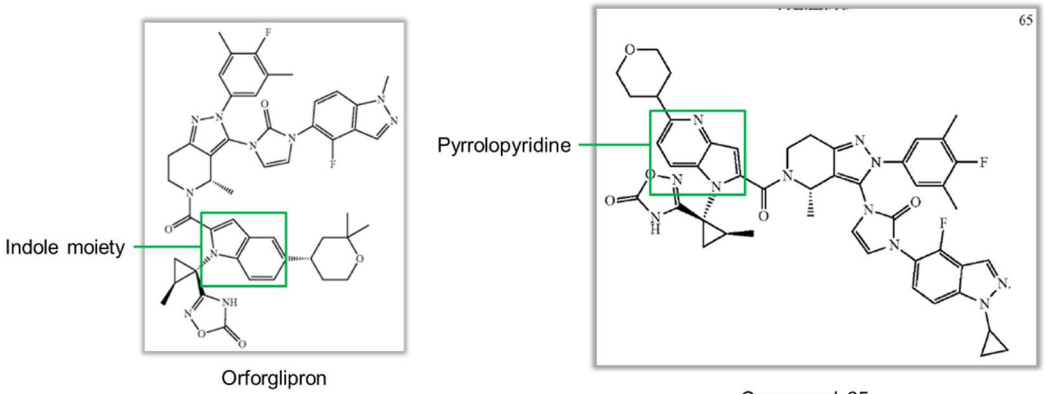
116. Nothing in Patel suggests converting the relevant benzene ring in orforglipron into a pyridine. Instead, a skilled artisan reading Patel would understand that a pyridine is just one of many different modifications and substitutions in the medicinal chemist's tool kit and that changing a benzene ring to a pyridine will affect every molecule in different ways.

117. Generally, Patel discloses exchanging a carbon in a ***benzene ring*** to a nitrogen to form a pyridine ring.



(EX1026, 2.) Patel is not focused on, and does not teach, substituting a nitrogen for a carbon in any particular position of the benzene ring, much less the substituted position in Compound 65. Similarly, Patel's reference to Pennington's "necessary nitrogen atom" is not focused on substituting a nitrogen atom in any particular position of the benzene ring of orforglipron. (EX1026, 1; EX1027.) In Compound 65, the nitrogen substitution is located on the indole moiety of orforglipron, and the

substitution converts the indole into a pyrrolopyridine, shown in the green boxes below.



Orforglipron Compound 65

Patel does not teach or address exchanging a carbon for a nitrogen in an indole moiety to form a pyrrolopyridine as required for Compound 65.

118. Moreover, the properties of indoles, which have a benzene ring fused to a pyrrole, and pyrrolopyridines, which have a pyridine ring fused to a pyrrole, can vary significantly. For example, Liu demonstrates that in analyzing structure-activity relationships for developing drugs that treat cancer metastasis through the inhibition of a transcription factor, hypoxia-inducible factor 1, pyridine rings showed much lower rates of inhibition than benzene groups. (EX1010, Table 4.) Similarly, Burnett illustrates that in analyzing indole-based inhibitors of p97, which has been linked to cancer and neurodegeneration, various substitutions on the indole resulted in over a 2000-fold variation in potency. (EX2039, 1.) Alverez also shows that small substitutions in the indole-based inhibitors of p97 can lead to over a 1000-fold

variation in potency. (EX2040, Table 1.) Patel does not address any of these differences.

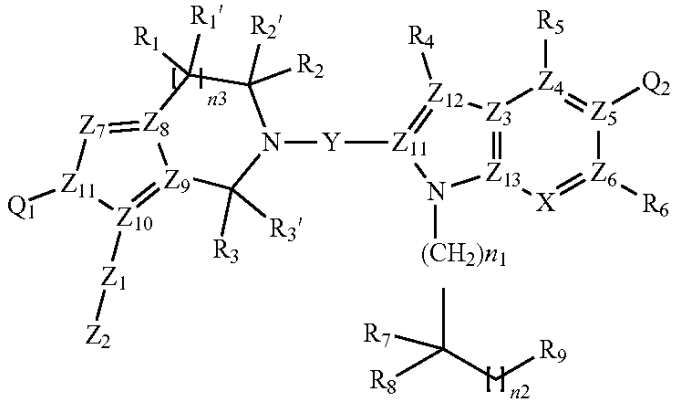
IV. THE ’236 PATENT (EX1001)

A. The ’236 Patent Discloses and Claims Novel GLP-1R Agonists with Improved Properties

119. The ’236 Patent issued from U.S. Non-Provisional Patent Application No. 18/884,965 (“the ’965 Application”), which was filed on September 13, 2024. It claims priority to fourteen provisional applications, including ten Chinese and four U.S. provisional applications, the earliest of which was filed on September 14, 2023. (EX1001, cover.)

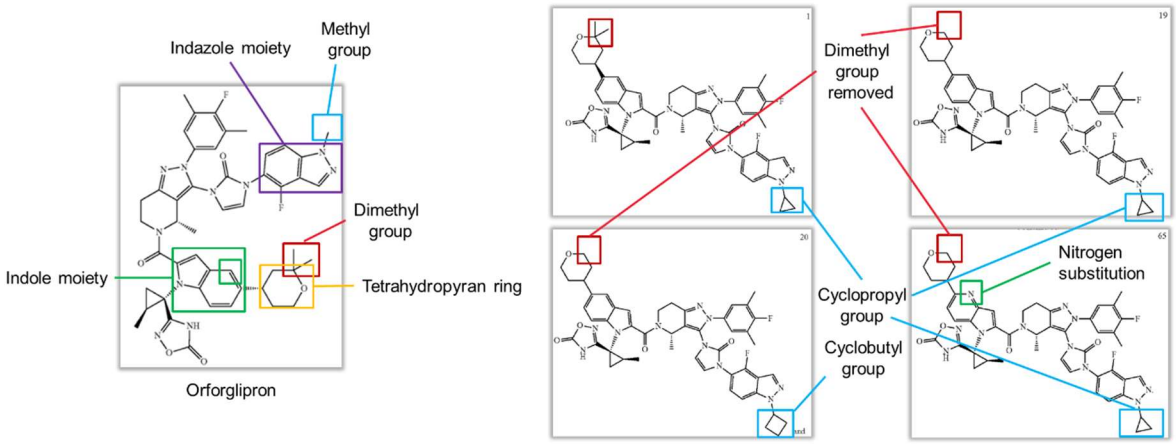
120. The ’236 Patent is directed to “compounds that bind to and act as agonists or modulators of the glucagon-like peptide-1 receptor (GLP-1R)” and the use of such compounds for the treatment of GLP-1R-mediated diseases and conditions. (EX1001, 1:49-55.) The ’236 Patent discloses eleven generic formulas, including Formula (I), shown below:

Formula (I)



121. The ’236 Patent discloses over 60 novel compounds. (EX1001, 167:38-200:48.) The challenged claims cover seven of the disclosed compounds: Compounds 1, 13, 18, 19, 20, 21 and 65. (EX1001, 204:10-220:58.) Out of the seven compounds, Dr. Pirrung only opines that four of those compounds, 1, 19, 20, and 65, are obvious (“the Challenged Compounds”).

122. Compared to orforglipron, Challenged Compounds 1, 19, 20, and 65 all have a cyclopropyl or cyclobutyl substituent in place of the methyl group on the indazole moiety of orforglipron, and Compounds 19, 20, and 65 also have one or more additional modifications, as shown below.



(EX1008, 99 (annotated); EX1001, 205:1-206:66 (annotated).)

123. The '236 Patent discloses unexpected, superior properties for the Challenged Compounds. (EX1001, 199:50-203:67.) The specification discloses the results of an *in vitro* activity study with EC_{50}[1] values for the claimed compounds:

TABLE 2

Bioactivity of different compounds in hGLP-1R agonist cAMP stimulation assay

Compounds	hGLP-1R CAMP: EC_{50} (nM)
1	0.094
13	0.228
18	0.265
19	0.012
20	0.018
21	0.044
24	0.868
29	0.063
35	0.025
36	0.05
37	0.06
55	0.15
65	0.092
66	0.014
70	0.064
76	0.019
77	0.022
78	0.012
79	0.171
80	0.038
81	0.042
82	0.011
84	0.08
50	0.028

[1] EC_{50} is a measure of a drug's potency. A lower EC_{50} indicates higher potency.

(EX1001, 201:1-27, Table 2 (annotated highlighted relevant compounds).) Claimed Compound 19 had an EC_{50} value of 0.012 nM, nearly eight times better than Compound 1. I understand that, although not shown in the '236 Patent, orforglipron demonstrated an EC_{50} value of 0.044 nm in the same assay. (EX2080, ¶8.)

124. The specification also includes the results of two studies comparing the pharmacokinetics[2] of the claimed compounds to orforglipron.

TABLE 3

Drug exposure of different compounds after a single-dose subcutaneous injection

Compounds	Dosing route	Dose, mg/kg	$AUC_{0\text{-}696h}$, ng · h/mL
1	Subcutaneous	30	60,272
13	Subcutaneous	30	23,399
18	Subcutaneous	30	51,234
19	Subcutaneous	30	234,473
20	Subcutaneous	30	77,688
21	Subcutaneous	30	61,479
Orforglipron	Subcutaneous	30	5,390

TABLE 4

Pharmacokinetic parameters of different compounds after a single-dose oral administration

Compounds	Dosing route	Dose, mg/kg	C_{max}, ng/ml	$AUC_{0\text{-}48h}$, ng · h/mL
19	Oral	5	4,460	60,043
20	Oral	5	1,900	16,982
65	Oral	5	10,993	71,836
Orforglipron	Oral	5	799	7,222

Note:
C_{max} refers to the maximum plasma concentration of a drug after administration

[2] The studies measure area under the curve ("AUC"), which represents total drug exposure, and maximum drug concentration ("C_{max}").

(EX1001, 201:31-202:50, Tables 3-4.) For instance, following a single-dose subcutaneous injection, Compound 19 demonstrated an $AUC_{0\text{-}696h}$ of 234,473 ng*h/mL, compared to 5,390 ng*h/mL for orforglipron and 60,272 ng*h/mL for Compound 1 (EX1001, 201:51-63, Table 3.) That represents an almost 4-fold increase compared to Compound 1 and an over 43-fold increase compared to orforglipron. Similarly, following a single oral dose, Compound 19 demonstrated a C_{max} of 4,460 ng/mL and $AUC_{0\text{-}48h}$ of 60,043 ng*h/mL, more than five times and eight times greater than orforglipron's respective values. (EX1001, 202:45.)

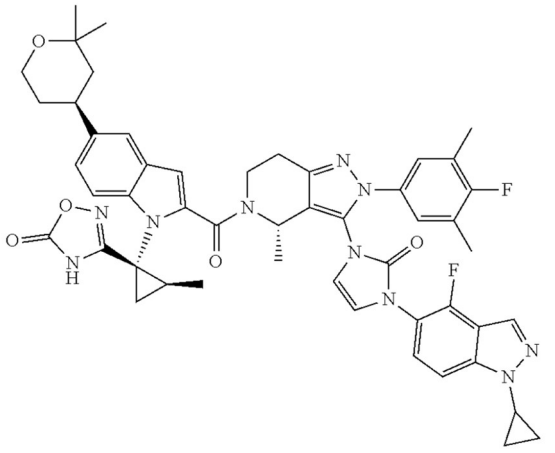
125. The '236 Patent has 25 claims. Claims 1 and 24 are independent claims. Claims 2-23 and 25 depend from claim 1. Independent claim 1 is directed to a compound or pharmaceutically acceptable salt thereof, where the compound is selected from one of Compounds 1, 13, 18, 19, 20, 21, and 65. The claims that depend from claim 1 narrow the claim to the seven claimed compounds and/or particular salts of those compounds. Independent claim 24 is directed to a compound selected from the group consisting of Compounds 1, 13, 18, 19, 20, 21, and 65. The chart below summarizes the subject matter of each of the Challenged Claims.

Claim	Compounds Claimed
1 (Independent)	1, 13, 18, 19, 20, 21, 65 Compound or pharmaceutically acceptable salt
2	1, 13, 18, 19, 20, 21, 65 Sodium, calcium, potassium, magnesium or lithium salt
3	1, 13, 18, 19, 20, 21, 65 - Sodium salt

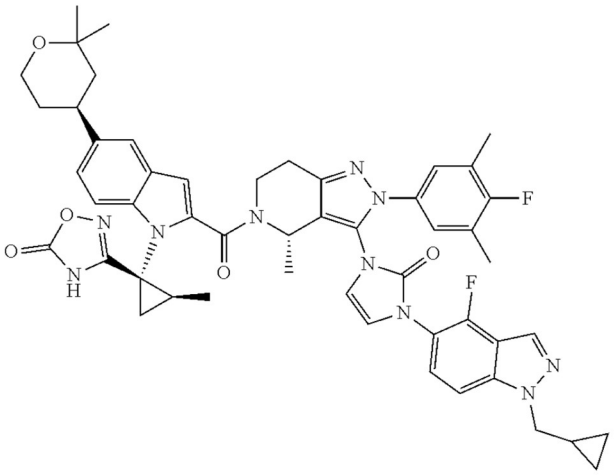
4	1, 13, 18, 19, 20, 21, 65 - Hemicalcium salt
5	1, 13, 18
6	19, 20, 21
7	1
8	1 - Sodium salt
9	1 - Hemicalcium salt
12	19
13	19 - Sodium salt
14	19 - Hemicalcium salt
15	20
16	20 - Sodium salt
17	20 - Hemicalcium salt
21	65
22	65 - Sodium salt
23	65 - Hemicalcium salt
24 (Independent)	1, 13, 18, 19, 20, 21, 65 - Compound only
25	1, 13, 18, 19, 20, 21, 65 - Pharmaceutical composition comprising compound and a pharmaceutically acceptable excipient

126. The structure of each of Compounds 1, 13, 18, 19, 20, 21, and 65 is shown below:

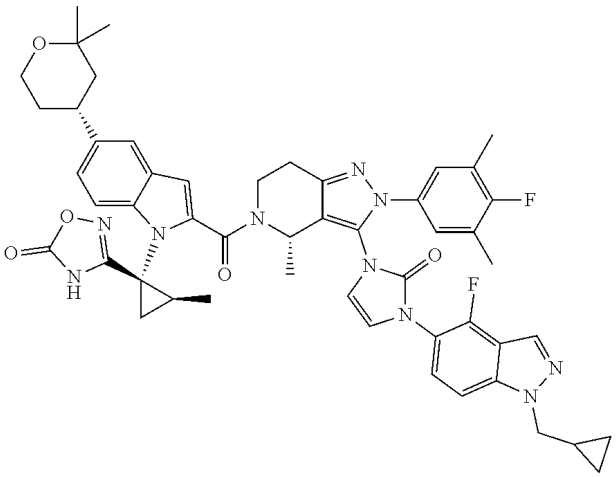
1



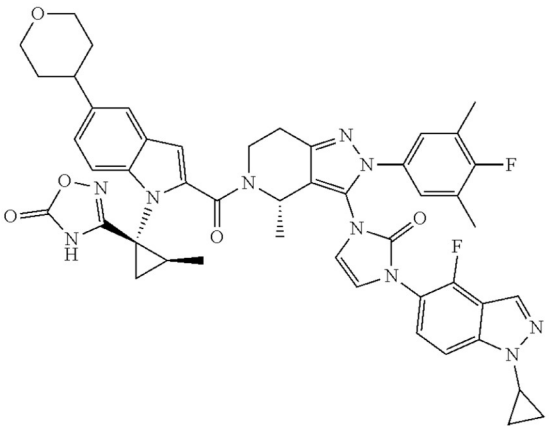
13



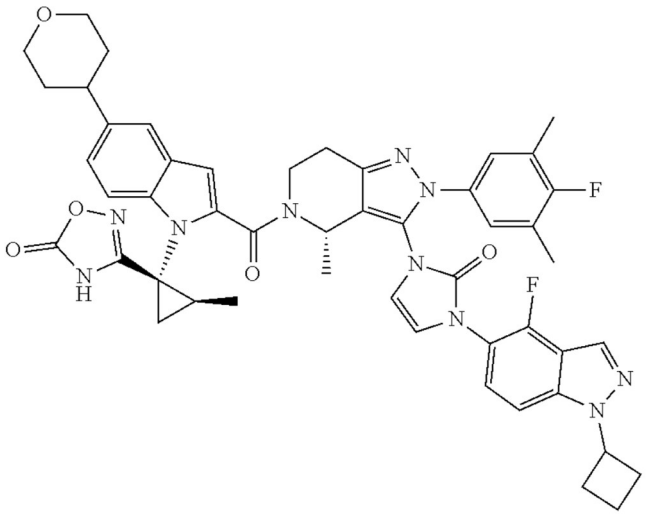
18



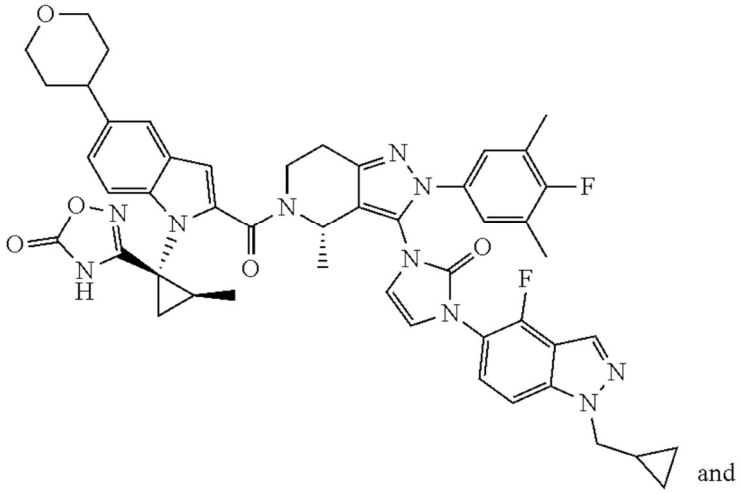
19



20

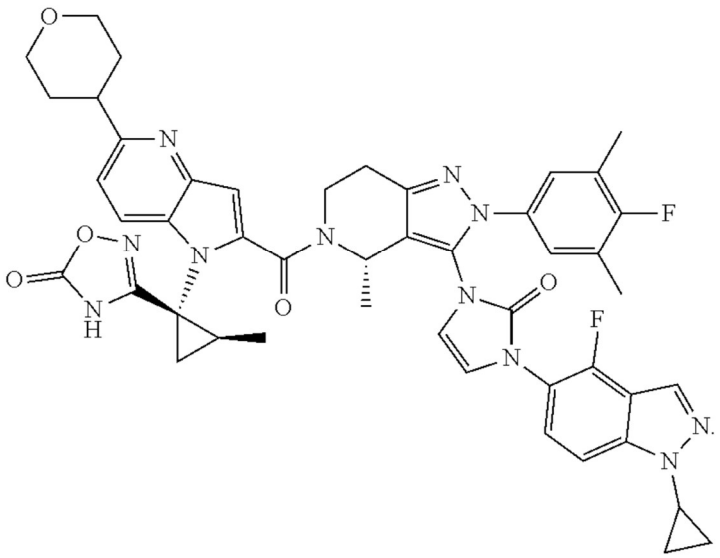


21



and

65



127. I understand that Patent Owner is developing one of the claimed compounds, named ASC30, for treatment of obesity.[3] (EX2022.) In Phase 1 studies, ASC30 showed promising efficacy and safety data, including a superior pharmacokinetic profile and a 6.5% mean reduction in body weight after just 28 days of treatment. (EX2022, 2.) I further understand that Patent Owner recently announced topline results in its 13-week Phase 2 study evaluating ASC30, which continued to show promising safety and efficacy data, including a 7.7% mean reduction in body weight. (EX2042, 1.)

[3] To my understanding, Ascletis has only publicly indicated that ASC30 is covered by the claims of the '236 Patent but has not yet publicly identified the structure of ASC30. (EX2066.)

B. Prosecution History of the ’236 Patent

128. The ’236 Patent issued from the ’965 application, filed on September 13, 2024. (EX1001, cover.) The ’965 application recited 25 claims, including independent claim 1. (EX2002, 154-165.) During prosecution, the Examiner conducted a search report based on the core structure of orforglipron. (EX2002, 312-839.) The search report included 39 references with 529 pages of orforglipron derivates, including WO 2024/169,952 (“Huang”), WO 2023/016,546, and WO 2024/153,070 (“Xu”), which disclose numerous orforglipron derivatives. (EX2002, 312-839; EX2019, [1496]-[1519]; EX2020, 206:14-213:8; EX2021, [251]-[253].)

129. The search report also included 156 pages identifying various structures and disclosures from Yoshino. (EX2002, 681-836, 686 (Yoshino Compound 67), 788 (Yoshino Compound 40), 697 (Yoshino Compound 22), 721 (Yoshino Compound 64), 705 (Yoshino Compound 35), 701 (Yoshino compound 28), 707 (Yoshino Compound 38), 702 (Yoshino Compound 30).) The search report also included Kawai, which the applicant had also disclosed in an IDS. (EX2002, 278, 679.) Ren was also identified in the Examiner’s search report, and applicant also disclosed a related patent publication to Ren in an IDS. (EX2002, 478-496, 273.) Applicant also disclosed Meng in an IDS. (EX2002, 274.) The Examiner initialed the IDS, indicating all references had been considered. (EX2002, 865-872.)

130. The Examiner ultimately allowed the claims, finding "Claims 1-25 are patentable over Yoshino" in the Notice of Allowance. (EX2002, 845.)

V. PERSON OF ORDINARY SKILL IN THE ART

131. Based on my review of the '236 Patent specification, the patent prosecution history, the prior art, and my experience and general knowledge, a skilled artisan is a person with a Bachelor's, Master's, or Doctoral degree in chemistry, medicinal chemistry, organic chemistry, pharmaceutical sciences, or a related field with one to three years of experience in small molecule drug discovery, including routine participation in compound synthesis, biological testing, and interpretation of SAR data, with a greater level of experience expected for a lower degree in education.

132. I qualified as a skilled artisan under this definition as of 2023 and well before that time.

133. Dr. Pirrung offers a slightly different definition of a skilled artisan. While, in my opinion, my definition of the skilled artisan is more appropriate, I also qualified as a skilled artisan under Dr. Pirrung's deposition as of 2023.

VI. PETITIONER HAS NOT PROVEN THAT ANY OF THE CHALLENGED CLAIMS WERE OBVIOUS

134. In the Grounds, Petitioner and Dr. Pirrung allege that Compounds 1, 19, 20, and 65 would have been obvious in view of the asserted prior art. In Ground

1, Dr. Pirrung asserts that claims 1-4, 6, 12-14, 24, and 25 are obvious only with respect to Compound 19 in view of Su, Yoshino, Kawai, and Talele. In Ground 2, Dr. Pirrung asserts that claims 1-9, 12-17, 24, and 25 are obvious only with respect to Compounds 1, 19, and 20 in view of Yoshino, Kawai, and Talele. In Ground 3, Dr. Pirrung focuses only on Compound 65 as claimed in claims 1-4 and 21-25 based on Grounds 1 and 2, and in further view of Meng, Patel, and Ren. In Ground 4, Dr. Pirrung alleges that the hemicalcium salt of Compound 1 as recited in claims 4 and 9 is obvious over Su and Bethel.

135. A summary chart of the asserted grounds is below. Ground 1 focuses only on Compound 19, whereas Ground 2 addresses Compounds 1, 19, and 20. Both Grounds assert Yoshino, Kawai, and Talele as prior art references, but an additional prior art reference, Su, is asserted in Ground 1 with respect to Compound 19 that is not asserted in Ground 2.

Ground	Claims	Asserted References	Compounds
1	1-4, 6, 12-14, 24, and 25	Su, Yoshino, Kawai, Talele	19
2	1-9, 12-17, 24, and 25	Yoshino, Kawai, Talele	1, 19, 20
3	1-4 and 21-25	Su, Yoshino, Kawai, Talele, Meng, Patel, Ren	65
4	4 and 9	Su, Bethel	1 – hemicalcium salt

136. I address each of Petitioner's ground in turn.

A. Ground 1: Compound 19 (Claims 1-4, 6, 12-14, 24, 25) Was Not Obvious Based on Su, Yoshino, Kawai and Talele

137. Ground 1 asserts that Compound 19 is obvious over Su, Yoshino, Kawai and Talele.

138. As explained below, Dr. Pirrung has not shown that Compound 19 is obvious based on Ground 1. First, a skilled artisan would not select Su Compound 44 or 175 as a lead compound. Second, whether starting with Su Compound 44 or 175 or starting with orforglipron, Dr. Pirrung provides no reason to combine the references or make their modifications in one compound, particularly given that Su did not make that combination. Third, even combining those compounds does not result in Compound 19. Fourth, Dr. Pirrung has not established a reasonable expectation of success. Finally, the objective evidence, particularly unexpected results and failure of others shows that Compound 19 is not obvious.

1. A Skilled Artisan Would Not Select Su Compound 44 or 175 as Lead Compounds

139. Although his declaration is not entirely clear, Petitioner and Dr. Pirrung seem to opine that a skilled artisan would view either Compound 44 or Compound 175 as a lead compound for further modification. (Pet., 54; EX1002, ¶¶149-154, 170.) I disagree.

140. Su is but one of numerous prior art references that disclose orforglipron derivatives. As described in Sections III and IV above, the prior art shows that skilled

artisans had already experimented with hundreds to thousands of orforglipron derivatives as of 2023. (EX1008; EX1006; EX1007; EX1028; EX1030; EX2019; EX2020; EX2021.) The asserted art that Dr. Pirrung relies on discloses numerous analogs to orforglipron with multiple potential substitutions on each derivative compound. (EX1008 (disclosing at least 159 exemplary compounds); EX1007 (disclosing at least 218 working examples); EX1028 (disclosing at least two working examples); EX1030 (disclosing at least 103 exemplary compounds).) Each of these references also discloses a generic formulation for GLP-1R agonists, encompassing millions of potential compounds, with innumerable possibilities for functional groups and substituents. (EX1008, 3:1-6:2; EX1007, 5:1-7:4; EX1028, [0007]; EX1030, 3:51-67.) Additional references disclose even more potential analog compounds of orforglipron. For example, WO 2024/169,952 ("Huang") discloses 238 exemplary orforglipron derivatives with extensive data on the biological activity, half-life, potency, permeability, exposure, and solubility of those compounds. (EX2019, [1496]-[1519].) WO 2023/016,546 discloses 150 additional orforglipron derivatives with biological activity for those compounds, as well as rat pharmacokinetic studies and glucose tolerance tests in non-human primates. (EX2020, 206:14-213:8.) WO 2024/153,070 ("Xu") discloses yet another 63 exemplary orforglipron derivatives with biological activity data. (EX2021, [251]-[253].)

141. Dr. Pirrung provides no reason that a skilled artisan would focus on Su out of the numerous prior art references a skilled artisan could have looked to if trying to develop a superior orforglipron derivative. As explained above, the Examiner's search report included 39 references with 529 pages of orforglipron derivates, which disclose millions of orforglipron derivatives. (EX2002, 312-839.) While many of those references include substantial potency and/or efficacy data, Su does not include ***any potency data*** for any of its 218 exemplary compounds and only includes pharmacokinetic data for five compounds that do not maintain the core orforglipron structure. (EX1007, 294-295.) Dr. Pirrung does not explain why a skilled artisan would focus on Su given its sparse data and the plethora of other sources of orforglipron derivatives. Instead, Dr. Pirrung appears to focus on Su based solely on the structural similarity of a small number of Su's compounds and Challenged Compound 19 using hindsight. I understand that approach is legally improper in identifying a lead compound for obviousness.

142. Even starting with Su, a skilled artisan would not select Su's Compounds 44 and 175 as lead compounds for further modification. Su includes 218 exemplary compounds and, as noted above, has data (pharmacokinetic data) for only five of them, Compounds 1, 3, 64, 173, and 174. (EX1007, 294:29-295:1.) In my opinion, if anything, a skilled artisan would reasonably prioritize the five exemplary compounds for which data are reported, out of the over 200 exemplary compounds

disclosed. That data provides important information about characteristics and properties relevant to drug development, such as pharmacokinetics. Second, a skilled artisan would understand that the inventors of Su likely selected these particular compounds for further testing for a reason, possibly reflecting greater interest in developing those compounds than the compounds for which no data is reported. While a skilled artisan would not completely ignore compounds lacking data, they would have no way to assess if the modifications made in those compounds result in better or worse properties and thus would not prioritize them as a lead for further modification.

143. Instead of focusing on the compounds more likely to be considered lead compounds in Su, Dr. Pirrung makes a series of unsupported assumptions to focus on Compounds 44 and 175, which I believe can only be the product of hindsight. In particular, Dr. Pirrung assumes that a skilled artisan would:

a. Ignore the compounds in Su with pharmacokinetic data;

b. Focus instead only on the seven compounds that are "deuterated" (EX1002, ¶¶61-62);

c. From those seven compounds, choose three that "share a common scaffold ring structure" to orforglipron (EX1002, ¶¶63-64);

d. Then from those three compounds, choose Su Compounds 44 and 176 over Compound 35 because of a supposedly "less favorable[] change in electronic character," that is unsupported by any data or disclosure in Su (EX1002, ¶67; EX2033, 92:2-93:1);

e. Then, instead of deuterated compound 176, focus on its non-deuterated counterpart, Compound 175, despite Petitioner and Dr. Pirrung's assertion that deuteration was supposedly performed to improve metabolic function. (EX1002, ¶¶62, 65.)

144. Ignoring Su's data, Dr. Pirrung states, with no support, that a skilled artisan would focus on a group of seven compounds in Su which are "deuterated." (EX1002, ¶¶61-62, 149-151; EX1007, Examples 176, 44, 35, 123, 139, 188, and 212.) Dr. Pirrung conclusively states that "a skilled artisan would have understood that the selection of specific compounds for deuteration studies reflects their heightened potential for lead optimization." (EX1002, ¶150.) But Su does not give any explanation or analysis as to why the seven compounds in particular were deuterated, and deuteration does not, by itself, imply any lead prioritization. Contrary to Dr. Pirrung's opinion, a skilled artisan would not understand Su's

deuterated compounds to be those that the inventors viewed as "of particular significance" and "promising candidates." (EX1002, ¶151.)

145. Dr. Pirrung asserts that the Su compounds were likely deuterated to improve their metabolic stability. (EX1002, ¶62.) While deuteration is one tool used by medicinal chemists to try to slow drug metabolism and increase stability and efficacy, there is no indication that the inventors of Su had any desire to deuterate the compounds for this reason. (EX2041, 5-6.) But even if Dr. Pirrung was correct, if anything, the deuteration would indicate to a skilled artisan that there was some metabolic problem with the non-deuterated "parent" compounds that the inventors were trying to fix, not that they were preferred compounds. Moreover, there is no data in Su to inform a skilled artisan as to whether the deuteration improved or worsened any metabolic properties of the compound. A skilled artisan would only know that Su chose to provide the pharmacokinetic data of Compounds 1, 3, 64, 173, and 174, none of which are deuterated. (EX1007, 294:29-295:1.)

146. Of the seven deuterated compounds, Dr. Pirrung, again using hindsight, opines that a skilled artisan would focus on Compounds 35, 44, and 176 because they have the same "common scaffold ring structure" as orforglipron, and a skilled artisan would have been motivated to only initially make "peripheral modifications" to this core structure. (EX1002, ¶¶63-69, 152.) Dr. Pirrung ignores that Su only discloses data for compounds that do not retain the "common scaffold ring structure"

as orforglipron (EX1007, 97, 98, 150, 243, 294-295), which would suggest to a skilled artisan that the Su inventors were not focused on only "peripheral modifications." Dr. Pirrung also provides no reason that a skilled artisan would think that the "common scaffold ring structure" of Compounds 35, 44, and 176 would make a skilled artisan think they would have desirable ***properties*** relative to the other deuterated compounds in Su. Again, Dr. Pirrung's opinion appears to be based solely on selecting compounds that have structural similarity to the Challenged Compounds using hindsight.

147. Dr. Pirrung then pushes Compound 35 aside because its modifications produce a "less favorable[] change in electronic character" than the modifications in Compounds 175 or 44. (EX1002, ¶67.) However, Dr. Pirrung provides no explanation of what he considers a resulting less favorable property. Further, even if there is a change in electronic character in Compound 35, Su does not provide any data as to the effect of that change, and a skilled artisan would therefore not know whether the change is favorable or unfavorable. Dr. Pirrung also admitted in his deposition that he did not consider any data when concluding that Compound 35 would have a "less favorable[] change in electronic character." (EX2033, 92:2-93:1; EX1002, ¶67.) It is therefore unclear why Dr. Pirrung discounts Compound 35 in favor of Compounds 44 and 176, except for the use of hindsight.

148. Dr. Pirrung next assumes, without explanation, that a skilled artisan would focus on Compound 175, which is the non-deuterated "parent" of Compound 176, instead of Compound 176 itself. (EX1002, ¶¶151, 153.) As Dr. Pirrung himself argues, however, deuteration involves "laborious synthetic procedures" and "often examined to enhance metabolic traits of drug candidates." (EX1002, ¶62.) Su does not disclose any data for Compounds 175 or 176 that would allow a skilled artisan to determine how the deuteration affects the properties of those compounds. Further, Dr. Pirrung gives no reason as to why a skilled artisan would first synthesize a deuterated compound, which is a laborious process and examined for metabolic properties, only to then remove them, particularly where there is no data demonstrating the properties of either Compound 175 or 176.

149. For all of the reasons above, a skilled artisan would not select Compounds 44 or 175 for lead optimization.

2. Dr. Pirrung Fails to Identify Any Specific Reason to Modify Orforglipron or the Su Compounds

150. Dr. Pirrung does not provide any specific reason to modify orforglipron or Su Compounds 44 and 175 or any property of those compounds that a skilled artisan would have been motivated to improve.

151. Instead, Dr. Pirrung's declaration praises the attributes of orforglipron. Dr. Pirrung admits that orforglipron was "orally bioavailable" and "[exhibited] full

agonist efficacy . . . comparable to native GLP-1." (EX1002, ¶¶48-49.) Further, Dr. Pirrung admits that orforglipron was "structurally optimized" for "once daily oral administration." (EX1002, ¶49.) Dr. Pirrung also cites to Phase 2 clinical trials of orforglipron, which "significantly reduced HbA1c and body weight compared to placebo, while maintaining a favorable safety profile." (EX1002, ¶51; EX1010, 4; EX1012, 2.) Based on that information, Dr. Pirrung calls orforglipron a "promising candidate" in Phase 3 clinical trials that had "the potential to transform treatment paradigms for patients with type 2 diabetes and obesity." (EX1002, ¶51; EX1012.) Dr. Pirrung thus does not identify any issues with orforglipron or motivation for a skilled artisan to seek to modify orforglipron (or Compounds 44 and 15 of Su) based on the prior art and clinical trials data.

152. Dr. Pirrung, instead, seems to identify two broad reasons a skilled artisan would not have been ***discouraged*** from the modifications in Challenged Compound 19. First, Dr, Pirrung opines that a skilled artisan would have understood from Kawai that the binding pocket "could accommodate a bulkier substituent without significantly disrupting the overall structure." (EX1002, ¶206.) Second, that a skilled artisan would understand that certain modifications to orforglipron would "maintain" or "preserve" biological activity. (EX1002, ¶¶208, 212-213.) I disagree that either argument would motivate a skilled artisan to modify orforglipron or Su's Compounds 44 or 175.

153. Dr. Pirrung's approach is contrary to the approach a medicinal chemist would take in seeking to modify a known compound. As discussed above, a skilled artisan would not seek to modify a compound such as orforglipron without defining the target compound profile ("TCP") or identifying a characteristic or property to be improved. *See* Section II.B. Dr. Pirrung does not identify any particular criteria for modifying orforglipron but, instead, appears to try to identify arguments why a skilled artisan would not be ***discouraged*** from making the substitutions in the claimed compounds. In my opinion, that approach uses improper hindsight.

154. As to the first reason, Dr. Pirrung opines that a skilled artisan would have understood from Kawai that the binding pocket "could accommodate a bulkier substituent without significantly disrupting the overall structure." (EX1002, ¶206.) Even if Kawai indicated that the binding pocket could allow for a bulkier substituent, which it does not, as discussed below, that does not provide a reason or motivation for a skilled artisan to modify orforglipron in the manner Dr. Pirrung opines. A skilled artisan would not modify an existing compound simply because a binding pocket "could accommodate" a different substituent. Instead, a skilled artisan would need a reason to think that a substitution at the relevant position might lead to some desired property.

155. As to the second reason, a skilled artisan would not synthesize and test newly modified compounds simply because they believed the modification would

preserve, maintain, or retain activity, or because the modification did not cause disruption in the structure and binding of the compound, unless they had some other defined goal. Dr. Pirrung cannot establish motivation simply by showing that a skilled artisan would not have expected the modifications to make the properties worse. For example, Dr. Pirrung opines that modifications to the indazole moiety on orforglipron "would not be expected to cause significant structural perturbation to the pocket and, therefore, would likely preserve binding potency." (EX1002, ¶208.) Similarly, he states that "Yoshino suggests that replacement of the methyl group with a ring structure can maintain the biological activity of the lead compound." (EX1002, ¶213.) A skilled artisan, however, would seek to achieve a desirable property, not synthesize compounds for the sake of making new compounds and maintaining activity.

156. In my opinion, Dr. Pirrung has failed to establish that a skilled artisan would be motivated to modify orforglipron (or Su Compounds 44 or 175) in a way that would lead to the Challenged Claims.

3. Starting with Orforglipron, Dr. Pirrung Fails to Prove that a Skilled Artisan Would be Motivated to Make the Specific Substitutions in Compound 19

157. A skilled artisan would need to make three changes to orforglipron to arrive at Compound 19. First, the skilled artisan would have to replace the methyl group on the indazole moiety of orforglipron with a cyclopropyl group. Second and

third, the skilled artisan would have to remove each of the two methyl groups on the tetrahydropyran ("THP") moiety of orforglipron. Dr. Pirrung has failed to establish a motivation to make those changes.

i. Dr. Pirrung Does Not Provide a Motivation to Replace the Methyl on the Indazole Moiety with Cyclopropyl

158. Starting with orforglipron, a skilled artisan would need to replace the methyl on the indazole moiety with a cycloalkyl, specifically a cyclopropyl, to achieve Compound 19. Dr. Pirrung has failed to show that a skilled artisan would be motivated to make that substitution.

159. A skilled artisan would know that there were numerous positions for potential modification or substitution on orforglipron. (Section III.A.) For example, as explained above, the Examiner's search report included 39 references with 529 pages of orforglipron derivates, which disclose millions of orforglipron derivatives. (EX2002, 312-839.) The indazole group on orforglipron, and specifically its methyl substituent, was no more than one among these options.

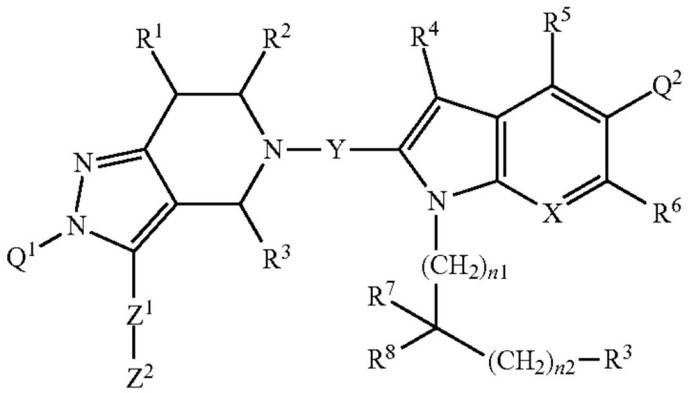
160. A skilled artisan would also have been aware of the "magic methyl effect" explained above in Section II.B. Because of that known effect, a skilled artisan would not have been particularly motivated to substitute the methyl group with alternate substituents on the indazole moiety, recognizing that the methyl effect would have a significant impact on the molecule's potency, selectivity, conformation

and pharmacokinetics. (EX2028.) Thus, without some specific reason to think that replacing the methyl group with a cyclopropyl group would lead to a desirable result, a skilled artisan would not have been motivated to consider alternative substituents to the methyl group on the indazole moiety. As discussed below, the prior art does not provide such a motivation.

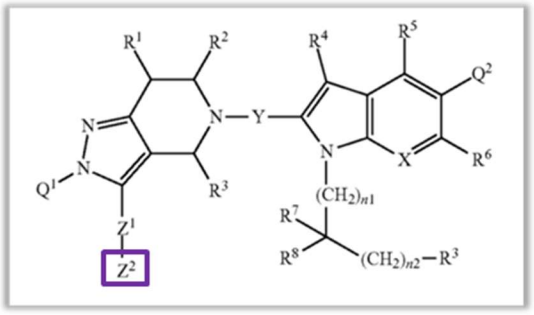
a. Yoshino

161. Yoshino fails to teach or suggest substituting the methyl on the indazole moiety with a cycloalkyl substituent. A skilled artisan, in fact, would read Yoshino to teach away from such a substitution. As described in more detail below, Yoshino does not allow for a cycloalkyl substituent on the indazole moiety. Further, none of the exemplary compounds in Yoshino that include an indazole moiety have a cycloalkyl substituent on the indazole.

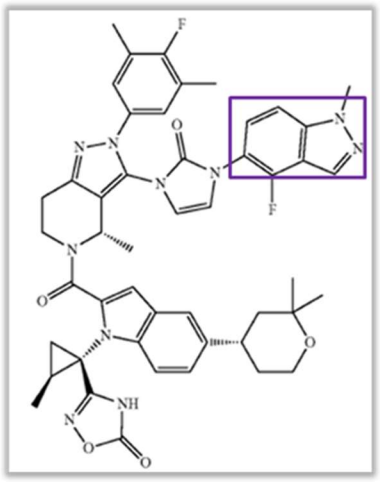
162. Yoshino discloses a general chemical structure of the invention, Formula (I):



(EX1008, 3:1-6:2.) In Formula (I), position Z^2 corresponds with the location of the indazole moiety in orforglipron (annotated in purple boxes).



Formula (I)



Orforglipron

Z^2 = indazole moiety

(EX1008, 3:5-15 (Formula (I)); EX1008, 99 (Example Compound 67).) Yoshino teaches that Z^2 can be selected from five possible classes of substituents, including "C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl and 5 to 10 membered heteroaryl." (EX1008, 5:21-26.) Yoshino goes on to teach that the "5 to 10 membered heteroaryl," which includes indazole, can be "optionally substituted with ***one to five substituents***" selected from eleven broad categories that include hundreds if not thousands of substituents. (EX1008, 5:21-6:2 (emphasis added).)

163. Despite the large number of options, ***Formula (I) does not allow for cycloalkyl groups*** on the indazole moiety at Z^2. While Z^2 itself specifically lists cycloalkyl as an option (EX1008, 5:21-26), the list of substituents allowed on the Z^2 group ***does not*** list cycloalkyl groups. Moreover, although the Z^2 substituents

include "C_{1-6} alkyl" and "3 to 12 membered heterocyclyl," the patent defines those terms to exclude cycloalkyl groups (EX1008, 5:21-6:2, 9:56-62, 10:39-64.) A skilled artisan would thus understand that cycloalkyls are excluded from the substituents allowed for at Z^2.

164. Yoshino also discloses 159 exemplary compounds, including orforglipron. (EX1008, 31-55, 89-90, 92-101, 120-121, 133-161.) Many of these compounds include an indazole moiety at Z^2 with substituents other than a methyl on the indazole. (*E.g.*, EX1008, Example Compounds 16, 126, 28, 26, 17, 120, 119, and 30.) None of the examples, however, include a cycloalkyl substituent.[4] This further reinforces a skilled artisan's understanding that Yoshino excludes, and teaches away from, cycloalkyl substituents on Z^2.

165. Ignoring this express exclusion, Dr. Pirrung instead opines that Yoshino generally teaches replacing the methyl group with a ring structure because certain exemplary compounds include a tetrahydrofuran ("THF") ring. (EX1002, ¶¶210-213.) I disagree with Dr. Pirrung's analysis.

166. First, cycloalkyl groups and THF rings have different properties that lead to different effects as substituents. THF rings are moderately polar because

[4] Further, Yoshino is not the only prior art reference claiming a large genus of orforglipron derivatives that does not allow for a cycloalkyl on the indazole moiety. As explained above, Meng similarly ***does not allow*** for a cycloalkyl group on the indazole moiety. (EX1029, [0010].)

they include an oxygen atom, whereas cycloalkyls, such as cyclopropyl or cyclobutyl, are non-polar because they include only carbon and hydrogen. (*Contrast* EX2024 *with* EX2025.) This means that the electrons on the atoms of a THF ring are not shared evenly, while the electrons on cycloalkyls are shared evenly. Polar groups, such as the THF ring, tend to be more hydrophilic, meaning they are attracted to water, and non-polar groups, such as cyclopropyl and cyclobutyl, are hydrophobic and are repelled by water. Generally, the oxygen atom on a THF ring also plays an important role in the ligand-binding site of a drug compound, which can change the interactions of the molecule. (EX2026, 2; EX2027, 2-6.) A skilled artisan would therefore not expect a polar THF ring and a non-polar cycloalkyl to have similar effects as a substituent. (EX2026, 2; EX2027, 2-6.) As a result, even if Yoshino motivated a skilled artisan to substitute a THF ring on the indazole moiety, it does not follow that it would motivate the same for all ring structures, particularly given Yoshino's exclusion of cycloalkyl groups on the indazole moiety.

167. Second, Yoshino does not actually teach that substituting a THF ring on the indazole moiety is beneficial. To the contrary, every compound disclosed by Yoshino with a THF substitution has ***less activity*** than orforglipron. (*See* EX1008, 162-163 (*contrast* Compound 8 (2.5 nM), Compound 14 (2.3 nM), Compound 22 (2.3 nM), Compound 40 (2.2 nM), and Compound 64 (2.0 nM) *with* Compound 67 (1.2 nM)).) For instance, Compound 40, which Dr. Pirrung points to as having

"comparable biological activity" actually has a nearly 2-fold decrease in activity. (EX1002, ¶210; EX1008 (*contrast* Compound 67 (1.2 nM) *with* Compound 40 (2.2 nM)).) Indeed, during his deposition, Dr. Pirrung admitted that the decrease in activity caused by the substitution of a THF ring in Yoshino's Compound 40 was "significant." (EX2033, 65:22-66:6 (acknowledging that Compound 40 has a 1.8-fold lower potency than orforglipron and is a "significant difference").) Dr. Pirrung does not explain why a skilled artisan would seek to modify orforglipron with a substituent that led to a significant decrease in activity.

168. Other compounds disclosed in Yoshino that do not contain the THF ring have up to four times greater activity. (EX1008, 162-163 (Compound 16 (0.51 nM), Compound 26 (0.77 nM), Compound 31 (0.74 nM), Compound 32 (0.94 nM)).) In my opinion, if anything, a skilled artisan would consider these compounds and substitutions rather than the THF-containing compounds when seeking to modify orforglipron. Dr. Pirrung's selection of the only modification disclosed in Yoshino that substitutes the methyl on the indazole moiety for a ring structure, without any reason for doing so, can only be explained by hindsight.

b. Kawai

169. Kawai likewise would not motivate a skilled artisan to substitute the methyl on the indazole moiety with a cycloalkyl.

170. There is no explicit teaching in Kawai to make any changes to orforglipron, and Dr. Pirrung does not contend otherwise. In fact, Kawai praises orforglipron (LY3502970), noting that it "displays a preclinical pharmacodynamic profile similar to marketed peptide-based GLP-1R agonists and possesses pharmacokinetic properties compatible with oral dosing in humans." (EX1004, 7.) Instead, Dr. Pirrung relies on a two-dimensional image in Kawai of a structural model of the interaction of orforglipron with the GLP-1 receptor. (EX1004, 2-4, Fig. 1I, 8.) In my opinion, Dr. Pirrung's conclusions based on that image are incorrect.

171. Dr. Pirrung states that Kawai teaches "which regions of the ligand-binding pocket exhibit conformational flexibility and could accommodate a bulkier substituent without significantly disrupting the overall structure of the binding pocket." (EX1002, ¶206.) Kawai's comments on confirmational flexibility, however, refer to GLP-1 receptors in general and do not suggest that the region surrounding the methyl group "could accommodate a bulkier substituent." (EX1004, 4 ("The unique conformation of TM2 observed in our structure and the binding mode of LY3502970 would be difficult to computationally predict even with prior structural information on GLP-1R, ***highlighting the conformational flexibility of GLP-1R and GPCRs in general***.") (emphasis added).)

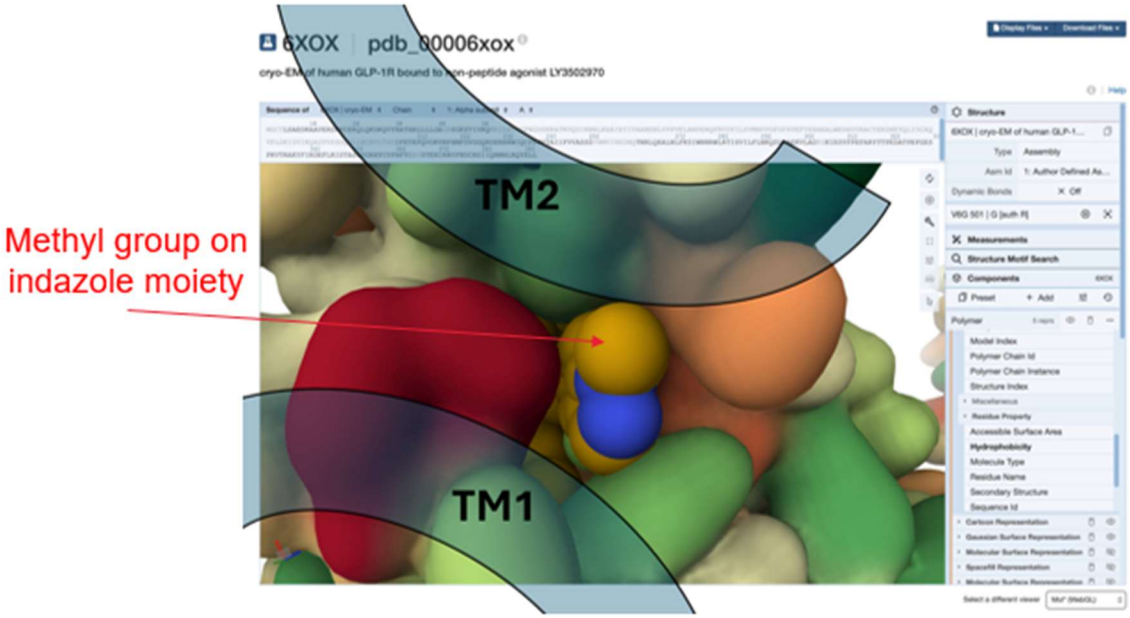
172. Kawai actually suggests that a bulkier substituent on the indazole moiety could have negative consequences. Kawai states that "the 4-fluoro-1-methyl-

indazole moiety (Fig. 1A, blue shading) of LY3502970 has aromatic interactions with Tyr205$^{2.75}$ and Tyr145$^{1.40}$ . . . .” (EX1004, 4.) Tyr205 and Try145 are two tyrosine amino acid residues on the GLP-1 receptor. (EX1004, Fig. 1I.) Tyrosine includes an aromatic, or benzene, ring. A skilled artisan would understand from this disclosure that the aromatic ring structure in the indazole moiety and the aromatic rings on the two tyrosine residues on the GLP-1 receptor interact and have a stabilizing effect on the protein structure. A skilled artisan would therefore understand that a bulkier substituent replacing the methyl group on the indazole ring could disrupt these aromatic, or stabilizing, interactions and lead to worse properties. (EX1002, ¶208.)

173. Dr. Pirrung also incorrectly opines that the two-dimensional image of the cryo-EM model in Kawai shows that the region surrounding the ligand-binding pocket where the methyl group on the indazole moiety binds is “spacious” and “characterized by a hydrophobic environment.” (EX1002, ¶209.) I disagree on both points.

174. As described above in Section III.A.3, a skilled artisan seeking to fully understand the ligand-binding interactions orforglipron and GLP-1 receptor would consider Kawai’s complete three-dimensional cryo-EM structure, which was deposited in the Protein Data Bank. (*See supra* Section III.A.3.) An image from that complete model showing the pocket where the methyl group on the indazole moiety

of orforglipron interacts with the GLP-1 receptor is shown below (referenced by the yellow sphere):

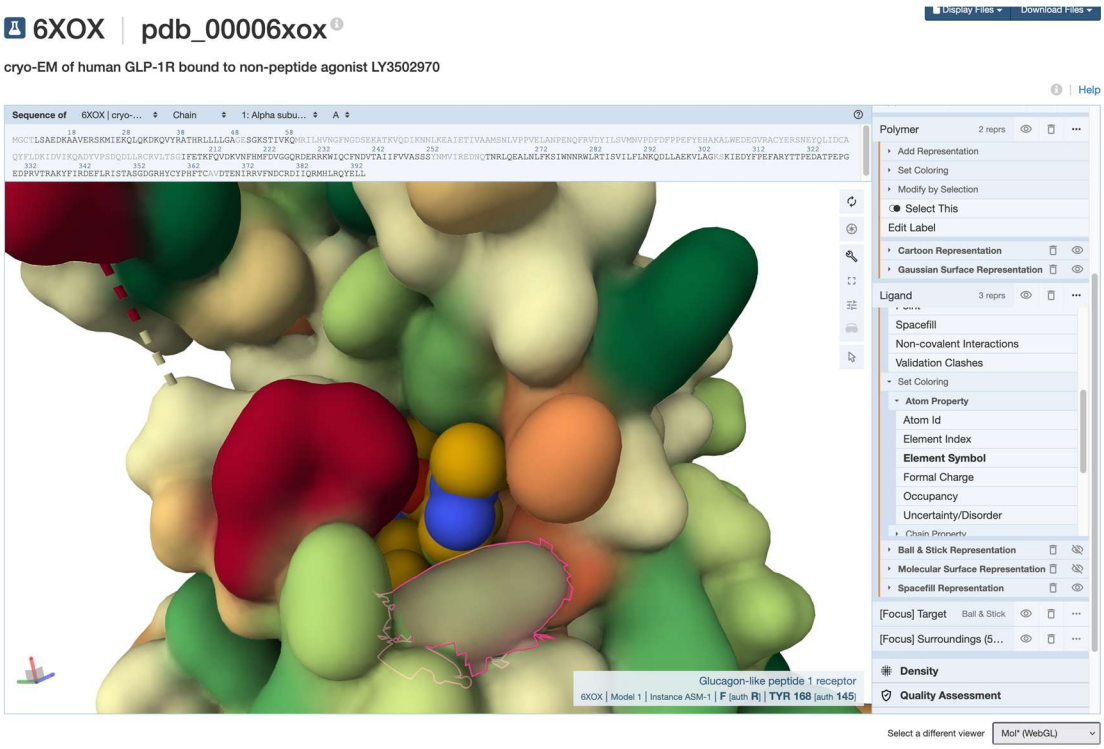


(EX2035, 2 (annotated indicating the TM1 and TM2 side chains and the methyl group on the indazole moiety).) Dr. Pirrung relies solely on the two-dimensional image of the cryo-EM structure depicted in Kawaii and does not acknowledge that a skilled artisan would analyze the complete three-dimensional nature of orforglipron binding to the GLP-1 receptor. (EX2033, 36:17-37:7, 38:1-12.)

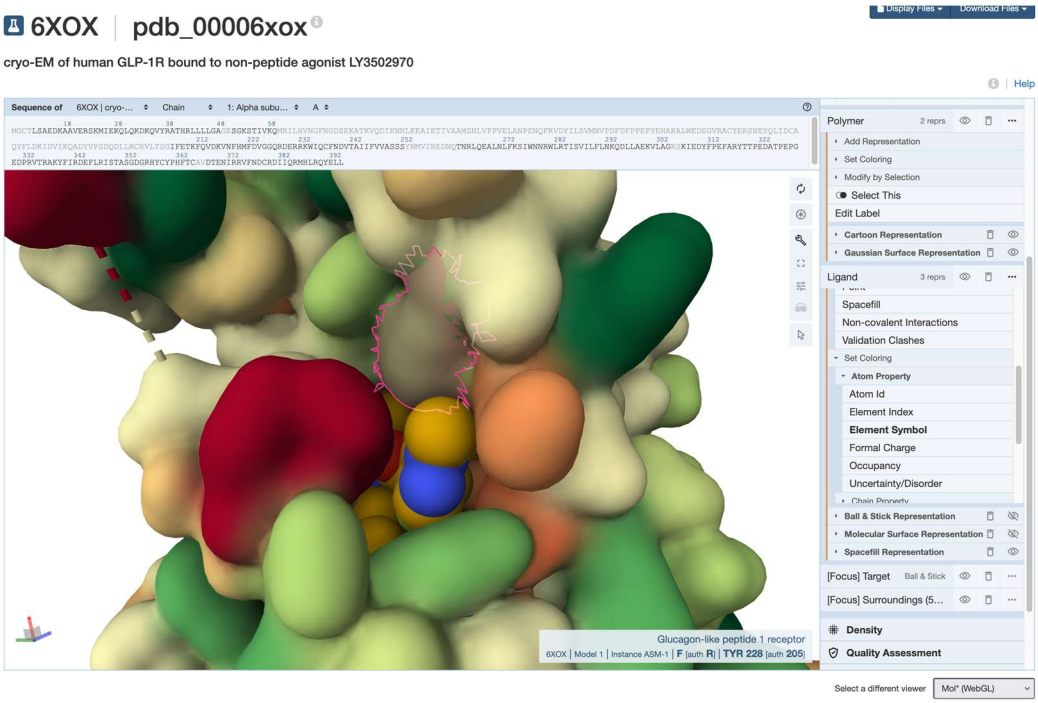
175. Based on the 3D cryo-EM structure in Protein Data Bank and the information in Kawai, a skilled artisan would not think that the binding pocket formed by TM1-TM2 strands is "spacious." In the cryo-EM structure above, the methyl group on the indazole moiety is represented by the yellow ball and the

various portions of the GLP-1R are shown in green, orange, and red. As a skilled artisan would see, the methyl group fits well in the area of the binding pocket on the GLP-1 receptor. A skilled artisan would understand that the binding pocket has adequate space for the indazole moiety with a methyl substituent, not that there is additional space to accommodate a bulkier substituent.

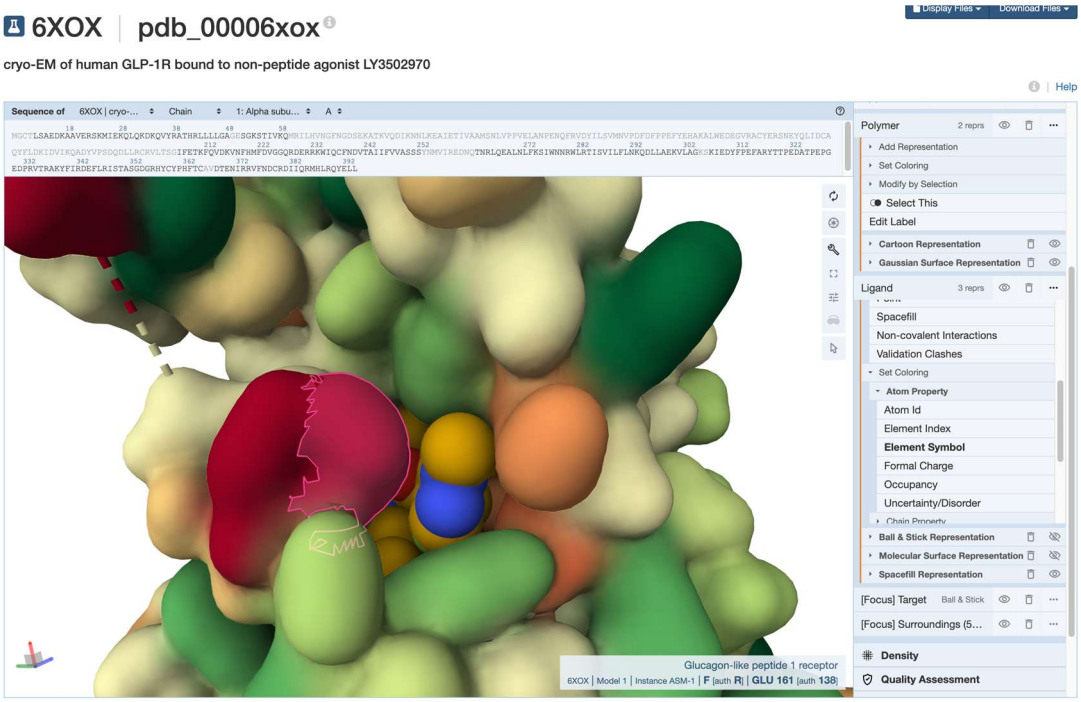
176. A skilled artisan would also not understand the binding pocket to be "hydrophobic" (i.e., non-polar). As Dr. Pirrung admits, Kawai discloses that the region is formed by tyrosine, glutamate, and lysine. (EX1002, ¶209; EX1004, Fig. 1I.) This is also confirmed by the cryo-EM structure in the Protein Data Bank, which shows the methyl group on the indazole moiety surrounded by two tyrosine residues, a glutamic acid, and a lysine, shown below.



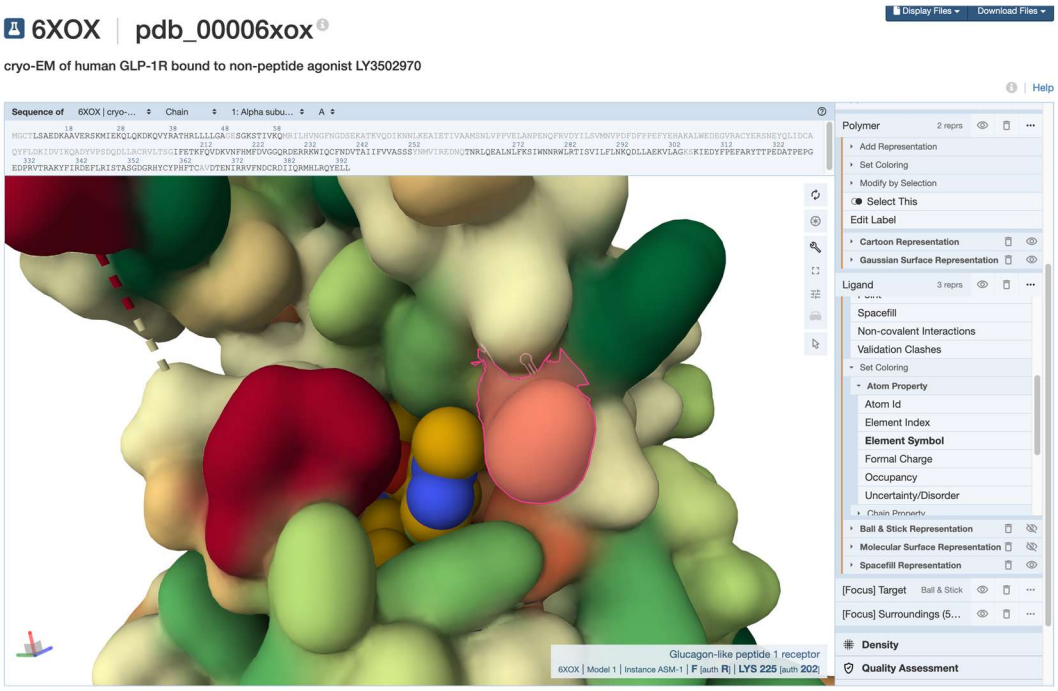
(EX2035, 5 (depicting a tyrosine residue below the methyl group).)



(EX2035, 6 (depicting a tyrosine residue above the methyl group).)



(EX2035, 3 (depicting a glutamic acid residue to the left of the methyl group).)

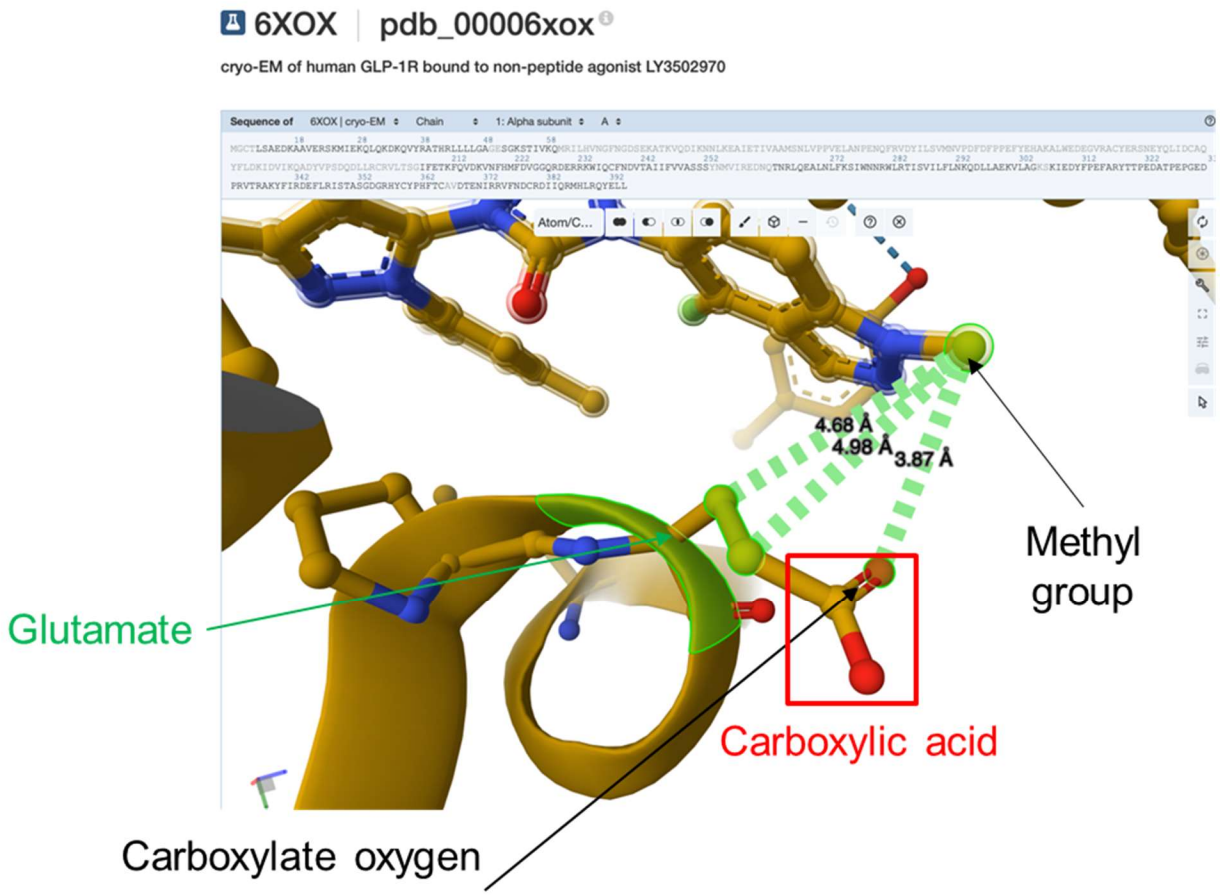


(EX2035, 4 (depicting a lysine residue to the right of the methyl group).)

177. A skilled artisan would know that glutamate and lysine are polar amino acids, and tyrosine is amphipathic, meaning it has polar and non-polar properties. (EX2036.) As described above, polar molecules tend to be hydrophilic and favor water. Further, as described above, the cryo-EM structure shows the hydrophobicity or hydrophilicity of the molecular surface of the GLP-1 receptor. Hydrophobic areas are shaded green and hydrophilic areas are shaded in red and orange. As is visible in the cryo-EM structure, the area immediately next to the methyl group on the indazole moiety is shaded in red and orange on either side, indicating hydrophilic surfaces, consistent with the disclosure in Kawai that the area surrounding the region where

the methyl group binds is hydrophilic. (EX1004, Fig. 1I (illustrating that the methyl group is flanked by polar amino acids, LYS202 and GLU138, and facing outwards towards the cellular environment).)

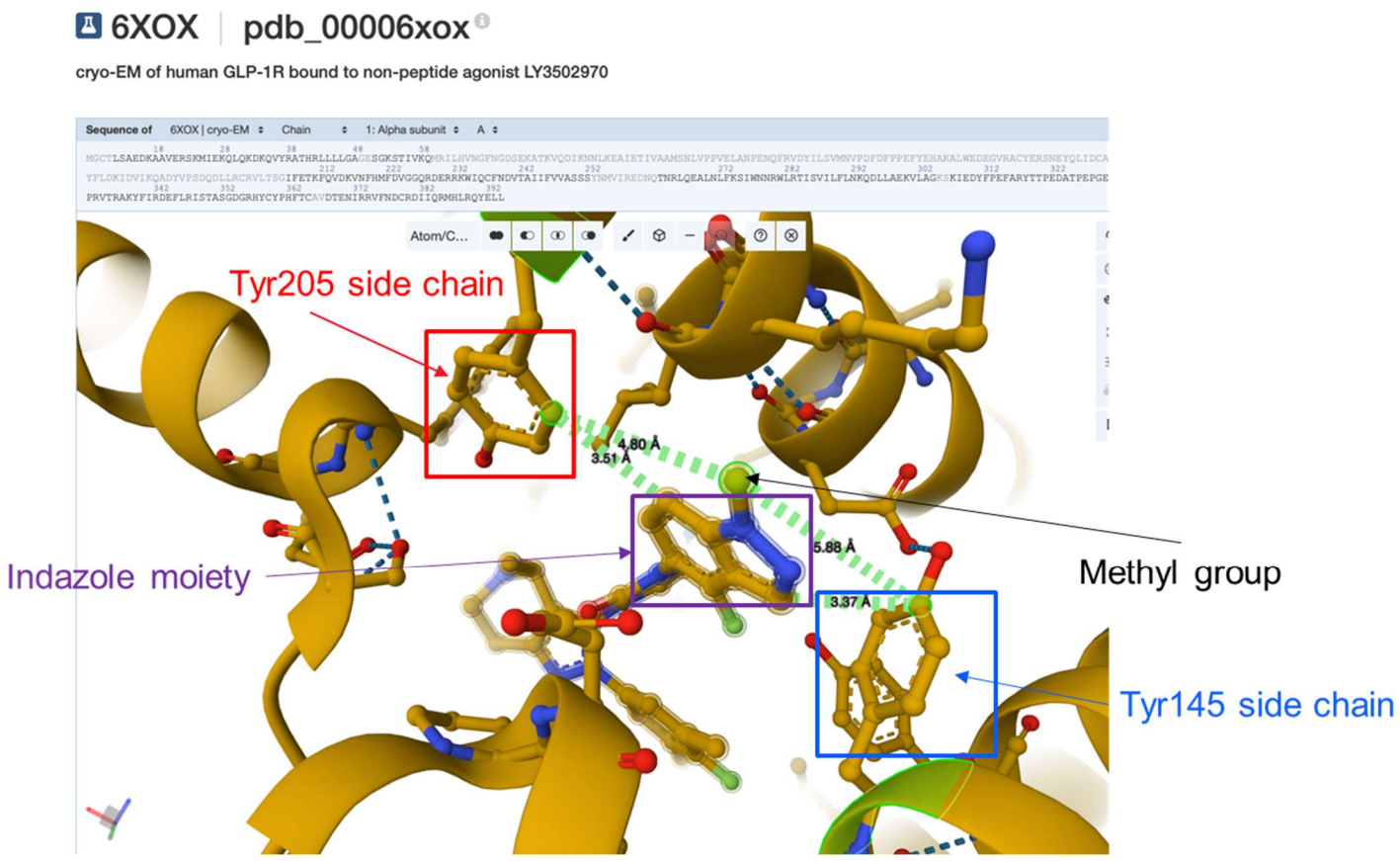
178. The cryo-EM structure further shows that the methyl group on the indazole moiety is close to the carboxylic acid on the side chain of the glutamate on the GLP-1 receptor.



(EX2035, 7 (annotated).) Contrary to Dr. Pirrung's opinion that the environment surrounding the methyl group is formed by the carbon atoms of the glutamate (GLU138) (EX1002, ¶209), the cryo-EM structure shows that the carboxylate

oxygen on the carboxylic acid is closer to the methyl groups than the carbon atoms of glutamate, forming a more polar and hydrophilic environment. Thus, if anything, a skilled artisan would believe this region would favor hydrophilic substituents, which tend to be polar, rather than non-polar, hydrophobic substituents, like cyclopropyl and cyclobutyl.

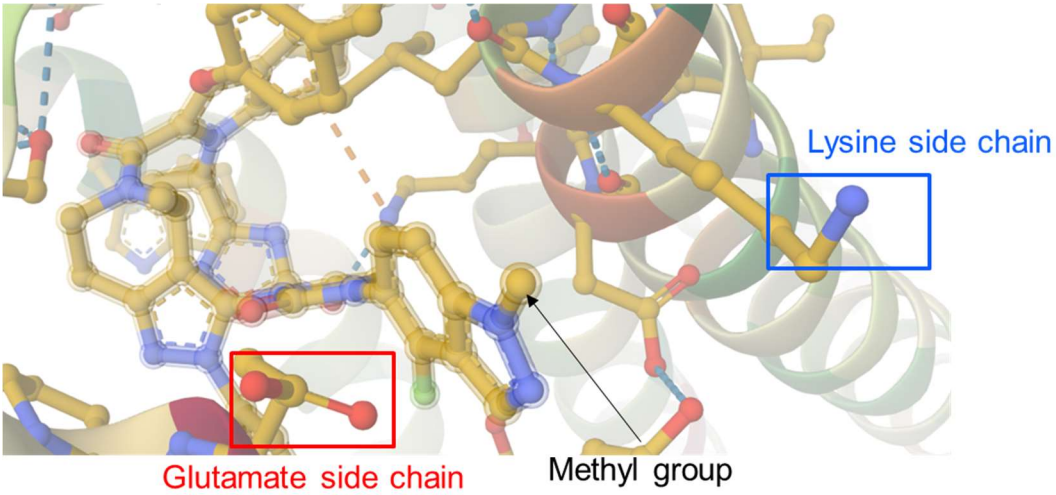
179. Dr. Pirrung also stated during deposition that Kawai's disclosure of Tyr205 interacting with the indazole moiety (EX1004, 4) is a "hydrophobic interaction." (EX2033, 40:8-23, 46:8-48:15.) As Dr. Pirrung further admitted, however, Kawai is silent on which portion of the indazole moiety the tyrosine residues have interactions with. (EX2033, 47:10-48:15; EX1004, 4 ("[T]he 4-fluoro-1-methyl-indazole moiety (Fig. 1A, blue shading) of LY3502970 has aromatic interactions with $Tyr205^{2.75}$ and $Tyr145^{1.40}$ . . . .").) A skilled artisan looking at the cryo-EM structure in the Protein Data Bank, as disclosed in Kawai, would see that the aromatic rings of Tyr145 and Tyr205 are closer to the aromatic ring of the indazole moiety than the methyl group. As Dr. Pirrung admits, the aromatic ring of tyrosine is the hydrophobic region of tyrosine. (EX2033, 46:2-4.) Therefore, a skilled artisan would understand that the aromatic rings of Tyr145 and Tyr205 do not interact with the methyl group on the indazole moiety, but rather with the aromatic ring on the indazole moiety itself.



(EX2035, 9 (annotated).)

180. I further disagree with Dr. Pirrung's opinion, expressed during his deposition, the glutamate and lysine in the receptor would form a salt bridge and "neutralize one another's charge." (EX2033, 40:8-16.) This is not supported by the disclosure in Kawai or the cryo-EM model in Protein Data Bank. In fact, Dr. Pirrung admits that he relied only on the two-dimensional image in Kawai for his opinions and assumed that the glutamate and lysine would form a salt bridge. (EX2033, 44:17-45:7.) Kawai makes no disclosure about whether a salt bridge forms and the two-dimensional image does not illustrate a salt bridge between the glutamate and

lysine. A skilled artisan would not jump to conclusions for how the amino acid side chains interact with each other and the functional groups on orforglipron from simply looking at the image in Kawai. Further, the three-dimensional cryo-EM structure in Protein Data Bank does not indicate that any salt bridge would form between the two amino acids, because the structure does not show any interactions between the glutamate and lysine side chains.



(EX2035, 8 (annotated indicating the glutamate side chain, lysine side chain).)

181. Because the region around the indazole is polar, and assuming they had any reason to modify the indazole moiety on orforglipron or Su Compound 44 in the first place, a skilled artisan would have been more likely to consider a polar substituent. The structural interactions and insight would not have led the skilled artisan to introduce a hydrophobic substituent, such as a cycloalkyl.

c. Talele

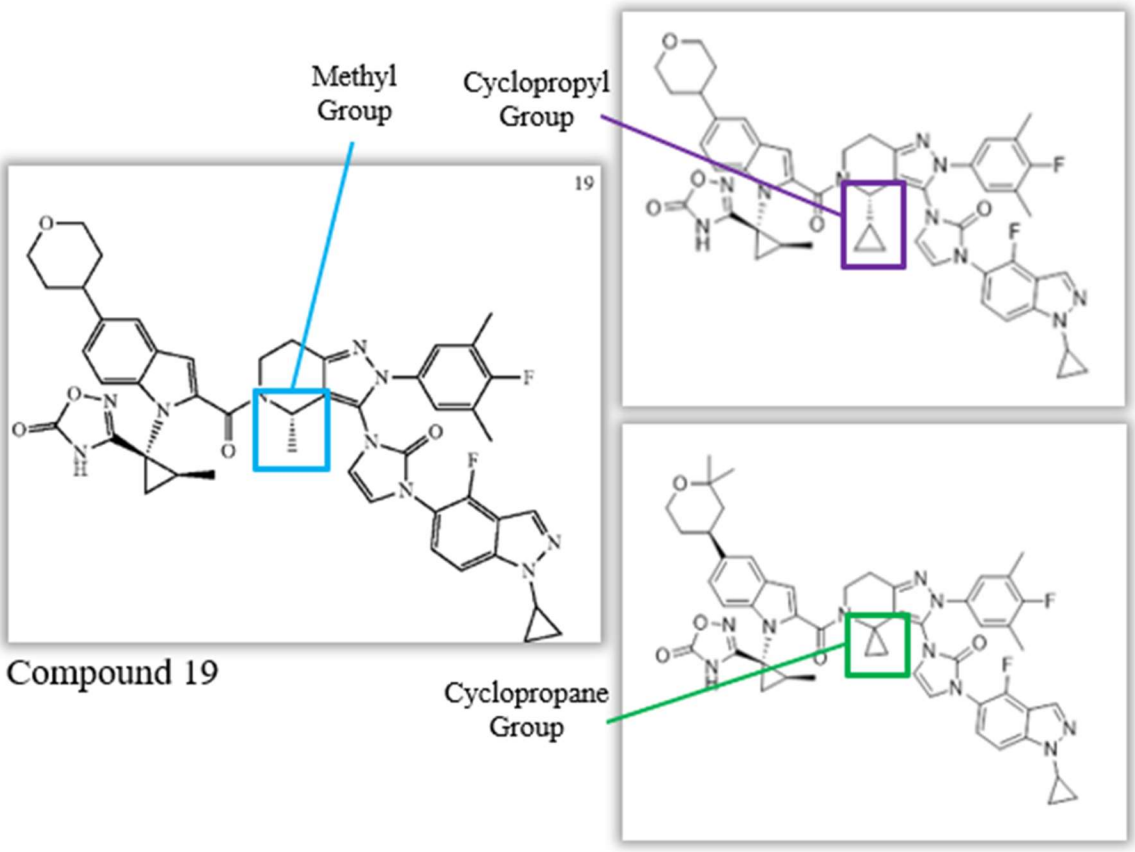
182. Dr. Pirrung also relies on Talele for the cycloalkyl substitution but offers no explanation as to why a skilled artisan would have been motivated to combine Talele with Su, Yoshino or Kawai. As Dr. Pirrung admits, Talele is a "review article," (EX1002, ¶80), that does not relate to orforglipron or GLP-1R agonists more generally.

183. Dr. Pirrung argues that Talele teaches that cyclopropyl rings can "enhanc[e] metabolic stability, improv[e] pharmacokinetic properties, or modulat[e] the biological activity of a drug molecule." (EX1002, ¶216.) But Dr. Pirrung does not point to any suggestion in the prior art that orforglipron had a shortcoming in any of those properties that would motivate a skilled artisan to implement Talele's teachings. Rather, Dr. Pirrung admits that orforglipron was "structurally optimized" for "once daily oral administration" and calls orforglipron a "promising candidate." (EX1002, ¶¶49-51.)

184. Moreover, as described in Section III.B.2, above, Talele also discloses that cyclopropyl substituents do not always lead to improved properties. (EX1009, 24.) Talele provides examples where the substitution with a cyclopropyl moiety resulted in a compound with worse properties. (EX1009, 20, 24.) As a result, Talele cautions that "[pharmacokinetic] properties can be modulated with a cyclopropyl

group" but "it is context dependent and one strategy does not work in all cases." (EX1009, 24.)

185. Ascletis's testing also shows that adding cyclopropyl groups to compounds does not always lead to desirable properties. The Gargiulo Declaration identifies two additional compounds that Ascletis synthesized and tested that are not specifically identified in the '236 Patent. (EX2080, ¶¶6-8.) Ascletis performed the same activity assay disclosed in Example 2 of the '236 Patent for these two additional compounds. (EX2080, ¶¶6-8.) In these compounds, a cyclopropyl or cyclopropane group was substituted for a methyl group at an additional position on Compound 19.



186. These substitutions significantly decreased potency in both compounds, where the compounds had an EC_{50} of 1.995 nM or greater than 10 nM, respectively, compared to an EC_{50} of 0.044 nM for orforglipron and 0.012 nM for Compound 19. (EX2080, ¶¶6-8.) Contrary to Dr. Pirrung's assumption based on Talele, a skilled artisan would have known that adding a cyclopropyl in place of a methyl would not always result in a compound with desirable properties but was simply one of many possible modifications that could be synthesized and tested.

187. A skilled artisan would also be aware that cycloalkyls can undergo reactions, such as oxidation of cyclopropyl rings, which can decrease drug potency.

(EX2074, 2.) A skilled artisan would thus well know that a cycloalkyl would not simply improve the properties of any compound but instead is one of innumerable functional groups modifications that a skilled artisan might experiment with depending on the context. Dr. Pirrung also admitted in deposition, "there are examples where introducing a [cyclopropyl] is not . . . beneficial as any structural change that is part of the toolbox of the medicinal chemist does not work in every single example." (EX2033, 97:22-98:4.) Talele, therefore, does not provide any motivation to make a cycloalkyl substitution in orforglipron.

188. There are also many other similar review articles on different substituents that may improve drug properties depending on the context. (EX2007, EX2008 (oxetanes); EX2009 (oxadiazoles); EX2010 (thiadiazoles); EX2011 (bicyclopentanes); EX2012 (nitrogen heterocycles); EX2013 (aromatic rings); EX2014 (8-11-membered rings); EX2015 (bicyclic rings).) Dr. Pirrung does not explain why a skilled artisan would look to Talele and its cyclopropyl groups as opposed to any of the numerous other substituents discussed in similar review articles.

189. Because Dr. Pirrung has not shown that Su, Yoshino, Kawai, and/or Talele would motivate a skilled artisan to substitute a cyclopropyl group for the methyl group on the indazole moiety in orforglipron, he has not shown that Compound 19 is obvious based on Ground 1 starting with orforglipron.

ii. Dr. Pirrung Does Not Articulate a Motivation to Remove the Two Methyl Groups on the Tetrahydropyran Moiety

190. Starting with orforglipron, a skilled artisan would have to remove each of the two methyl groups on the tetrahydropyran ("THP") moiety to arrive at Compound 19. Dr. Pirrung has failed to show that a skilled artisan would be motivated to remove those two groups.

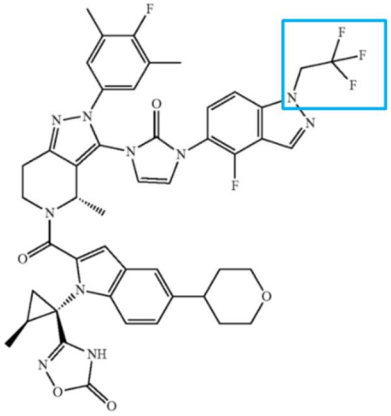
191. A skilled artisan would know that there were many, many positions for potential modification or substitution on orforglipron. The asserted prior art references themselves disclose numerous options as potential substituents to the THP moiety. (EX1008, 3:32-42; EX1007, 6:19-25; EX1030, 5:50-64.) The THP moiety on orforglipron was no more than one of numerous positions where a skilled artisan could have experimented with orforglipron.

192. Dr. Pirrung points only to Yoshino as teaching the removal of each methyl from the THP moiety of orforglipron. (EX1002, ¶¶219-221.) Specifically, Dr. Pirrung opines that Compounds 28 and 30, which do not include the dimethyl group, "retain[] comparable activity" and thus would encourage a skilled artisan to make that substitution. (EX1002, ¶220.) I disagree.

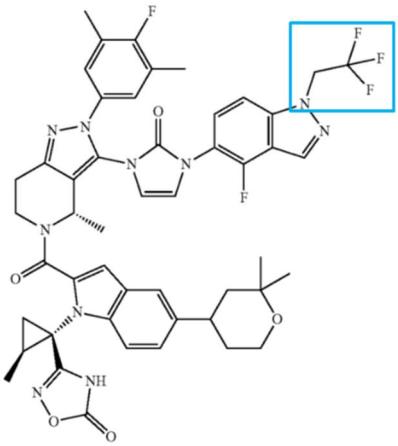
193. First, Dr. Pirrung does not explain why a skilled artisan would be motivated to make a modification to orforglipron that simply "retains" activity.

Unless they identified some other potential benefit, a skilled artisan would not make such a substitution without the benefit of hindsight.

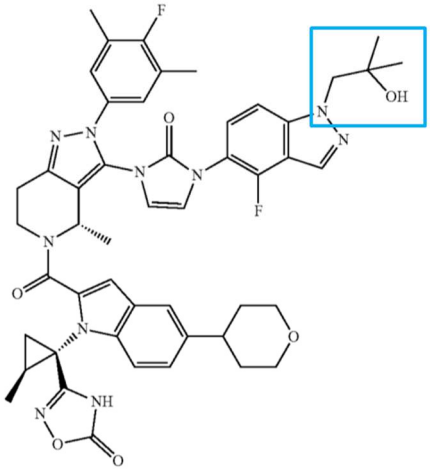
194. Second, both Compounds 28 and 30 have additional modifications other than the removal of the dimethyl group compared to orforglipron. Compounds 28 and 30, as well as their respective counterparts (Compounds 35 and 38) which have the dimethyl group on the THP ring, also include a polar functional group on the indazole, as shown below in blue boxes.



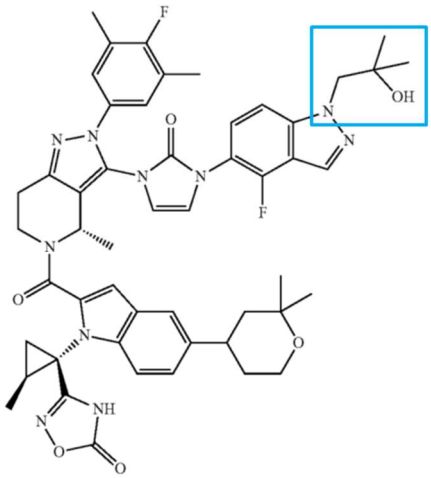
Compound 28



Compound 35



Compound 30



Compound 38

A skilled artisan would understand that the polar substituents on these compounds could affect the properties of the compound and possibly compensate for the removal of the dimethyl group on Compounds 28 and 30, as compared to Compounds 35 and 38. As a result, a skilled artisan would not have been able to directly assess if the removal of the dimethyl group even "maintained activity" relative to orforglipron based on the activity of Compounds 28 and 30.

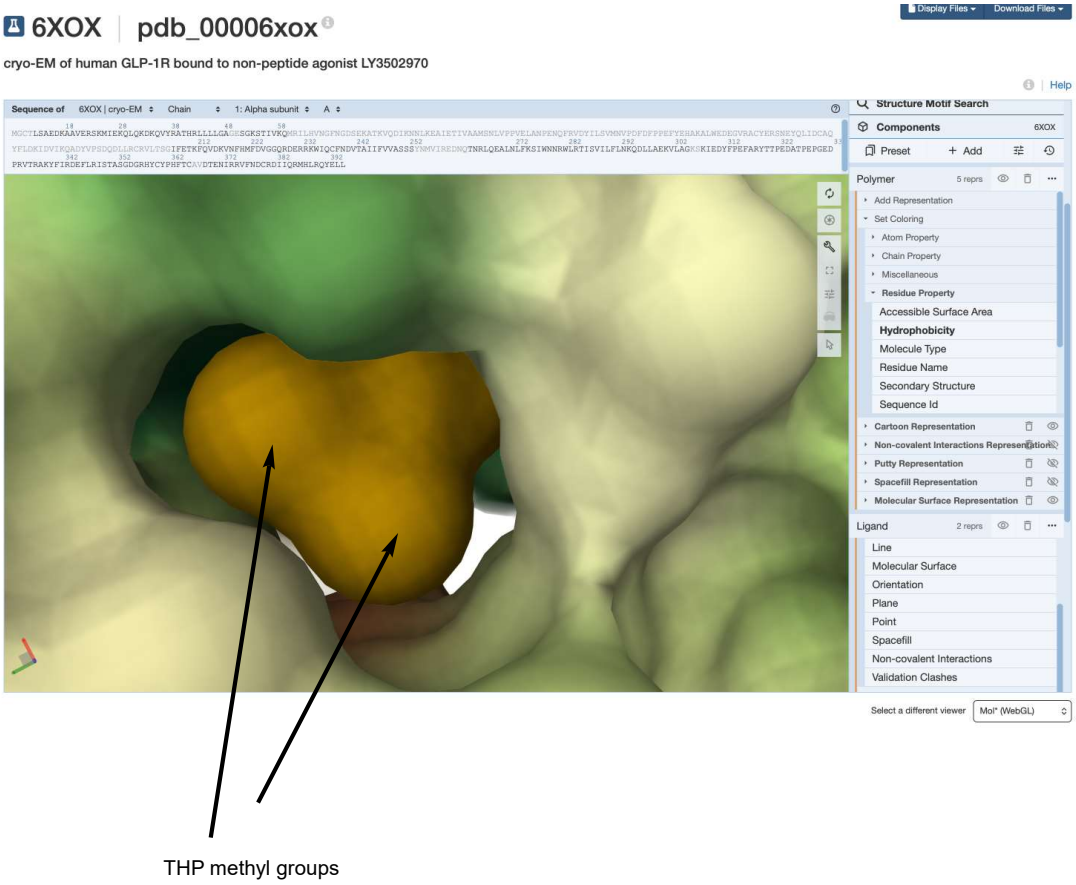
195. Third, many of the examples in Yoshino that do not have a dimethyl group on the THP moiety have decreased potency. Among the 80 compounds with potency data in Yoshino (Table 3), 30 possess a non-substituted achiral THP ring and many of those do not retain potency compared to orforglipron. (EX1002, ¶221.) For example, Compound 25 has an EC_{50} of 4.0 nM, and Compound 57 has an EC_{50} of 8.1 nM. (EX1008, 310:41-311:51.) A skilled artisan would understand from this

data that removing a dimethyl group would often lead to worse pharmacological properties.

196. Fourth, despite experimenting extensively with different THP moiety substitutions, Yoshino ultimately chose to move forward with Compound 67 as its lead compound, which includes the dimethyl group on the THP moiety. (EX1008, 311:51-313:34.) In addition to the 30 compounds with the dimethyl group removed, Yoshino also discloses numerous compounds with different THP moiety substitutions, including stereoisomers of monomethyl (Compounds 41, 61, and 52), ethyl (Compound 77), and cyclobutyl (Compound 113). (EX1008, 31-55, 89-90, 92-101, 120-121, 133-161.) Despite this extensive experimentation with different substitutions on the THP moiety, Yoshino opted to move forward with Compound 67. (EX1008, 311:51-313:34.) Thus, a skilled artisan would understand that, after experimenting with extensive THP substituents, the Yoshino inventors found the dimethyl group favorable over removing that group or making a different substitution. Moreover, a skilled artisan would understand that synthesizing the THP moiety with the dimethyl substitution is more challenging, and a skilled artisan would have been unlikely to do so without a perceived benefit from the dimethyl group.

197. Fifth, the cryo-EM structure of orforglipron binding to the GLP-1R would discourage a skilled artisan from removing the dimethyl group on the THF

moiety. As explained above, the three-dimensional cryo-EM structure disclosed in Kawai was deposited in the Protein Data Bank. The binding and interactions of the dimethyl group to the GLP-1 receptor are shown below. The dimethyl group on the THF moiety of orforglipron is represented by the two conjoined yellow spheres (as noted by the two black arrows), and the region of the GLP-1 receptor that binds to the dimethyl group is represented in green and white.



(EX2035, 11.) The dimethyl group sits in the binding pocket as shown in the image above. This region of the binding pocket is a hydrophobic environment, as denoted by the green coloring in the cryo-EM structure.

198. Based on the cryo-EM structure, a skilled artisan would understand that the dimethyl group fits well in the hydrophobic cavity of the protein receptor. A skilled artisan would further understand that removing the dimethyl group would considerably reduce the fit in this region of the binding pocket. This, in turn, would decrease the structural complementarity between the receptor protein and orforglipron.

iii. Dr. Pirrung Fails to Show Any Motivation to Make Both Changes

199. Even if Dr. Pirrung had shown a skilled artisan would be motivated to substitute a cyclopropyl group for the methyl on the indazole of orforglipron or remove both methyl groups from the indole moiety (which he has not for all the reasons above), he does not articulate any motivation for a skilled artisan to make both of those changes in the same compound. In my opinion, a skilled artisan would have no reason to make both of those changes without the benefit of hindsight.

4. Starting with Su, Dr. Pirrung Does Not Establish a Motivation to Make the Specific Substitutions in Compound 19

200. Starting with Su Compound 44, a skilled artisan would have to substitute a cyclopropyl for the methyl group on the indazole moiety ***and*** remove both deuterium atoms from the THP moiety. Starting with Su Compound 175, a skilled artisan would need to remove both methyl groups from the THP moiety. Dr.

Pirrung has not established a motivation to make those changes when starting with either Su Compound 44 or 175.

i. Dr. Pirrung Fails to Identify any Motivation to Combine Compounds 44 and 175

201. Dr. Pirrung offers no reason or explanation why a skilled artisan would combine Compounds 44 and 175 to arrive at Compound 19 as claimed in the ’236 Patent. Instead, Dr. Pirrung states in conclusory manner that “a POSA seeking to modify orforglipron would have been motivated to incorporate peripheral modifications guided by Compounds 175 and 44.” (EX1002, ¶170.)

202. Notably, despite Su disclosing a compound with a cyclopropyl group on the indazole moiety and a separate compound with the dimethyl group on the indole moiety replaced by deuterium atoms, Su itself does not exemplify a compound combining these substitutions. And Su further makes no suggestion to combine Compounds 44 and 175, and Dr. Pirrung does not identify one.

203. A skilled artisan also would not be motivated to combine Su Compounds 44 and 175 because Su discloses no data for those compounds, as previously discussed. Because there is no data for either Compound 44 or 175, there is no way for a skilled artisan to know the pharmacological properties and characteristics for either compound or to assess the effect that the relevant substitution. Thus, a skilled artisan would not know what specific modifications to

select, if any, or if the modifications as described in Compounds 44 and 175 might lead to desirable results.

204. Finally, as explained in more detail below, none of Yoshino, Kawai, or Talele suggest combining Su Compounds 44 and 175 to achieve Compound 19.

ii. Dr. Pirrung Fails to Establish a Motivation to Modify Compound 44 to Replace the Methyl on the Indazole Moiety with Cyclopropyl

205. Starting with Su's Compound 44, a skilled artisan would have to substitute a cyclopropyl for the methyl on the indazole moiety and remove the deuterium atoms from the THP moiety to make Challenged Compound 19. Petitioner has failed to establish a motivation to make either modification.

206. For the same reasons explained above, Yoshino, Kawai, and Talele would not motivate a skilled artisan to replace the methyl group on the indazole moiety with cyclopropyl. (Section VI.A.3.i.)

207. Moreover, combining Compounds 44 and 175 of Su would not result in Compound 19 because the THP ring would be deuterated. In order to arrive at Compound 19 as claimed in the '236 Patent, a skilled artisan would need to make another modification to Compound 44 to remove the deuterium atoms.

208. Su does not teach or suggest removal of the deuteration of Compound 44. For instance, Su does not present a non-deuterated version of that compound despite providing deuterated and non-deuterated versions of other compounds.

209. Dr. Pirrung states only that removing the deuterium atoms could offer synthetic simplicity and the absence of a chiral center in the THP ring. (EX1002, ¶154.) I disagree that a skilled artisan would remove the deuterium atoms for that reason. As explained above, a skilled artisan would understand that compounds are deuterated to probe drug metabolism and potentially increase efficacy. Thus, a skilled artisan would understand that deuterated Compound 44 was likely deuterated for a reason, such as addressing potential metabolic issues, and that removal of those atoms could negatively impact the compounds properties. Thus, particularly without any data on the deuterated compound, a skilled artisan would not be motivated to remove the deuterium atoms from Compound 44.

210. Nor do Yoshino, Kawai, or Talele encourage the removal of the dimethyl group on the THP moiety. As explained above, Yoshino discloses 30 compounds in which the THP ring is not substituted, the majority of which exhibit worse potency than orforglipron. (EX1008, 310:41-311:51.) Kawai makes no comment or disclosure regarding the dimethyl group on the THP moiety, and, as explained above, a skilled artisan analyzing the cryo-EM structure would understand that the dimethyl group fits well in binding pocket of the protein receptor. Talele is a general review article that discloses no teachings regarding the removal of the dimethyl group. Thus, Yoshino, Kawai, Talele do not provide a motivation to remove the deuterium atoms from Su Compound 44.

iii. Dr. Pirrung Fails to Establish a Motivation to Remove the Dimethyl Group from the THP Moiety of Su Compound 175

211. Starting with Su Compound 175, a skilled artisan would have to remove the dimethyl group from the THP moiety to arrive at Challenged Compound 19. Dr. Pirrung has failed to show a motivation to make that change.

212. For the same reasons discussed above, Yoshino, Kawai, and Talele would not motivate a skilled artisan to remove the dimethyl group on the THP moiety of Su Compound 175. (Section VI.A.3.ii.)

5. Dr. Pirrung Has Not Shown That Compound 19 Was Obvious to Try

213. Dr. Pirrung further has not shown that Compound 19 was "obvious to try." As explained above, I understand that, to show an invention is invalid as "obvious to try," the possible combinations must be (1) sufficiently small in number so as to be reasonable to conclude that the combination would have been selected; and (2) such that the combination would have been believed to be one that would produce predictable and well understood results. The opposite is true here.

214. A skilled artisan looking to modify orforglipron would understand that there were nearly infinite potential ways to modify the molecule. As the prior art shows, skilled artisans knew that there were many positions on orforglipron that one could look to modify. Moreover, at each position, there were millions of potential

substitutions that a skilled artisan could experiment with. This certainly is not a scenario where the prior art presented a finite number of predictable solutions.

215. As described in Section III.A, above, the prior art shows that skilled artisans had already experimented with hundreds to thousands of orforglipron derivatives as of 2023. (EX1008; EX1006; EX1007; EX1028; EX1030; EX2019; EX2020; EX2021.) The asserted art that Dr. Pirrung relies on discloses numerous analogs to orforglipron with multiple potential substitutions on each derivative compound. (EX1008 (disclosing at least 159 exemplary compounds); EX1007 (disclosing at least 218 working examples); EX1028 (disclosing at least two working examples); EX1030 (disclosing at least 103 exemplary compounds).) Each of these references also disclose a generic formulation for GLP-1R agonists, encompassing millions of potential compounds, with innumerable possibilities for functional groups and substituents. (EX1008, 3:1-6:2; EX1007, 5:1-7:4; EX1028, [0007]; EX1030, 3:51-67.) Additional references disclose even more potential analog compounds of orforglipron. For example, WO 2024/169,952 ("Huang") discloses 238 exemplary orforglipron derivatives with extensive data on the biological activity, half-life, potency, permeability, exposure, and solubility of those compounds. (EX2019, [1495]-[1519].) WO 2023/016,546 discloses 150 additional orforglipron derivatives with biological activity for those compounds, as well as rat pharmacokinetic studies and glucose tolerance tests in non-human primates.

(EX2020, 206:14-213:8.) WO 2024/153,070 ("Xu") discloses yet another 63 exemplary orforglipron derivatives with biological activity data. (EX2021, [251]-[253].)

216. These references show that there were many positions on orforglipron that a skilled artisan might have attempted to modify, not just the positions Dr. Pirrung focuses on with the use of hindsight. For instance, Kawai discloses other pockets on the GLP-1 receptor that a skilled artisan could potentially look to for modifying orforglipron. Specifically, Kawai identifies four different moieties of orforglipron that interact with the GLP-1 receptor. (EX1004, 3.) Dr. Pirrung focuses on the position interacting with the indazole moiety and methyl substituent but does not explain why a skilled artisan would focus on that particular position and not others. (EX1002, ¶206.) Yoshino and Su reinforce the understanding that a skilled artisan would look to positions other than the methyl substituent and different modifications, demonstrating that a skilled artisan had no particular direction when seeking to modify the core structure of orforglipron. (*See, e.g.*, EX1008, 100 (Compound 69), 101 (Compound 72); EX1007, 115-116 (Compound 31), 120 (Compound 40); EX2021, 47 (Compound 6), 48 (Compound 13).)

217. Even focusing on the positions modified in the Challenged Compounds, the prior art disclosed hundreds to thousands of possible options. For example, as explained above, Yoshino disclosed hundreds of potential substituents for the

position of the indazole moiety. (EX1008, 5:21-67.) Other prior art references likewise disclose a wide array of potential substitutions that a skilled artisan could consider on the indazole moiety. (*See, e.g.*, EX1007, 253-254 (Compound 181), 255 (Compound 182), 272 (Compound 198), 273 (Compound 199); EX2020, 63 (Compound 112); EX2021, 53 (Compound 54).) And, unlike the references Dr. Pirrung relies on for cyclopropyl analogs, many of these references actually have biological data for their compounds, giving skilled artisans some information about the substitutions' effects. (*See, e.g.*, EX2019, [1496]-[1519]; EX2020, 206:14-213:8; EX2021, [251]-[253].) Dr. Pirrung provides no reason why a skilled artisan would choose cyclopropyl or cyclobutyl out of all these potential options.

218. Likewise, Yoshino discloses hundreds of potential substituents for the position of the THP ring. (EX1008, 3:32-42 (disclosing that the THP ring can be optionally substituted with one to three substituents selected from four classes of molecules, including a halogen atom and a C_{1-6} alkyl).) As explained above, Yoshino extensively explored substitutions on the THP ring, and selected Compound 67 as its lead compound. (EX1008, 31-55, 89-90, 92-101, 120-121, 133-161.) Other asserted prior art references also disclose numerous options as potential substituents of the THP ring. For example, Su discloses that the THP ring can be substituted at two positions, selected from one of 20 classes of molecules, which can then be further substituted, resulting in thousands of variations. (EX1007, 6:19-25.)

Similarly, Ren teaches that a potential THP ring can be optionally substituted with one or more substituents selected from eleven different classes of molecules, resulting in thousands of different compounds. (EX1030, 5:50-64.)

219. As described in detail above in Section III.A, the asserted prior art teaches an enormous breadth of options for functional groups and substituents on the disclosed general structures for a GLP-1R agonist. A skilled artisan would understand that any number of modifications could be made to orforglipron, resulting in billions of different compounds. Focusing on the indazole moiety, THP ring, and indole moiety alone, a skilled artisan would understand that there are millions of different possible modifications to orforglipron. Nothing in the asserted prior art points a skilled artisan to any one particular modification. Rather, a skilled artisan would understand that there are numerous possibilities to choose from, design, and test.

220. Thus, Dr. Pirrung's analysis and focus on the exact substitutions made in Challenged Compound 19, without any explanation as to why a skilled artisan would make those modifications out of the many possible options available, is the epitome of impermissible hindsight.

6. Dr. Pirrung Fails to Establish a Reasonable Expectation of Success of Achieving Compound 19

221. Dr. Pirrung fails to provide any analysis or establish a reasonable expectation of success for achieving Compound 19. Rather, throughout his declaration, Dr. Pirrung merely states in conclusory manner that the prior art would give a skilled artisan a reasonable expectation of success. (EX1002, ¶¶152-154, 225, 312.)

222. Dr. Pirrung does not identify any particular property of orforglipron that a skilled artisan would seek to improve or any issues with orforglipron. Moreover, Dr. Pirrung does not offer any analysis that establishes that a skilled artisan would reasonably expect the modifications required by the claimed compounds to actually result in any desired properties.

223. In my opinion, a skilled artisan would not have any reasonable expectation, based on the asserted prior art, that the modifications needed to arrive at Challenged Compound 19 would lead to desirable properties.

224. Su does not provide a reasonable expectation that Compound 19 would achieve any desirable properties because it does not include any data on Su Compounds 44 and 175. Su thus does not provide a skilled artisan any way to assess the effect of the modifications made in each of those compounds, much less a reasonable expectation that Challenged Compound 19 (with the modifications in

both Su compounds plus removal of the deuterium atoms) would have desirable properties.

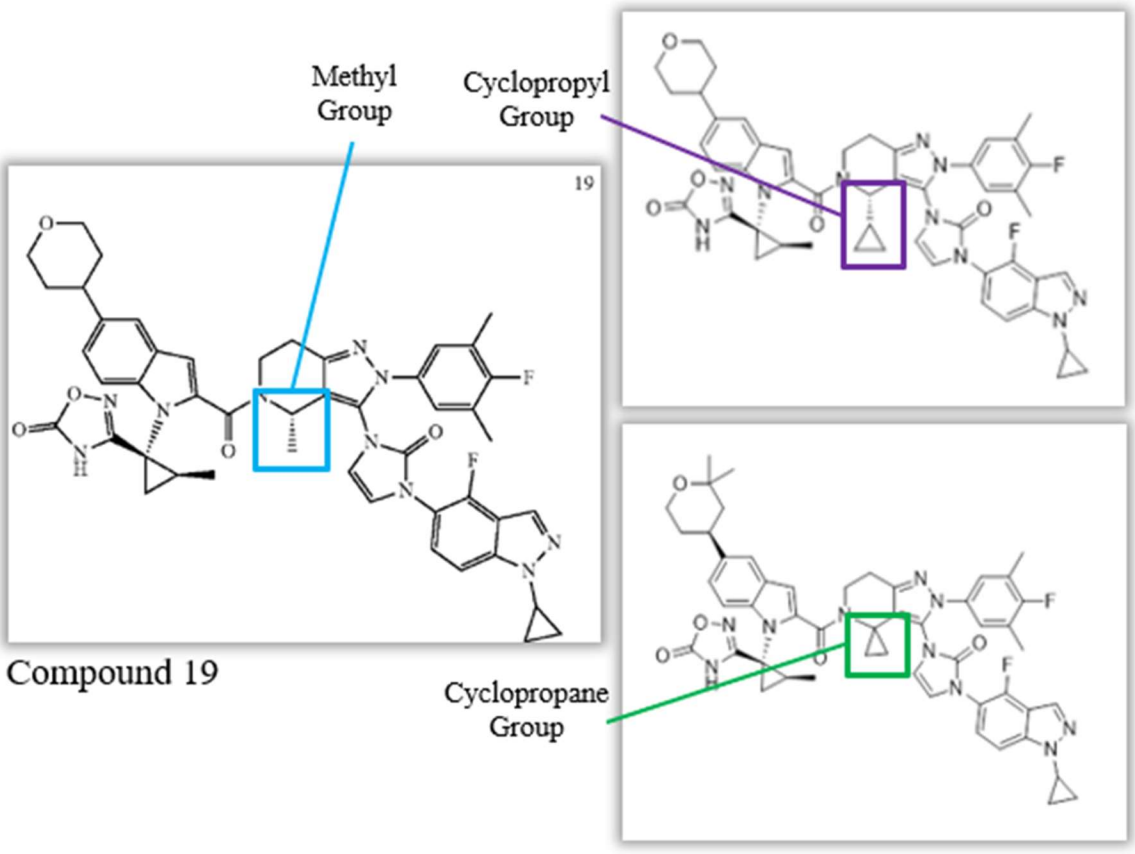
225. Yoshino likewise does not provide a reasonable expectation that Compound 19 would achieve any desirable properties. First, Yoshino does not include any compound with a cyclopropyl substitution on the indazole moiety and, in fact, teaches away from that substitution. Second, while they all include additional substitutions that complicate the analysis, the Yoshino compounds without a dimethyl group on the THP moiety generally show reduced activity relative to orforglipron, not any improved property. (EX1008, 310:41-311:51, Table 3.) Finally, Yoshino only has pharmacokinetic data on orforglipron and thus does not lead a skilled artisan to expect that any particular modification would lead to an improvement in those properties.

226. Kawai and Talele also do not provide a reasonable expectation that Compound 19 would achieve any desirable properties. Kawai only has pharmacokinetic data on orforglipron and does not suggest making any modification to it. And Talele has nothing to do with GLP-1R agonists and does not suggest that adding a cyclopropyl group to orforglipron at any position, much less on the indazole moiety, would lead to desirable properties.

227. Moreover, as discussed in Section II.B, above, a skilled artisan would also know that small structural changes can result in big differences in compound

properties, such as potency, target selectivity, and/or pharmacokinetics. For example, a skilled artisan would know that the addition of a methyl group in one position of a compound could lead to complete inhibition of activity for a compound. (EX2034, 111, Fig. 11.14.) Moving the methyl group to another position, however, could lead to a more desirable level of activity. (EX2034, 111, Fig. 11.14.) A skilled artisan would have no way of knowing the effect of the change, however, or whether it is successful in achieving desired properties, without synthesizing and testing the modification.

228. In addition, Ascletis's testing also shows that replacing substituents with cyclopropyl groups in the orforglipron structure does not always lead to desirable properties, as Dr. Pirrung assumes from Talele's disclosure. As shown in the Gargiulo Declaration, Ascletis evaluated the activity of two additional compounds not specifically identified in the '236 Patent in the same activity assay disclosed in Example 2. (EX2080, ¶¶6-8.) In these compounds, a cyclopropyl or cyclopropane group was substituted for a methyl group at an additional position on the orforglipron core structure.



229. These substitutions significantly decreased potency in both compounds, where the compounds had an EC_{50} of 1.995 nM or greater than 10 nM (indicating no activity), compared to an EC_{50} of 0.012 nM for Compound 19. (EX2080, ¶¶6-8.) A skilled artisan would therefore not have had a reasonable expectation of success that adding a cyclopropyl would result in a compound with desirable properties based on the prior art. Rather, a skilled artisan would need to synthesize and test each modification to orforglipron.

230. The failures of others in developing a small molecule GLP-1R agonist would also cut against a skilled artisan having a reasonable expectation of success.

Small molecule GLP-1R agonists have a history of poor potency and toxicity preventing viable drug candidates, particularly Boc5. (EX2046, 4.) Additionally, as described in further detail below, Pfizer has discontinued multiple small molecule GLP-1R agonists for safety reasons and after reviewing the results of initial clinical trial data. (EX2048; EX2050; EX2051.) Based on the continued failures in small molecule GLP-1R agonist development, a skilled artisan would be less likely to reasonably expect that any modifications would lead to a GLP-1R agonist with desired properties.

231. Thus, a skilled artisan would not have a reasonable expectation of success in achieving Compound 19 based on the prior art.

7. The Objective Evidence Shows that Compound 19 Is Not Obvious

232. For the reasons discussed below in Section VI.E., the objective indicia also strongly support the non-obviousness of Compound 19.

8. Dr. Pirrung Further Fails to Show that the Salts in Claims 2-4 and 22-23 Are Obvious

233. Dr. Pirrung points to the disclosures in Yoshino and Su to support his assertion that the salts of Challenged Compound 19 are obvious. Neither of those references provides a motivation to make the claimed salts of Challenged Compound 19. Dr. Pirrung does provide any separate motivation or establish a reasonable expectation of success for formulating such salts.

234. Yoshino does no more than disclose a list of potential counterions for the numerous compounds disclosed in Yoshino itself. Yoshino does not teach whether the inventors actually successfully formed salts of any compound in Yoshino.

235. A skilled artisan would understand that the formation of salts that form stable solids, have suitable polymorphism or hydration, and produce acceptable pharmaceutical properties is unpredictable. As explained above, in Section II.C, salt formation is unpredictable. A skilled artisan has no way of knowing whether a particular compound will form a crystalline salt with a particular counterion in advance, nor whether any such crystalline form will possess suitable physical properties. The only way for a skilled artisan to determine whether a particular salt will provide acceptable pharmaceutical properties is to conduct a salt screen with the particular compound and explore the properties of the resulting compounds.

236. Further, as shown in Gupta et al., different salts can show dramatically different properties, including solubility, stability, hygroscopicity, bioavailability, toxicity, polymorphism, and ease of manufacture. (EX2073.) Additionally, as Suresh et al. demonstrates, even minor structural changes in the free acid or base can alter the coordination geometry of a salt, stoichiometry, and solid-state behavior. (EX2075, Abstract.) Thus, a skilled artisan would know that salts are unpredictable

and even molecules that are close analogs of each other as salts could have significantly different properties.

237. Dr. Pirrung also relies on Yoshino's disclosure of sodium and calcium salts, but Yoshino only discloses these salt forms generally and does not disclose any compound in sodium or calcium salt form. As explained above, a skilled artisan would know that salt formation is unpredictable and would not understand Yoshino to teach any particular salt for the compounds disclosed, much less for the Challenged Compounds.

238. For these additional reasons, Dr. Pirrung has not shown that the salts claimed in claims 2-4 and 22-23 of the '236 Patent are obvious.

B. Ground 2: Compounds 1, 19, and 20 (Claims 1-9, 12-17, 24, and 25) Were Not Obvious Based on Ground 2

239. In Ground 2, Dr. Pirrung asserts that claims 1-9, 12-17, 24, and 25 are obvious with respect to Compounds 1, 19, and 20 in view of Yoshino, Kawai, and Talele. Dr. Pirrung's opinions for Ground 2 are substantively similar to his opinions on Ground 1.

240. For similar reasons as to Ground 1, Dr. Pirrung has not shown that Compounds 1, 19, or 20 are obvious based on Ground 2. As explained below, first, Dr. Pirrung has not established any motivation or reason in the prior art that would lead to the Challenged Compounds. More specifically, Dr. Pirrung does not

articulate any reason that a skilled artisan would seek to modify orforglipron or any characteristic of that molecule they would seek to improve. Dr. Pirrung also fails to show that a skilled artisan would be motivated to make the specific modifications needed to arrive at Compounds 1, 19, and 20. Second, Dr. Pirrung has failed to establish that a skilled artisan would have a reasonable expectation of success in achieving Compounds 1, 19, and 20. Finally, objective considerations further show that Compounds 1, 19, and 20 were not obvious.

1. Dr. Pirrung Fails to Establish a Motivation to Make the Substitutions Required by Compounds 1, 19, and 20

i. Compound 1

241. A skilled artisan would have to replace the methyl group on the indazole moiety of orforglipron with a cyclopropyl group to arrive at Challenged Compound 1.

242. As explained above in Section VI.A.2, Dr. Pirrung has failed to establish any reason that a skilled artisan would modify orforglipron or identify any property of orforglipron that a skilled artisan would have sought to improve. (Section VI.A.2.)

243. In addition, for the same reasons discussed above, a skilled artisan would not have been motivated to replace the methyl group on the indazole moiety of orforglipron. (Section VI.A.3.i.)

244. For the same reasons explained in Section VI.A.5, Dr. Pirrung has failed to show that Challenged Compound 1 would have been obvious to try. (Section VI.A.5.)

245. Accordingly, in my opinion, Dr. Pirrung has failed to establish a motivation to make Challenged Compound 1.

ii. Compound 19

246. A skilled artisan would need to make multiple changes to orforglipron to arrive at Challenged Compound 19. First, the skilled artisan would have to replace the methyl group on the indazole moiety of orforglipron with a cyclopropyl group. Second and third, the skilled artisan would have to remove each of the two methyl groups on the tetrahydropyran ("THP") moiety of orforglipron.

247. As explained above in Section VI.A.2., Dr. Pirrung has failed to establish any reason that a skilled artisan would modify orforglipron or identify any property of orforglipron that a skilled artisan would have sought to improve. (Section VI.A.2.)

248. In addition, for the same reasons discussed above, a skilled artisan would not have been motivated to replace the methyl group on the indazole moiety of orforglipron. (Section VI.A.3.i.)

249. In addition, for the same reasons discussed above, a skilled artisan would not have been motivated to remove the dimethyl group on the THP moiety of orforglipron. (Section VI.A.3.ii.)

250. Even if Dr. Pirrung had shown a skilled artisan would be motivated to replace the methyl group on the indazole moiety with a cyclopropyl group or remove both methyl groups on the THP moiety, he does not articulate any motivation for a skilled artisan to make both of those changes in the same compound.

251. Finally, as explained in Section VI.A.5, Dr. Pirrung has failed to show that Challenged Compound 19 would have been obvious to try starting with orforglipron. (Section VI.A.5.)

252. Accordingly, in my opinion, Dr. Pirrung has failed to establish a motivation to make Challenged Compound 19.

iii. Compound 20

253. Similar to Compound 19, Challenged Compound 20 requires multiple modifications from orforglipron. First, the skilled artisan would have to replace the methyl group on the indazole moiety of orforglipron with a cyclobutyl group. Further, the skilled artisan would have to remove each of the two methyl groups on the THP moiety of orforglipron.

254. For the same reasons discussed above, a skilled artisan would not have been motivated to replace the methyl on the indazole moiety with a cycloalkyl, such

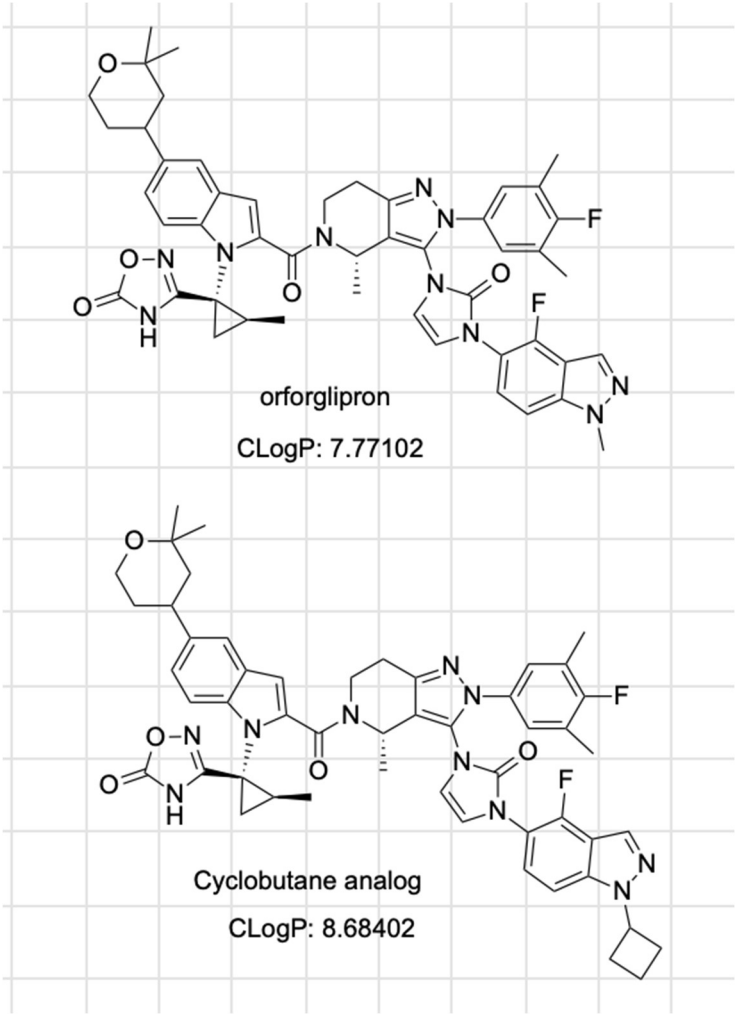
as cyclobutyl. (Section VI.A.3.i.) In addition, for the reasons discussed above, a skilled artisan would not have been motivated to remove the dimethyl group on the THP moiety. (Section VI.A.3.ii.)

255. Further, Dr. Pirrung does not point to any teaching in Yoshino, Kawai, or Talele that would motivate a skilled artisan to substitute a cyclobutyl group for the methyl on the indazole moiety. Indeed, Talele speaks only to cyclopropyl groups, and Dr. Pirrung does not specifically point to that reference for cyclobutyl.

256. Dr. Pirrung states, with no support, that a "four-membered ring cycloalkyl group [is] more resistant to metabolism than simply alkyl groups." (EX1002, ¶225.) To the contrary, a skilled artisan would have known that cyclobutyl groups can make molecules more susceptible to metabolic oxidation and lower potency. (EX2076, 3-4.) A skilled artisan would also recognize that a cyclobutyl ring can open in some circumstances and therefore increase instability.

257. Finally, a skilled artisan would understand that replacing the methyl group with the cyclobutyl on orforglipron would increase lipophilicity, which lowers the bioavailability of the drug. (*See* EX2072, 6-7 (describing modifications in a potential drug candidate for treatment of immunological diseases, where a more rigid linker, i.e., cyclobutane, modified lipophilicity).) Lipophilicity can be calculated as the CLogP value. As CLogP, or lipophilicity, increases in orforglipron, bioavailability decreases.

258. I conducted calculations of the lipophilicity of orforglipron compared to an analog compound substituting the methyl group on the indazole moiety for a cyclobutyl. As shown in the calculation below, the cyclobutyl group increases the CLogP value, indicating that bioavailability is decreasing.



A skilled artisan would understand that higher lipophilicity in orforglipron could lead to lower oral bioavailability. Thus, a skilled artisan would not be motivated to modify orforglipron, which is orally administered, to have reduced bioavailability,

without a specific reason to believe that the cyclobutyl substitution would lead to a desired property.

259. Finally, even if Dr. Pirrung had shown a skilled artisan would be motivated to replace the methyl group on the indazole moiety with a cyclobutyl group or remove both methyl groups on the THP moiety, he does not articulate any motivation for a skilled artisan to make both of those changes in the same compound.

2. Dr. Pirrung Fails to Establish a Reasonable Expectation of Success of Achieving Compounds 1, 19 or 20

260. Dr. Pirrung fails to provide any analysis or establish a reasonable expectation of success for achieving Compounds 1, 19, or 20. Rather, throughout his declaration, Dr. Pirrung merely states in conclusory manner that the prior art would give a skilled artisan a reasonable expectation of success. (EX1002, ¶¶152-154, 225, 312.)

261. For the same reasons I previously explained, a skilled artisan would not have any reasonable expectation, based on the asserted prior art, that the modifications needed to arrive at Challenged Compound 19 would lead to desirable properties. (Section VI.A.6.) Those same reasons apply to Challenged Compounds 1 and 20.

262. In addition, for Challenged Claim 20, Dr. Pirrung does not point to any data that would lead a skilled artisan to reasonably expect that substitution a

cyclobutyl for the methyl on the indazole moiety of orforglipron would lead to desirable results. Indeed, Dr. Pirrung does not point to anything in Yoshino, Kawai, or Talele that discloses a cyclobutyl substitution or suggests such a substitution would be beneficial.

263. Thus, a skilled artisan would not have a reasonable expectation of success in achieving Compounds 1, 19, and 20 based on the prior art.

3. The Objective Evidence Shows that Compounds 1, 19 and 20 Are Not Obvious

264. For the reasons discussed below in Section VI.E., the objective indicia also strongly support the non-obviousness of Compound 1, 19 and 20.

4. Dr. Pirrung Further Fails to Show that the Salts in Claims 2-4, 8-9, 13-14, and 16-17 Obvious

265. Dr. Pirrung points to the disclosures in Yoshino and Su to support his assertion that the salts of Compounds 1, 19, and 20 are obvious. Neither of those references provides a motivation to make the claimed salts of the Challenged Compounds. Dr. Pirrung does provide any separate motivation or establish a reasonable expectation of success for formulating such salts.

266. Yoshino does no more than disclose a list of potential counterions for the numerous compounds disclosed in Yoshino itself. Yoshino does not teach whether the inventors actually successfully formed salts of any compound in Yoshino.

267. A skilled artisan would understand that salts are unpredictable. As explained above, in Section II.C, salt formation is unpredictable. A skilled artisan has no way of knowing whether a particular compound will form a salt with a particular counterion in advance. The only way for a skilled artisan to determine whether a particular salt will form is to conduct a salt screen with the particular compound. Even if Yoshino disclosed successful salts for any of the compounds disclosed, which it does not, a skilled artisan would not have necessarily been motivated to attempt the same salts of a modified compound.

268. Further, as shown in Gupta et al., different salts can show dramatically different properties, including solubility, stability, hygroscopicity, bioavailability, toxicity, polymorphism, and ease of manufacture. (EX2073.) Additionally, as Suresh et al. demonstrates, even minor structural changes in the free acid or base can alter the coordination geometry of a salt, stoichiometry, and solid-state behavior. (EX2075, Abstract.) Thus, a skilled artisan would know that salts are unpredictable, and even molecules that are close analogs of each other as salts could have significantly different properties.

269. Dr. Pirrung also relies on Yoshino's disclosure of sodium and calcium salts, but Yoshino only discloses these salt forms generally and does not disclose any compound in sodium or calcium salt form. As explained above, a skilled artisan would know that salt formation is unpredictable and would not understand Yoshino

to teach any particular salt for the compounds disclosed, much less for the claimed compounds.

270. For these additional reasons, Dr. Pirrung has not shown that the salts claimed in claims 2-4, 8-9, 13-14, and 16-17 of the '236 Patent are obvious.

C. Ground 3 Does Not Show that Compound 65 (Claims 1-4 and 21-25) Was Obvious

271. Compound 65 differs from Compound 19 in the substitution of a nitrogen in the benzene ring fused to the pyrrole ring. In chemical terms, Compound 65 contains a 1*H*-pyrrolo[3,2-*b*]pyridine (or 4-azaindole) whereas Compound 19 contains an indole. (EX1002, ¶273.) In Ground 3, Dr. Pirrung opines that Compound 65 is obvious over a combination of Su, Yoshino, Kawai, Talele, Meng, Patel, and/or Ren.

272. I disagree for the reasons set forth below. Dr. Pirrung relies on his opinions in Grounds 1 and 2, and begins his analysis with Compound 19. For the same reasons discussed in Grounds 1 and 2, Compound 19 is not obvious. Dr. Pirrung further fails to establish why a skilled artisan would have been motivated to make the multiple modifications to orforglipron or Su required to achieve Compound 65 based on the prior art. Moreover, the prior art does not establish that a skilled artisan would have had a reasonable expectation of success in achieving Compound 65.

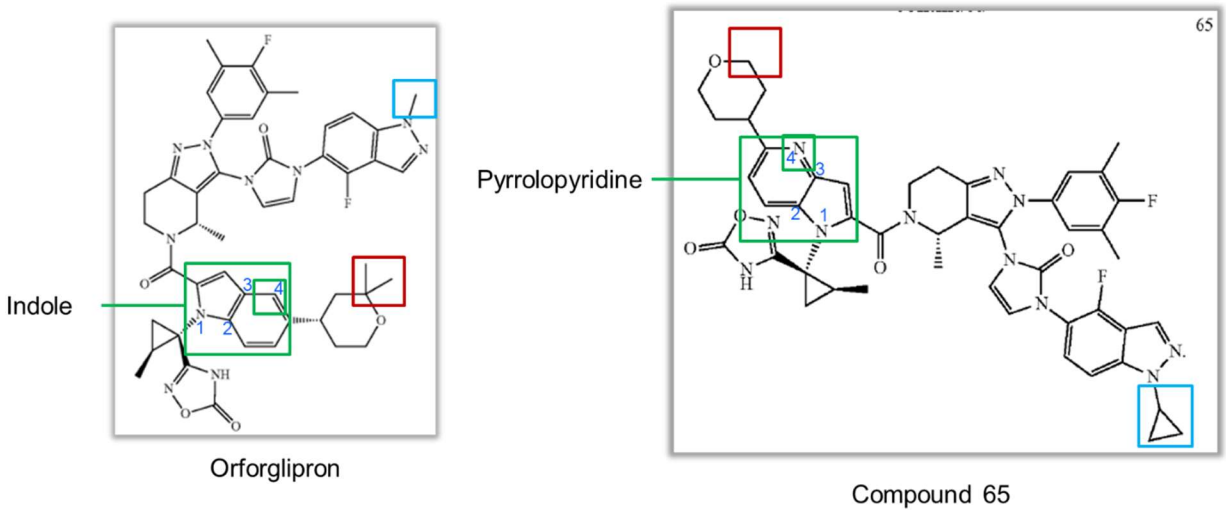
1. Ground 3 Depends on Ground 2 and Fails for the Same Reasons

273. Dr. Pirrung relies on his analysis in Grounds 1 and 2 to arrive at Compound 19 and then relies on Meng, Patel, and Ren to support his claim that a skilled artisan would substitute a nitrogen atom in the benzene ring to which the pyrrole is attached. (EX1002, ¶¶274-285.) Thus, Dr. Pirrung's analysis in Ground 3 depends on the success of Grounds 1 and 2, as he begins his analysis with Compound 19. As explained above, however, Dr. Pirrung fails to show that Su, Yoshino, Kawai, and/or Talele provide a motivation to make Compound 19 or that a skilled artisan would have a reasonable expectation of success. Thus, I disagree with Dr. Pirrung that a skilled artisan would "begin" with Compound 19 because the prior art does not teach or render Compound 19 obvious.

2. Dr. Pirrung Failes to Identify a Motivation to Make the Multiple Changes Needed to Arrive at Compound 65

274. Challenged Compound 65 has multiple modifications compared to orforglipron, as depicted below in the green, red, and blue boxes.[5]

[5] As explained above, a skilled artisan would not select Compound 175 of Su as a lead compound, but even starting with that compound, multiple modifications would still be required to arrive at Challenged Compound 65.



As shown above in the green boxes, Compound 65 includes a nitrogen atom at the 4-position on the indole of orforglipron, resulting in a pyrrolopyridine.

275. Dr. Pirrung does not show that a skilled artisan would have been motivated to replace the C-H group at the 4-position of the indole with a nitrogen atom to make a pyrrolopyridine to achieve Compound 65. Dr. Pirrung relies on Meng, Patel, and Ren for this substitution but, in my opinion, none of those references would motivate a skilled artisan to replace the relevant C-H group on the indole moiety of orforglipron with a nitrogen.

276. Dr. Pirrung, initially, does not identify any characteristic of orforglipron (or Compound 175 of Su) that a skilled artisan would seek to change or improve. As discussed above, a skilled artisan would not seek to modify a compound such as orforglipron without defining the target compound profile ("TCP") or

identifying a property to be improved. Dr. Pirrung does not identify any particular criteria or property for modifying orforglipron or Su Compound 175.

277. A skilled artisan would not have been motivated to replace any C-H group much less that specific C-H group with a nitrogen in the indole of the core structure of orforglipron in the first place for two reasons. First, a skilled artisan would know that substituting a nitrogen atom in an benzene ring often leads to decreased activity in compounds. As explained in Koovits, replacing a benzene core structure with a pyridine, or replacing a carbon in a benzene ring with a nitrogen, can lead to decreased biological activity or increases in metabolic degradation. (EX2078, 6 (illustrating that pyridine analogs showed significant loss of potency), Table 1.) Second, a skilled artisan would understand that substituting a nitrogen atom for a carbon atom would be synthetically more challenging. As Huestis states, "[c]ompared to indoles, however, [pyrrolopyridines] are far more challenging to prepare, especially in highly functionalized form." (EX2052, 1-2.) Thus, a skilled artisan would not be motivated to modify orforglipron and introduce a nitrogen on the indole to form a pyrrolopyridine without a specific reason to think the change would lead to a desired property.

278. A skilled artisan would further understand that substitutions on moieties such as the indole in a compound can modify the fundamental properties of the compounds in different and significant ways. Wermuth teaches that "[a] typical

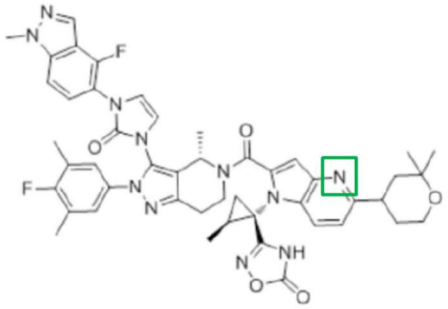
lead optimization program often involves a trial-and-error process of replacing chemical functionality, including rings, and in most cases this intellectual exercise is based on a chemist's knowledge and recollection of his or her past experience." (EX2034, 47.) Moreover, Table 8.10 in Wermuth shows six possibilities for replacement of an indole ring, none of which is a pyrrolopyridine, which is the replacement in Compound 65. (EX2034, 57, Table 8.10.) This reinforces a skilled artisan's understanding from the asserted art that there could be many other potential modifications to the ring structure of orforglipron, not just the substitution of a specific C-H group with a nitrogen atom.

279. Meng does not provide the requisite motivation for a skilled artisan to make the specific nitrogen substitution. Initially, Meng is just one of numerous patent documents that disclose potential modifications to the core structure of orforglipron. Dr. Pirrung provides no reason why a skilled artisan would select this particular reference from the sea of orforglipron-related prior art.

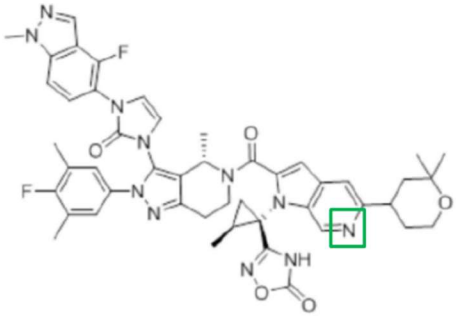
280. Meng discloses a general structure for a GLP-1 receptor agonist that encompasses thousands of potential structures. (EX1029, [0007]-[0019].) Despite the broad disclosure, Dr. Pirrung relies exclusively on Meng's Compound (II), which incorporates a nitrogen atom on the indole moiety in the same location as Compound 65. (EX1002, ¶275.) Dr. Pirrung opines that a skilled artisan would look to Compound (II) because it is one of only two compounds (along with Compound

(III)) "that are structurally and functionally characterized" in Meng. (EX1002, ¶276.) Dr. Pirrung admitted in his deposition that a skilled artisan would understand that compounds that were "functionally characterized" are more likely to be "lead candidates" for further development. (EX2033, 61:1-63:6.) This contradicts Dr. Pirrung's approach in Ground 1 regarding Su, where he ignores the "functionally characterized" compounds, further establishing that Dr. Pirrung relied on hindsight in his analysis.

281. Dr. Pirrung also does not explain why a skilled artisan would focus on Compound (II) instead of Compound (III), when Meng discloses data showing that Compound (III) is more potent than Compound (II). Compound (II) and Compound (III) differ in the location of the nitrogen substitution in the core structure of orforglipron:



(II) or



(III).

(EX1029, [0020]-[0021] (annotated, depicting Compounds II and III).)

282. In my opinion, if anything, a skilled artisan would focus on Compound (III) from Meng, not Compound (II). (EX1029, [0027]–[0192], Examples 1–3.) Meng discloses a comparative study evaluating Compounds (II) and (III) against orforglipron. (EX1002, ¶276; EX1029, [0186]-[0192].) The data from the comparison study reported in Meng demonstrates that Compound III is more potent than both orforglipron and Compound (II). (EX1029, [0186]-[0192].) In my opinion, if considering Compounds (II) and (III) from Meng, a skilled artisan would focus on the compound with better activity, Compound (III). Dr. Pirrung ignores this data and fails to provide any explanation why a skilled artisan would look to Compound (II). The only reason is hindsight.

283. Patel also would not motivate a skilled artisan to substitute a nitrogen on the benzene ring of the indole in orforglipron. Patel is a general review article that discusses the use of pyridines, generally, in medicinal chemistry. (EX1002, ¶278.) As explained above, Patel is not directed to GLP-1R agonists, and Dr. Pirrung does not explain why a skilled artisan would look to Patel in the first place. Patel also does not focus on substituting a nitrogen for a carbon in any particular position of a benzene, and does not address substitutions of an indole moiety at all, much less suggest the specific substitution in Compound 65.

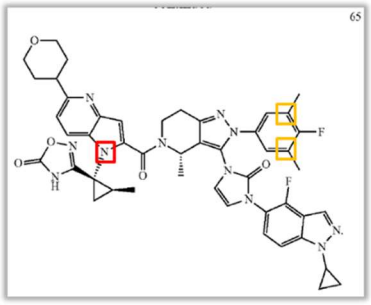
284. Moreover, Patel is just one of many review articles that generally discuss different functional ring groups used in medicinal chemistry. For example, other articles discuss the potential benefits of pyridines, piperidines, piperazines, pyrimidines, pyrazoles, triazoles, imidazoles, and fused and monocyclic heterocycles. (EX2053-EX2064.) Dr. Pirrung's reliance on Pennington's "necessary nitrogen atom" would also not motivate a skilled artisan to substitute a nitrogen specifically on the benzene ring of the indole on orforglipron, because Pennington is also not directed to GLP-1R agonists, does not teach that a nitrogen substitution will lead to desirable properties in every instance, and does not teach the specific substitution on the indole moiety as on Compound 65. (EX1002, ¶279; EX1027.) A skilled artisan could consider any of these ring structures for substitution purposes. Dr. Pirrung provides no reason why a skilled artisan would focus on Patel and ignore all of these other potential changes to the orforglipron ring structure.

285. Ren likewise would not have motivated a skilled artisan to make the required nitrogen substitution. Ren is another of numerous patent documents that disclose potential modifications to the core structure of orforglipron. Dr. Pirrung provides no reason why a skilled artisan would select this particular reference from the sea of orforglipron-related prior art.

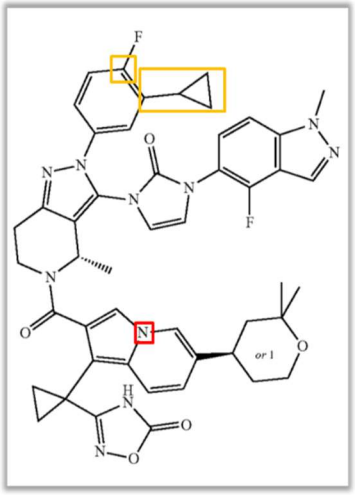
286. Dr. Pirrung opines that Ren shows "additional support for the beneficial effects of nitrogen substitution." (EX1002, ¶281.) Dr. Pirrung, however, relies on

two compounds in Ren (compounds 76 and 90) that do not even make the same substitution as seen in Challenged Compound 65. Rens's Compound 76 incorporates a nitrogen atom in a different position than Compound 65 (EX1002, ¶281), and Ren's Compound 90 includes ***two*** nitrogen substitutions on the indole moiety. (EX1002, ¶¶281-282.) Thus, even if Ren encouraged a skilled artisan to make the substitutions from Compounds 76 and 90, those substitutions would not lead to Challenged Compound 65.

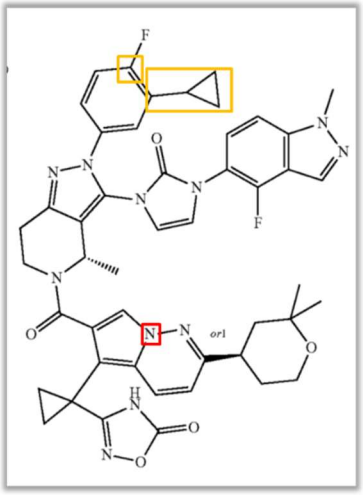
287. Further, Compounds 76 and 90 have different substituents on the fluorobenzyl ring from the Challenged Compounds, where one methyl is missing and the other methyl has been substituted with a cyclopropyl (annotated in yellow boxes below).



Compound 65



Compound 76
(Ren)



Compound 90
(Ren)

288. A skilled artisan reading the entirety of Ren would understand from its disclosure that there were other potential modifications to orforglipron, such as on the fluorophenyl ring, not just the substitution of the nitrogen on the indole moiety. Dr. Pirrung focuses only on the nitrogen substitution and ignores the other modifications made in Compounds 76 and 90 without any explanation as to why a skilled artisan would only make the substitution on the indole moiety and not the substitutions on the fluorophenyl ring. Dr. Pirrung's focus on solely the modification on the indole moiety, and not the modifications on the compounds as a whole in Ren, further shows the impermissible use of hindsight.

289. If anything, a skilled artisan would focus on Compound 73 from Ren, instead of Compounds 76 and 90, based on its pharmacokinetic data. Dr. Pirrung points to Table 30 in Ren to support his opinion that a skilled artisan would have incorporated a nitrogen atom in the indole moiety based on the data disclosed for Compound 90, which is better than the data disclosed for Compound 76. (EX1002, ¶¶282-283.) Compound 73, however, has a higher C_{max} and AUC than both Compounds 90 and 76, and its oral bioavailability, F, is 90% compared to 59% for Compound 90 and 30% for Compound 76.

TABLE 30-continued

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

(EX1030, Table 3.)

290. A skilled artisan would therefore, if they would look to Ren at all, focus on Compound 73 over Compound 90.

291. Finally, even if a skilled artisan would be motivated to make the very specific modification to the orforglipron ring structure in Compound 65, Dr. Pirrung fails to explain why they would also be motivated to make ***all of the modifications*** needed to achieve Compound 65. There is simply nothing in the prior art that suggests substituting the methyl group on the indazole moiety for a cyclopropyl, removing the dimethyl group on the THP ring, and making a nitrogen substitution in the indole moiety, all in the same compound or that those three modifications would lead to desirable results. A skilled artisan would have understood that a compound's biological activity results from the structure as whole and individual modifications do not lead to a predictable result when made together. Thus, a skilled artisan would not have been able to predict the effect of any of the modifications to orforglipron, much less the properties of a compound with all of the modifications

seen in Compound 65. The only way to determine the effect of multiple modifications to orforglipron would be to make and test the compounds.

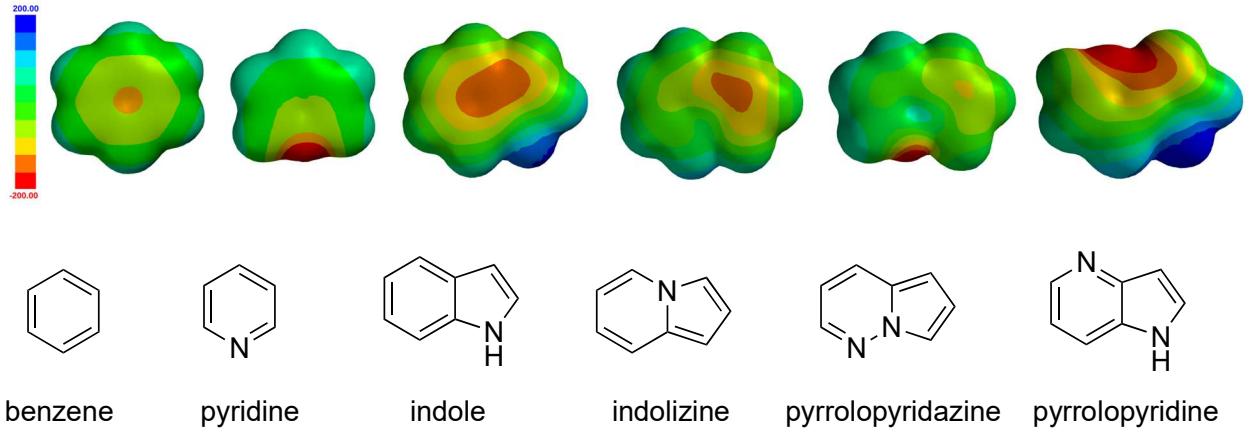
3. Dr. Pirrung Fails to Establish a Reasonable Expectation of Success in Achieving Compound 65

292. Similar to Grounds 1 and 2, Dr. Pirrung fails to provide any analysis or establish a reasonable expectation of success for achieving Compound 65. Rather, throughout his declaration, Dr. Pirrung merely states in conclusory manner that the prior art would give a skilled artisan a reasonable expectation of success. (EX1002, ¶¶152-154, 225, 312.)

293. Dr. Pirrung does not identify any particular property of orforglipron that a skilled artisan would seek to improve or any issues with orforglipron. Moreover, Dr. Pirrung does not offer any analysis that establishes that a skilled artisan would reasonably expect the modifications required by the claimed compounds to actually result in any desired properties. Rather, a skilled artisan would not have any reasonable expectation, based on the asserted prior art, that any of the modifications to orforglipron resulting in the claimed compounds would lead to desired properties. On the contrary, as explained above, the data disclosed in Yoshino suggests, if anything, to a skilled artisan that the modifications would not result in improved properties. (EX1008, 310:41-311:51, Table 3.) Further, Su has no data for Compounds 44 or 175 and thus does not teach that making the modifications in those

compounds would lead to desired properties. Likewise, none of Petitioner's other prior art references provide such a teaching. Thus, a skilled artisan would not have a reasonable expectation of success in achieving Compound 65 based on the prior art.

294. Moreover, a skilled artisan would know that modifying the orforglipron ring structure could significantly change the properties of the compound. A skilled artisan would need to consider the properties of each different ring moiety and test each one to determine how it affects the properties of the overall drug compound. 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." (EX2077, 1.) Using Spartan 24, I calculated the electron density surfaces encoded with the electrostatic potential maps for benzene, pyridine, indole, indolizine, pyrrolopyridazine and pyrrolopyridines, shown below.



295. The electron density surfaces encoded with the electrostatic potential maps illustrate the vastly different nature of each type of ring structure's electronic and steric properties that a skilled artisan would need to consider when making choices about suitable replacements of core structures in orforglipron. As shown in the calculations above, the indole and pyrrolopyridine have different electronic and steric properties that a skilled artisan would know affect the structural and physical properties and protein binding interactions of these compounds. 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.

4. The Objective Evidence Shows that Compound 65 Is Not Obvious

296. For the reasons discussed below in Section VI.E., the objective indicia also strongly support the non-obviousness of Compound 65.

5. Dr. Pirrung Further Fails to Show that the Salts in Claims 2-4 and 22-23 Obvious

297. Dr. Pirrung points to the disclosures in Yoshino and Su to support his assertion that the salts of Challenged Compound 65 are obvious. Neither of those references provides a motivation to make the claimed salts of Challenged Compound 65. Dr. Pirrung does provide any separate motivation or establish a reasonable expectation of success for formulating such salts.

298. Yoshino does no more than disclose a list of potential counterions for the numerous compounds disclosed in Yoshino itself. Yoshino does not teach whether the inventors actually successfully formed salts of any compound in Yoshino.

299. A skilled artisan would understand that salts are unpredictable. As explained above, in Section II.C, salt formation is unpredictable. A skilled artisan has no way of knowing whether a particular compound will form a salt with a particular counterion in advance. The only way for a skilled artisan to determine whether a particular salt will form is to conduct a salt screen with the particular compound.

300. Further, as shown in Gupta et al., different salts can show dramatically different properties, including solubility, stability, hygroscopicity, bioavailability, toxicity, polymorphism, and ease of manufacture. (*See generally* EX2073.)

Additionally, as Suresh et al. demonstrates, even minor structural changes in the free acid or base can alter the coordination geometry of a salt, stoichiometry, and solid-state behavior. (EX2075, Abstract.) Thus, a skilled artisan would know that salts are unpredictable and even molecules that are close analogs of each other as salts could have significantly different properties.

301. Dr. Pirrung also relies on Yoshino's disclosure of sodium and calcium salts, but Yoshino only discloses these salt forms generally and does not disclose any compound in sodium or calcium salt form. As explained above, a skilled artisan would know that salt formation is unpredictable and would not understand Yoshino to teach any particular salt for the compounds disclosed, much less for the claimed compounds.

302. For these additional reasons, Dr. Pirrung has not shown that the salts claimed in claims 2-4 and 22-23 of the '236 Patent are obvious.

D. Ground 4: Dr. Pirrung Has Not Shown the Hemi-Calcium Salt of Compound 1 (Claims 4 And 9) Was Not Obvious

303. Claims 4 and 9 claim a hemicalcium salt of Compounds 1, 13, 18, 19, 20, 21, and 65 and a hemicalcium salt of Compound 1, respectively. In Ground 4, Dr. Pirrung claims they are obvious over Su and Bethel.

304. Dr. Pirrung offers no reason that a skilled artisan would select Su's Compound 175 to make a hemicalcium salt. To the contrary, as explained in detail

above, a skilled artisan would have no reason to pick Su out of the sea of orforglipron prior art or select Su's Compound 175 as a lead compound. (Section VI.A.1.) Thus, a skilled artisan would not begin with Compound 175 based on the disclosures in Su.

305. Even starting with Su's Compound 175, the prior art would not motivate a skilled artisan to try to make its hemicalcium salt. Su does not disclose any salts of its Compound 175. And Bethel only discloses a hemicalcium salt of orforglipron. Neither reference teaches or suggests to a skilled artisan to make a hemicalcium salt of Su Compound 175.

306. Further, a skilled artisan would have known that salt selection is unpredictable, and that a screening process would be necessary to identify an optimal salt. (EX2070.) As explained above in Section II.C, there are a large number of potential counterions and hundreds of solvents and solvent mixtures a skilled artisan must choose from to try to form a salt, each of which is tested individually to determine if a salt can be formed. To achieve this, a skilled artisan may also conduct a salt screen to prepare a wide range of salts. (EX2070, Abstract.)

307. A skilled artisan would also understand the unpredictability of salt formation. As explained above, there is no way for a skilled artisan to be able to predict which salts will form. Moreover, each compound has different properties, resulting in different salts. (EX2070, Abstract.) Thus, changes to a compound would

result in different properties of the compound, which would affect salt forms and salt selection. A skilled artisan would therefore not be able to predict which salts will form, even for compounds that are structural analogs of each other.

308. Finally, a skilled artisan would not be motivated to form a hemicalcium salt of the claimed compounds based on the disclosures in Bethel. There is nothing in Bethel that suggests that the hemicalcium salt of orforglipron is better or has improved properties compared to any other salt of orforglipron. Bethel does not disclose any stability data or other properties of the hemicalcium salt of orforglipron that would lead a skilled artisan to select a hemicalcium salt for a different compound. Thus, a skilled artisan would have no reason to try to make a hemicalcium salt of the claimed compounds based on Bethel. Dr. Pirrung also does not offer any motivation as to why a skilled artisan would choose to make a hemicalcium salt based on the disclosure in Bethel.

E. Grounds 1-4: Objective Evidence Shows the Challenged Compounds Are Not Obvious

309. I have also considered the objective evidence in providing my opinions on the validity of the ’236 Patent. In my opinion, at least unexpected results and failures of others further show that the Challenged Claims are not obvious.

1. Unexpected Results

310. The Challenged Compounds demonstrate unexpectedly superior properties to the closest prior art. (EX1001, 199:50-203:67.) Compounds 1, 20 and 65 demonstrate unexpectedly improved properties over orforglipron. Compound 19 also demonstrates unexpectedly improved properties over both orforglipron and Compound 175 of Su (i.e., Compound 1 of the Challenged Patent).

311. Example 2 and Table 2 of the '236 Patent disclose the results of an *in vitro* activity study with EC_{50} values for the claimed compounds.

TABLE 2

Bioactivity of different compounds in hGLP-1R agonist cAMP stimulation assay

Compounds	hGLP-1R CAMP: EC_{50} (nM)
1	0.094
13	0.228
18	0.265
19	0.012
20	0.018
21	0.044
24	0.868
29	0.063
35	0.025
36	0.05
37	0.06
55	0.15
65	0.092
66	0.014
70	0.064
76	0.019
77	0.022
78	0.012
79	0.171
80	0.038
81	0.042
82	0.011
84	0.08
50	0.028

(EX1001, 201:1-27, Table 2.) I understand that Ascletis also tested orforglipron in the same assay disclosed in Example 2 and demonstrated an EC50 value of 0.044 nM. (EX2080, ¶8)

312. Example 3 and Table 3 of the '236 Patent disclose pharmacokinetic results for Compounds 1, 19, 20, and orforglipron following a single-dose subcutaneous injection.

TABLE 3

Drug exposure of different compounds after a single-dose subcutaneous injection

Compounds	Dosing route	Dose, mg/kg	$AUC_{0\text{-}696h}$, ng · h/mL
1	Subcutaneous	30	60,272
13	Subcutaneous	30	23,399
18	Subcutaneous	30	51,234
19	Subcutaneous	30	234,473
20	Subcutaneous	30	77,688
21	Subcutaneous	30	61,479
Orforglipron	Subcutaneous	30	5,390

(EX1001, 201:50-63, Table 3.) I understand that Ascletis also evaluated the clearance (Cl_F) and observed concentration (C_{max}) for Compounds 1 and 19 in the same assay disclosed in Example 3. (EX2080, ¶¶9-11.) The chart below summarizes the additional data for Compounds 1 and 19 from the assay.

	Compound 1	**Compound 19**
Cl_F, mL/min/kg	7.27	2.03
Cmax , ng/mL	561	2603

313. Example 3 and Table 4 disclose pharmacokinetic results for Compounds 19, 20, 65, and orforglipron following a single-dose administration.

TABLE 4

Pharmacokinetic parameters of different compounds after a single-dose oral administration

Compounds	Dosing route	Dose, mg/kg	C_{max}, ng/ml	$AUC_{0\text{-}48h}$, ng · h/mL
19	Oral	5	4,460	60,043
20	Oral	5	1,900	16,982
65	Oral	5	10,993	71,836
Orforglipron	Oral	5	799	7,222

(EX1001, 201:31-202:50, Table 4.)

314. Based on the above data, Compound 1 shows superior pharmacokinetics to orforglipron following a subcutaneous injection. Compound 1's $AUC_{0\text{-}696h}$ after a subcutaneous injection was 60,272 ng*h/mL compared to 5,390 ng*h/mL for orforglipron. (EX1001, 201:50-63, Table 3.) Compound 1's $AUC_{0\text{-}696h}$ is thus ***11-fold*** that of orforglipron.

315. Compound 19's potency and pharmacokinetics are both unexpectedly superior to orforglipron and Compound 1. The data for Compound 19 compared to those compounds are summarized in the table below.

	Compound 19	**Orforglipron**	**Compound 1**
EC_{50}, (nm)	0.012 nm	0.044 nm *Over 3-fold less potent*	0.094 nm *Over 7-fold less potent*

Single Dose Subcutaneous Injection			
$AUC_{0\text{-}696h}$	234,473 ng*h/mL	5,390 ng*h/mL *Over 43-fold worse*	60,272 ng*h/mL *Nearly 4-fold worse*
Cl_F	2.03 mL/min/kg		7.27 mL/min/kg *Over 3-fold worse*
C_{max}	2603 ng/mL		561 ng/mL *Over 4-fold worse*
Single Dose Oral Administration			
C_{max}	4,460 ng/mL	799 ng/mL *Over 5-fold worse*	
$AUC_{0\text{-}48h}$	60,043 ng*h/mL	7,222 ng*h/mL *Over 8-fold worse*	

316. As shown above, Compound 19 demonstrated an EC_{50} of 0.012 nM, while orforglipron and Compound 1 measured 0.044 nM and 0.094 nM, respectively. (EX1001, 201:1-27, Table 2; EX2080, ¶¶6-8.) The EC_{50} value of Compound 19 is thus more than 3-fold the EC_{50} of orforglipron and over 7-fold the EC_{50} value of Compound 1. (EX2080, ¶¶9-11.) These increases in EC_{50} indicate a significant improvement in potency.

317. Compound 19 also demonstrates unexpectedly superior pharmacokinetics to Compound 1 and orforglipron following a single-dose subcutaneous injection. Compound 19 demonstrated an $AUC_{0\text{-}696h}$ of 234,473

ng*h/mL, while Compound 1 and orforglipron measured 60,272 ng*h/mL and 5,390 ng*h/mL, respectively. (EX1001, 201:50-63, Table 3.) Additional data shows that Compound 19 has a superior clearance rate of 2.03 mL/min/kg compared to 7.27 mL/min/kg for Compound 1. (EX2080, ¶¶9-11.) Compound 19's C_{max} was also superior to Compound 1's, measuring at 2,603 ng/mL compared to 561 ng/mL, respectively. Thus, Compound 19's $AUC_{0\text{-}696h}$ exceeds Compound 1 and orforglipron by over 3-fold and 43-fold, respectively.

318. Compound 19 shows superior pharmacokinetic properties to orforglipron following a single-oral administration as well. Compound 19's C_{max} was 4,460 ng/mL and $AUC_{0\text{-}48h}$ was 60,043 ng*h/mL. (EX1001, 201:31-202:50, Table 4.) Orforglipron's C_{max} was 799 ng/mL and $AUC_{0\text{-}48h}$ was 7,222 ng*h/mL. (EX1001, 201:31-202:50, Table 4.) Compound 19 demonstrated a C_{max} more than 5-fold orforglipron's and an $AUC_{0\text{-}48h}$ more than 8-fold orforglipron's after a single-dose oral administration. (EX1001, 201:31-202:50, Table 4.)

319. Compound 20 also shows superior pharmacokinetics to orforglipron in both a subcutaneous and oral dose. These results are summarized the table below.

	Compound 20	**Orforglipron**
EC_{50}, (nm)	0.018 nm *Over 2.4-fold greater*	0.044 nm
Single Dose Subcutaneous Injection		

$AUC_{0\text{-}696h}$, ng*h/mL	77,688 ng*h/mL	5,390 ng*h/mL
Single Dose Oral Administration		
C_{max}, ng/mL	1,900 ng/mL	799 ng/mL
$AUC_{0\text{-}48h}$, ng*h/mL	16,982 ng*h/mL	7,222 ng*h/mL

320. As shown above, Compound 20 demonstrated an EC_{50} of 0.018 nM, compared to 0.044 nM for orforglipron. (EX1001, 201:1-27, Table 2; EX2080, ¶¶6-8.) The EC_{50} value of Compound 20 is almost 2.5-fold the EC_{50} of orforglipron. This increase in EC_{50} indicates a significant improvement in potency over orforglipron.

321. Following the subcutaneous dose, Compound 20 measured an $AUC_{0\text{-}696h}$ of 77,688 ng*h/mL, whereas orforglipron measured 5,390 ng*h/mL. (EX1001, 201:50-63, Table 3.) Compound 20's $AUC_{0\text{-}696h}$ exceeds orforglipron by over 14-fold, evidencing superior subcutaneous pharmacokinetics.

322. Following the oral dose, Compound 20's C_{max} was 1,900 ng/mL and $AUC_{0\text{-}48h}$ was 16,982 ng*h/mL. (EX1001, 201:31-202:50, Table 4.) Orforglipron's C_{max} was 799 ng/mL and $AUC_{0\text{-}48h}$ was 7,222 ng*h/mL. (EX1001, 201:31-202:50, Table 4.) Compound 20 thus demonstrated a C_{max} more than 2-fold orforglipron's and an $AUC_{0\text{-}48h}$ more than 2-fold orforglipron's after a single-dose oral administration. (EX1001, 201:31-202:50, Table 4.) Compound 20 shows increased pharmacokinetics across all methods of administration.

323. Compound 65 shows improved pharmacokinetic results following a single-dose oral administration. Compound 65's C_{max} was 10,993 ng/mL and $AUC_{0\text{-}48h}$ was 71,836 ng*h/mL. (EX1001, 201:31-202:50, Table 4.) Orforglipron's C_{max} was 799 ng/mL and $AUC_{0\text{-}48h}$ was 7,222 ng*h/mL. (EX1001, 201:31-202:50, Table 4.) Compound 65 thus demonstrated a C_{max} more than 13-fold orforglipron's and an $AUC_{0\text{-}48h}$ more than 10-fold orforglipron's after a single-dose oral administration. (EX1001, 201:31-202:50, Table 4.)

324. I understand that Patent Owner measured the solubility of Challenged Compound 1 compared to Challenged Compound 65. (EX2081; EX2080, ¶¶12-13.) Higher solubility improves a compound's druggability, increasing bioavailability and allowing for faster absorption. Based on Patent Owner's experiments, Challenged Compound 1 has a solubility of 0.0587 mg/mL at pH 11, compared to a solubility of 6.650 mg/mL from Challenged Compound 65. (EX2081; EX2080, ¶¶12-13.) Compound 65 thus shows an over 100-fold increase in solubility compared to Compound 1. This is a significant increase in solubility that may facilitate formulation and could offer advantages for pharmaceutical development of Compound 65 compared to Compound 1.

325. Nothing in the prior art suggests that the substitutions made in the Challenged Compounds would lead to the superior potency and pharmacokinetic results discussed above. Su and Yoshino do not provide any potency data for

compounds with the modifications in the Challenged Compounds. Moreover, Yoshino and Kawai do not provide pharmacokinetic data for any compound other than orforglipron, and while Talele suggests cyclopropyl groups can affect the properties of a compound, it is not directed to orforglipron and does not suggest the significant improvement in pharmacokinetics shown by the Challenged Compounds. (EX1008; EX1004; EX1009.) Meng only provides potency data for its Compounds (II) and (III), compared to orforglipron and does not disclose any pharmacokinetic data for any compounds. (EX1029, [0186]-[0192].) Ren, on the other hand, does not disclose any potency data, and only provides pharmacokinetic data for five compounds compared to orforglipron, none of which have the same modifications as the Challenged Compounds. (EX1030, Table 30.) Neither Meng nor Ren would suggest that the modifications made in the Challenged Compounds would result in any superior potency or pharmacokinetic properties.

326. I further understand that the Patent Owner is developing a drug named ASC30 for treatment of obesity. (EX2022.) Furthermore, the ’236 Patent’s claims cover ASC30. (EX2066). ASC30 has demonstrated safety and efficacy data in Phase 1 and 2 clinical trials, including a 6.5% mean reduction in body weight after just 28 days of treatment. (EX2023; EX2022, 2.) ASC30’s recent Phase 2 trial also shows good tolerability. (EX2042, 1.) Over a 13-week study, only 22-30% of patients reported vomiting. (EX2042, Table 1.) ASC30 also had promising GI tolerability

profiles for nausea, diarrhea, and constipation. (EX2042.) While early, these results are positive indicators for ASC30's safety and efficacy and consistent with the superior properties demonstrated by the preclinical data in the '236 Patent.

327. Moreover, I understand that Ascletis is pursuing ASC30 in both a once-daily oral dosing regimen and a once-monthly subcutaneous dosing regimen. (EX2042.) The superior potency and pharmacokinetics seen in the Challenged Compounds likely enable that flexibility in dosing regimen, which I understand is not being pursued with orforglipron.

2. Failure of Others

328. In my opinion, the difficulty of achieving a small-molecule GLP-1R agonist for oral administration like the compounds disclosed in the '236 Patent is underscored by the efforts and failure of others in the field.

329. Many companies are currently developing non-peptide GLP-1R agonists for oral administration. Before the current generation of GLP-1 receptor agonists, others had also failed to create non-peptide GLP-1 receptor agonists. In 2007, scientists at the Institute of Materia Medica in Shanghai discovered a non-peptidic GLP-1R agonist, titled Boc5. (EX2067, 7-8.) Boc5 never moved to clinical development due to low bioavailability and poor pharmacokinetics. (EX2067, 7-8; EX2046, 4.) After performing SAR studies, which expectedly improved on Boc5's potency, the new drug's properties still did not prompt development. (EX2046, 4.)

330. A trio of Pfizer programs developing small-molecule GLP-1R agonists were discontinued after at least a Phase 1 clinical trial. Pfizer's lotiglipron was discontinued after discovering concerning "transaminase elevations" in Phase 1 and Phase 2 studies. (EX2048.) Transaminases are enzymes created by damaged liver cells. An elevation in transaminase levels indicates liver stress. In the Phase 2 study, elevated transaminase levels were observed in "6.6% and 6.0% of participants on lotiglipron in the T2D and obesity cohorts, respectively, compared with 1.6% on placebo in the obesity cohort." (EX2049, Abstract.)

331. In addition to lotiglipron, Pfizer also advanced danuglipron to Phase 2 clinical trials and expected to begin Phase 3 testing. (EX2050.) Instead, Pfizer also discontinued danuglipron after a "potential drug-induced liver injury" occurred. (EX2050, 1.)

332. Finally, Pfizer discontinued its third GLP-1R agonist, PF-06954522, after reviewing data from their Phase 1 study. (EX2051.)

333. Companies have continued to invest significant capital and effort into developing small molecule GLP-1R agonists but none have yet received FDA approval.

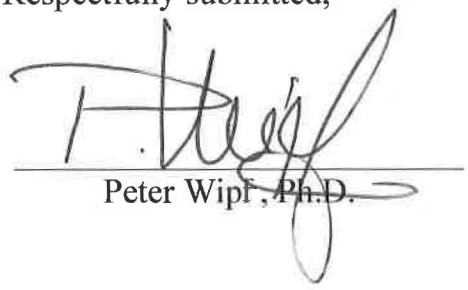
VIII. CONCLUSION

In my opinion, Petitioner and Dr. Pirrung have failed to show that any claim of the challenged patent is unpatentable in light of the prior art asserted.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001.

Dated: March 5, 2026

Respectfully submitted,



Peter Wipf, Ph.D.

APPENDIX A

BIOGRAPHICAL SKETCH

PETER WIPF

PERSONAL DATA

Contact Inf.:	University of Pittsburgh	Phone:	(412) 624 8606/(412) 624 8065
	Department of Chemistry	@wipf_group	
	Chevron Science Center	E-Mail:	PWIPF@PITT.EDU
	Pittsburgh, PA 15260		
Homepage:	http://ccc.chem.pitt.edu/wipf/index.html		

Number of peer-reviewed publications: >640; number of issued US patents: >125.
Total citations (source: Google Scholar): 44,000 *(11,500 since 2020)*; *h*-index: 106 *(44 since 2020)*; *i10*-index: 569 *(310 since 2020)*.
ORCID Identifier: 0000-0001-7693-5863

EDUCATION

Swiss National Science Foundation Postdoctoral Fellow: University of Virginia, Department of Chemistry (1/1988-8/1990). Research Topics: Total Synthesis of FK-506; Stereoselectivity in the Ester-Enolate Claisen Rearrangement. Advisor: Prof. R. E. Ireland.

Ph. D. (1987) University of Zürich, Department of Chemistry. Thesis title: Synthesis and Conformational Analysis of Peptides with α,α-Disubstituted α-Amino Acids. Advisor: Prof. H. Heimgartner.

Dipl. Chem. (1984) University of Zürich, Department of Chemistry. Thesis title: Synthesis and 1,3-Dipolar Cycloadditions of Arylthio-Substituted Nitrile Ylids. Advisor: Prof. H. Heimgartner.

PROFESSIONAL EXPERIENCE

Distinguished University Professor of Chemistry (7/2004-present), **Professor** (2/1997-6/2004), **Associate Professor** (8/1995-1/1997), **Assistant Professor** (9/1990-8/1995), University of Pittsburgh.

Co-Leader (7/2012-present), Cancer Therapeutics Program, UPMC Hillman Cancer Center.

Director: Combinatorial Chemistry Center (11/1997-present), University of Pittsburgh Center for Chemical Methodologies and Library Development (10/2002-present).

Subject Matter Expert, UPMC Enterprises (12/2018-present).

Professor of Pharmaceutical Sciences (11/2001-present), University of Pittsburgh, School of Pharmacy, Department of Pharmaceutical Sciences.

Professor of Bioengineering (1/2014-present), University of Pittsburgh, Swanson School of Engineering, Department of Bioengineering.

PRIMARY RESEARCH INTERESTS

- The Total Synthesis of Natural Products
- Synthetic Organic and Medicinal Chemistry
- Discovery of Innovative Methods in Heterocyclic and Strain-Release Chemistry

- Computational Analysis of Small Molecule Properties

AWARDS AND HONORS

- Fellow of the National Academy of Inventors (2024)
- ACS Award for Creative Work in Synthetic Organic Chemistry (2023)
- Internal Advisory Board, UPMC Hillman Cancer Center Heme-Onc T32 Fellowship Program (2022-present)
- Visiting Professor, University of Eastern Finland, Kuopio, Finland (2021-present)
- Vice President, Organic Syntheses, Inc. (2021-present).
- Stanford University Ranking in Top 0.04% of Scientists in the World (2020)
- Adjunct Professor, Duke University, Department of Chemistry, Durham, North Carolina (7/2002-7/2019).
- Visiting Professor (Gast Professur), RWTH Aachen, Aachen, Germany (October-November 2015, August-September 2016, and May-June 2017)
- Provost's Award for Excellence in Mentoring (2015)
- Chair-Elect, Chair, and Retiring Chair of the Section on Pharmaceutical Sciences of the American Association for the Advancement of Science (2015-2018)
- Humboldt Research Award of the Alexander von Humboldt Foundation (2014)
- Harry and Carol Mosher Award of the Santa Clara Valley Section of the ACS (2013)
- Edward W. Morley Award of the Cleveland Section of the ACS (2013)
- ACS Pittsburgh Award (2012)
- Fellow of the American Chemical Society (2010)
- ACS Ernest Guenther Award in the Chemistry of Natural Products (2009)
- Chancellor's Senior Scholar Distinguished Research Award (2008)
- Novartis Chemistry Lectureship (2005)
- Fellow of the Royal Society of Chemistry (FRSC, 2004)
- Visiting Professor (Professeur Associé), École Supérieur de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI), Paris, France (September 2004)
- Long Range Planning Committee, ACS Division of Medicinal Chemistry (2004-2006)
- ISHC Katritzky Award in Heterocyclic Chemistry (2003)
- Fellow of the American Association for the Advancement of Science (AAAS, 2002)
- Chair, Gordon Research Conference on Stereochemistry, Salve Regina University, Newport, Rhode Island (June 9-14, 2002)
- Visiting Professor (Professeur Associé), Université de Paris-Sud, Orsay, France (November 2001)
- Member-at-Large, Organic Division Executive Committee of the ACS (2001-2003)
- Novartis Research Award (2000, 2001)
- Japan Society for the Promotion of Science Fellow (2000)
- Akron Section ACS Award (1998)
- ACS Arthur C. Cope Scholar Award (1998)
- NIH Medicinal Chemistry Study Section, Member (1998-2003), Chairman (2001-2003)
- Chancellor's Junior Scholar Distinguished Research Award (1997)
- Phi Eta Sigma, Honorary Member (1996)

- Merck Young Investigator Award (1995)
- Zeneca Award for Excellence in Chemistry (1995)
- Camille Dreyfus Teacher-Scholar Award (1995)
- UCI-Allergan Visiting Lecturer, University of California, Irvine, California (May, 1995)
- American Cancer Society Junior Faculty Research Award (1995-1998)
- NSF Presidential Faculty Fellow (1994-1999)
- ETH Ruzicka Award (1994)
- Alfred P. Sloan Research Fellow (1994-1996)
- American Cyanamid Faculty Award (1994)
- Eli Lilly Grantee (1993-1995)
- University of Zürich, Distinguished Dissertation Award (1987)

SCIENTIFIC, EDITORIAL, AND PROFESSIONAL BOARDS

- External Advisory Committee, Purdue Institute for Cancer Research (PICR), West Lafayette, IN (2024-present)
- External Monitor for Emory College of Arts and Sciences (2022)
- Editorial Advisory Board, ACS Medicinal Chemistry Letters (2021-present)
- Organizing Committee, *Workshop on Synthetic Organic Chemistry for Young Investigators, Sponsored by Organic Syntheses, Inc.* (2019-2023)
- Member of Panel Assessing Research and Teaching Activities of the Institute of Pharmacy, Innsbruck University, Austria (2019)
- Editorial Advisory Board, *Helvetica Chimica Acta* (2016-2022)
- ACS National Awards Selection Committee (2015-2022)
- Guest Editor for *Israel Journal of Chemistry* Special Issue on "Flow Chemistry" (2014).
- Organic Syntheses, Inc., Board of Directors (2013-present)
- Editorial Advisory Board, Diversity Oriented Synthesis (http://www.versita.com/dos; 2012-2015)
- Nominating Committee for Board of Directors of Organic Synthesis (2011, 2015)
- Guest Editor for Molecules Special Issue on "Diversity Oriented Synthesis" (2011)
- Facilitator for Arkivoc "Commemorative Issue in Honor of Prof. Heinz Heimgartner on the Occasion of his 70th Anniversary" (2011)
- External Advisory Committee, Purdue University Center for Cancer Research, West Lafayette, IN (2010-2023)
- Associate Editor, ACS Medicinal Chemistry Letters (2009-2020)
- Honorary Editorial Board, International Journal of High Throughput Screening (2009-present)
- Organic Reactions, Inc., Board of Directors (2007-2023)
- External Advisory Board, Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, FL (2007-2012)
- International Advisory Editorial Board, Organic & Biomolecular Chemistry (2007-present)
- Faculty of 1000 Biology; Drug Discovery & Design Section of the Pharmacology & Drug Discovery Section, Biology Reports Ltd (http://www.f1000biology; 2006-2011)

- Oncology Advisory Board, Wyeth (2005-2009)
- Member of the Editorial Board, Chemical Biology & Drug Design (CB&DD, 2005-present)
- Guest Editor for Tetrahedron Symposium in Print No. 102 on "Recent Advances in the Chemistry of Zirconocenes" (2004)
- Progress in Heterocyclic Chemistry Editorial Advisory Board (2004-2007)
- International Society of Heterocyclic Chemists (ISHC) Advisory Board (2003-2007)
- Scientific Advisory Board, Fluorous Technologies, Inc., U-PARC, 970 William Pitt Way, Pittsburgh, Pennsylvania 15238 (2000-2010)
- Associate Editor for North America, Organic & Biomolecular Chemistry (2002-2006)
- Member of the Board of Editors of Organic Syntheses, Inc. (2002-2010)
- Scientific Advisory Board, Lexicon Genetics, Inc., The Woodlands, Texas (2001-2002)
- Member of the Editorial Advisory Board, Chirality (2000-present)
- Member of the Advisory Board, Molecules (http://www.mdpi.org/molecules/; 2000-2019)
- Scientific Advisory Board, Xenoport, Santa Clara, California (1999-2006)
- Member of the Advisory Board, Journal of Organic Chemistry (1999-2003)
- Executive Editor, Electronic Encyclopedia of Reagents in Organic Synthesis, J. Wiley (1999-2004)
- Member of the Editorial Board, Organic Reactions, Inc. (1997-2012)
- Series Editor (with Ted Taylor), The Chemistry of Heterocyclic Compounds, J. Wiley (1997-2015)
- Scientific Advisory Board, Coelacanth Chemical Corporation, Inc., New York (1997-2001)
- Chemistry Advisory Board, Arpida AG, Münchenstein, Switzerland (1997-2008)

COMMITTEES/NATIONAL PANELS

- NIH Chemical Biology and Probes Study Section, June 23-24, 2025.
- NSF SYN ORG 1 Review Panel, February 1-2, 2024.
- UPMC Hillman Cancer Center Developmental Pilot Program Review Panel, June 21, 2023.
- NIH Special Emphasis Panel; Small Business: Respiratory Sciences ZRG1 CVRS-B (11) Study Section, November 29-30, 2022.
- Chemistry External Review Panel, Purdue University, West Lafayette, Indiana, September 11-13, 2022.
- 3rd Organic Syntheses Workshop on Organic Synthesis and Natural Products Chemistry, Organizer, Steamboat Springs, Colorado, August 16-19, 2022.
- 2nd Organic Syntheses Workshop on Organic Synthesis and Natural Products Chemistry, Organizer, Steamboat Springs, Colorado, August 10-13, 2021.
- NIH Special Emphasis Panel/Scientific Review Group 2020/01 ZRG1 CB-B (55) R Study Section, November 14-15, 2019.
- 1st Organic Syntheses Workshop on Organic Synthesis and Natural Products Chemistry, Organizer, Steamboat Springs, Colorado, August 6-9, 2019.
- NIH Special Emphasis Panel/Scientific Review Group ZRG1 BCMB-A (50) Study Section, March 31, 3017.

- AAAS 2017 Annual Meeting, Symposium Organizer of Session on: Impact of Drug Shortages and Pricing on the Health of Americans, Hynes Convention Center, Chicago, Illinois, February 18, 2017.
- NIH Special Emphasis Panel/Scientific Review Group ZRG1 BCMB-A (50) Study Section, March 30, 2016.
- Pacifichem 2015, Symposium Organizer and Fund Raiser, BIOL: Heat Shock Proteins: The Next Target in the Disease Frontier (#91), Honolulu, Hawaii, December 18, 2015.
- ACS National Award Selection Committee 2015-present.
- NIH Special Emphasis Panel/Scientific Review Group ZRG1 BCMB-W (02) M Study Section, December 10, 2014.
- NIH Special Emphasis Panel/Scientific Review Group ZRG1 BCMB-A 02 M Study Section, August 15, 2014.
- NIH Special Emphasis Panel/Scientific Review Group 2014/01 ZRG1 BCMB-P (02) Study Section, December 5-6, 2013.
- 8th National CMLD Meeting, National Institutes of Health, Bethesda, Maryland, Chair, June 12, 2012.
- NIH Special Emphasis Panel/Scientific Review Group 2012/01 ZRG1 BCMB-P (02) Study Section, November 17-18, 2011.
- NIH Synthetic and Biological Chemistry B (SBCB) Study Section, June 1-2, 2011.
- NIH Special Emphasis Panel/Scientific Review Group 2011/05 ZRG1 BCMB-P (02), April 4-5, 2011.
- Chair, Department of Chemistry & Biochemistry Review Panel, University of Notre Dame, South Bend, Indiana, November 22-23, 2010.
- NIH Special Emphasis Panel/Scientific Review Group 2010/05 ZAI1 RB-M (M1), March 18, 2010.
- NSF Chemical Synthesis SYN-2 Review Panel, October 26-27, 2009.
- NIH ZRG1 BCMB-P 58 R Editorial Board Review Panel, July 20-21, 2009.
- NIH Special Emphasis Panel ZRG1 BCMB-B, June 4-5, 2009.
- NIMH Technical Evaluation Panel ZMH1 ERB-S C6 S "NIMH Chemical Synthesis and Drug Supply Program", June 25, 2008.
- 31st ACS National Medicinal Chemistry Symposium, Pittsburgh, PA, Program Co-Chair, June 15-19, 2008.
- NIH Roadmap: Defining the Role of Informatics within the Molecular Libraries Program (MLP) Workshop, Bethesda, Maryland, Co-Chair, May 17, 2008.
- NIH Special Emphasis Panel ZRG1 BCMB-B, February 28-29, 2008.
- 2007 ACS/EFMC Congress on "Frontiers in CNS and Oncology Medicinal Chemistry", Siena, Italy, Member of the Organizing Committee, October 7-9, 2007.
- 1st Latin American Meeting on Medicinal Chemistry (LatQuiMed), Montevideo, Uruguay, Member of the Scientific Committee, April 22-25, 2007.
- 2007 ACS Medicinal Chemistry Division Student Fellowship Selection Committee.
- 2007 ACS David W. Robertson Award Selection Committee.

- NIH ZCA1 GRB-P M1 S Discovery and Development Special Emphasis Panel (PO1), February 7-9, 2007.
- 2006 ACS Medicinal Chemistry Division Student Fellowship Selection Committee.
- 2006 ACS David W. Robertson Award Selection Committee.
- ACS Symposium on "Hepatitis C Inhibitors" (ACS Medicinal Chemistry Division), 232nd National Meeting, San Francisco, CA, Co-Organizer (with S. Venkatraman), September, 2006.
- ACS Symposium on "Peptide Bond Isosteres" (ACS Organic Division), 232nd National Meeting, San Francisco, CA, Co-Organizer (with D. Huryn), September, 2006.
- 2006 "Heinz Heimgartner Ehren Symposium" Committee.
- Pacifichem 2005 Symposium on "Prospects for Automated and Microreactor Synthesis" (Environmental and Green Chemistry Division), Hilton Hawaiian Village, Honolulu, HI, Co-Organizer (with J. Yoshida), December 15-16, 2005.
- Special Emphasis Panel/Scientific Review Group 2006/01 ZRG1 BCMB-R, Synthetic and Biological Chemistry, Chairman, October 25, 2005.
- SBIR/STTR Phase II Virtual Panel Combinatorial Biotechnology/Drug Delivery, March 31, 2005.
- NIH ZRG1 BCMB-B Conflicts in Biological Chemistry and Macromolecular Biophysics Special Emphasis Panel, March 10, 2005.
- American Association for Cancer Research (AACR) Think Tank on "Opportunities and Challenges of Chemistry in Cancer Research", Philadelphia, PA, February 10-11, 2005.
- ACS Symposium on "Molecular Chirality: Theory, Synthesis and Spectroscopy" (Organic ACS Division), 56th Southeastern Regional Meeting, Research Triangle Park, NC, Co-Organizer (with D. N. Beratan), November 13, 2004.
- ACS Symposium on "Diversity-Oriented Synthesis and Chemogenomic Drug Discovery" (co-sponsored by Medicinal Chemistry and Organic ACS Divisions), 228th National Meeting, Philadelphia, PA, Organizer, August 23, 2004.
- ACS Symposium on "Half-A-Century of Organozirconium Chemistry" (co-sponsored by Organic and Inorganic ACS Divisions), 227th National Meeting, Anaheim, CA, Co-Organizer (with E. Negishi), March 28-29, 2004.
- NSF Division of Chemistry Committee of Visitors (COV), February 3-5, 2004.
- NIH Oncological Science Study Section, Ad-hoc member, March 17, 2003.
- NSF Organic Chemistry Workshop, Organizing Committee, 2001-2003.
- American Chemical Society, Division of Organic Chemistry Predoctoral Fellowship Committee, Member, 2001-2002; Chair, 2002.
- NIH Medicinal Chemistry Study Section, Member, 1998-2003, Chairman, 2001-2003.
- NIH Medicinal Chemistry Study Section, Ad-hoc member, October 15-16, 1997.
- NIH Bio-Organic & Natural Products Chemistry Study Section, Chairman of Chemistry & Related Sciences Special Emphasis Panel, November 7-8, 1996.
- NSF Chemistry Division Postdoctoral Fellowships Review Panel, Washington, DC, April 15-16, 1996.

- NIH Bio-Organic & Natural Products Chemistry Study Section, Ad-hoc member, October 19-21, 1995.
- NSF-NATO Postdoctoral Fellowship Review Panel, Washington, DC, April 25-27, 1995.

CONSULTING RELATIONSHIPS AND SCIENTIFIC ADVISORY BOARDS

- Continuously since 1995, with a total of >30 pharmaceutical and chemical companies
- Coelacanth Chemical Corporation, Inc., New York, NY (1997-2001).

RESEARCH PUBLICATIONS

636. "**Antitumor Efficacy of 1,2,4-Triazole-Based VCP/p97 Allosteric Inhibitors**." Green, N.; LaPorte, M. G.; Paquette, W.; Joyasawal, S.; Mondal, P.; Vaughn, Z.; Carder, E. J.; Liang, M.; Shan, L.; Wang, F.; Tomaino, F.; Srivastava, A.; Flint, A.; Moore, W. J.; Chou, T.-F.; Stott, G. M.; Wolf, M.; Wipf, P.; Huryn, D. M. *J. Med. Chem.* **2025**, *68*(14), 14465–14494.
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SELECTED PATENTS (TOTAL NUMBER OF PATENTS: >135)

(FOR AN EXTENDED LISTING, SEE: https://patentscope.wipo.int/search/en/structuredSearch.jsf)

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RESEARCH PRESENTATIONS

Invited Symposia Presentations and Major Lectureships

2025

- International Society Of Vascularized Composite Allotransplantation (ISVCA), Midnight Sun Meeting, Helsinki, Finland, June 27-29.

2024

- ACS National Meeting, Division of Organic Chemistry, State of the Art in sp3-Rich Bioisosteres, Denver, Colorado, August 21.
- CSBC2024, Chemical Solutions for Biological Challenges, Turku, Finland, June 10-12.

2023

- The 10th Pharmaron Symposium on Synthetic and Medicinal Chemistry, Ningbo, China, September 23.
- ACS Award for Creative Work in Synthetic Organic Chemistry, Division of Organic Chemistry, ACS Spring 2023 National Meeting, Indianapolis, March 29.

2022

- Gordon Research Conference on Heterocyclic Compounds, Salve Regina University, Newport, Rhode Island, June 24.
- 1st Virtual Symposium on Chirality, John Wiley & Sons Ltd., February 22.

2021

- FinPharma Research Seminar, October 27.
- UEF DrugTech RC Ruska-Event 2021, Koli, Finland, September 6.
- Organic Synthesis Workshop on Organic Synthesis and Natural Products Chemistry, Steamboat Springs, Colorado, August 10.
- Keynote Speaker, VIII European Workshop in Drug Synthesis, May 21.

2020

- International Conference on Chemical Science for Drug Discovery & Therapy, Department of chemistry VNIT Nagpur, Nagpur, India, July 22-26.
- 8th Vertex Day Lecturer, University of California at Irvine, Departments of Chemistry and Pharmaceutical Sciences, Irvine, California, February 28.

2019

- Organic Syntheses Lecturer, Virginia Commonwealth University, Department of Chemistry and Department of Chemical Engineering, Richmond, Virginia, August 16.

2018

- Organic Syntheses Lecturer, City University of New York Hunter College, Department of Chemistry, New York, New York, October 19.
- Organic Syntheses Lecturer, Old Dominion University, Department of Chemistry and Biochemistry, Norfolk, Virginia, October 5.
- Symposium on Projects of NCI Chemical Biology Consortium: A Unique, Collaborative Approach to Cancer Drug Discovery, 256th ACS National Meeting in Boston, Massachusetts, August 21.
- PancreasFest, Sheraton Station Square, Pittsburgh, Pennsylvania, July 26.

- Annual Meeting of the American Society of Pharmacognosy (ASP), Lexington, Kentucky, July 22.
- 41st Annual Conference on Shock, Scottsdale, Arizona, June 9-12.
- Plenary Lecturer, VII European Workshop in Drug Synthesis, Certosa di Pontignano, Siena, Italy, May 23.
- Cardio Pulmonary Vascular Biology Center of Biological Research Excellence, Providence VA Medical Center, Providence, Rhode Island, January 12.

2017

- Plenary Lecturer, PSRC-8, 8th Pacific Symposium on Radical Chemistry, Queensland University of Technology, Brisbane, Queensland, Australia, July 18-22.
- Plenary Lecturer, ISSX 2017, 14th European Meeting of The International Society for the Study of Xenobiotics, Gürzenich, Cologne, Germany, June 26-29.
- Hillger-Roberts-Kranbuehl Lectureship, College of William and Mary, Williamsburg, Virginia, April 7.
- Plenary Lecturer, 29. Irseer Naturstofftage, Schwäbisches Tagungs- und Bildungszentrum Irsee, Germany, February 22-24.
- Michael H. Benn Distinguished Lectureship, University of Calgary, Calgary, Canada, February 8-10.

2016

- International Conference for the 70th Anniversary of the Pharmaceutical Society of Korea (PSK), Seoul, South Korea, October 18.
- 2016 Chung-Ang SRC International Symposium, Center for Metareceptome Research, Seoul, South Korea, October 17.

2015

- Pacifichem 2015, Symposium on Molecular Design in Medicine: Concept to Commerce, Honolulu, Hawaii, December 20.
- Pacifichem 2015, Symposium on Heat Shock Proteins: The Next Target in the Disease Frontier, Honolulu, Hawaii, December 18.
- NSF REU Symposium, Department of Chemistry, Western Washington University, Bellingham, Washington, August 14.
- Bristol–Myers Squibb Symposium, Department of Chemistry, University of California Irvine, Irvine, California, June 25.
- Children's Hospital of Pittsburgh Molecular Medicine Research Seminar, Rangos Research Center, Pittsburgh, Pennsylvania, June 9.
- 43rd Alexander von Humboldt Awards Symposium, Bamberg, Germany, March 28.
- BMS Smissman Symposium, Division of Medicinal Chemistry, 249th American Chemical Society National Meeting, Denver, Colorado, March 24.
- International Conference on Exploring New Avenues in Medicinal Chemistry: Opportunities and Challenges, Forman Christian College, Lahore, Pakistan, January 21.

2014

- Society of Chemical Industry (SCI) A Celebration of Organic Chemistry 2014, Erl Wood, United Kingdom, September 22.
- Innovation Seminar Series, Biolake Development Area, Wuhan, China, September 12.
- Tsinghua University Frontiers in Biological Sciences Seminar Series, Beijing, China, September 9.
- Gordon Research Conference on Natural Products, Proctor Academy, Andover, New Hampshire, July 20-24.
- V EWDSy - Fifth European Workshop in Drug Synthesis, Certosa di Pontignano, Siena, Italy, May 18-23.
- The 2014 Paquette Legacy Symposium, Department of Chemistry and Biochemistry, The Ohio State University, Columbus, OH, May 9.
- Harry and Carol Mosher Award Lecture, Biltmore Hotel, Santa Clara, California, January 16.

2013

- Madeleine Joullié Lectureship, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, September 19.
- TGH Jones Lectureship, Department of Chemistry, University of Queensland, Brisbane, Queensland, Australia, July 15.
- 6th Heron Island Conference on Reactive Intermediates and Unusual Molecules, Heron Island (off Gladstone), Great Barrier Reef, Queensland, Australia, July 7-13.
- 2013 National Organic Symposium, University of Washington, Seattle, Washington, June 23-27.
- Howard E. Smith Lecture on Stereochemistry, 14th International Conference on Chiroptical Spectroscopy, Vanderbilt University, Nashville, Tennessee, June 10.
- Morley Lecture, 57th Annual May Conference, The Cleveland Section of the Society for Applied Spectroscopy, Microscopy Society of NE Ohio, The American Vacuum Society, and The Cleveland Section of the American Chemical Society, Dolan Science Center, John Carroll University, University Heights, Ohio, May 16.
- 2013 Hecht Lecture, University of Virginia, Department of Chemistry, Charlottesville, Virginia, April 19.
- 2nd Annual Conference on Laboratory Automation and Screening (slas 2013), Symposium on Assay Development and Screening Libraries, Orlando, Florida, January 16.

2012

- DFG (Deutsche Forschungsgemeinschaft) FOR 934 Meeting, Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, Darmstadt, Germany, December 4-5.
- Asymchem Fall Symposium for Pharmaceutical CMC, Tianjin, China, September 20-21.
- 244th National ACS Meeting, Symposium on "Molecular and Supramolecular Chirality", ACS Organic/Analytical Chemistry Division, Philadelphia, PA, August 20.
- Plenary Lecturer, 19th International Conference on Organic Synthesis in conjunction with the 24th Royal Australian Chemical Institute Organic Conference, Melbourne, Australia, July 1-6.
- Plenary Lecturer, Australian Workshop for Chemical Biology, University of Melbourne, Melbourne, Australia, June 29.

- 29th Herbert C. Brown Lectures in Organic Chemistry, Purdue University, West Lafayette, June 9.
- SCI/RSC Symposium on Advances in Synthesis and Medicinal Chemistry, BioPark, Welwyn Garden City, United Kingdom, May 1.
- Prof. Dr. Manfred Hesse Memorial Symposium, University of Zürich-Irchel, Zürich, Switzerland, March 22.

2011

- The 30th Annual Esther and Bingham J. Humphrey Memorial Symposium in Chemistry, University of Vermont, Burlington, VT, September 24.
- 14th Brazilian Meeting on Organic Synthesis (BMOS), Brasilia, Brazil, September 1-5.
- NSF Workshop on "Physical Frameworks for Sampling Chemical Compound Space", Instiute for Pure & Applied Mathematics, University of California at Los Angeles, Los Angeles, May 16-20.
- 241st National ACS Meeting, Symposium on "Drug Discovery Centers", ACS Medicinal Chemistry Division, Anaheim, CA, March 29.
- Eli Lilly Lecturer, Imperial College, Organic Synthesis Group, London, United Kingdom, January 18.

2010

- EFMC-ISMC XXIst International Symposium on Medicinal Chemistry, Brussels, Belgium, September 5-9.
- Novartis Central Europe Lecturer, June 14-18.
- Bürgenstock/45th Euchem Conference on Stereochemistry, Brunnen, Switzerland, May 2-7.

2009

- AstraZeneca Symposium on Excellence in Chemistry, AstraZeneca, Wilmington, Delaware, October 14.
- 3rd Nature Chemical Biology Symposium, Chemical Biology in Drug Discovery, Boston, Massachusetts, September 19-20.
- 238th National ACS Meeting, Symposium on "Small Molecules Therapeutic Agents", ACS Organic Chemistry Division, Washington, DC, August 18.
- Gordon Research Conference on Natural Products, Tilton School, Tilton, New Hampshire, July 30.
- Journées Thématiques – Novel Methods in Organic Synthesis; New Organometallic and Catalytic Methods, University of Neuchatel, Department of Chemistry, Neuchatel, Switzerland, June 19.
- 3° Cycle with Lectures at the Universities of Basel, Fribourg, Lausanne, and Neuchatel, Switzerland, June 15-18.
- 237th National ACS Meeting, Symposium on "Ernest Guenther Award in the Chemistry of Natural Products", ACS Organic Chemistry Division, Salt Lake City, Utah, March 25.

2008

- 4th International BASF Boron Conference, The Heldrich, New Brunswick, New Jersey, November 12-13.

- Boehringer Ingelheim Lectureship, Department of Chemistry, Yale University, New Haven, Connnecticut, December 17.
- "Illinois Frontiers Symposium", Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois, October 3.
- "Frontiers in Chemical Research" Lecturer, Department of Chemistry, Texas A&M University, College Station, Texas, September 29 to October 1.
- Gordon Research Conference on Stereochemistry, Salve Regina University, Newport, Rhode Island, July 28.
- Gordon Research Conference on Heterocyclic Compounds, Salve Regina University, Newport, Rhode Island, June 19.
- French-American Chemical Society, 12th Meeting on Synthetic Organic and Bioorganic Chemistry, Santa Barbara, California, June 8-12.
- II EWDSy - Second European Workshop in Drug Synthesis, Certosa di Pontignano, Siena, Italy, May 26.
- "Natural Products in Anticancer Drug Discovery", 2008 Annual Meeting of the American Association for Anticancer Research (AACR), San Diego, California, April 12.
- 52nd Annual Julius A. Koch Memorial Lecturer, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania, March 26.
- 9th Annual Florida Heterocyclic and Synthetic Conference (Flohet-9), University of Florida, Gainesville, FL, March 9-12.
- abc Technologies 2008: Automation beyond Chemistry, Basel Hilton, Basel, Switzerland, January 16-17.

2007

- The Sixth Princess Chulabhorn International Science Congress (PC VI), Shangri-La Hotel, Bangkok, Thailand, November 27.
- 2007 ACS/EFMC Congress on "Frontiers in CNS and Oncology Medicinal Chemistry", Siena, Italy, October 7.
- Roche Colorado Corporation Peptide Symposium (RCCPS-07), Boulder, Colorado, September 26-27.
- Chemistry & Biology of Bioactive Natural Products, Competence Center for Integrated Natural Products Research Mainz/Kaiserslautern, TU Kaiserslautern, Kaiserslautern, Germany, September 20.
- Oppolzer Lectures 2007, University of Geneva, Geneva, Switzerland, September 14.
- 2nd Negishi-Brown Lectures on "Catalytic, Asymmetric, and Other Selective Syntheses", Purdue University, Lafayette, Indiana, August 30.
- 234th National ACS Meeting, Symposium on "Peptide Natural Products", ACS Organic Chemistry Division, Boston, Massachusetts, August 21.
- Chirality 2007, ISCD-19, 19th International Symposium on Chirality, San Diego, California, July 8-11.
- Gordon Research Conference on Combinatorial Chemistry – Accelerated Drug Discovery, Colby-Sawyer Collge, New Hampshire, June 3-8.

- 1st Latin American Meeting on Medicinal Chemistry (LatQuiMed), Montevideo, Uruguay, April 25, 2007.

2006

- IVth Lilly Graduate Students Awards Symposium, Madrid Alcobendas, Spain, October 27.
- 232nd National ACS Meeting, Symposium on "Parallel Medicinal Chemistry", ACS Medicinal Chemistry Division, San Francisco, California, September 13.
- ICOB-5 & ISCNP-25 IUPAC International Conference on Biodiversity and Natural Products, Symposium on Mode of Action and Chemical Biology, Kyoto International Conference Hall, Kyoto, Japan, July 25.
- Prof. H. Heimgartner Ehren Symposium, Department of Chemistry, University of Zürich, Zürich, Switzerland, June 9.
- Pfizer Symposium, Department of Chemistry, University of Toronto, Toronto, Canada, May 17.
- BioNEt 2006, Symposium on Natural Products as Potential Medicines, University of Durham, Durham, United Kingdom, January 16.

2005

- Pacifichem 2005, Symposium on Combinatorial Chemistry, Hilton Hawaiian Village, Honolulu, Hawaii, December 17.
- Pacifichem 2005, Symposium on Prospects for Automated and Microreactor Synthesis, Hilton Hawaiian Village, Honolulu, Hawaii, December 15.
- 27th Gulf Coast Chemistry Conference, Pensacola Beach, Florida, September 15-17.
- 54th Gordon Research Conference on Natural Products Chemistry, Tilton, New Hampshire, July 24-28.
- Modern Synthetic Methods and CHIRAL USA 2005, The Westin Princeton at Forrestal Village, Princeton, NJ, July 13.
- 17th Lakeland Heterocyclic Symposium, Grasmere Village, Cumbria, United Kingdom, May 5-9.
- 4th Symposium International de Synthèse Organique de l'Université de Montréal (SISOUM 2005), Montreal, April 28-29.
- ACS Symposium "Award for Creative Research and Applications of Iodine Chemistry", 229th National Meeting, San Diego, California, March 13.

2004

- 38th Sheffield Stereochemistry Meeting 2004, Department of Chemistry, University of Sheffield, Sheffield, United Kingdom, December 21.
- Asymmetric Synthesis: A Symposium in Honor of Ernest Eliel, 56th Southeastern Regional ACS Meeting, Research Triangle Park, North Carolina, November 13.
- 4èmes Journées École Doctorale de Chimie Moléculaire Paris Centre, University Pierre et Marie Curie, Paris VI - Jussieu, France, September 16.
- Plenary Speaker, Journées de Chimie Organique 2004, École Polytechnique Palaiseau, French Chemical Society, Palaiseau, September 9.
- 11th Symposium on the Latest Trends in Organic Synthesis (LTOS-11), Brock University, St. Catherine, Canada, August 14.

- Gordon Research Conference on Heterocyclic Compounds, Salve Regina University, Newport, Rhode Island, July 5.
- Gordon Research Conference on Stereochemistry, Salve Regina University, Newport, Rhode Island, June 22.
- Merck Synthesis Symposium, University of California at Irvine, Irvine, California, June 5.
- 2004 CU-Roche Colorado Symposium on Synthetic Organic Chemistry, University of Colorado, Boulder, Colorado, June 3.
- Keynote Lecture, 34th Annual Spring Organic Synthesis Symposium, University of Ottawa, Ottawa, Ontario, Canada, May 4.
- Lilly Lectureship, Purdue University, Department of Chemistry, West Lafayette, Indiana, April 27.
- Tripartite Symposium on Drug Discovery, Duquesne University, Pittsbugh, Pennsylvania, April 3.
- ACS Symposium on Half-A-Century of Organozirconium Chemistry, 227th National Meeting, Anaheim, California, March 29.
- Distinguished Alumni Speaker, 2004 Lilly Grantee Symposium, Eli Lilly & Co., Indianapolis, Indiana, March 1.

2003

- 2003 Iddles Lecturer, University of New Hampshire, Durham, New Hampshire, November 5 & 6.
- 23rd Gregynog Young Chemists Organic Synthesis Workshop, Powys, Wales, September 26-28.
- Katritzky Junior Award Lecture, 19th International Congress of Heterocyclic Chemistry, Fort Collins, Colorado, August 14.
- Gordon Research Conference on Organic Reactions & Processes, Roger Williams University, Bristol, Rhode Island, July 21.
- Gordon Research Conference on Combinatorial Chemistry, Tilton, New Hampshire, July 6.
- 4th Annual Boston University Symposium on Advances in Streamlined Synthesis, Boston, Massachusetts, June 27.
- Krano Memorial Lectures, University of Akron, Akron, Ohio, April 17.
- 123rd Annual Symposium of the Pharmaceutical Society of Japan, Nagasaki, March 28.
- Roche Lectureship, Colorado State University, Fort Collins, Colorado, February 24.
- ACS ProSpectives on Process Chemistry in the Pharmaceutical Industry, San Juan, Puerto Rico, February 4.
- 2003 Connecticut Organic Chemistry Symposium, New Haven, Connecticut, January 10.

2002

- UCSD/La Jolla Pharma Symposium on Organic Chemistry, La Jolla, California, December 16.
- 14th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Workshop on Combinatorial Chemistry, Frankfurt, Germany, November 20.

- 8th International Conference on Chemistry of Antibiotics and Related Microbial Products (ICCA-8), Waseda University, Tokyo, Japan, October 24.
- 2002 Pfizer Chemistry Forum, Pfizer Inc. Global Research & Development, Groton, Connecticut, July 30.
- 14th IUPAC ICOS, Symposium on Automation in Synthesis, Christchurch, New Zealand, July 18.
- 1st Lilly Foundation Symposium, Madrid, Spain, May 29.
- 36th European Symposium on Bioorganic Chemistry, "Chemical Biology of Cellular Signalling and Localization", Gregynog, Powys, Wales, May 10-13.
- 14th Conference on Combinatorial Chemistry (JCCF-14), Osaka, Japan, April 22.
- Symposium on Natural Products Combinatorial Chemistry, 223rd ACS National Meeting, Orlando, Florida, April 7. ORGN 31
- Abbott Lectureship, University of Minnesota, Department of Chemistry, Minneapolis, Minnesota, February 15.
- Lilly Lectureship, University of Notre Dame, Department of Chemistry and Biochemistry, South Bend, Indiana, January 30.

2001

- Gordon Research Conference on Natural Products Chemistry, Tilton, New Hampshire, August 2.
- New Jersey ACS Organic Group Spring Symposium, Iselin, New Jersey, April 16.
- Combinatorial Chemistry, High-Throughput Screening and Contemporary Pharmacology, Experimental Biology 2001, Orlando, Florida, April 1.
- Combinatorial Chemistry Applications in Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania, March 15.
- McGill Chemical Society Lectureship, McGill University, Montreal, Canada, February 13.

2000

- Pacifichem 2000, Symposium on Marine Natural Products, The Paul J. Scheuer Symposium, Hilton Hawaiian Village, Honolulu, Hawaii, December 18.
- Pacifichem 2000, Symposium on Discovery and Development of Asymmetric Synthesis and Chiral Technology, Hilton Hawaiian Village, Honolulu, Hawaii, December 16.
- Sixth Wyeth-Ayerst Chemistry Lectureship, Princeton University, Department of Chemistry, Princeton, New Jersey, November 31.
- New York Academy of Sciences, New York, New York, October 3.
- 33rd Annual Mid-Atlantic Graduate Student Symposium in Medicinal Chemistry, Duquesne University, Pittsburgh, Pennsylvania, July 11.
- The Sixth Michigan Symposium on Contemporary Challenges in Molecular Medicine, Ann Arbor, Michigan, May 12.
- Ireland Lectureship, University of Virginia, Charlottesville, Virginia, April 7.
- Symposium on Analytical Challenges and Opportunities in Combinatorial Chemistry, Pittcon 2000, New Orleans, Louisiana, March 16.
- Marine Natural Products Gordon Research Conference, Ventura, California, February 27-March 3.

1999

- Van Cleave Lectureship, University of Regina, Regina, Canada, November 5 & 6.
- 11th International Symposium on Chiral Discrimination (ISCD '99), Chicago, Illinois, July 27.
- 16th International Symposium on Synthesis in Organic Chemistry, Churchill College, Cambridge, UK, July 21.
- Symposium on Synthesis and Synthetic Methodology, 31st American Chemical Society Central Regional Meeting, The Ohio State University, Columbus, OH, June 23.
- Symposium on Combinatorial Synthesis, 82nd Canadian Society for Chemistry Conference, Toronto, Ontario, Canada, June 2.
- Symposium on Solid-Phase Organic Chemistry, 32nd American Chemical Society Middle Atlantic Regional Meeting (MARM '99), Fairleigh Dickinson University, Madison, NJ, May 19.
- Moffatt Lectureship, University of British-Columbia, Department of Chemistry and Biochemistry, Vancouver, Canada, March 22.
- 21st Akron Section ACS Award Lecture, Akron, OH, March 17.
- Second International Conference on Combinatorial Library Methods for Basic Research and Drug Discovery, Tucson, Arizona, January 10-12.

1998

- IVth U.S. – Japan Symposium on Marine Bioorganic Chemistry, Santa Cruz, California, December 14-18.
- Merck Lecturer, Department of Chemistry, University of Nottingham, Nottingham, United Kingdom, November 23.
- IBC's International Symposium on New Synthetic Methods, Sanibel Harbour, Ft. Myers, Florida, September 15-16.
- Arthur C. Cope Awards Symposium, American Chemical Society, 216th National Meeting, Boston, Massachusetts, August 23-27. ORGN 323
- Gordon Research Conference on Reactions and Processes, New England College, Henniker, New Hampshire, July 12-17.
- 5th International Conference on Heteroatom Chemistry (ICHAC-5), London, Ontario, Canada, July 6-10.
- Basel Chemical Society Lectureship, Universität Basel, Basel, June 25.
- Berliner GdCH Lectureship, Humboldt Universität, Berlin, June 22.
- Gordon Research Conference on Stereochemistry, Salve Regina University, Newport, Rhode Island, June 7-12.
- French-American Chemical Society, 7th Meeting on Synthetic Organic and Bioorganic Chemistry, Cannes, France, June 2-6.
- Tripartite Symposium, Chemistry in Medicine - Today and Tomorrow, Pittsburgh, Pennsylvania, April 25.
- Experimental Biology '98, Symposium on Implications of Combinatorial Chemistry on Pharmacological Sciences, San Francisco, April 20.
- Seventeenth Mona Symposium, Natural Products & Medicinal Chemistry, University of the West Indies, Mona, Jamaica, January 5-9.

1997

- Twentieth Gulf Coast Chemistry Conference, Pensacola Beach, Florida, September 18-20.
- BASF Research Workshop "Reactivity and Selectivity", St. Johann/Pfalz, Germany, September 15-19.
- 16th International Congress of Heterocyclic Chemistry, Bozeman, Montana, August 10-15.
- 9th IUPAC Symposium on Organometallic Chemistry, Göttingen, Germany, July 20-25.
- Fifth Annual Visions in Chemistry Symposium, Rhone-Poulenc Rorer Research and Development, Collegeville, Pennsylvania, May 1.
- Chemistry and its Applications to Medicine. A Symposium in Honor of Professor Madeleine Joullié. University of Pennsylvania, Philadelphia, Pennsylvania, March 17.
- Eighth Annual Frontiers in Chemistry Lecture Series, The Scripps Research Institute, La Jolla, California, February 21.

1996

- Plenary Speaker of the Royal Australian Chemical Institute at the 10th Brisbane Organic Chemistry Symposium, Queensland University of Technology, November 29, the 17th Sydney Organic Synthesis Symposium, University of Sydney, December 3, the Australian National University, Canberra, December 4, the 21st Melbourne Organic Synthesis Symposium, University of Melbourne, Melbourne, December 6, and the 6th Adelaide Organic Synthesis Symposium, Flinders University, Adelaide, December 9.
- Symposium on Current Tactics and Methods for Natural Product Synthesis, 48th ACS Southeast Regional Meeting, Greenville, South Carolina, November 12.
- 1996 Otsuka Symposium, Kawauchi, Tokushima, Japan, September 23-25.
- Eleventh Nozaki Conference, Osaka, Japan, September 20-21.
- 11th IUPAC International Conference on Organic Synthesis, Amsterdam, The Netherlands, June 30 - July 4.
- 3° Cycle with Lectures at the Universities of Fribourg, Lausanne, Neuchatel, and Geneva, Switzerland, June 24-27.
- ACS E. Guenther Award Symposium on the Chemistry of Natural Products, New Orleans, LA, March 26.
- Sandoz Chemistry Lectureship, Basel, Switzerland, March 13.
- Seventh Biennial Lilly Grantee Symposium in Organic Chemistry, Indianapolis, Indiana, March 4-5.

1995

- Symposium on Advances in Methods and Strategies for Complex Molecule Synthesis, 25th ACS Northeast Regional Meeting, Rochester, New York, October 23.
- The 1995 Princeton ACS Fall Organic Chemistry Symposium, Princeton, New Jersey. September 22.
- The First Annual Procter & Gamble Pharmaceuticals *Lectures in Organic Chemistry*, Procter & Gamble, Cincinnati, Ohio, August 17.
- IVth International Symposium on Carbanion Chemistry, Colorado State University, Fort Collins, Colorado August 12-16.

- Gordon Research Conference on Heterocyclic Chemistry, New Hampton, New Hampshire, July 9-14.
- 28th Annual Mid-Atlantic Graduate Student Symposium in Medicinal Chemistry, Duquesne University, Pittsburgh, Pennsylvania, June 27.
- Symposium on Recent Developments in Organic Synthesis, 27th ACS Central Regional Meeting, Akron, Ohio, May 31.

1994

- Gordon Research Conference on Organic Reactions & Processes, New Hampton, New Hampshire, July 17-22.
- Symposium on Reagents and Mechanisms in Organic Chemistry, Joint 26th Central and 27th Great Lakes ACS Regional Meeting, Ann Arbor, Michigan, June 2.
- NSF - Former Soviet Union (FSU) Workshop on Organic Synthesis, Stanford University, Palo Alto, California, March 10-12.

1993

- The 1993 Josef Fried Symposium of Bioorganic Chemistry, University of Chicago, Chicago, Illinois, November 19.
- Symposium on Pharmaceutical Chemistry, 25th ACS Central Regional Meeting, Pittsburgh, Pennsylvania, October 6.
- Second Canadian Workshop on Organic Synthesis, Jouvence, Québec, May 25-28.

1992

- Third Hoffmann-LaRoche Symposium on New Synthetic Methods, Engelberg, Switzerland, September 20-23.

Presentations at National and Regional Meetings

2025

- Center for Protein Conformational Disease, Pittsburgh, PA, March 21.

2024

- Oncology Graduate Program Mini-Symposium, UPMC Hillman Cancer Center, Pittsburgh, PA, February 17.

2023

- UEF DrugTech RC Ruska-Event 2023, Koli, Finland, December 12.
- ORGN 3919195, ACS Fall 2023 National Meeting, San Francisco, CA, August 13.
- Natural Sciences for Sustainability 2023, Jyväskylä, Finland, June 14-16.
- UPMC Enterprises Translational Sciences Meeting, Pittsburgh, May 8.
- Cancer Therapeutics Program, UPMC Hillman Cancer Center, Pittsburgh, PA, March 17.
- Cancer RC & DrugTech RC Joint Meeting, University of Eastern Finland, Kuopio, Finland, March 15.

2022

- DrugTech RC SAB Meeting, University of Eastern Finland, Kuopio, Finland, September 26.

- CVRC Seminar Series, Cardiovascular Institute and the Warren Alpert Medical School at Brown University, Providence, Rhode Island, March 24.

2019

- UPMC Enterprises, Pittsburgh, Pennsylvania, August 19.

2018

- Inaugural Chemical Biology Consortium Symposium: Bridging the Gaps of Drug Discovery, University of California at San Francisco, Mission Bay Conference Center, San Francisco, California, November 16.
- Cardiovascular Research Center, Brown University Medical Center, Providence, Rhode Island, January 12.

2017

- Center for Protein Conformational Diseases, University of Pittsburgh, Pittsburgh, Pennsylvania, December 8.

2016

- Basic and Traditional Research in Lung Disease Lecture Series, UPMC Division of Pulmonary, Allergy & Critical Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, November 29.
- Duke University, Faculty Colloquium, Durham, North Carolina, November 10.
- Chemical Biology Consortium (CBC) Kickoff Meeting, National Institutes of Health, Bethesda, Maryland, June 23-24.
- Brackenridge Faculty Lecture, University Honors College, University of Pittsburgh, Pittsburgh, Pennsylvania, June 13.
- MBSB Research Symposium, University of Pittsburgh, Pittsburgh, Pennsylvania, May 13.

2015

- Gesellschaft Deutscher Chemiker (GDCh), RWTH Aachen, Aachen, Germany, October 20.
- NERM 2016, Symposium on Progressive Methodology for Organic Synthesis, Ithaca College, Ithaca, New York, June 11.
- University of Pittsburgh Innovation Institute, Investor Presentation, Pittsburgh, Pennsylvania, April 16.
- University of Puerto Rico, Lecture on Advanced Topics in Biomedical Sciences: Biotechnology and Drug Development (CBIO 8506), UP Medical School, San Juan, Puerto Rico, April 9.
- TCC Joint Update Meeting, Duquesne University Power Center Ballroom, Pittsburgh, Pennsylvania, April 1.

2014

- Workshop on Mitochondria and Metabolic Signaling in Ataxia-Telangiectasia, A-T Childrens Project, Tarrytown, New York, December 15-16.
- Basic Biology of Aging Work Group; Mitochondria, Aging & Metabolism Seminar Series, Bridgeside Point Building, University of Pittsburgh, Pittsburgh, Pennsylvania, December 3.
- Center for the Discovery of New Medicines, University of Michigan, Ann Arbor, Michigan, November 14.

- Cope Symposium in Honor of Jeff Johnston, ACS 45th Central Regional Meeting, Pittsburgh Greentree, Pennsylvania, October 30.
- CRC Work Group, Hillman Cancer Center, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, September 17.
- UPCI Satellite Conference on Aging and Cancer, University of Pittsburgh at Greensburg, Greensburg, Pennsylvania, June 18.
- Mitochondrial Medicine 2014, The United Mitochondrial Disease Foundation (UMDF), Sheraton Station Square, Pittsburgh, Pennsylvania, June 5.
- University of Pittsburgh School of Medicine MD/PhD Program, Pittsburgh, Pennsylvania, February 18.
- University of Pittsburgh School of Medicine Physician Scientist Training Program, Pittsburgh, Pennsylvania, January 9.

2013

- Actelion, Resaerch Building H89 Inaguration Event, Allschwil, Switzerland, October 10.
- Chemical Biology Consortium (CBC) Steering Committee Meeting, NIH Campus, Bethesda, Maryland, July 17.
- 2nd Annual University of Pittsburgh-Tsinghua University Joint Symposium on Medical Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, April 30.

2012

- Molecular Therapeutics Drug Development – Translational Scinece Meeting, Hillman Cancer Center, Pittsburgh, Pennsylvania, November 26.
- Translation Science 2012, Spotlight Session on "Mitochondria-Metabolism, Moonlighting, and Death, University of Pittsburgh, Pittsburgh, Pennsylvania, October 4.
- 8th Annual Symposium of the Centers for Chemical Methodologies & Library Development (CMLD), Lister Hill Auditorium, NIH Bethesda, Maryland, June 12.

2011

- Panel Member, Bioengineering Innovation and Commercialization Program, Pitt Biomedical Engineering Society, Center for Bioenginering, Pittsburgh, Pennsylvania, July 28.
- 7th Annual Symposium of the Centers for Chemical Methodologies & Library Development (CMLD), University of Chicago Gleacher Center, Chicago, Illinois, July 22.
- 2011 UPCI Satellite Conference, Molecular Therapeutics and Drug Discovery Program, Pittsburgh, Pennsylvania, June 15.

2010

- Colloquium on "Research in Progress on the Basic Biology of Aging, University of Pittsburgh, Department of Microbiology and Molecular Genetics, Pittsburgh, Pennsylvania, October 15.

2009

- 5th Annual Symposium of the Centers for Chemical Methodologies & Library Development, Boston University CMLD, Boston, Massachusetts, August 10.
- Workshop in Organic Chemistry, Ohio State University, Columbus, Ohio, April 25.
- First Unitarian Church of Pittsburgh, Sunday Forum, Pittsburgh, Pennsylvania, January 4.

2008

- Philadelphia Organic Chemists' Club (POCC), Department of Chemistry, University of Pennsylvania, Pennsylvania, December 4.
- 4th Annual Symposium of the Centers for Chemical Methodologies & Library Development, Kansas CMLD, Lawrence, Kansas, October 27-28.

2007

- 42nd Midwest Regional ACS Meeting, Symposium on Chemical Methods & Library Design, Hotel Intercontinental, Kansas City, Kansas, November 8.
- 3rd Annual Symposium of the Centers for Chemical Methodologies & Library Development, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, July 23.

2006

- Science2006, Spotlight Session 7 on Nature's Pharmacopoeia, University of Pittsburgh, October 6.
- 2nd Annual Symposium of the Centers for Chemical Methodologies & Library Development, Pittsburgh, Pennsylvania, August 14.
- Gordon Research Conference on Organic Reactions & Processes, Bryant University, Smithfield, Rhode Island, July 29.
- Wine & Whimsy, Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, June 16.
- Pharmacology Wednesday Lunch & Lecture Series, Department of Pharmacology, University of Pittsburgh, Pittsburgh, Pennsylvania, June 14.
- MLSC Program Meeting, Hotel Hershey, Hershey, Pennsylvania, April 15.

2005

- CMLD Program Meeting, Boston University, Boston, Massachusetts, August 9.
- Symposium on Green Chemistry, 37th American Chemical Society Middle Atlantic Regional Meeting (MARM '05), Busch Campus, Rutgers University, Piscataway, New Jersey, May 23.
- New Developments in Parkinson's Disease, Udall Parkinson's Disease Research Center of Excellence and Pittsburgh Institute for Neurodegenerative Disease, Pittsburgh, Pennsylvania, May 23.

2004

- Centers of Excellence in Chemical Methodologies and Library Development (CMLD), 2004 Annual Meeting, National Institutes of Health, Bethesda, Maryland, August 17.

2003

- Centers of Excellence in Chemical Methodologies and Library Development (CMLD), 2003 Annual Meeting, National Institutes of Health, Bethesda, Maryland, July 18.
- NSF Organic Chemistry Workshop, Asilomar Conference Center, Pacific Grove, California, July 10.
- ACS Student Affiliates, University of Pittsburgh, Department of Chemistry, Pittsburgh, Pennsylvania, January 17.

2002

- ACS ProSpectives, Combinatorial Chemistry: Conventional Tools from Revolutionary Technologies, Lansdowne Conference Center, Leesburg, Virginia, September 23.

- NSF Organic Chemistry Workshop, Minary Conference Center, Holderness, New Hampshire, June 30.

2001

- NSF Organic Chemistry Workshop, Gold Lake Resort, Ward, Colorado, July 16.

2000

- Meeting of the Experimental Therapeutics Program, Kansas Cancer Institute, University of Kansas, Lawrence, Kansas, September 22.
- Gordon Research Conference on Stereochemistry, Salve Regina University, Newport, Rhode Island, June 10-15.
- NIH Grantsmanship Workshop, 220th ACS National Meeting, Washington, DC, August 22.

1999

- North Jersey ACS Organic Topical Group Fall Meeting, Seton Hall University, South Orange, New Jersey, September 27.
- NIH Grantsmanship Workshop, 218th ACS National Meeting, New Orleans, Louisiana, August 22.
- R. E. Ireland 70th Birthday Symposium, Anaheim, CA, March 26.
- NIH Grantsmanship Workshop, 217th ACS National Meeting, Anaheim, CA, March 24.

1998

- Seminar on Combinatorial Chemistry, Pittsburgh Chemist's Club, Pittsburgh, Pennsylvania, May 26.
- Tutorial on Role of Mass Spectrometry in Drug Discovery, Mass Spectrometry Discussion Group, Pittsburgh, Pennsylvania, April 17.

1996

- ORGN 177, presented at the 211th ACS National Meeting, New Orleans, Louisiana, March 26.

1995

- ORGN 1015, presented at the 1995 International Chemical Congress of Pacific Basin Societies, Honolulu, Hawaii, December 21.
- NSF Workshop on Organic Synthesis and Natural Products Chemistry, Marconi Conference Center, Tomales Bay, California, July 26-30.
- Gordon Research Conference on Natural Products Chemistry, Henniker, New Hampshire, July 3.

1994

- ORGN 149, presented at the 207th ACS National Meeting, San Diego, CA, March 14.

1993

- ORGN 184, presented at the 206th ACS National Meeting, Chicago, Illinois, August 25.
- ORGN 185, presented at the 206th ACS National Meeting, Chicago, Illinois, August 25.
- Gordon Research Conference on Natural Products, New Hampton, New Hampshire, July 18-23.

1992

- ORGN 163, presented at the 204th ACS National Meeting, Washington, DC, August 23-28.
- ORGN 162, presented at the 204th ACS National Meeting, Washington, DC, August 23-28.
- Gordon Research Conference on Organic Reactions & Processes, New Hampton, New Hampshire, July 13 & 15.

1991

- MEDI 52, presented at the 4th Chemical Congress of North America, New York, August 25-30.
- ORGN 89, presented at the 4th Chemical Congress of North America, New York, August 25-30.

Seminars at Universities, Colleges & Institutes

2025

- Texas A&M University, Department of Chemistry, College Station, Texas, May 1.
- University of Eastern Finland, School of Pharmacy, Kuopio, Finland, February 6.
- DrugTech, University of Eastern Finland, Kuopio, Finland, February 4.

2024

- University of Eastern Finland, School of Pharmacy, Kuopio, Finland, February 23.
- Hong Kong University of Science and Technology, Hong Kong, February 20.

2023

- UPMC Enterprises Translational Sciences Meeting, Pittsburgh, December 11.
- Emory University, Department of Chemistry, Atlanta, Georgia, December 5.
- The College of William & Mary, Department of Chemistry, Williamsburg, Virginia, November 3.
- University of Pittsburgh and Carnegie Mellon University, Molecular Biophysics/Structural Biology Program, Pittsburgh, Pennsylvania, February 16.
- University of Puerto Rico, Medical Sciences Campus, School of Medicine, San Juan, Puerto Rico, February 13.
- University of Houston, Department of Chemistry, Houston, Texas, January 24.
- Oregon Health & Science University, Department of Chemical Physiology and Biochemistry, Portland, Oregon, January 17.

2022

- University of Eastern Finland, Drug Discovery and Delivery (DrugTech) Institute, Kuopio, Finland, February 23.

2021

- University of Eastern Finland, Drug Discovery and Delivery (DrugTech) Institute, Kuopio, Finland, May 31.
- University of California at Los Angeles, Department of Chemistry and Biochemistry, Los Angeles, California, February 25.

2020

- Cleveland State University, Department of Chemistry, Cleveland, Ohio, September 4.

- University of Texas at Arlington, Department of Chemistry and Biochemistry, Arlington, Texas, March 12.
- University of Texas at Arlington, Department of Chemistry and Biochemistry, Arlington, Texas, March 11.

2019

- Michigan State University, Department of Pharmacology and Toxicology, East Lansing, Michigan, September 20.
- University of Virginia, Department of Pharmacology, School of Medicine, Charlottesville, Virginia, April 30.

2018

- Memorial Sloan-Kettering Cancer Center, Chemical Biology Program, New York, New York, December 19.
- University of Puerto Rico, Medical Sciences Campus, NIGMS-RISE Program, San Juan, Puerto Rico, June 20.
- University of Pittsburgh, Department of Human Genetics, School of Public Health, Pittsburgh, Pennsylvania, February 2.

2017

- Sewanee- The University of the South, Department of Chemistry and Biochemistry, Sewanee, Tennessee, December 1.
- Ecole Supérieur de Physique et Chimie Industrielles (ESPCI), Laboratoire de Chimie Organique, Paris, France, June 23.
- Technische Universität Kaiserslautern, Institute for Organic Chemistry, Kaiserslautern, Germany, June 8.
- RWTH Aachen, Organisch-Chemisches Institut, Aachen, Germany, May 30.
- Eberhard-Karls-Universität Tübingen, Institute for Pharmaceutical and Medicinal Chemistry, Tübingen, Germany, May 15.
- University Hospital RWTH Aachen, Institute of Biochemistry and Molecular Biology, Aachen, Germany, May 11.
- University of Alberta, Department of Chemistry, Edmonton, Canada, February 8.

2016

- North Carolina State University, Department of Chemistry, Raleigh, North Carolina, November 11.
- Duke University, Department of Chemistry, Durham, North Carolina, November 10.
- RWTH Aachen, Organic Chemistry Colloquium, Aachen, Germany, September 29.
- University of Zürich, Department of Chemistry, Zürich, Switzerland, September 27.
- Purdue University, Department of Chemistry, West Lafayette, May 5.
- New York University, Department of Chemistry, New York, New York, April 1.
- University of Colorado, Department of Chemistry, Boulder, Colorado, February 22.
- Messiah College, Department of Chemistry, Mechanicsburg, Pennsylvania, February 19.
- Juniata College, Department of Chemistry, Huntingdon, Pennsylvania, January 27.

2015

- RWTH Aachen, Organisch-Chemisches Institut, Aachen, Germany, November 20.

- Westfälische Wilhelms Universität Münster, Organisch-Chemisches Institut, Münster, Germany, October 22.
- Forschungszentrum Jülich GmbH, Jülich, Germany, October 8.
- University of Puerto Rico, Medical Sciences Campus, MBRS-RISE Program, San Juan, Puerto Rico, April 10.
- University of Virginia, Department of Pharmacology, School of Medicine, Charlottesville, Virginia, March 16.
- Saint Vincent College, Department of Chemistry, Latrobe, Pennsylvania, January 23.

2014
- University of Michigan, College of Pharmacy, Ann Arbor, Michigan, November 13.
- University of Notre Dame, Department of Chemistry and Biochemistry, South Bend, Indiana, November 12.
- Duke University, Department of Chemistry, Durham, North Carolina, October 23.
- Rochester Institute of Technology, School of Chemistry & Materials Science, Rochester, New York, February 6.
- Virginia Tech, Department of Chemistry, Blacksburg, Virginia, January 31.
- Duquesne University, Department of Medicinal Chemistry, Pittsburgh, Pennsylvania, January 23.

2013
- The Scripps Research Institute, Florida Campus, Department of Metabolism & Aging, Jupiter, Florida, November 14.
- John Carroll University, Chemistry Department, University Heights, Ohio, March 20.
- Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, Georgia, February 27.

2012
- Institut für Organische Chemie, RWTH Aachen, Aachen, Germany, December 6.
- University of Wisconsin, Department of Chemistry, Madison, Wisconsin, November 6.
- Chulabhorn Research Institute, Bangkok, Thailand, May 10.
- Chulabhorn Graduate Institute, Bangkok, Thailand, May 10.
- Allegheny College, Department of Chemistry, Meadville, Pennsylvania, February 10.

2011
- University of Southern California, Department of Chemistry, Los Angeles, California, March 30.
- University of Rochester, Department of Chemistry, Rochester, New York, March 16.

2010
- Facultad de Química, UdelaR, Montevideo, Uruguay, December 15.
- Institut Pasteur de Montevideo, Uruguay, December 14.
- Department of Chemistry, Southern Methodist University, Dallas, October 1.
- Department of Chemistry, Texas Christian University, Fort Worth, September 30.
- Institute of Chemistry, Slovak Academy of Sciences, Bratislava, Slovakia, June 17.
- Chemical Research Center, Hungarian Academy of Sciences, Budapest, Hungary, June 16.

- Institute for Technical Chemistry and Academy of Sciences, Prague, Czech Republic, June 14.
- NIDDK, Laboratory of Bioorganic Chemistry, National Institutes of Health, Bethesda, Maryland, March 5.
- Duke University, Department of Chemistry, Durham, North Carolina, February 15.
- Albert Einstein College of Medicine of Yeshiva University, Jack and Pearl Resnick Campus, Bronx, New York, January 12.

2009

- University of Neuchatel, Institute of Organic Chemistry, Neuchatel, Switzerland, June 18.
- EPFL, Department of Chemistry, Lausanne, Switzerland, June 17.
- University of Fribourg, Department of Chemistry, Fribourg, Switzerland, June 16.
- University of Basel, Institute of Organic Chemistry, Basel, Switzerland, June 15.
- Ohio State University, Department of Chemistry, Columbus, Ohio, April 24.
- Michigan State University, Department of Chemistry, East Lansing, Michigan, April 2.
- Louisiana State University, Department of Chemistry, Baton Rouge, Louisiana, March 13.
- University of Pittsburgh at Johnstown, Department of Chemistry, Johnstown, Pennsylvania, March 6.
- University of Pittsburgh, ACS Student Affiliates, Department of Chemistry, Pittsburgh, Pennsylvania, February 27.
- University of South Florida, Department of Chemistry, Tampa, Florida, January 21.

2008

- Boehringer-Ingelheim Lectureship, Yale University, Department of Chemistry, New Haven, Connecticut, December 17.
- Bryn Mawr College, Department of Chemistry, Bryn Mawr, Pennsylvania, December 5.
- Indiana University, Department of Chemistry, Bloomington, Indiana, September 8.
- University of Alabama, Department of Chemistry, Tuscaloosa, Alabama, January 31.

2007

- University of Barcelona, Facultat de Química, Barcelona, Spain, December 12.
- University of Barcelona, Facultat de Farmàcia, Barcelona, Spain, December 11.
- Scripps Florida, Drug Discovery-Biochemistry & Medicinal Chemistry, Jupiter, Florida, May 15.
- University of Sao Paulo, Instituto de Química, Sao Paulo, Brazil, April 27.
- Universidad de la Republica, School of Chemistry, Montevideo, Uruguay, April 26.
- H. Lee Moffitt Cancer Center & Research Institute, Drug Discovery Program, Tampa, Florida, March 7.

2006

- University of North Carolina, Department of Chemistry & Division of Medicinal Chemistry and Natural Products, Chapel Hill, North Carolina, December 18.
- Structural Biology/Molecular Biophysics Seminar Series, University of Pittsburgh, Pittsburgh, Pennsylvania, December 14.
- Memorial Sloan-Kettering Cancer Center, Molecular Pharmacology and Chemistry Program, New York, New York, November 20.
- University of Michigan, Department of Chemistry, Ann Arbor, Michigan, May 22.

- Duke University, Department of Chemistry, Durham, North Carolina, January 26.

2005

- University of Pittsburgh Cancer Institute, Hillman Cancer Center, Pittsburgh, Pennsylvania, November 15.

2004

- University of Pittsburgh, School of Arts & Sciences, Pittsburgh, Pennsylvania, December 16.
- West Virginia University, Department of Chemistry, Morgantown, West Virginia, December 1.
- Duke University, Department of Chemistry, Durham, North Carolina, November 11.
- Université de Rennes 1, Campus de Beaulieu, Department of Chemistry, Rennes, France, September 22.
- Université de Paris-Sud, Institut de Chimie Moléculaire, Orsay, France, September 21.
- Université Paul Cézanne (Aix-Marseille III), Laboratory of Synthetic Chemistry, Marseille, France, September 17.
- University of Arkansas, Department of Chemistry and Biochemistry, Fayetteville, Arkansas, July 26.
- Technion-Israel Institute of Technology, Department of Chemistry, Haifa, Israel, May 20.
- Weizmann Institute of Science, Organic Chemistry Department, Rehovot, Israel, May 19.
- SUNY Buffalo, Department of Chemistry, Buffalo, New York, March 5.
- University of California at San Diego, Department of Chemistry and Biochemistry, La Jolla, California, January 19.

2003

- University of Iowa, College of Pharmacy, Division of Medicinal and Natural Products Chemistry, Iowa City, Iowa, December 9.
- Universidad de la Republica, School of Chemistry, Montevideo, Uruguay, October 29.
- University of Nottingham, Department of Chemistry, Nottingham, United Kingdom, September 25.
- SUNY College at Fredonia, Department of Chemistry, Fredonia, New York, September 18.
- University of Arizona, Department of Chemistry, Tucson, Arizona, May 9.
- University of Tokyo, Faculty of Pharmaceutical Sciences, Tokyo, March 25.
- University of South Florida, Department of Chemistry, Tampa, Florida, March 20.
- UT Southwestern Medical Center, Department of Biochemistry, Dallas, Texas, January 21.

2002

- Stanford University, Department of Chemistry, Palo Alto, California, October 29.
- Niigata University, Graduate School of Science and Technology, Niigata, Japan, October 25.
- University of Pittsburgh, Department of Pharmaceutical Sciences, School of Pharmacy, Pittsburgh, Pennsylvania, October 15.
- St. Jude Children's Research Hospital, Department of Molecular Pharmacology, Memphis, Tennessee, July 8.
- University of Illinois at Chicago, Department of Chemistry, Chicago, Illinois, March 26.

- University of California at Santa Barbara, Department of Chemistry, Santa Barbara, California, March 22.
- Wayne State University, Department of Chemistry, Detroit, Michigan, February 27.

2001

- Peking University, Department of Chemistry, Beijing, China, December 20.
- Shanghai Institute of Materia Medica, Shanghai, China, December 17.
- University Claude-Bernard, Department of Chemistry, Lyon, France, November 22.
- Ecole Polytechnique, Department of Chemistry, Palaiseau, France, November 21.
- Westfälische Wilhems-Universität Münster, GdCH Lecture, Münster, Germany, November 19.
- University of Reims, Department of Chemistry, Reims, France, November 16.
- Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France, November 15.
- Ecole Supérieur de Physique et Chimie Industrielles (ESPCI), Laboratoire de Chimie Organique, Paris, France, November 14.
- University of Paris-Sud, Institut de Chimie Moléculaire, Orsay, France, November 13.
- University Pierre et Marie Curie, Department of Chemistry, Paris Jussieu, France, November 12.
- University Louis Pasteur, Institut de Chimie, Strasbourg, France, November 9.
- University of Paris-Sud, Faculty of Pharmacy, Chatenay-Malabry, France, November 8.
- University of Versailles-St-Quentin, Department of Chemistry, Versailles, France, November 7.
- Louisiana State University, Department of Chemistry, Baton Rouge, Louisiana, October 4.
- University of Zürich, Institute of Organic Chemistry, Zürich, Switzerland, June 19.
- Stanford University, Department of Chemistry, Palo Alto, California, May 10.
- Bucknell University, Department of Chemistry, Lewisburg, Pennsylvania, March 28.
- Texas Tech University, Department of Chemistry and Biochemistry, Lubbock, Texas, March 7.
- University of Texas at Arlington, Department of Chemistry and Biochemistry, Arlington, Texas, March 6.

2000

- Rutgers University, Department of Chemistry, Newark, New Jersey, December 1.
- Oregon State University, Department of Chemistry, Corvallis, Oregon, October 9.
- Wright State University, Department of Chemistry, Dayton, Ohio, October 6.
- University of Kansas, Department of Medicinal Chemistry, Lawrence, Kansas, September 22.
- North Carolina State University, Department of Chemistry, Raleigh, North Carolina, September 15.
- University of Illinois at Urbana-Champaign, Department of Chemistry, Urbana, Illinois, July 24.
- Tokyo Institute of Technology, Department of Chemistry, Tokyo, Japan, May 27.
- University of Tokyo, Graduate School of Pharmaceutical Sciences, Tokyo, Japan, May 25.
- Okayama University of Science, Department of Chemistry, Faculty of Science, Okayama, Japan, May 23.

- Kyoto University, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto, Japan, May 22.
- Japan Advanced Institute of Science and Technology, Graduate School of Materials Science, Hokuriku, Ishikawa, Japan, May 19.
- Nagoya City University, Faculty of Pharmaceutical Sciences, Nagoya, Japan, May 17.
- Tohoku University, Graduate School of Science, Sendai, Japan, May 15.
- University of Washington, Department of Chemistry, Seattle, Washington, April 21.
- University of Tennessee, Department of Chemistry, Knoxville, Tennessee, March 30.
- University of North Carolina, Department of Chemistry, Chapel Hill, North Carolina, February 3.
- Ohio State University, Department of Chemistry, Columbus, Ohio, January 20.

1999

- Emory University, Department of Chemistry, Atlanta, Georgia, December 8.
- Boston University, Department of Chemistry, Boston, Massachusetts, November 29.
- University of Maryland, Department of Chemistry, College Park, Maryland, November 18.
- University of Connecticut, Department of Chemistry, Storrs, Connecticut, April 28.
- University of Rochester, Department of Chemistry, Rochester, New York, April 9.
- University of British-Columbia, Department of Chemistry and Biochemistry, Vancouver, Canada, March 22.
- Boston College, Department of Chemistry, Boston, Massachusetts, March 9.
- University of Chicago, Department of Chemistry, Chicago, Illinois, January 4.

1998

- Michigan State University, Department of Chemistry, East Lansing, Michigan, December 10.
- Imperial College, Department of Chemistry, London, United Kingdom, November 25.
- SUNY Geneseo, Department of Chemistry, Geneseo, New York, November 13.
- University of Arkansas, Department of Chemistry, Fayetteville, Arkansas, October 26.
- Carnegie Mellon University, Department of Chemistry, Pittsburgh, Pennsylvania, October 6.
- Florida State University, Department of Chemistry, Tallahassee, Florida, September 22.
- The College of William & Mary, Department of Chemistry, Williamsburg, Virginia, September 4.
- University of Pittsburgh, Department of Chemistry, Pittsburgh, Pennsylvania, March 23.
- Rutgers University, Department of Chemistry, Piscataway, New Jersey, March 3.

1997

- University of Wisconsin, Department of Chemistry, Madison, Wisconsin, November 20.
- Gettysburg College, Sceptical Chemists Club, Gettysburg, Pennsylvania, November 6.
- University of Pennsylvania, Department of Chemistry, Philadelphia, Pennsylvania. August 4.
- Northwestern University, Department of Chemistry, Evanston, Illinois, May 13.
- University of Kentucky, Department of Chemistry, Lexington, Kentucky, April 11.
- University of Pennsylvania, Department of Chemistry, Philadelphia, Pennsylvania. March 18.

- Purdue University, Department of Chemistry, West Lafayette, Indiana, March 4.
- Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts, February 27.
- University of Missouri, Department of Chemistry, Columbia, Missouri, February 7.
- Washington University, Department of Chemistry, St. Louis, Missouri, February 6.

1996

- University of Alabama, Department of Chemistry, Tuscaloosa, Alabama, October 29.
- Vanderbilt University, Department of Chemistry, Nashville, Tennessee, October 28.
- Okayama University of Science, Department of Applied Chemistry, Okayama, Japan, September 19.
- Duke University, Department of Chemistry, Durham, North Carolina, August 1.
- Technical University of Munich, Institute of Organic Chemistry, Garching, Germany, June 19.
- Memorial Sloan-Kettering Cancer Center, Molecular Pharmacology and Therapeutics Program, Bio-Organic Chemistry Series, New York, New York, May 16.
- West Virginia University, Department of Chemistry, Morgantown, West Virginia, April 24.
- Miami University, Department of Chemistry, Oxford, Ohio, April 4.
- University of Basel, Institute of Organic Chemistry, Basel, Switzerland, March 14.
- University of Karlsruhe, Institute of Organic Chemistry, Karlsruhe, Germany, March 12.
- University of California at Santa Barbara, Department of Chemistry, Santa Barbara, California, February 16.
- University of California at Los Angeles, Department of Chemistry, Los Angeles, California, February 15.
- University of Buffalo, Department of Chemistry, Buffalo, New York, February 2.
- Harvard University, Department of Chemistry, Cambridge, Massachusetts, January 22.
- Youngstown State University, Department of Chemistry, Youngstown, Ohio, January 12.

1995

- Boston University, Department of Chemistry, Boston, Massachusetts, December 4.
- University of Toronto, Department of Chemistry, Toronto, Canada, November 17.
- ETH, Department of Chemistry, Zürich, Switzerland, November 10.
- Columbia University, Department of Chemistry, New York, New York, November 2.
- University of Illinois at Chicago, Department of Chemistry, Chicago, Illinois, October 3.
- Penn State University, Department of Chemistry, State College, Pennsylvania, September 19.
- McGill University, Department of Chemistry, Montréal, Canada, September 12.
- University of Montréal, Department of Chemistry, Montréal, Canada, April 5.
- University of Illinois at Urbana-Champaign, Department of Chemistry, Urbana, Illinois, March 29.
- Indiana University, Department of Chemistry, Bloomington, Indiana, March 27.
- University of Texas, Department of Chemistry, Austin, Texas, March 17.
- Texas A&M, Department of Chemistry, College Station, Texas, March 16.
- Rice University, Department of Chemistry, Houston, Texas, March 15.

- University of Houston, Department of Chemistry, Houston, Texas, March 14.
- University of Delaware, Department of Chemistry, Newark, Delaware, March 1.
- University of Minnesota, Department of Chemistry, Minneapolis, Minnesota, February 3.
- Cornell University, Department of Chemistry, Cornell, New York, January 30.
- Yale University, Department of Chemistry, New Haven, Connecticut, January 18.
- University of California at San Diego, Department of Chemistry, La Jolla, California, January 16.

1994

- State University of New York at Stony Brook, Department of Chemistry, Stony Brook, December 15.
- Johns Hopkins University, Department of Chemistry, Baltimore, Maryland, December 13.
- Northwestern University, Department of Chemistry, Evanston, Illinois, November 16.
- University of Utah, Department of Chemistry, Salt Lake City, Utah, October 4.
- University of Colorado, Department of Chemistry and Biochemistry, Boulder, Colorado, October 3.
- ETH, Department of Chemistry, Zürich, Switzerland, September 30.
- Ohio University, Department of Chemistry, Athens, Ohio, September 24.
- Allegheny College, Department of Chemistry, Meadville, Pennsylvania, September 15.
- University of California at San Diego, Department of Chemistry, La Jolla, California, August 1.
- Princeton University, Department of Chemistry, Princeton, New Jersey, May 3.
- University of Frankfurt, Institute of Organic Chemistry, Frankfurt, Germany, April 28.
- Swarthmore College, Department of Chemistry, Swarthmore, Pennsylvania, March 25.
- City University of New York, Hunter College, Department of Chemistry, New York, New York, March 4.
- Northwestern University, Department of Chemistry, Evanston, Illinois, January 20.

1993

- University of Toledo, Department of Chemistry, Toledo, Ohio, November 22.
- University of Dayton, Department of Chemistry, Dayton, Ohio, October 23.
- University of Virginia, Department of Chemistry, Charlottesville, Virginia, October 1.
- Stanford University, Department of Chemistry, Palo Alto, California, September 22.
- University of California at Berkeley, Department of Chemistry, Berkeley, California, September 21.
- University of Marburg, Institute of Organic Chemistry, Marburg, Germany, September 2.
- Kent State University, Department of Chemistry, Kent, Ohio, March 11.
- University of Pittsburgh, Department of Pharmacology, Pittsburgh, Pennsylvania, March 5.
- University of Zürich, Institute of Organic Chemistry, Zürich, Switzerland, February 5.
- University of Würzburg, Institute of Organic Chemistry, Würzburg, Germany, February 3.
- University of West Virginia, Department of Chemistry, Morgantown, West Virginia, January 27.

- University of Pennsylvania, Department of Chemistry, Philadelphia, Pennsylvania. January 18.

1992

- Westminster College, Department of Chemistry, New Wilmington, Pennsylvania, February 18.
- Duquesne University, Department of Medicinal Chemistry, Pittsburgh, Pennsylvania, January 30.
- Fairmont State College, Department of Chemistry, Fairmont, West Virginia, January 23.

Seminars at Industrial & Government Laboratories

2024

- Johnson & Johnson, Spring House, Pennsylvania, May 15.

2023

- XWPharma, East Lake, Wuhan, China, September 25.
- TCG GreenChem, Process R&D Center, Ewing, NJ, June 29.

2022

- Corteva External Innovation Lectureship Series, Indianapolis, IN, February 8.

2021

- Roche Pharmaceutical Research and Early Development, Basel, Switzerland, September 23.
- 3M Global R&D Services, 3M Center, St. Paul, Minnesota, April 22.

2019

- AMRI, Chemical Development and Medicinal Chemistry, Albany, New York, January 10.

2018

- XW Laboratories, Wuhan Optics Valley, Wuhan, China, December 6.
- Sterling, Solomeo di Corciano, Perugia, Italy, May 21.
- XW Laboratories, Wuhan Optics Valley, Wuhan, China, May 11.
- XW Laboratories, Wuhan Optics Valley, Wuhan, China, May 12.

2017

- XW Laboratories, Wuhan Optics Valley, Wuhan, China, November 7.
- XW Laboratories, Wuhan Optics Valley, Wuhan, China, November 6.
- Boehringer Ingelheim Pharmaceuticals Inc., Process Research, Ridgefield, Connecticut, October 13.
- Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland, September 25.
- Actelion, Discovery Chemistry, Allschwil, Switzerland, May 8.

2016

- Actelion, Discovery Chemistry, Allschwil, Switzerland, September 26.
- Boehringer-Ingelheim Pharma GmbH & Co. KG, Chemical Development, Biberach, Germany, September 23.
- Sanofi Deutschland GmbH, Diabetes Research Division, Frankfurt, Germany, September 8.

- Boehringer-Ingelheim, Process Development, Ingelheim, Germany, August 30.
- Lycera Corp., Ann Arbor, Michigan, July 1.
- National Institute on Aging, Translational Gerontology Branch, Biomedical Research Center, Baltimore, Maryland, June 8.

2015

- Bayer CropScience, Industriepark Höchst, Frankfurt, Germany, November 19.
- Bayer Pharma AG, CWL-Institutskolloquium**,** Research Center, Wuppertal, Germany, November 17.
- Bayer HealthCare Berlin, Germany, November 12.
- Grünenthal GmbH, Global Preclinical R&D, Aachen, Germany, October 13.
- Gilead, Sciences 2015 Medicinal Chemistry Colloquium, Foster City, California, September 22.

2014

- GSK, Upper Merion, King of Prussia, Pennsylvania, August 6.

2013

- Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, August 8.
- Polyphor Ltd., Allschwil, Switzerland, March 11.

2012

- Grünenthal GmbH, Global Preclinical R&D, Aachen, Germany, December 3.
- Eli Lilly, Process Chemistry, Indianapolis, Indiana, November 2.
- L'Oréal, Advanced Research Chemistry & Performance Materials Department, Aulnay-sous-Bois, France, September 24.
- Molecular Discovery Program, National Cancer Institute, Frederick, Maryland, May 24.

2011

- Bristol-Myers Squibb Co, Pharmaceutical Research Institute, Wallingford, Connecticut, November 21.
- Amgen, Inc., Process and Medicinal Chemistry Colloquium, Cambridge, Massachussetts, August 18.
- Sunovion Pharmaceuticals Inc., Process and Medicinal Chemistry Colloquium, Marlborough, Massachussetts, June 9.
- Principia Biopharma, Molecular Medicine Research Institute, Sunnyvale, California, May 17.
- Sanofi-Aventis, Diabetes Division Colloquia, Frankfurt, Germany, February 1.
- Merck-Serono KGaA, Organic Chemistry Seminar Series, Darmstadt, Germany, January 20.
- Eli Lilly & Co., Discovery Chemistry Colloquia, Erl Wood Manor, Windlesham, Surrey, United Kingdom, January 19.

2010

- Gilead, Medicinal Chemistry Colloquia, Foster City, California, November 11.
- Actelion, Discovery Chemistry, Allschwil, Switzerland, January 19.

2009

- Givaudan Flavors Inc., Cincinnati, Ohio, May 14.

2008
- Actelion, Discovery Chemistry, Allschwil, Switzerland, November 6.
- Abbott Laboratories, Medicinal Chemistry & Process Research, Abbott Park, Illinois, October 16.
- Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, August 7.
- Amgen, Small Molecule Drug Discovery, Thousand Oaks, California, June 10.
- Merck Research Laboratories, Rahway, New Jersey, May 6.

2007
- Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, United Kingdom, December 10.
- Actelion, Discovery Chemistry, Allschwil, Switzerland, September 17.

2006
- OSI Pharmaceuticals, Cancer Research, Farmingdale, New York, November 16.
- Vertex Pharmaceuticals, Medicinal Chemistry, Cambridge, Massachusetts, November 9.
- Actelion, Discovery Chemistry, Allschwil, Switzerland, October 25.
- Sanofi-Aventis Combinatorial Technologies Center (SACTC), Tucson, Arizona, October 5.
- Novartis Institutes for BioMedical Research, Basel, Switzerland, June 7.
- Novartis Institutes for BioMedical Research, Vienna, Austria, June 6.
- Novartis Institutes for BioMedical Research, Horsham Research Centre, Horsham, United Kingdom, April 24.
- Actelion, Discovery Chemistry, Allschwil, Switzerland, March 31.
- Shionogi Co., Medicinal and Process Chemistry Research Laboratories, Osaka, Japan, March 8.
- Sankyo Co., Ltd., Medicinal Chemistry Research Laboratories, Shinagawa-ku, Tokyo, Japan, March 7.
- Novartis Tsukuba Research Institute, Tsukuba, Japan, March 6.
- Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, February 7.
- AstraZeneca R&D, Waltham, Massachusetts, January 19.

2005
- Hoffmann-La Roche Inc., Nutley, New Jersey, November 10.
- GSK, Synthetic Chemistry, King of Prussia, Pennsylvania, October 20.
- Boehringer-Ingelheim, Process Research and Medicinal Chemistry, Biberach, Germany, June 24.
- Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, United Kingdom, May 10.
- Syrrx, Medicinal Chemistry, San Diego, California, March 15.

2004
- AstraZeneca, Alderley Park, United Kingdom, December 20.
- Sepracor Inc, Process R&D, Marlborough, Massachusetts, October 21.
- Scios Inc., Medicinal Chemistry, Newark, California, October 15.
- Gilead Sciences, Medicinal Chemistry Colloquia, Foster City, California, October 14.

- Pfizer Michigan Laboratories, Ann Arbor, Michigan, June 10.
- Actelion, Discovery Chemistry, Allschwil, Switzerland, May 16.
- Sepracor Inc., Process R&D, Marlborough, Massachusetts, May 6.
- Bristol-Myers Squibb, Chemical Process Research & Development, New Brunswick, New Jersey, April 29.
- FMC Co., Discovery Chemistry, Princeton, New Jersey, January 26.

2003

- Albany Molecular Research Institute, Syracuse, New York, October 9.
- Center for Cancer Research, National Cancer Institute, Ft. Detrick, Frederick, Maryland, October 2.
- Schering-Plough Research Institute, Kenilworth, New Jersey, September 23.
- Abbott Bioresearch Center, Department of Medicinal Chemistry, Worcester, Massachusetts, June 26.
- GE Corporate Research & Development, Niskayuna, New York, May 15.
- Novartis Pharma K.K., Tsukuba Research Institute, Ibaraki, Japan, March 26.
- Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, January 9.
- Sugen, Inc., South San Francisco, California, January 23.

2002

- Pharmacia, St. Louis, Missouri, December 11.
- Axovan Ltd, Allschwil, Switzerland, November 21.
- Aventis Pharma Germany GmbH, Frankfurt, Germany, November 19.
- Aventis Pharmaceuticals, Bridgewater, New Jersey, November 6.
- Fujisawa Pharmaceutical Co., Exploratory Research Laboratories, Tsukuba, Japan, October 28.
- UCB Pharma Research, Inc., Medicinal Chemistry, Cambridge, Massachusetts, August 20.
- Merck Research Laboratories, Medicinal Chemistry, Rahway, New Jersey, May 23.
- Biogen, Medicinal Chemistry, Cambridge, Massachusetts, April 4.
- Amgen, Small Molecule Drug Discovery, Thousand Oaks, California, March 21.
- 3M, Corporate Research Center, Maplewood, Minnesota, February 14.
- Celera, Department of Medicinal Chemistry, South San Francisco, California, January 24.

2001

- Lilly Pharmaceuticals (Sphinx), Research Triangle Park, North Carolina, December 7.
- Lilly Forschung GMBH, Discovery Chemistry Research, Hamburg, Germany, November 20.
- Eastman Kodak Co., Research & Development Laboratories, Rochester, New York, October 25.
- Albemarle Corporation, Research & Development, Baton Rouge, Louisiana, October 5.
- Dow Agrosciences, Department of Chemistry, Indianapolis, Indiana, May 21.
- Bristol-Myers Squibb, Discovery Chemistry, Lawrenceville, New Jersey, May 17.
- Roche Bioscience, Department of Chemistry, Palo Alto, California, May 9.
- AstraZeneca Pharmaceuticals, Department of Chemistry, Wilmington, Delaware, March 14.

- AstraZeneca-MethylGene Joint Chemistry Seminar Program, Ville St.-Laurent, Québec, Canada, February 14.

2000

- Wyeth-Ayerst, Princeton, New Jersey, November 30.
- XenoPort, Inc., Palo Alto, California, November 20.
- Sphinx Pharmaceuticals, Research Triangle Park, North Carolina, November 17.
- Sphinx Pharmaceuticals, Research Triangle Park, North Carolina, September 14.
- Bayer, Departments of Medicinal Chemistry and Process Research, West Haven, Connecticut, August 28.
- Abbott Laboratories, Process R&D, North Chicago, Illinois, July 20.
- Abbott Laboratories, Medicinal Chemistry, Abbott Park, Illinois, July 19.
- Takeda Chemical Industries, Ltd., Pharmaceutical Discovery Research Division, Osaka, Japan, May 18.
- Sphinx Pharmaceuticals, Research Triangle Park, North Carolina, April 6.
- Eastman Chemicals, Fine Chemicals Division, Kingsport, Tennessee, March 29.

1999

- Sphinx Pharmaceuticals, Research Triangle Park, North Carolina, September 24.
- Sphinx Pharmaceuticals, Research Triangle Park, North Carolina, May 7.
- Lord Corporation, R&D, Cary, North Carolina, January 25.

1998

- Merck, Sharp & Dohme, Terlings Park, Essex, United Kingdom, November 24.
- R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, February 17.
- DuPont Organic Synthesis Seminar Series, Stine Haskell Research Center, Newark, Delaware, June 30.
- Wyeth-Ayerst Research, Radnor, Pennsylvania, May 20.
- Eli Lilly, Department of Medicinal Chemistry, Indianapolis, Indiana, May 12.
- Pharmacia&Upjohn, Department of Medicinal Chemistry, Kalamazoo, Michigan, May 4.
- Pressure Chemical Co., Pittsburgh, Pennsylvania, March 21.
- Merck & Co., Medicinal Chemistry, West Point, Pennsylvania, March 6.
- Biogen, Medicinal Chemistry, Cambridge, Massachusetts, February 6.
- Bio-Mega/Boehringer Ingelheim, Department of Medicinal Chemistry, Laval, Québec, Canada, January 30.

1997

- BASF Central Research, Luwigshafen, Germany, July 17.
- Bayer Pharma Research, Wuppertal, Germany, July 16.
- Schering-Plough Research Institute, Kenilworth, New Jersey, May 29.
- Affymax Research Institute, Palo Alto, California, May 22.
- Cubist Pharmaceuticals, Chemistry Research, Cambridge, Massachusetts, March 7.
- Glaxo Wellcome Co., Cell Biology Department, Research Triangle Park, North Carolina, January 24.
- Astra Arcus USA, Medicinal Chemistry, Rochester, New York, January 15, 1997.

1996
- Bristol-Myers Squibb Co, Pharmaceutical Research Institute, Wallingford, Connecticut, October 15.
- Biogen, Medicinal Chemistry, Cambridge, Massachusetts, October 8.
- Sepracor Inc, Process R&D, Marlborough, Massachusetts, October 7.
- Boehringer Ingelheim Pharmaceuticals Inc., Chemical Development, Ridgefield, Connecticut, September 11.
- BASF Bioresearch Center, Department of Medicinal Chemistry, Worcester, Massachusetts, September 10.
- SmithKline Beecham Pharmaceuticals, Department of Medicinal Chemistry, King of Prussia, Pennsylvania, August 19.
- Albany Molecular Research, Albany, New York, May 24.
- DuPont, Central Research Laboratories, Experimental Station, Wilmington, Delaware, March 20.
- Hoffmann-La Roche Inc., Nutley, New Jersey, February 22.

1995
- Merck Research Laboratories, Rahway, New Jersey, November 1.
- Zeneca Pharmaceuticals, Department of Medicinal Chemistry, Wilmington, Delaware, October 24.
- Merck Frosst, Department of Medicinal Chemistry, Pointe Claire, Canada, September 13.
- DuPont Merck, Chemical Process R&D, Deepwater, New Jersey, June 23.
- Searle, Departments of Medicinal Chemistry and Chemical Research, Skokie, Illinois, June 7.
- Syntex Discovery Research, Palo Alto, California, May 15.
- Wyeth-Ayerst Lederle Laboratories, Pearl River, New York, April 14.
- PPG Industries, Coatings and Resins R&D, Allison Park, Pennsylvania, February 21.

1994
- Bristol-Myers Squibb, Chemical Process Research & Development, New Brunswick, New Jersey, December 14.
- Bio-Mega/Boehringer Ingelheim Research Inc., Department of Chemistry, Laval, Québec, Canada, October 12.
- Glaxo Research Institute, Departments of Medicinal Chemistry and Process Research, Research Triangle Park, North Carolina, June 23.
- Miles, Departments of Medicinal Chemistry and Process Research, West Haven, Connecticut, May 5.
- Pfizer, Medicinal Chemistry, Groton, Connecticut, April 21.
- Parke-Davis, Medicinal Chemistry, Ann Arbor, Michigan, April 12.
- Zeneca Pharmaceuticals, Medicinal Chemistry, Wilmington, Delaware, March 17.
- R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, February 17.
- Eisai Research Institute, Special Seminar Series, Andover, Massachusetts, February 10.
- Merck & Co., Medicinal Chemistry, West Point, Pennsylvania, January 13.

1993
- Upjohn Co., Medicinal Chemistry Research, Kalamazoo, Michigan, December 1.

- Sandoz Research Institute, Department of Medicinal Chemistry, East Hanover, New Jersey, June 14.
- Eli Lilly, Departments of Medicinal Chemistry and Process Research, Indianapolis, Indiana, June 18.
- SmithKline Beecham, Department of Medicinal Chemistry, King of Prussia, Pennsylvania, May 7.
- Ciba-Geigy, Department of Medicinal Chemistry, Summit, New Jersey, March 23.
- Merck & Co., Process Research, Rahway, New Jersey, February 17.
- Hoffmann-LaRoche Inc., Process Research (Pharmaceuticals), Basel, Switzerland, February 4.

1992

- Ciba-Geigy AG, Central Research, Basel, Switzerland, September 24.

PROFESSIONAL MEMBERSHIPS

American Chemical Society
Swiss Chemical Society
UPMC Hillman Cancer Center
American Association for the Advancement of Science
International Society of Heterocyclic Chemistry
Royal Society of Chemistry
Finnish Society For Synthetic Chemistry

TEACHING EXPERIENCE

Graduate Level Courses:

- Synthetic Organic Chemistry (Chem 2320)
- Techniques of Organic Research (Chem 2380)
- Biological Chemistry II (Chem 2820)
- Special Topics in Organic Chemistry: Sigmatropic Rearrangements (Chem 3320)
- Combinatorial Chemistry (Chem 3300)
- Drug Development I (Pharm 5119)
- Molecular Pharmacology 2370 and 3360 (MSMPHL 2370 and 3360)
- Medicinal Chemistry (Pharm 3032)
- Heterocyclic Chemistry (Chem 3300, ESPCI, Chem 3310)
- Computational Chemistry for Organic Chemists (Chem 3330)
- Marine Natural Products - Structure, Bioactivity & Synthesis (UCI)
- Graduate Research Seminar (Chem 2700)
- Chemical Hazards (Chem 3300)
- Drug Development I (Pharm 5119)

Undergraduate Level Courses:

- Techniques of Organic Research (Chem 1380)
- Advanced Organic Chemistry (Chem 1310/2370)
- Organic Chemistry 1 (Chem 0310, Chem 0730 (honors))

- Organic Chemistry 2 (Chem 0320, Chem 0740 (honors))
- Biosynthesis (Chem 1310/2370)
- Inorganic Synthesis Lab & Lecture (Chem 1140)

Spring 1991:	- Techniques of Organic Research (Chem 1380/2380)
Fall 1991:	- Synthetic Organic Chemistry (Chem 1310/2370)
	- Special Topics in Organic Chemistry: Sigmatropic Rearrangements (Chem 3320)
Spring 1992:	- Techniques of Organic Research (Chem 1380/2380)
Fall 1992:	- Organic Chemistry 2 (Chem 0320)
	- Computational Chemistry for Organic Chemists (Chem 3330)
Spring 1993:	- Techniques of Organic Research (Chem 1380/2380)
Fall 1993:	- Synthetic Organic Chemistry (Chem 1310/2370)
Spring 1994:	- Techniques of Organic Research (Chem 1380/2380)
Fall 1994:	- Organic Chemistry 1 (Chem 0310)
	- Computational Methods in Organic Chemistry (Chem 3330)
Spring 1995:	- Organic Chemistry 2 (Chem 0320)
	- Marine Natural Products - Structure, Bioactivity & Synthesis (UCI)
Fall 1995:	- Synthetic Organic Chemistry (Chem 1310/2370)
Spring 1996:	- Synthetic Organic Chemistry (Chem 2320)
Spring 1997:	- Synthetic Organic Chemistry (Chem 2320)
	- Computational Methods in Organic Chemistry (Chem 3330)
Fall 1997:	- Synthetic Organic Chemistry and Biosynthesis (Chem 1310/2370)
Spring 1998:	- Synthetic Organic Chemistry (Chem 2320)
Spring 1999:	- Organic Chemistry 2 (Chem 0320)
Summer 1999:	- Synthetic Organic Chemistry (Chem 2320)
	- Polarimetry & Calculations as part of a shortcourse on the Measurement of Enantiopurity and Assignment of Absolute Configuration (11th International Symposium on Chiral Discrimination, Chicago, Illinois)
	- ACS Shortcourse on Combinatorial Chemistry, New Orleans, Louisiana
Fall 1999:	- Synthetic Organic Chemistry (Chem 1310/2370)
	- Biological Chemistry (Chem 3590, section on biosynthesis)
	- Shortcourse on Combinatorial Chemistry, Zeneca Pharmaceuticals, Wilmington, Delaware
Spring 2000:	- Techniques of Organic Research (Chem 1380/2380)
Summer 2000:	- ACS Short Course on Combinatorial Chemistry, Washington, DC
Fall 2000:	- Honors Organic Chemistry 1 (Chem 0730)
	- ACS Short Course on Frontiers in Organic Chemistry; Part 2: Chemical Discovery, Washington, DC

	- Molecular Pharmacology (MSMPHL 2310); Section on Molecular Diversity and Combinatorial Chemistry
Spring 2001:	- Honors Organic Chemistry 2 (Chem 0740)
	- Introduction to Combinatorial Chemistry (Chem 3300)
Summer 2001:	- Short Course on Combinatorial Chemistry, Dow AgroSciences, Indianapolis, Indiana
Fall 2001:	- Synthetic Organic Chemistry (Chem 1310/2370)
	- Heterocyclic Chemistry (Chem 3300)
	- Graduate Research Seminar (Chem 2700)
	- ACS Short Course on Chemical Discovery, Philadelphia, PA
	- Highlights of Heterocyclic Chemistry (University of Paris-Sud)
	- Molecular Pharmacology 3360; Section on Molecular Diversity and Combinatorial Chemistry
	- Introduction to Heterocyclic Chemistry (Shanghai Institute of Materia Medica, Chinese Academy of Sciences)
Spring 2002:	- Drug Development I (Pharm 5119)
Fall 2002:	- Computational Chemistry for Organic Chemists (Chem 3310)
	- Graduate Research Seminar (Chem 2700)
	- ACS Short Course on Accelerated Chemical Discovery, Philadelphia, PA
Spring 2003:	- Biological Chemistry II (Chem 2820)
Fall 2003:	- Graduate Research Seminar (Chem 2700)
	- ACS Short Course on Accelerated Chemical Discovery, Boston, MA.
	- Minicourse in Modern Organic Synthesis, Universidad de la Republica, Montevideo, Uruguay
	- Molecular Pharmacology 3360; Section on Drug Discovery, Department of Pharmacology, University of Pittsburgh Medical School
Spring 2004:	- Organic Chemistry 1 (Chem 0310)
	- Pharm 5119 Drug Development I
Summer 2004:	- Short Course on Organozirconium Chemistry, Department of Chemistry, Technion, Haifa, Israel
Fall 2004:	- Short Course on Heterocyclic Chemistry – Concepts, Syntheses & Applications, Department of Chemistry, École Supérieure the Physique et de Chimie Industrielles de la Ville de Paris (ESPCI), Paris, France
	- Molecular Pharmacology 3360 (MSMPHL 3360); Section on Drug Discovery/The Origin of Drugs, Department of Pharmacology, University of Pittsburgh Medical School
Spring 2005:	- Inorganic Synthesis Lab & Lecture (Chem 1140)
	- Drug Development I (Pharm 5119)
	- ACS ProSpectives Short Course on Heterocyclic Chemistry, Miami, FL
Summer 2005:	- Short Course on Heterocyclic Chemistry, Pharmacore, High Point, NC.
Fall 2005:	- Organic Chemistry 2 (Chem 0320)

	- Molecular Pharmacology 3360 (MSMPHL 3360); Section on Drug Discovery/The Origin of Drugs, Department of Pharmacology, University of Pittsburgh Medical School
Spring 2006:	- Synthetic Organic Chemistry (Chem 2320)
	- Drug Development I (Pharm 5119)
Fall 2006:	- Molecular Pharmacology 3360 (MSMPHL 3360); Section on Drug Discovery/The Origin of Drugs, Department of Pharmacology, University of Pittsburgh Medical School
Spring 2007:	- Synthetic Organic Chemistry (Chem 2320)
	- Drug Development I (Pharm 5119)
Spring 2008:	- Synthetic Organic Chemistry (Chem 2320)
	- Drug Development I (Pharm 5119)
	- Molecular Pharmacology 2370 (MSMPHL 2370); Section on Drug Discovery/The Origin of Drugs, Department of Pharmacology, University of Pittsburgh Medical School
	- Short Course on Heterocyclic Chemistry, Actelion, Basel, Switzerland
Fall 2008:	- Synthetic Organic Chemistry (Chem 1310/2370)
	- Molecular Pharmacology 3360 (MSMPHL 3360); Section on Drug Discovery/The Origin of Drugs, Department of Pharmacology, UPMC
Spring 2009:	- Advanced Topics in Organic Chemistry – Heterocyclic Chemistry (Chem 3300)
	- Drug Development I (Pharm 5119)
Fall 2009:	- Synthetic Organic Chemistry (Chem 1310/2370)
	- Medicinal Chemistry (Pharm 3032)
Spring 2010:	- Drug Development I (Pharm 5119)
Summer 2010:	- Short Course on Heterocyclic Chemistry, Pfizer, Groton, Connecticut
Fall 2010:	- Synthetic Organic Chemistry (Chem 1310/2370)
	- Medicinal Chemistry (Pharm 3032)
	- Short Course on Heterocyclic Chemistry, Department of Chemistry, UdelaR, Montevideo, Uruguay
Spring 2011:	- Drug Development I (Pharm 5119)
Fall 2011:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
Spring 2012:	- Organic Chemistry 1 (0310)
	- Drug Development I (Pharm 5119)
Fall 2012:	- Molecular Pharmacology (MSMPHL 2370)
	- Medicinal Chemistry (Pharm 3032, Chem 3310)
Spring 2013:	- Organic Chemistry 1 (0310)
	- Drug Development I (Pharm 5119)
Fall 2013:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
Spring 2014:	- Organic Chemistry 2 (Chem 0320)
Fall 2014:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
	- Drug Discovery – Challenges and Opportunities (MSMPHL 2370)

Spring 2015:	- Heterocyclic Chemistry (Chem 3310)
Fall 2015:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
Spring 2016:	- Organic Chemistry 2 (Chem 0320)
Fall 2016:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
Spring 2017:	- Synthetic Organic Chemistry (Chem 2320)
Fall 2017:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
Spring 2018:	- Synthetic Organic Chemistry (Chem 2320)
Summer 2018:	- Chemical Hazards (Chem 3300)
Fall 2018:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
Spring 2019:	- Synthetic Organic Chemistry (Chem 2320)
Fall 2019:	- Medicinal Chemistry (Pharm 3032, Chem 3310)
	- Cancer Biology and Therapeutics (MSMPHL3310)
Spring 2020:	- Organic Chemistry 2 (Chem 0320)
Spring 2021:	- Organic Chemistry 2 (Chem 0320)
Fall 2022:	- Synthetic Organic Chemistry (Chem 1310/2370)
	- Medicinal Chemistry (Pharm 3032)
Fall 2023:	- Synthetic Organic Chemistry (Chem 1310/2370)
Fall 2024:	- Synthetic Organic Chemistry (Chem 1310/2370)

STUDENTS SUPERVISED

Total Students Supervised: 438
Graduate Students: 114
Postdoctoral Students: 115
Undergraduate and Rotation Students: 209

STAFF SUPERVISED

Total Staff Supervised: 57