UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

ASTRAZENECA
Patent Owner.

Patent No. RE44,186

DECLARATION OF DAVID P. ROTELLA, PH.D.

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I, David P. Rotella, declare as follows:

I. QUALIFICATIONS

1. My name is David P. Rotella. I am currently the Margaret and Herman Sokol Professor of Chemistry in the Department of Chemistry and Biochemistry and in the Sokol Institute of Pharmaceutical Life Sciences at Montclair State University. I have been a member of the faculty of this university since 2011.

2. I am currently an adjunct professor in the Department of Pharmaceutical Sciences at the University of Pittsburgh, in the Center for Drug Discovery at Northeastern University, and in the Department of Medicinal Chemistry at the University of Mississippi. I have been a member of the faculty of these departments since 2010, 2010, and 2009, respectively.

3. I am currently a registered pharmacist in the Commonwealth of Pennsylvania.

4. I was formerly a research scientist at multiple pharmaceutical companies during the years 1991-2010, including at Bristol-Myers Squibb PRI, Lexicon Pharmaceuticals, and Wyeth Research/Pfizer. My industry experience focused on drug discovery and development.

5. I received my B.S. Pharm. from the University of Pittsburgh in 1981 and Ph.D. in Medicinal Chemistry from The Ohio State University in 1985. I was a Postdoctoral Scholar in the Department of Chemistry at The Pennsylvania State University from 1985 to 1987.

6. My current research focuses on protein kinase inhibitors for anti-infective and anti-inflammatory applications. Specifically, I work on the discovery of new agents useful for the potential treatment of parasitic and neurodegenerative diseases, including the synthesizing of new analogs of a lead structure as potential protein kinase inhibitors and investigation of structure-activity relationships in a product that has HSP90 inhibitor activity.

7. I have authored or co-authored more than 20 abstracts for presentation at professional meetings, 40 peer-reviewed journal articles, and seven book chapters. I have also edited or co-edited five books in the field of Medicinal Chemistry. I have received numerous honors, fellowships and awards, and am an inventor or co-inventor on seven granted patents.

8. A summary of my education, experience, publications, awards and honors, patents, publications, and presentations is provided in my CV, a copy of which is submitted separately (Ex. 1004).

II. SCOPE OF WORK

9. I understand that a petition is being filed with the United States Patent and Trademark Office for *Inter Partes* Review of U.S. Reissued Patent No. RE44,186 (hereinafter, "the '186 patent," Ex. 1001). I have been retained by Mylan Pharmaceuticals Inc. as a technical expert to provide opinions regarding the '186 patent. I have reviewed the '186 patent and relevant sections of its prosecution history in the US Patent and Trademark Office (Ex. 1006). I have also reviewed and considered other documents in arriving at my opinions, and cite them in this declaration. For convenience, documents cited in this declaration are listed

in the Appendix in Section XI.

10. I am compensated at the rate of $500/hour for my work. I have no financial interest in the outcome of this matter.

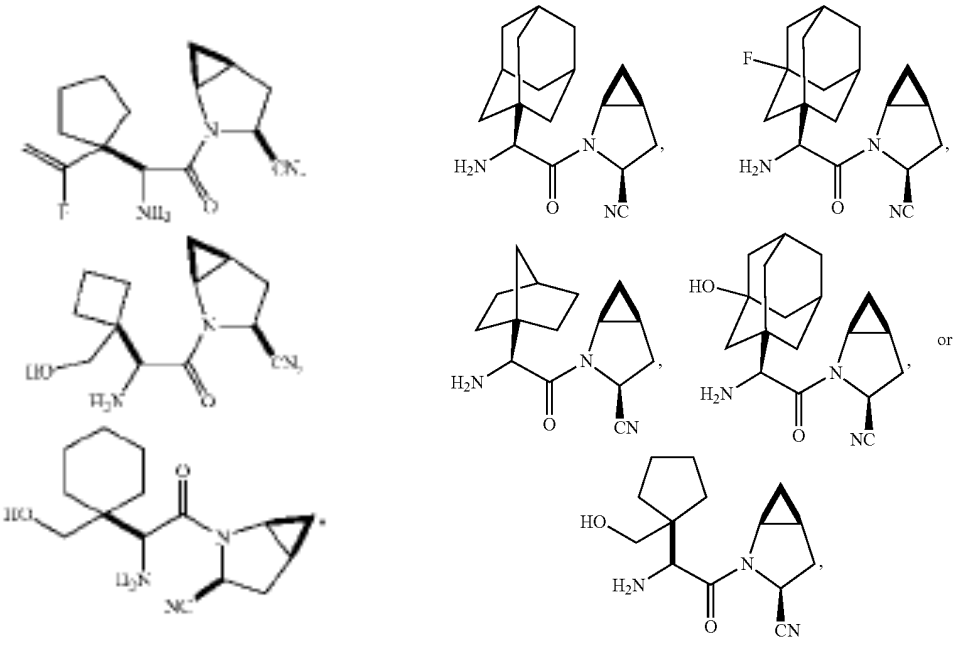
III. OVERVIEW OF THE '186 PATENT

11. The '186 patent is entitled "Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method" and was issued on April 30, 2013. I have been advised that the '186 patent issued from U.S. Application No. 13/308,658, which was filed on December 1, 2011, as a reissued application of U.S. Application No. 09/788,173, which was filed on February 16, 2001 and issued as U.S. Patent No. 6,395,767 on May 28, 2002. I have also been advised that U.S. Application No. 09/788,173 claims priority to U.S. Provisional Application No. 60/188,555, which was filed on March 10, 2000.

12. The '186 patent is generally directed to cyclopropyl-fused pyrrolidine-based compounds with a variety of optional substituents, as well as pharmaceutical combinations and methods for treating diabetes and additional diseases. According to the '186 patent, the "cyclopropyl-fused pyrrolidine-based compounds [of the '186 patent are] inhibitors of dipeptidyl peptidase IV [(DP-IV)] . . . for treating diabetes, especially Type II diabetes." Ex. 1001 col. 1, ll. 19-21. The '186 patent describes the mechanism by which DP-IV inhibition treats type 2 diabetes as follows: "[DP-IV] has been shown to be the primary degrading enzyme of GLP-1(7-36) in vivo . . . [t]hus, inhibition of [DP-IV] in vivo should potentiate endogenous levels of GLP-1(7-36) and . . . thus serve to ameliorate the diabetic condition." *Id.* at Col. 1, ll. 59-67.

13. Independent claim 1 discloses a genus of chemical compounds comprising a cyclopropyl-fused pyrrolidine-based core with a variety of optional substituents. Dependent claims 2-7 and independent claims 8 and 10 further limit the substituent groups of the compound of claim 1. For example, independent claim 8 recites the following:

A compound having the structure:

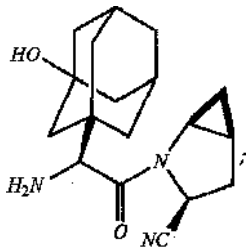


or a pharmaceutically acceptable salt thereof.

Dependent claim 9 is directed to the hydrochloride or trifluoroacetic acid salts of the compounds of claim 8. Dependent claim 11 is directed to a pharmaceutical composition comprising a compound within the scope of claim 1. Claims 12-21 recite pharmaceutical combinations comprising a compound within the scope of claim 1 and an antidiabetic agent for treating diabetes and/or additional agents for

treating related diseases. Claim 22 recites pharmaceutical combinations comprising a compound within the scope of claim 1 and an agent for treating obesity or other related diseases. Claims 23 and 24 were canceled upon reissue.

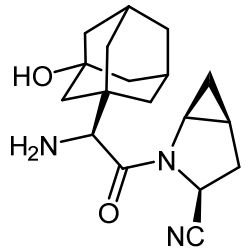
14. Independent claim 25 recites a single compound as follows:



or a pharmaceutically acceptable salt thereof.

The compound of claim 25 also falls within the scope of composition claims 1, 2, 4, 6, 7, 8 and 10. Dependent claim 26 recites the hydrochloride salt of the compound of claim 25. Dependent claims 27 and 28 further recite pharmaceutical compositions of the compound of claim 25. Dependent claims 29-31 recite a combination of the compound of claim 25 and an antidiabetic agent other than a DP-IV inhibitor. Claims 32-43 recite various methods of treatment using the compound of claim 25, alone or in combination with an antidiabetic agent other than a DP-IV inhibitor.

15. The compound of claim 25 is also known as (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile. For convenience, this compound will be referred to as “saxagliptin” as shown below:



Saxagliptin

16. In my opinion, and as explained in detail below, the claims of the ’186 patent would have been obvious to individuals of ordinary skill in the field prior to and at the time of the earliest possible priority filing date of the ’186 patent, i.e., prior to March 10, 2000.

IV. FILE HISTORY OF THE ’186 PATENT

17. I have been advised that the determination of the right to priority is controlled by the written description requirement of 35 U.S.C. § 112, and to satisfy the written description requirement the disclosure of the prior application must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventors were in possession *of the invention*. I have been further advised that the prior application must indicate to a person skilled in the art that the inventor was “in possession” of the invention as later claimed.

18. I understand that U.S. Patent No. RE44,186, entitled “Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method” (“the ’186 patent”), issued April 30, 2013. I further understand that the ’186 patent issued from U.S. Application Serial No. 13/308,658, filed December 1, 2011 as a reissue application of U.S. Application Serial No. 09/788,173, filed February 16, 2001 and issued as U.S. Patent No. 6,395,767 on May 28, 2002. U.S. Application

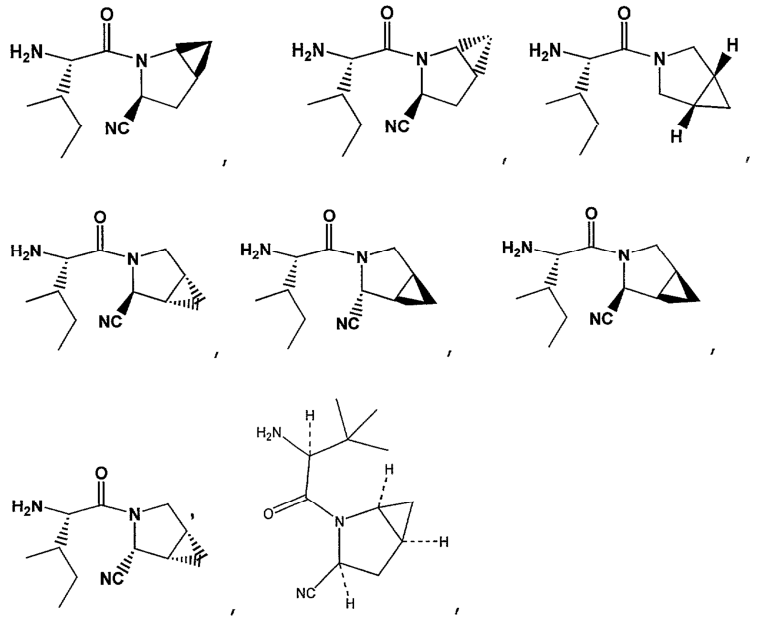
Serial No. 09/788,173 (“the ’173 application”) and claims priority to U.S. Provisional Application No. 60/188,555, filed on March 10, 2000 (“the ’555 application”).

19. Several claim elements of the ’186 patent are not described in the earliest-filed ’555 application, and instead appear for the first time in the later-filed ’173 application. For example, there is no description in the ’555 application of: (i) the genus of compounds recited in claim 6; (ii) the specific compounds recited in claim 8 or (iii) the specific compound of claim 25.

20. There is no disclosure in the earlier-filed ’555 application of the specific genus of claim 6, in which claim 1 is further limited to:

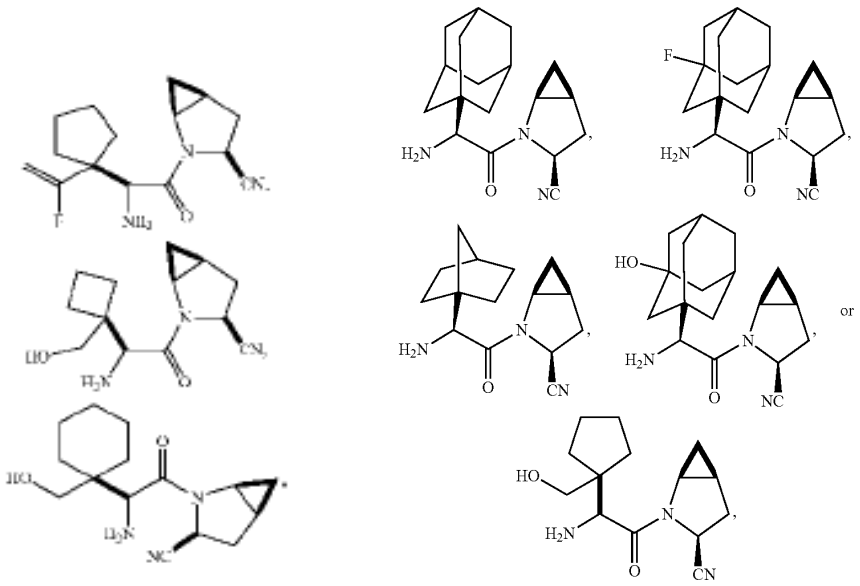
> R^3 is H, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,
> R^2 is H or alkyl, n is 0,
> X is CN.

See, e.g., Ex. 1027, p. 0008, ll. 8-11; claim 6. Further, the ’555 application exemplifies only short, straight and/or branched alkyl substituents at the 2-position as shown below:



See, e.g., Ex. 1027, p. 0056; claim 13. Accordingly, one of ordinary skill in the art would have understood that the inventors were not in possession of the genus recited in claim 6 at the time of the '555 application's filing.

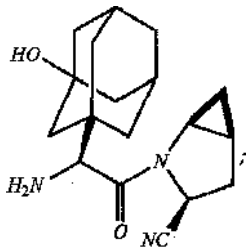
21. Claim 8 of the '186 patent recites a compound as defined in claim 1 having the structure:



or a pharmaceutically acceptable salt thereof.

The only specific compounds described in the ’555 application are directed to short, straight and/or branched alkyl substituents at the 2-position. *See*, e.g., Ex. 1027, p. 0056; claim 13. The compounds of claim 8 were first disclosed in the ’173 application. *See*, e.g., Ex. 1005, p. 0010.

22. Similarly, the compound of claim 25 is also not specifically disclosed in the specification of the ’555 application. Independent claim 25 recites the following:



or, a pharmaceutically acceptable salt thereof.

As discussed above, the only specific compounds described in the ’555 application are directed to short, straight and/or branched alkyl substituents at the 2-position as depicted in the preceding paragraph. *See*, e.g., Ex. 1027, p. 0056; claim 13. The compound of claim 25 was first disclosed in the ’173 application. *See*, e.g., Ex. 1005, p. 0010. Accordingly, one of ordinary skill in the art could surmise that the inventors were not in possession of the compounds of claims 8 or 25 at the time of the ’555 application’s filing.

23. As discussed in detail above, several claim elements of the ’186 patent are not described in the earliest-filed ’555 application, and instead appear for the first time in the later-filed ’173 application. Accordingly, one of ordinary skill in

the art would have understood that the inventors were not in possession of the claimed subject matter at the time of the ’555 application’s filing.

V. LEGAL STANDARDS

24. I have been informed that a claimed invention is not patentable under 35 U.S.C. § 103 (2012), for obviousness, if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the field to which the subject matter pertains.

25. I have been instructed that a determination of obviousness requires inquiries into (i) the scope and content of the art when the invention was made; (ii) the differences between the art and the claims at issue; (iii) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent they exist, any secondary considerations.

26. I understand that a claim can be found to have been obvious if all the claimed elements were known in the prior art and one skilled in the field could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable and expected results to one of ordinary skill in the art.

27. I understand that improper hindsight must not be used when comparing the prior art to the invention for obviousness. Thus, a conclusion of obviousness must be firmly based on knowledge and skill of a person of ordinary skill in the field at the time the invention was made without the use of post-filing knowledge.

28. I understand that in order for a claimed invention to be considered obvious, there must be some supporting rationale for combining cited references as proposed.

29. I have been informed that obviousness may be established by showing that it would have been obvious to combine the teachings of more than one item of prior art. In determining whether a piece of prior art could have been combined with other prior art or with other information within the knowledge of one of ordinary skill in the art, the following are examples of approaches and rationales that may be considered: (i) combination of prior art elements according to known methods to yield predictable results; (ii) simple substitution of one known element for another to obtain predictable results; (iii) use of a known technique to improve similar methods or products in the same way; (vi) application of a known technique to a known method or product ready for improvement to yield predictable results; (vii) application of a technique or approach that would have been "obvious to try" (choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success); (viii) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; or (ix) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

30. I also understand that evidence of "secondary considerations" may be weighed against evidence of the scope and content of, and the level of skill in, the art to rebut a conclusion of *obviousness* where appropriate.

31. I understand that such secondary considerations when in evidence may include: (i) commercial success of a product due to the merits of the claimed invention; (ii) a long-felt, but unsatisfied need for the invention; (iii) failure of others to find the solution provided by the claimed invention; (iv) deliberate copying of the invention by others; (v) unexpected results achieved by the invention; (vi) praise of the invention by others skilled in the art; (vii) lack of independent simultaneous invention within a comparatively short space of time; and (viii) teaching away from the invention in the prior art. Secondary considerations are relevant where there is a connection, or relationship, between the evidence and the claimed invention.

VI. LEVEL OF ORDINARY SKILL AND RELEVANT TIME

32. I have been advised that the '186 patent claims priority to U.S. provisional application number 60/188,555 ("the '555 application)," which was filed on March 10, 2000. I further understand, however, that the '186 patent may not be entitled to that 2000 priority date. Each of the opinions expressed in this declaration apply regardless of whether the priority date is March 10, 2000 (the filing date of the '555 application) or February 16, 2001 (the filing date of the '173 application).

33. As discussed above, "a person of ordinary skill in the relevant field" is a hypothetical person who is presumed to have typical knowledge and experience

in the relevant field at the time of the invention. A person of ordinary skill in the field is also a person of ordinary creativity. I have been asked to use the time prior to March 10, 2000, as the relevant timeframe for assessing validity of the ’186 patent. When I refer to March 2000, I am referring specifically to prior to March 10, 2000.

34. By virtue of my education, experience, and training, I am familiar with the level of skill in the field of the ’186 patent on or about March 10, 2000.

35. One of ordinary skill in the field would likely have some combination of the following skills and experience: (i) designing target compounds towards drug discovery; (ii) designing and preparing formulations of drugs that exhibit inhibitory activity; (iii) understanding the biological aspects of drug development, including the drug’s effect on the whole animal; and (iv) understanding work presented or published by others in the field, including the patents and printed publications discussed in this declaration.

36. Typically, a person of ordinary skill in the relevant field in March 2000 could have an advanced degree (e.g., a Ph.D.) in pharmaceutics, pharmaceutical chemistry, medicinal chemistry or a related field and at least 2-3 years of practical experience in the design of drugs. Alternatively, a person of ordinary skill in the relevant field could have less education but considerable professional experience.

37. My understanding of the level of ordinary skill in the art is corroborated by the specification of the ’186 patent, which in many instances provides general rather than specific guidance regarding how the invention would be practiced. For example, the ’186 patent lacks specific guidance of the various

pharmaceutical combinations that it claims. There are no validated or tested dosages for those combinations, nor any examples describing any actual combinations produced by the inventors. Rather than providing specific guidance regarding dosages for the claimed combinations, the ’186 patent invites those of ordinary skill in the art to turn to the knowledge and resources readily available to them when selecting and formulating appropriate combinations of known drugs. For example, rather than providing specific guidance for the combination dosages, the ’186 patent provides very broad dosage ranges (*see*, e.g., Ex. 1001, col. 4, ll. 48-53), which provide essentially no guidance for selecting actual dosages or treatment regimens. The lack of specific guidance provided in the specification reflects the high level of skill in the art.

38. WO Patent App. Pub. No. 98/19998 to Villhauer (pub’d May 14,1998) (hereinafter “Villhauer,” Ex. 1008) similarly indicates a high level of skill in the art by relying on that skill to select from the many options disclosed in the specification or known to those in the art. *See*, e.g., *id.* at pp. 2-3 (disclosing large and diverse R groups), *id.* at 3, ll. 20-27 (disclosing pharmaceutically acceptable salts and isomers), *id.* at 7, ll. 22 (teaching that “[t]he process of the invention may be effected in conventional manner.”), *id.* at 8, ll. 1-10 (disclosing starting materials known or prepared in known or conventional manner) and *id.* at 20 (disclosing pharmaceutically acceptable carriers, adjuvants and modes of administration, and conventional preparation of same). Villhauer thus reflects the conventional approach in the art to prepare promising variants of lead compounds and compare the results.

39. Claims 13-22 of the ’186 patent recite various combinations of DP-IV inhibitors and additional therapeutic agents (e.g., other antidiabetic agents, anti-obesity agents, lipid-modulating agents, etc.). At multiple instances, the ’186 patent invites those of ordinary skill in the art to select additional agents or mechanisms beyond those disclosed in the specification for use in combination with the claimed DP-IV inhibitors, for example:

> The term “lipid-modulating” agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol **and/or other known mechanisms** for therapeutically treating lipid disorders.

Ex. 1001, col. 4, ll. 43-47 (emphasis added).

> The other antidiabetic agent may also preferably be a sulfonyl urea . . ., **other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β-cells** . . .

Id. at col. 15, ll. 5-11 (emphasis added).

> The squalene synthetase inhibitors suitable for use herein include, but are not limited to, a-phosphono-sulfonates . . . **as well as other known squalene synthetase inhibitors** . . .

Id. at col. 17, ll. 47-52 (emphasis added).

> Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives . . . **and other known serum cholesterol lowering agents**.

Id. at col. 18, ll. 1-20 (emphasis added).

> The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) **or other known beta 3 agonists** . . .

Id. at col. 20, ll. 12-18 (emphasis added). The '186 patent's repeated reliance on knowledge available outside the specification itself reflects the high level of skill in the art.

40. Furthermore, the '186 patent defers in several instances to resources readily available to those of ordinary skill in the art for determining dosages and other treatment parameters for the claimed combinations, including 15 citations to the Physician's Desk Reference (PDR). *See*, e.g., Ex. 1001, col. 15, ll. 60-61; col. 16, ll. 4-5; col. 19, ll. 3 and 35; col. 20, ll. 43, 50, 57, and 67; col. 21, ll. 9, 15, 24, 41, 47, and 54. For example, the '186 patent states that "[t]he amounts and dosages employed will be as indicated in the Physician's Desk Reference . . ." *id.* at col. 19, ll. 2-4. I agree that the PDR is a resource often used in the art for established dosing and treatment regimens for FDA approved drugs.

41. The '186 patent provides a reasonable expectation of success for practicing the claimed invention to the extent it is enabled by the specification. The background section of the '186 patent defines the mechanism by which DP-IV inhibitors treat type 2 diabetes, for example, by providing that "[DP-IV] has been shown to be the primary degrading enzyme of GLP-1(7-36) in vivo . . . [t]hus, inhibition of [DP-IV] in vivo should potentiate endogenous levels of GLP-1(7-36)

and . . . thus serve to ameliorate the diabetic condition." *id.* at col. 1, ll. 59-67. Villhauer provides evidence for what was generally known in the art by teaching that because "GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal, [DP-IV] inhibition . . . represent[s] an attractive approach for treating non-insulin-dependent diabetes mellitus (NIDDM)." Ex. 1008, p. 1. In addition, the '186 patent teaches that the claimed DP-IV inhibitors can be used "for treating diabetes, especially Type II diabetes." Ex. 1001, col. 3, l. 53 – col. 4, l. 1. Given the high level of skill in the art and the advanced knowledge in the art regarding the activity of DP-IV inhibitors, one of ordinary skill in the art would have had a reasonable expectation for treating diabetes to the same extent the claims of the '186 are enabled by the specification.

VII. CLAIM CONSTRUCTION

42. I have been advised that, in the present proceeding, the '186 patent claims are to be given their broadest reasonable interpretation in view of the specification. I also understand that, absent some reason to the contrary, claim terms are typically given their ordinary and accustomed meaning as would have been understood by one of ordinary skill in the art. I have followed these principles in my analysis described throughout this declaration. The '186 patent provides definitions for certain claim terms. In my opinion, those definitions are conventional.

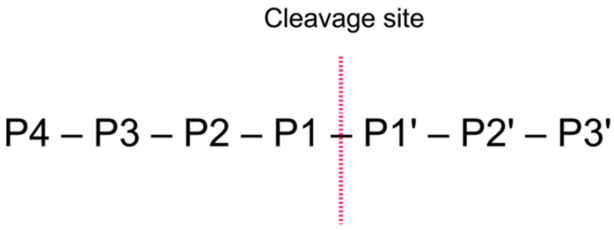
VIII. THE STATE OF THE PRIOR ART

43. Below I describe the details of what was generally known in the art as of March 2000, including: (i) the structure and activity of known DP-IV inhibitors;

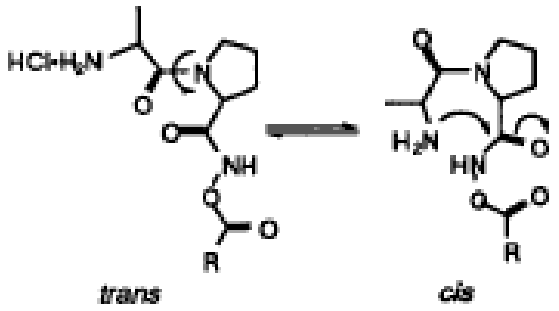
(ii) principles for improving a compound's drug-likeness and suitability as an orally bioavailable drug and (iii) standard strategies for assessing and modulating compound potency.

44. As set forth above, the Background section of the '186 patent discloses that "inhibitors of dipeptidyl peptidase IV [(DP-IV) are known to] . . . treat[ ] diabetes, especially Type II diabetes." Ex. 1001 col. 1, ll. 19-21. The Background of the '186 patent also describes what was well known about the mechanism by which DP-IV inhibitors treat type 2 diabetes: "[DP-IV] has been shown to be the primary degrading enzyme of GLP-1(7-36) in vivo . . . [t]hus, inhibition of [DP-IV] in vivo should potentiate endogenous levels of GLP-1(7-36) and . . . thus serve to ameliorate the diabetic condition." *Id.* at col. 1, ll. 59-67.

45. Lin describes what was well known in the art in March 2000 regarding the substrate structural elements required by DP-IV. Jian Lin et al., *Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics*, 95 PROC. NATL. ACAD. SCI. USA 14020 (1998) at 14020 (hereinafter "Lin," Ex. 1015). For example, Lin reports that "[DP-IV] substrates require the presence of a proline at the P_1 position as well as a protonated free N terminus." *Id.* The P_1, etc. positions are depicted schematically below:



46. Lin also describes what was generally known in the art in March 2000 regarding DP-IV's preferred substrate and inhibitor conformations. For example, Lin reports that "[DP-IV] possesses a high conformational specificity for a trans amide bond between the P_1 and N-terminal P_2 residues." Ex. 1015 at 14020. Where the P_1 residue is the C-terminal residue and the P_2 residue is the N-terminal residue (*see* schematic above for P_1 and P_2 position designations). The trans and cis conformations of the Lin prolyl dipeptides are depicted below:



47. *Id*., p. 14022. Lin addresses the importance of the trans conformation for compound stability and its effect on DP-IV inhibition as follows:

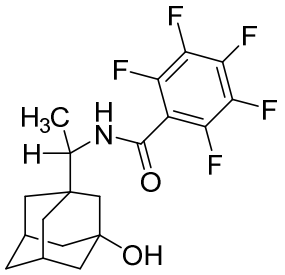
> Many of the problems associated with inefficient inactivation of [DP-IV] are a consequence of the **importance of the trans conformation** of the P_1-P_2 amide bond and the requirement for a protonated free N terminus. **The cyclization reaction of the free N-terminal amino group with the reactive inhibitor . . . require[s] the molecule assume the cis conformation**.

Id., at 14020-14021. Lin reports K_i values of 14,000 nM for a dipeptide in the cis conformation and 188 nM for a dipeptide of otherwise identical structure in the

trans conformation. Comparison of these K_i values for DP-IV inhibition reveals the significantly greater potency of, and preference for, inhibitors in the trans conformation. *See*, e.g., *id.* at 14023 and Table 2.

48. Lin also describes what was well known in the art in March 2000 regarding the effect of conformation on dipeptide stability. Specifically, Lin describes "the cyclization reaction of the free N-terminal amino acid group with the reactive site of the inhibitor" for related dipeptide compounds (*id.* at 14020-14021), which negatively impacts compound stability. Lin also observed that intramolecular cyclization was minimized by selecting the trans instead of cis conformation. *Id.* Thus from these teachings, a person of ordinary skill in the art would have understood that intramolecular cyclization could be reduced by both selecting against a conformation that favors intramolecular cyclization (i.e., the cis conformation) and through the addition of a large, steric group to the compound, which would also limit the interaction between the free N-terminal amine and the reactive inhibitor.

49. Howared E. Hoffman et al., *Pharmacokinetics and Metabolism of Rimantadine Hydrochloride in Mice and Dogs*, 32(11) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 1699 (1988) (hereinafter "Hoffman," Ex. 1016), describes the use of a large, steric adamantyl group in the antiviral drug, rimantadine. As described by Hoffman, the adamantyl moiety was known to be metabolized to a hydroxylated derivative at the 3-position as shown below:



3-hydroxy rimantidine

Hoffman thus serves as further basis that adamantane was generally known in the art to undergo metabolism to yield a 3-hydroxylated adamantyl group.

50. Lipinski (Ex. 1017), Hansch (Ex. 1018), Cates (Ex. 1019) and other references available to one of ordinary skill in the art describe well-known guidelines and strategies for enhancing the drug-like properties of a compound, such as by reducing a compound's partition coefficient, and thus potentially increasing its solubility in aqueous solution. The partition coefficient (P) is a ratio of concentrations of un-ionized compound between two liquid phases, and Log P is a measure of a compound's lipophilicity. For example, addition of a hydroxyl group at the 3-position of an adamantyl moiety would improve the Lipinski parameters, such as reducing Log P and improving permeability as discussed below.

51. According to Christopher A. Lipinski et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*, 23 ADV. DRUG DELIV. REV. 3 (1996) (hereinafter "Lipinski," Ex. 1017), the use of hydroxyl groups on drugs increases their water solubility. *See*, e.g., *id.* at 17. Also according to Lipinski, adding a hydroxyl group to a lipophilic group should also reduce the compound's Log P and

thus improve its solubility. *See*, e.g., *id.* at 8 and 15. These positions are consistent with the knowledge generally available in the art, as evidenced by at least by the Lipinski, Hansch or Cates disclosures.

52. Hansch et al., *Cluster Analysis and the Design of Congener Sets, in* SUBSTITUENT CONSTANTS FOR CORRELATION ANALYSIS IN CHEMISTRY AND BIOLOGY 48 (John Wiley & Sons1979) (hereinafter "Hansch," Ex. 1018), describes a process of drug design, in particular molecular modification. *Id.* at 48-49. Hansch describes well-characterized Log P fragment values (Fr) for aliphatic substituents (e.g., hydroxyl = -1.64). *Id.*, p. 52. Thus according to Hansch, hydroxyl groups have the effect of lowering Log P when added as a compound substituent.

53. Cates, "Calculation of Drug Solubilities by Pharmacy Students," *American Journal Of Pharmaceutical Education*, 45, pp. 11-13 (hereinafter "Cates," Ex. 1019), 1981describes a process of approximating whether or not a drug is soluble in water and how modifications to such a drug will affect the solubility of the drug. *See*, e.g., *id.* at 11-12. Cates discloses, "[t]his procedure involves correlation of partition coefficient values using the octanol/water system and aqueous solubility." *Id.*, Abstract. Referring to partition coefficients based on the octanol/water system expressed as log P, Cates discloses, "[a]lthough this is a measure of the solubility characteristics of the whole molecule, one normally uses the sum of the fragments of the molecule which have been assigned relative hydrophilic-lipophilic values, (π), to calculate log P. Using this procedure, a positive value for π means the substituent, relative to H, favors the octanol phase (i.e., lipophilic). And negative π value indicates its greater affinity for water (*i.e.*,

hydrophilic)." *Id.*, p. 11. Cates also discloses a number of π values that can be used for calculations involving whole molecules, and thus to calculate an approximate log P, which will be indicative of relative solubility. Thus, Cates discloses a method of approximating solubilities, and in particular teaches that addition of hydrophilic substituents increases the solubility of a drug in water.Furthermore, in March 2000, it was also known that an understanding of candidate drug metabolites "can guide structural modifications, thereby improving the activity and/or bioavailability." *See* Walter A. Korfmacher et al., *HPLC-API/MS/MS: a powerful tool for integrating drug metabolism into the drug discovery process*, 2 DRug Disc. Today 532 (1997) (hereinafter "Korfmacher," Ex. 1020). 3-Hydroxy adamantane is a known metabolite of adamantane. Further, Korfmacher teaches the following advantages of metabolite identification:

> Metabolite identification in drug discovery provides early information that can lead to structural changes in the current lead compound, improving such pharmacokinetic parameters as oral bioavailability, half-life ($t_{1/2}$), or C_{max}. Often these parameters can be changed by improving the metabolic stability of the compound. In order to improve metabolic stability, it is very important to know how a compound is metabolized. The goal of drug discovery is to progress a lead compound into a final candidate drug that can be placed in the development stage. . . **Early metabolite identification can provide information on how to improve the metabolic stability of the lead structure. In this way, future lead compounds might be a metabolite identified from the previous lead drug or an analog of the previous drug designed to block the major route of metabolism**.

Id., at 534 (emphasis added). Thus according to Korfmacher, one of ordinary skill in the art would have been motivated to make and test a known metabolite when optimizing a lead.

54. As discussed above, the significance of dipeptide conformation on the effective interaction between DP-IV and its substrates and inhibitors was well understood in the art. For example, Lin reported that "[DP-IV] possesses a high conformational specificity for a trans amide bond" and noted "the importance of the trans conformation." Ex. 1015, p. 14020. As would have been understood by one of ordinary skill in the art, the orientation of certain functional groups in the DP-IV inhibitor would be distinct for the cis and trans conformations. *Id.* at 14020-14021.

55. The standard strategy in March 2000 for modulating the orientation of a ring-bound substituent by one of ordinary skill in the art would have been through fusion of the substituent-bearing ring with another ring. *See*, e.g., Ex. 1021, p. 243. Fusion between two rings can result in significant changes in ring flexibility, including ring flattening. *Id.* These changes in turn would have been expected by one of ordinary skill in the art to affect the orientation of ring-bound substituents. *Id.* The smallest ring that can be used for fusion is a cyclopropyl ring. *Id.*

56. Cyclopropyl is one of the most commonly used ring fusion agents because: (i) addition of a cyclopropyl ring has a negligible effect on compound molecular weight, which is an important contributor to better drug-like qualities

(*see*, e.g., *id.* at 243); (ii) cyclopropyl has an exceedingly small footprint, meaning it adds a minimal steric effect on the rest of the compound to which it is attached (*see*, e.g., *id.* at 243) and (iii) cyclopropyl provides greater conformational restriction than larger ring fusions, resulting in fewer conformations (*see*, e.g., *id.* at 243).

57. C. Y. Chiou et al., *The Cholinergic Effects and Rates of Hydrolysis of Conformationally Rigid Analogs of Acetylcholine*, 166 *J. Pharm. Exp. Ther*. 243 (1969), 243 (hereinafter "Chiou," Ex. 1021) explored the fusion of a cyclopropyl ring onto acetylcholine (ACh) in order to produce a compound that was "1) structurally as close to ACh as possible and 2) conformationally as rigid as possible." According to Chiou, cyclopropyl rings "are considered the smallest chemical structure . . . capable of conferring conformational rigidity." *Id.* at 243.

58. As would have been well appreciated by one of ordinary skill in the art in March 2000, an enzyme and its respective substrates and inhibitors typically fit together in a manner analogous to a hand in a glove. *See*, e.g., Ex. #, p. 2377 (Koshland). Closer degrees of matching often result in greater affinity (with respect to a substrate) or greater inhibition (with respect to an inhibitor). *See*, e.g. *Id.* at 2376. Thus inhibitor conformation and functional group orientation are important to effective interactions between enzymes and their inhibitors. *See*, e.g., *Id*. Like other enzymes, DP-IV inhibition would have been expected to be improved when the active site and inhibitor fit closely.

IX. PRIOR ART REFERENCES DISCLOSE OR SUGGEST EACH OF THE CLAIMED FEATURES OF THE '186 PATENT

59. As set forth in detail below, each element of claims 8, 9, 25, and 26 is taught in the combination of Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009) and Hanessian (Ex. 1010) and one of ordinary skill in the art would have been motivated to combine these teachings by March 10, 2000, as set forth below.

A. Brief Overview of the Prior Art References

60. I have reviewed several references that I believe teach or suggest the compounds, pharmaceutical compositions, pharmaceutical combinations, and methods recited in claims 8, 9, 25, and 26 of the '186 patent. By the virtue of their publication dates, I understand that these references, described in more detail below, are considered prior art relative to the '186 patent.

Doreen M. Ashworth et al., *2-cyanopyrrolidides as potent, stable inhibitors of dipeptidyl peptidase IV*, 6 BIOORG. & MED. CHEM. LTRS. 1163 (1996) (hereinafter "Ashworth," Ex. 1007)

61. Ashworth shows a publication date of May 21, 1996. Ex. 1007. I understand that Ashworth can be applied in assessing the validity of the '186 patent claims.

62. Ashworth discloses a series of stable, potent inhibitors of dipeptidyl peptidase IV (DP-IV), which incorporate a 2-cyanopyrrolidide moiety into the structure of the inhibitor. Ashworth describes DP-IV inhibitors as having the following activity:

> [DP-IV] is a serine protease which catalyses the cleavage of dipeptides from the N-terminus of proteins with the sequence H-X-Pro-Y or H-X-Ala-Y (where X, Y= any amino acid, Y ≠ Pro).

Id. at 1163.

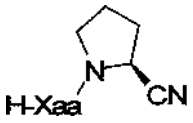
63. DP-IV inhibitors were known to be useful for the treatment of conditions such as type 2 diabetes. *See*, e.g., Villhauer, Ex. 1008, Abstract, discussed in more detail below.

64. DP-IV inhibitors are typically graded according to their stability and potency. *See*, e.g., Ex. 1007, Table II. Overall stability is a sum of chemical and metabolic stability, both of which ultimately impact the quantity of active inhibitor available for interaction with an enzyme target. *See*, e.g., E.J. Ariëns & A. M. Simonis, *Optimalization of Pharmacokinetics – An Essential Aspect of Drug Development – by Metabolic Stabilization*, *Pharmacochem. Lib.*, *in* 4 PHARMACOCHEM. LIB. 165 (1982), 173-178 (hereinafter "Ariens," Ex. 1023). Inhibitor stability is generally measured in terms of an inhibitor's half-life ($t_{1/2}$), with longer half-lives representing greater stability. *See*, e.g., R. Scott Obach, *Prediction of Human Clearance of Twenty-nine Drugs from Hepatic Microsomal Intrinsic Clearance Data: An Examination of In Vitro Half-life Approach and Nonspecific Binding to Microsomes*, 27 DRUG METAB. DISPOS. 1350 (1999), 1354-1355 (hereinafter "Obach," Ex. 1024). Potency reflects the degree to which an inhibitor acts on its target. Inhibitor potency is generally measured in terms of its dissociation constant (K_i) or using an IC_{50} concentration (i.e., a concentration of a potential inhibitor at which enzyme activity is reduced by 50% from control),

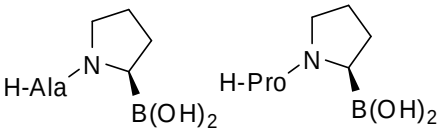
which represents the propensity of dissociation between an inhibitor and its target, with smaller K_i or IC_{50} values representing greater potency. Yung-chi Cheng & William H. Prusoff, *Relationship Between the Inhibition Constant (K_I) and the Concentration of Inhibitor which Causes 50 Per Cent Inhibition (I_{50}) of an Enzymatic Reaction*, 22 Biochem. Pharmacol. 3099 (1973), 3099 (hereinafter "Cheng," Ex. 1025).

65. Some of the compounds described in Ashworth have K_i values of less than 5 nM versus human DP-IV and chemical stability half-lives of greater than 48 hours in aqueous solution at pH 7.4. Ex. 1007, p. 1163. Thus some of the compounds of Ashworth have both high potency and high stability, making them desirable drug candidates and leads.

66. Ashworth discloses 29 compounds, six of which contain the 2-cyanopyrrolidide moiety, as follows:



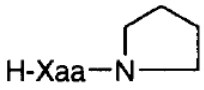
where Xaa represents various amino acid substituents as specified in Table II. *Id.* at 1166. Ashworth discloses that the most potent DP-IV inhibitors previously known were the boroproline analogues **1**, and **2**,



1 **2**

which had K_i values of 2 nM and 3 nM respectively. *Id.* at 1163. Ashworth concludes that the 2-cyanopyrrolidide analogues "possessed activity comparable to the boroprolines, 1 and 2." *Id.* at 1165. In addition, Ashworth teaches that the 2-cyanopyrrolidide analogues exhibited "superior stability in aqueous solution" relative to boroprolines **1** and **2**. *Id*. at 1164.

67. Ashworth discloses the DP-IV inhibition activity of 19 aminoacyl pyrrolidides (lacking the 2-cyano moiety) in Table I:



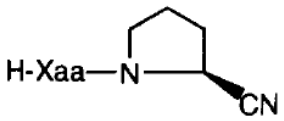
Compound N°	Xaa	K_i (μM)[13]
5	Cyclohexylglycine [Chg]	0.064 ± 0.01
6	(R,S)-Cyclopentylglycine [Cpg]	0.21 ± 0.04
7	Ile	0.41 ± 0.01
8	*allo*-Ile	0.44 ± 0.04
9	Val	0.47 ± 0.02
10	Lys(Cbz)	0.52 ± 0.07
11	tert-Butylglycine [Tbg]	0.88 ± 0.20
12	Thr(Me)	0.90 ± 0.15
13	Orn(Cbz)	0.91 ± 0.20
14	2-Aminohexanoic acid [Aha]	1.20 ± 0.20
15	Glu	2.00 ± 0.40
16	Pro	2.10 ± 0.20
17	Cyclohexylalanine [Cha]	2.15 ± 0.50
18	Glu(OBn)	2.70 ± 0.30
19	Thr	4.90 ± 0.90
20	Phenylglycine [Phg]	5.30 ± 0.10
21	Ser(Bn)	6.00 ± 1.50
22	Ala	7.00 ± 1.00
23	Asp	14.50 ± 1.90

Id. at 1164.

The compounds of Table I exhibit inhibition activity in the 0.064 μM to 14.50 μM range. Ashworth notes that the most active of these compounds was compound **5**,

"[i]n particular, β-branched α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino acid, **(S)-cyclohexylglycine providing the most active pyrrolidide** (compound **5** possessing a K_i value of 64 nM)." *Id.*, at 1165 (emphasis added).

68. By comparison, Table II of Ashworth discloses the DP-IV inhibition activity of six analogues having the 2-cyano moiety:



Compound N°	Xaa	K_i (nM)[13]	$t_{½}$ (h)[19]
24	Cpg	1.1 ± 0.2	48
25	Chg	1.4 ± 0.5	>48
26	Ile	2.2 ± 0.5	48
27	Tbg	3.8 ± 0.8	>48
28	Lys(Z)	5.2 ± 1.0	24
29	Pro	22.0 ± 4.0	7.5

Id. at 1166. The compounds of Table II (having a 2-cyanopyrrolidide moiety) exhibit inhibition activity in the 1.1 nM to 22 nM range, which in some cases equates to a 50-fold increase in inhibition activity relative to compounds **5** and **25**, which lack the 2-cyano moiety.

69. Ashworth teaches that, "[s]ubstrates and inhibitors of DP-IV require a free N-terminus, which means that potential dipeptide serine protease inhibitors (e.g., C-terminal aldehydes, boronic acids, a-ketoacids, trifluoromethylketones, or chloromethylketones) are inherently unstable at neutral pH due to intramolecular cyclisation." *Id.* at 1163.

70. Table II of Ashworth shows the chemical stability data of DP-IV

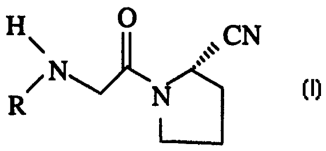
inhibitors in aqueous solution (pH of 7.4), as measured in half-life ($t_{1/2}$). *Id.* at 1166. When changing the substituent at the 2-position of the acetyl-pyrrolidine-2-carbonitrile from a straight chain alkyl moiety, for example compound **28** (lysine moiety), to a moiety having at least one branch at the α-carbon, such as the cyclohexyl moiety in Ashworth compound **25**, the stability dramatically increases from 24 hours to greater than 48 hours. *Id.* at 1166. Ashworth discloses that substitution at this position improves the potency of an aminoacyl pyrrolidide compound as shown in Table 1 of Ashworth. *Id.* at 1163 and 1166 (compare Tables I and II).

71. Specifically, compound **5** (having a cyclohexyl group) of Table I shows at least a 100-fold increase in potency compared to compound **7** (having a 1-methyl propyl group) or compound **9** (having an isopropyl group). Ashworth confirms this observation by noting, "[a]s expected, from the substrate specificity of DP-IV, only (S)-amino acid derivatives showed any activity and, as can be seen in Table I, lipophilic amino acids gave more potent compounds. In particular, β-branched α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino acid, (S)-cyclohexylglycine providing the most active pyrrolidide (compound **5** possessing a K_i value of 64 nM)." *Id.* at 1165.

WO Patent App. Pub. No. 98/19998 to Villhauer (pub'd May 14,1998) (hereinafter "Villhauer," Ex. 1008)

72. Villhauer was published May 14, 1998. Ex. 1008. I understand that Villhauer can be applied in assessing the validity of the '186 patent claims.

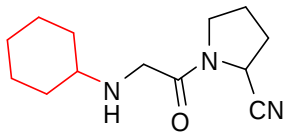
73. Villhauer discloses numerous DP-IV serine protease inhibitor compounds. The dipeptide compounds of Villhauer are N-(N'-substituted glycyl)-2-cyanopyrrolidines having the following structure of formula (I):



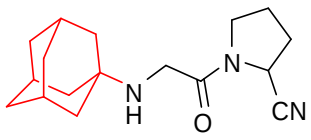
(I)

Id. at abstract.

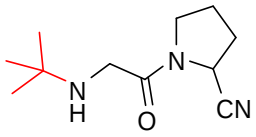
74. Villhauer discloses various substituents at position "R" of formula (I) above. For example, Villhauer discloses compounds having cycloalkyl groups attached to the amino moiety of 2-cyano pyrrolidides, including a cyclohexyl group:



(*id.* at 12, Example No. 28); adamantyl groups attached to the amino moiety of 2-cyano pyrrolidines:



(*id.* at 13, Example No. 47); and alkyl groups attached to the amino moiety of 2-cyano pyrrolidides:



(*id.* at 13,Example No. 52). Villhauer also teaches how the compounds shown directly above were prepared. *See*, e.g., *id.* at 8-10.

75. Villhauer discloses the use of DP-IV inhibitors, such as N-(N'-substituted glycyl)-2-cyanopyrrolidines, for "the treatment of conditions mediated by DPP-IV, such as non-insulin-dependent diabetes melitus." *Id.* at Abstract. As disclosed in Villhauer, "DPP-IV is responsible for inactivating glucagon-like peptide-1 (GLP-1) . . . [and] [s]ince GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal, DPP-IV inhibition [is] an attractive approach for treating non-insulin-dependent diabetes mellitus (NIDDM)." *Id.* at 1, ll. 6-13.

76. Villhauer discloses that the DP-IV inhibitor compound may be in free form or in acid addition salt form, where the salt could be from any pharmaceutically acceptable acid, with hydrochloride as a preferred option. *Id.* at 3. Similarly, Villhauer discloses that any pharmaceutically acceptable carriers, adjuvants and enteral or parenteral administration forms (prepared by conventional means) could be used with any of the disclosed agents of the invention. *Id.* at 20.

77. Villhauer further discloses the use of DP-IV inhibitors, such as N-(N'-substituted glycyl)-2-cyanopyrrolidines, for "use in **treating conditions mediated by DPP-IV** [such as] **non-insulin-dependent diabetes mellitus** . . . [and] **obesity** . . ." *Id.* at 18, ll. 18-21 (emphasis in original).

Reetta Raag & Thomas L. Poulos, *Crystal Structure of Cytochrome P-450$_{CAM}$ Complexed with Camphane, Thiocamphor, and Adamantane: Factors Controlling P-450 Substrate Hydroxylation*, 30 BIOCHEMISTRY 2674 (1991) (hereinafter "Raag," Ex. 1009)

78. Raag shows a publication date of March 1, 1991. Ex. 1009. I understand that Raag can be applied in assessing the validity of the '186 patent claims.

79. Raag describes a study of the metabolism of adamantane by cytochrome P-450$_{cAm}$ and corresponding X-ray crystal structures for complexes of cytochrome P450$_{cAm}$ with adamantane as the substrate. Raag describes the hydroxylation of adamantane, as well as other substrates. Table III from Raag, presented below, shows the various molecules that underwent hydroxylation, where the adamantane group is shown in the third column:

Table III: Various Substrate-Dependent Parameters[a]

	 camphor	 adamantanone	 adamantane	 thiocamphor	 camphor/Y96F	 norcamphor	 camphane
molec vol	315 Å^3	300 Å^3	293 Å^3	322 Å^3	315 Å^3	236 Å^3	309 Å^3
hydrogen bond to Y96	yes[a]	yes[b]	no	no	no	yes[b]	no
no. of iron ligands	5[a]	5[b]	6	6		6[b]	6
redox pot. Fe^{3+}/Fe^{2+}	−170 mV[c]	−175 mV[c]				−206 mV[c]	
high-spin %	94–97%[c–e]	96–98%[c,d]	99%[d]	65%[e]	59%[e]	46%[c]	46%[e]
regiospecif of substr hydroxylatn	5-exo (100%)[d–f]	5 (100%)[d]	1 (100%)[d]	5-exo (64%)[e] 6-exo (34%) 3-exo (2%)	5-exo (92%)[e,f] 4 (1%) 6-exo (2–4%) 3-exo (0–4%) 9 (<1%)	5-exo (45%)[f] 6-exo (47%) 3-exo (8%)	5-exo (90%)[e] 6-exo (10%)
substr temp factor (Fe^{3+})	16.2 Å^2[a]	16.5 Å^2[b]	24.7 Å^2	23.5 Å^2		33.5 Å^2[b]	30.1 Å^2
substr hydrophilic groups	yes	yes	no	yes	yes	yes	no
hydroxylatn "efficiency"	100%[e,f]			98%[e]	100%[e]	12%[f]	8%[e]
L6–substr dist	NA	NA	2.63 Å	2.35 Å (70%) 3.35 Å (30%)		3.0 Å[b]	2.88 Å
L6–iron dist	NA	NA	1.95 Å	1.35 Å		1.73 Å[b]	1.67 Å
L6 occupancy	NA	NA	1.00	0.90		0.97[b]	1.00
L6 temp factor	NA	NA	14.3 Å^2	19.6 Å^2		3.8 Å^2[b]	7.7 Å^2
cation occupancy	1.00[a]	1.00[b]	0.89	0.91		1.00[b]	0.72
cation temp factor	12.1 Å^2[a]	10.0 Å^2[b]	15.5 Å^2	14.2 Å^2		7.9 Å^2[b]	21.7 Å^2

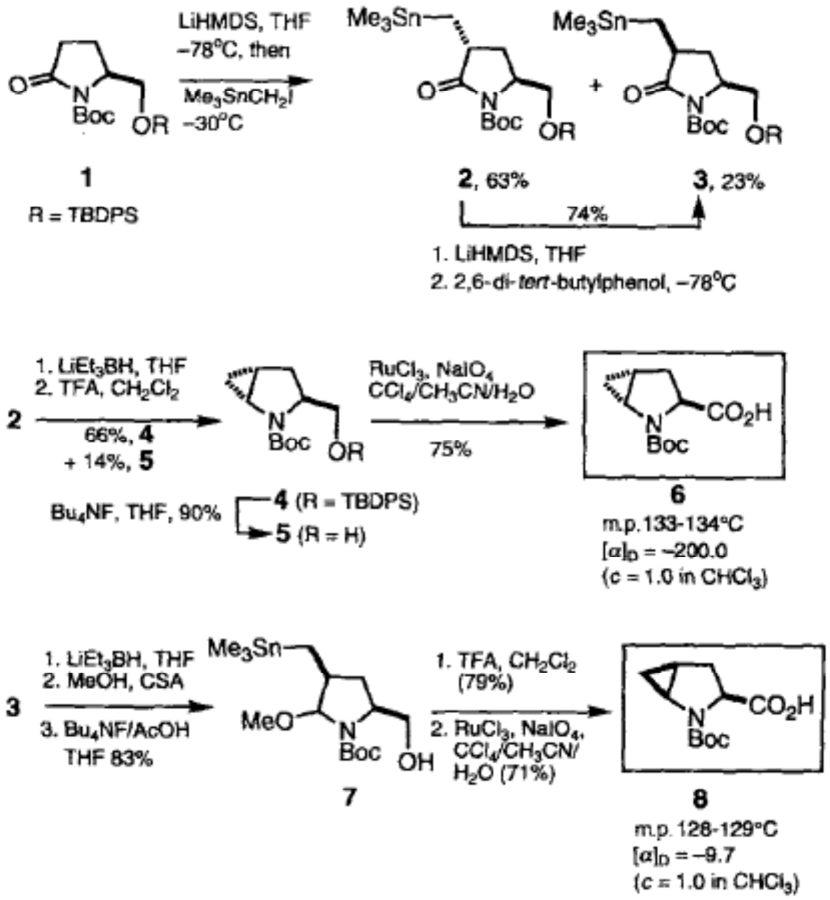
[a] Poulos et al. (1985, 1987). [b] Raag and Poulos (1989a). [c] Fisher and Sligar (1985). [d] White et al. (1984). [e] Atkins and Sligar (1988b). [f] Atkins and Sligar (1989). [g] Carbon numbering for each substrate begins with C-1 at the top of the six-membered ring which is in the plane of the table. Numbering proceeds counterclockwise such that the carbonyl carbon is C-2 and C-5 is in the lower right-hand portion of the ring. Note that C-5 is a secondary carbon in some substances and a tertiary carbon in others.

80. Raag, Table III, shows that substrates that undergo regiospecific hydroxylation of adamantane by cytochrome P450 (a xenobiotic metabolizing enzyme). Hydroxylation occurs at the a specific position, i.e., at a tertiary carbon site (and not the secondary carbon site). Raag also teaches that "[a]damantane is . . . metabolized to a single product despite having a relatively high active site mobility. The single product can be attributed to the existence of only two types of unique carbon atoms in adamantane, together with the greater reactivity of tertiary versus secondary carbons." *Id.* at 2678.

Stephen Hanessian et al., ***The Synthesis of Enantiopure ω-Methanoprolines and ω-Methanopipecolic Acids by a Novel Cyclopropanation Reaction: The "Flattening" of Proline,*** **36 ANGEW. CHEM. ED. ENGL. 1881 (1997) (hereinafter "Hanessian," Ex. 1010)**

81. Hanessian shows a publication date of September 17, 1997. Ex. 1010. I understand that Hanessian can be applied in assessing the validity of the '186 patent claims.

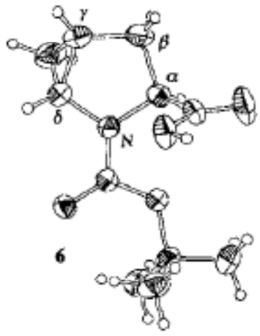
82. Hanessian describes the synthesis of enantiopure ω-methanoproline acids by a cyclopropanation reaction. Hanessian teaches that the use of conformationally constrained analogues of proline were well known in the peptidomimetic research area at the time the application which led to the '186 patent was filed. Hanessian describes the "highly stereocontrolled syntheses of the diastereomeric 4,5-methano-L-prolines and 5,6-methano-L-pipecolic acids by a novel intramolecular cyclopropanation reaction of iminium ions . . . ." *Id.* at 1882. One such example shown by Hanessian is compound **8** which was synthesized according to Scheme 1 below:



Id. at 1882.

83. The structure and conformation of compound **8** in the solid state were unambiguously confirmed by single X-ray analysis. Further, Table 1 of Hanessian, as reproduced below, shows selected torsion angles for compound **8** where "considerable 'flattening' of the pyrrolidine ring is observed relative to *N*-Boc-L-proline." *Id.* at 1882. Thus, Hanessian provides evidence for a conformational change resulting from cyclopropane fusion to a substituted pyrrolidine ring.

Table 1. Selected torsion angles and root-mean-square deviations from fitted atoms in a given plane of X-ray crystal structures, and ^{13}C NMR chemical shifts ($CDCl_3$).



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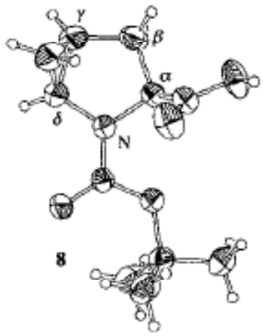


8

	N-Boc-L-proline [20]	**6**	**8**
$\tau(NC_\alpha)$	−17	−5.6	−14.4
$\tau(C_\alpha C_\beta)$	+31	+4.8	+15.3
$\tau(C_\beta C_\gamma)$	−35	−2.6	−11.4
$\tau(C_\gamma C_\delta)$	+24	−0.7	+2.9
$\tau(C_\delta N)$	−4	+4.1	+7.6
$\tau(BocNC_\alpha CO_2H)$	−72	−64.0	−67.1
rms deviation of fitted atoms	0.018 C_α, N, C_δ, C_γ	0.003 C_β, C_γ, C_δ, N	0.013 C_β, C_γ, C_δ, N
	δ(cis/trans)	*δ(cis/trans)*	*δ(cis/trans)*
COOH	178.35/176.60	177.7/175.5	179.1/176.1
NC=O	153.95/155.39	157.1/154	155.7/154.1
C_α	58.8	60.8/60.1	59.5/59.1
C_β	30.75/29.53	32.0	31.5/29.1

Id. at 1882.

84. Hanessian confirms the "flattening" of the pyrrolidine ring by determining the root-mean-square values for the C_β and N atoms from the plane defined by C_β, C_γ, C_δ and N (*see* Table 1 above). *Id.* Hanessian determined that for compound **8**, the out-of-plane carbon was the carbon bearing the carboxyl group (C_α) when compared to *N*-Boc proline. *Id.* Hanessian thus observed that by flattening the pyrrolidine ring, the orientation of the out-of-plane carbon was modified with respect to the ring.

WO Patent App. Pub. No. 99/38501to Bachovchin et al. (pub'd Aug. 5, 1999) (hereinafter "Bachovchin," Ex. 1011)

85. Bachovchin was published August 5, 1999. Ex. 1011. I understand that Bachovchin can be applied in assessing the validity of the '186 patent claims.

86. Bachovchin discloses improved methods for reducing in animal subjects (including humans) at least one type of insulin resistance, hyperinsulinemia, and Type II diabetes. In particular, Bachovchin describes the use of DP-IV inhibitors in an amount effective to treat, among other indications, Type II diabetes. Claim 4 of Bachovchin recites, "A method for treating Type II diabetes, comprising administering to an animal a composition including one or more inhibitors of dipeptidylpeptidase IV [(DP-IV)]." *Id.* at claim 4. Moreover, various examples of DP-IV inhibitors are listed in Bachovchin. For example, a class of DP-IV inhibitors shown in Bachovchin are compounds based on the dipeptide (D)-Ala-(L)-Ala. Bachovchin also discloses the use of pharmaceutical compositions of DP-IV inhibitors, "another aspect of the present invention relates to pharmaceutical compositions of dipeptidylpeptidase inhibitors, particularly [DP-IV] inhibitors." *Id.* at 7, ll. 29-30. Thus, the use of DP-IV inhibitors for treating type 2 diabetes was well known at least one year before the application which led to the '186 patent was filed.

87. Bachovchin also discloses that "[i]n particular, it is an object of the invention to provide methods for producing long lasting beneficial changes . . . to provide effective treatments for diabetes [and] obesity . . ." *Id.* at 4, ll. 7-11. Bachovchin also discloses "administration of a [DP-IV] inhibitor . . . in an amount effective to improve one or more aberrant indices associated with glucose

metabolism disorders . . . [such as] Type II diabetes . . . [and] obesity." *Id.* at 6, ll. 16-22.

88. Furthermore, the use of DP-IV inhibitors in combination therapy with various antidiabetic agents other than a DP-IV inhibitor for treating type 2 diabetes is also described extensively in Bachovchin:

> The [DP-IV] inhibitors used according to the invention can also be used conjointly with agents acting on the ATP-dependent potassium channel of the β-cells, such as glibenclamide, **glipizide**, **gliclazide** and AG-EE 623 ZW. The DPIV inhibitors may also advantageously be applied in combination with other oral agents such as **metformin** and related compounds or glucosidase inhibitors as, for example, **acarbose**.

Id. at 46 (emphasis added.)

XENICAL Label (available by FOIA Aug. 9, 1999) (hereinafter "the Xenical Label," Ex. 1013)

89. The Xenical Label was published August 9, 1999 after approval of Xenical by the FDA. Ex. 1013. I understand that the Xenical Label can be applied in assessing the validity of the '186 patent claims. .

90. The Xenical Label discloses the FDA-approved uses of the anti-obesity agent, Xenical (i.e., orlistat), and supporting studies. In one such study, patients with type 2 diabetes were treated with Xenical. As indicated in the Xenical Label, "XENICAL is indicated for obesity management . . . in the presence of other risk factors (e.g., . . . diabetes)." *Id.* at 0018. According to the Xenical Label, "epidemiological studies have established a relationship between obesity and

visceral fat and the risks for cardiovascular disease [and] type 2 diabetes." *Id.* at 0013. The Xenical Label also provides dosages for Xenical as follows: "[t]he recommended dose of XENICAL is one 120 mg capsule three times a day." *Id.* at 0024.

MEVACOR Label (available by FOIA Sept. 15, 1994) (hereinafter "the Mevacor Label," Ex. 1014)

91. The Mevacor Label was published September 13, 1994 after approval of Mevacor by the FDA. Ex. 1014. I understand that the Mevacor Label can be applied in assessing the validity of the '186 patent claims.

92. The Mevacor Label discloses the FDA-approved uses of the lipid-modulating agent, Mevacor (i.e., lovastatin), and supporting studies. As indicated in the Mevacor label, "poorly controlled diabetes mellitus" was considered a "secondary cause[ ] for hypercholesterolemia . . ." *Id.* at 0010. The Mevacor Label also provides dosages for Mevacor as follows: "[t]he recommended dosing range is 20-80 mg/day in a single or two divided doses; the maximum recommended dose is 80 mg/day." *Id.* at 0014.

GLUCOPHAGE Label (available by FOIA Jan. 8, 1998) (hereinafter "the Glucophage Label," Ex. 1012)

93. The Glucophage Label was published January 8, 1998 after approval of Glucophage by the FDA. Ex. 1012. I understand that the Glucophage Label can be applied in assessing the validity of the '186 patent claims.

94. The Glucophage Label discloses the FDA-approved uses of the antihyperglycemic agent, Glucophage (i.e., metformin), and supporting studies. The Glucophage label describes a "29-week double-blind, placebo-controlled study

of GLUCOPHAGE and glyburide, alone and in combination . . . in obese patients with type 2 diabetes," (*Id.* at 0017) where glyburide is also an antihyperglycemic agent for use in treating patients with type 2 diabetes. The Glucophage Label also provides dosages for Glucophage as follows: "[i]n general, clinically significant responses are not seen at doses below 1500 mg per day . . . [and] GLUCOPHAGE may be given to a maximum daily dose of 2550 mg per day." *Id.* at 0048.

B. THE PRIOR ART TEACHES AND SUGGESTS EVERY ELEMENT OF CLAIMS 1, 2, 4, 6-22, 25-30, 32-37 AND 39-42 OF THE '186 PATENT

95. As explained in detail below, each and every feature of claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 of the '186 patent can be found in the prior art, specifically in the references identified below, and one of ordinary skill in the art would have been motivated to combine them to arrive at the subject matter of each of the respective claims of the '186 patent.

96. Each of claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 is presented below in bold text followed by my analysis of the claim or claims. The analysis below identifies exemplary disclosure of the cited references with respect to the corresponding claim elements, and is not meant to be exclusive or exhaustive.

97. Where reference is made to additional publications below, those publications are intended to provide additional bases regarding what was generally known in the art in March 2000 and provide factual basis for my statements. Those references are not intended to serve as additional grounds for invalidity.

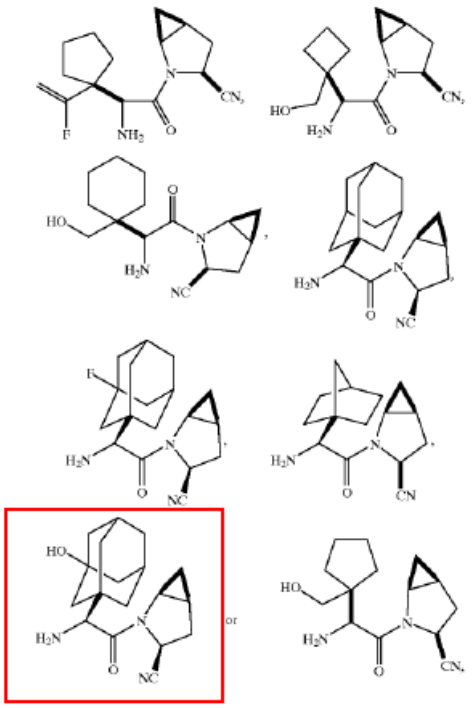
EACH FEATURE OF CLAIMS 1, 2, 4, 6-11, 25-28, 32-35, 39 AND 40 IS DISCLOSED BY ASHWORTH, VILLHAUER, RAAG AND HANESSIAN

98. As discussed above, Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009) and Hanessian (Ex. 1010) can be considered prior art to the '186 patent.

99. Specific compounds recited in claims 8 and 25 of the '186 patent fall within the scope of compound claims 1, 2, 4, 6, 7 and 10 of the '186 patent. Therefore, claims 8 and 25 will be addressed first, followed by claims 1, 2, 4, 6, 7 and 10.

Claim 8:

"A compound having the structure:

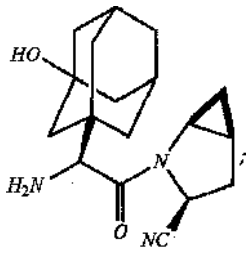


or a pharmaceutically acceptable salt thereof."

The red box outline is provided for illustration purposes and does not appear in the original claim, but the structure shown therein is equivalent to the compound of claim 25.

Claim 25:

"A compound that is

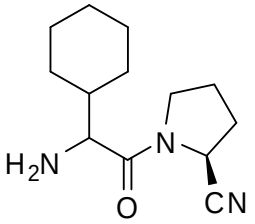


or a pharmaceutically acceptable salt thereof."

100. As will be discussed in greater detail below, the prior art provides specific motivation to select Ashworth compound **25** as a lead compound for further optimization. *See* Ex. 1007. One of ordinary skill in the art would understand that certain core features of Ashworth compound **25** should be retained in the ultimate compound, including the glycyl-proline core, free amine, and cyano components of Ashworth compound **25**. *See* Ex. 1007. As explained below, one of ordinary skill also would have been motivated to adopt the trans orientation of the dipeptide in order to enhance its activity and stability. *See* Ex. 1015. There was also motivation to substitute the cyclohexyl group of Ashworth compound **25** with a hydroxylated adamantyl group in order to improve the compound's chemical and metabolic stability. *See* Ex. 1007 and Ex. 1008. One would have further been motivated to fuse a cyclopropyl ring onto the pyrrolidine ring of Ashworth

compound **25** to improve compound stability and modulate the interaction between the active 2-cyano moiety with the DP-IV enzyme. *See* Ex. 1010. Thus, as evidenced by prior art references (including Ashworth, Villhauer, Raag and Hanessian), claims 8 and 25 of the ’186 patent would be considered obvious to one of ordinary skill in the art in view of the knowledge and motivation provided by the references to the skilled artisan.

101. The prior art provided ample motivation for one of skill in the art to select the Ashworth’s compound **25** as a lead compound to develop a composition as an inhibitor of DP-IV enzyme, as claimed in claims 8 and 25 of the ’186 patent.

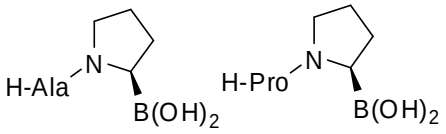


Ashworth Compound **25**

102. Ashworth discloses potent dipeptide analogues incorporating a 2-cyanopyrrolidide moiety useful as inhibitors of dipeptidyl peptidase IV. *See* Ex. 1007, p. 1163 (disclosing, “[a] novel series of stable, potent inhibitors of [DP-IV] has been developed. A number of dipeptide analogues, incorporating a 2-cyanopyrrolidide, were found to have K_i values of less than 5 nM versus human DP-IV and half-lives of >48h in aqueous solution . . . .”). Because Ashworth explicitly discloses the use of the 2-cyanopyrrolidide compounds as inhibitors of DP-IV, a person of skill in the art had express motivation to select the disclosed

compounds with a reasonable expectation of success for developing improved compositions useful as inhibitors of DP-IV.

103. Further, Ashworth provides motivation to select the 2-cyanopyrrolidine analogues. For example, Ashworth teaches that the 2-cyanopyrrolidide analogues "possessed activity comparable to the boroprolines, 1 and 2" which were previously known as the most potent DP-IV inhibitors as shown below:



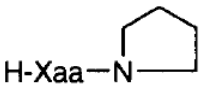
1 **2**

Id. at 1165. The boroprolines **1** and **2** had K_i values of 2 nM and 3 nM respectively. *Id.*, p. 1163. Because the Ashworth reference teaches that 2-cyanopyrrolidide analogues have activity comparable to the boroproline analogues, one of ordinary skill in the art had express motivation to select the 2-cyanopyrrolidide analogues as lead compounds to arrive at the compound in claims 8 and 25 of the '186 patent with a reasonable expectation of success. Furthermore, one of ordinary skill in the art would select the 2-cyanopyrrolidide analogues as lead compounds because they were more synthetically accessible than the boroprolines and metabolic considerations (boronic acid vs. cyano group) would make them more desirable. *Id.*

104. Further, Ashworth provided ample motivation to specifically select compound **25** as a lead from the limited compounds described therein (*see* below,

id. at 1166, Table II) because (i) compound **25** is one of only six 2-cyanopyrrolidide analogues (i.e., dipeptide nitriles) described by Ashworth (*see id.*, Table II, listing only six compounds); and (ii) compound **25** , which contains a 2-cyano moiety, exhibits high potency and excellent stability compared to aminoacyl pyrrolidides lacking the 2-cyano moiety (*id.* at 1164 and 1166, compare Tables I and II).

105. For example, Ashworth discloses the DP-IV inhibition activity of 19 aminoacyl pyrrolidides (lacking the 2-cyano moiety) in Table I:



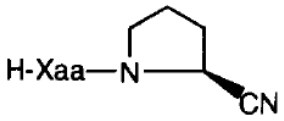
Compound N°	Xaa	K_i (μM)[13]
5	Cyclohexylglycine [Chg]	0.064 ± 0.01
6	(R,S)-Cyclopentylglycine [Cpg]	0.21 ± 0.04
7	Ile	0.41 ± 0.01
8	*allo*-Ile	0.44 ± 0.04
9	Val	0.47 ± 0.02
10	Lys(Cbz)	0.52 ± 0.07
11	tert-Butylglycine [Tbg]	0.88 ± 0.20
12	Thr(Me)	0.90 ± 0.15
13	Orn(Cbz)	0.91 ± 0.20
14	2-Aminohexanoic acid [Aha]	1.20 ± 0.20
15	Glu	2.00 ± 0.40
16	Pro	2.10 ± 0.20
17	Cyclohexylalanine [Cha]	2.15 ± 0.50
18	Glu(OBn)	2.70 ± 0.30
19	Thr	4.90 ± 0.90
20	Phenylglycine [Phg]	5.30 ± 0.10
21	Ser(Bn)	6.00 ± 1.50
22	Ala	7.00 ± 1.00
23	Asp	14.50 ± 1.90

Id. at 1164.

The compounds of Table I (i.e., dipeptides lacking the 2-cyano moiety) have

inhibition activity in the 0.064 µM to 14.50 µM range. Ashworth notes that the most active of these compounds was compound **5,** "[i]n particular, β-branched α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino acid, **(S)-cyclohexylglycine providing the most active pyrrolidide** (compound **5** possessing a K_i value of 64 nM)." *Id.* at 1165 (emphasis added).

106. In comparison, Table II of Ashworth discloses the DP-IV inhibition activity of six analogues having the 2-cyano moiety:



Compound N°	Xaa	K_i (nM)[13]	$t_{½}$ (h)[19]
24	Cpg	1.1 ± 0.2	48
25	Chg	1.4 ± 0.5	>48
26	Ile	2.2 ± 0.5	48
27	Tbg	3.8 ± 0.8	>48
28	Lys(Z)	5.2 ± 1.0	24
29	Pro	22.0 ± 4.0	7.5

Id. at 1166. The six compounds of Table II (all having a 2-cyanopyrrolidide moiety) have inhibition activity in the 1.1 nM to 22 nM range, which in some cases equates to a 50-fold increase in inhibition activity over the same compounds lacking the 2-cyano moiety. *Id.* at 1164 and 1166. For example, compound **5** has a K_i value of 0.064 µM, which decreases to 1.4 nM in compound **25** solely through the addition of a 2-cyano moiety. This decrease in inhibition activity represents significantly greater DP-IV inhibition potency for compound **25** relative to compound **5**. This illustrates the beneficial effect on potency of the cyano moiety

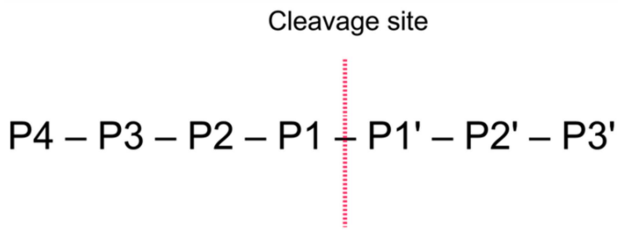
in DP-IV inhibitors.

107. Taken as a whole, the Ashworth reference contains ample and explicit motivation for one of skill in the art to select compound **25** as a lead for designing DP-IV inhibitors such as the compounds recited in claims 8 and 25 of the '186 patent. As evidenced by Ashworth, the inventors of the '186 patent were not the first to recognize the use of this core structure in designing DP-IV inhibitor compounds.

108. One of ordinary skill in the art would have been motivated to retain certain structural elements of Ashworth compound **25** when optimizing it toward the ultimate compound. For example, by March 2000, it was well known in the art that proline dipeptides and mimetics were therapeutically useful for a variety of purposes, including DP-IV inhibition. *See*, e.g., Ex. 1007. Early work with pyrrolidinyl dipeptides revealed high inhibitor potency when coupling a pyrrolidine-containing amino acid with cyclohexylglycine. Ex. 1008 at 1165. Villhauer also identified dipeptide glycyl-cyanopyrrolidines as inhibitors of DP-IV. *See, id.* at Abstract. Therefore, one of ordinary skill in the art would have been motivated to retain the dipeptide structure of Ashworth compound **25**.

109. One of ordinary skill in the art would have been motivated to retain the P_1 proline, free amine, and 2-cyano moieties of the Ashworth compound **25** based on the knowledge generally available in the art. For example, Ashworth states that "[s]ubstrates and inhibitors of DP-IV require a free N-terminus" (Ex. 1007, p. 1163) and describes superior potency with the 2-cyano moiety versus without it (*id.*, 1164 and 1166, compare Tables I and II). Lin provides additional

basis for retaining these elements by reporting that "[DP- IV] substrates require the presence of a proline at the P_1 position as well as a protonated free N terminus." Ex. 1015 at 14020. The P_1, etc. positions are depicted schematically below:



Thus one of ordinary skill in the art would have been motivated to retain the free amine and 2-cyano moieties in the lead compound and would have had a reasonable expectation of success that the ultimate compound having these features would be an active DP-IV inhibitor.

110. One of ordinary skill in the art would have been motivated to select the trans conformation when optimizing Ashworth compound **25**. It was well known in the art in March 2000 that DP-IV has selectivity for substrates and inhibitors in the trans conformation relative to the cis conformation. Lin represents what was generally known in the art in March 2000 regarding DP-IV's preferred substrate and inhibitor conformations. Lin reports that "[DP-IV] possesses a high conformational specificity for a trans amide bond between the P_1 and N-terminal P_2 residues." Ex. 1015 at 14020. Lin reports K_i values of 14,000 nM for dipeptides in the cis conformation and 188 nM for otherwise structurally identical dipeptides in the trans conformation. Comparison of these K_i values for DP-IV inhibition reveals the significantly greater potency of, and preference for, inhibitors in the trans conformation. *See,* e.g., *id.* at 14023 and Table 2.

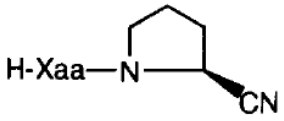
111. One of ordinary skill in the art would have been motivated to limit intramolecular cyclization when optimizing Ashworth compound **25**. It was generally understood in the art that intramolecular cyclization was a source of dipeptide instability in DP-IV inhibitors. For example, Ashworth teaches that, "[s]ubstrates and inhibitors of DP-IV require a free N-terminus, which means that potential dipeptide serine protease inhibitors (e.g., C-terminal aldehydes, boronic acids, a-ketoacids, trifluoromethylketones, or chloromethylketones) are inherently unstable at neutral pH due to intramolecular cyclisation." Ex. 1007 at 1163. As further basis for what was known in the art, Lin describes "the cyclization reaction of the free N-terminal amino acid group with the reactive site of the inhibitor" for related dipeptide compounds (Ex. 1015, pp. 14020-14021), which negatively impacts compound stability. Lin further teaches that "[t]he cyclization reaction of the free N-terminal amino group with the reactive inhibitor . . . require[s] the molecule assume the cis conformation. *Id.* at 14020-14021.

112. One of ordinary skill would have understood that intramolecular cyclization could be reduced by both selecting against a conformation that favors intramolecular cyclization (i.e., selecting against the cis conformation) and through the addition of a large, steric group to the compound. *See*, e.g., Debnath Pal & Pinak Chakrabarti, *Cis Peptide Bonds in Proteins: Residues Involved, their Conformations, Interactions and Location*, 294 J. of Mol. Biol. 271 (1999), 274 (hereafter "Pal," Ex. 1026). Selection of the trans conformation advantageously places the reactive cyano and amine groups farther from each other, thereby limiting intramolecular cyclization. Adding a steric group to the compound would

be expected to restrict its range of motion, thereby limiting intramolecular cyclization. *Id.*

113. One of ordinary skill in the art would have understood that a large steric group could be added to Ashworth compound **25** in order to increase its stability. Further, one of ordinary skill in the art would have been motivated to substitute the cyclohexyl group at the 2-position of the acetyl-pyrrolidine-2-carbonitrile compound **25** with a tricyclo[3.3.1.1]dec-1-y1 group (also referred to as the "adamantyl group") in order to optimize the compound, e.g., to increase the stability of the compound and to bias the compound toward the trans conformation. Ashworth provides the motivation to do so because it shows increased potency for compounds having larger substituents at the 2-position. *See*, e.g., Ex. 1007, p. 1166, Table II (compare compounds **24** and **25**).

114. Ashworth provides motivation to optimize the 2-position of the acetyl-pyrrolidine-2-carbonitrile compound **25** with a suitable substituent to enhance stability. Table II of Ashworth shows the chemical stability data of DP-IV inhibitors in aqueous solution (pH of 7.4), as measured in half-life ($t_{1/2}$).

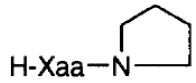


Compound N°	Xaa	K_i (nM)[13]	$t_{½}$ (h)[19]
24	Cpg	1.1 ± 0.2	48
25	Chg	1.4 ± 0.5	>48
26	Ile	2.2 ± 0.5	48
27	Tbg	3.8 ± 0.8	>48
28	Lys(Z)	5.2 ± 1.0	24
29	Pro	22.0 ± 4.0	7.5

Id. at 1166.

115. When changing the substituent at the 2-position of the acetyl-pyrrolidine-2-carbonitrile from a straight chain alkyl moiety, for example compound **28** (a lysine moiety), to a more bulky cycloalkyl moiety such as a cyclohexyl moiety, for example compound **25**, the stability dramatically increases from 24 hours to greater than 48 hours. Given this teaching, one of ordinary skill in the art would have been motivated to try even larger, bulkier alkyl groups, such as substituting the cyclohexyl group at the 2-position of the acetyl-pyrrolidine-2-carbonitrile compound **25** with an adamantyl group, in order to further minimize cyclization and increase the stability of the compound under similar conditions. Adamantyl was well known and studied in the art. For example, as discussed in more detail below, Raag, published in 1991, taught hydroxylated adamantane. Ex. 1009, p. 2678.

116. One of ordinary skill in the art also would have been motivated to substitute the cyclohexyl group at the 2-position of the acetyl-pyrrolidine-2-carbonitrile compound **25** with an adamantyl group because, e.g., Ashworth discloses that substitution at this position improves the potency of an aminoacyl pyrrolidide compound as shown in Table 1 of Ashworth:



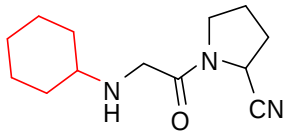
Compound N°	Xaa	K_i (μM)[13]
5	Cyclohexylglycine [Chg]	0.064 ± 0.01
6	(R,S)-Cyclopentylglycine [Cpg]	0.21 ± 0.04
7	Ile	0.41 ± 0.01
8	*allo*-Ile	0.44 ± 0.04
9	Val	0.47 ± 0.02
10	Lys(Cbz)	0.52 ± 0.07
11	tert-Butylglycine [Tbg]	0.88 ± 0.20
12	Thr(Me)	0.90 ± 0.15
13	Orn(Cbz)	0.91 ± 0.20
14	2-Aminohexanoic acid [Aha]	1.20 ± 0.20
15	Glu	2.00 ± 0.40
16	Pro	2.10 ± 0.20
17	Cyclohexylalanine [Cha]	2.15 ± 0.50
18	Glu(OBn)	2.70 ± 0.30
19	Thr	4.90 ± 0.90
20	Phenylglycine [Phg]	5.30 ± 0.10
21	Ser(Bn)	6.00 ± 1.50
22	Ala	7.00 ± 1.00
23	Asp	14.50 ± 1.90

Id. at 1164. Specifically, compound **5** (having a cyclohexyl group) of Table I shows at least a 100-fold increase in potency compared to compound **7** (having a 1-methyl propyl group) or compound **9** (having an isopropyl group). Ashworth confirms this observation by noting, "[a]s expected, from the substrate specificity of DP-IV, only (S)-amino acid derivatives showed any activity and, as can be seen in Table I, lipophilic amino acids gave more potent compounds. In particular, β-branched α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino acid, **(S)-cyclohexylglycine providing the most active pyrrolidide** (compound **5** possessing a K_i value of 64 nM)." *Id.* at 1165.

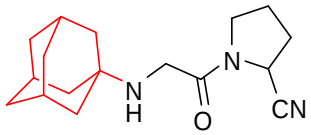
117. Therefore, Ashworth describes and teaches: (i) the advantage of replacing a smaller **straight chain alkyl moiety** (i.e., a 4-amino-butyl group) at the

2-position of an aminoacyl pyrrolidine with **a larger cycloalkyl moiety** (e.g., a cyclohexyl group) to produce an aminoacyl pyrrolidine-carbonitrile with **increased stability** under physiological pH conditions; and (ii) the advantage of replacing a **smaller branched alkyl moiety** (i.e.,1-methyl propyl group or isopropyl group) at the 2-position of an aminoacyl pyrrolidine by a **larger cycloalkyl moiety** (cyclohexyl group) to produce an aminoacyl pyrrolidine with **superior activity** in inhibiting DP-IV.

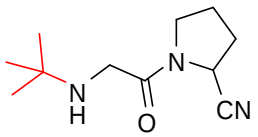
118. Additionally, one of ordinary skill in the art would have been motivated to substitute the cyclohexyl group at the 2-position of compound **25** with an adamantyl group because the art taught adamantyl as an obvious alternative to cyclohexyl. For example, Villhauer discloses compounds having cycloalkyl (e.g., adamantyl groups) or alkyl groups attached to the amino moiety of 2-cyano pyrrolidides for use as DP-IV inhibitors. Specifically, Villhauer discloses a cyclohexyl group attached to the amino moiety of 2-cyano pyrrolidides:



(Ex. 1008, p. 12, Example No. 28); adamantyl groups attached to the amino moiety of 2-cyano pyrrolidides:



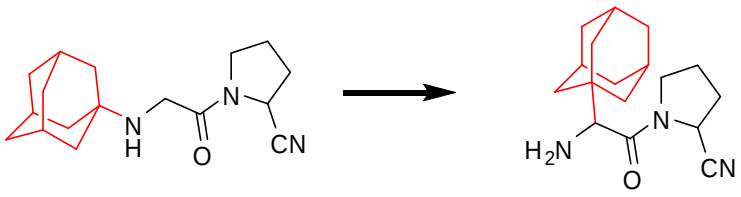
(*id.* at 13, Example No. 47) and alkyl groups attached to the amino moiety of 2-cyano pyrrolidides:



(*id.* at 13, Example No. 52). Villhauer performed a pairwise comparative analysis between cyclohexyl and adamantyl groups, along with a small number of other substituents. Villhauer thus provides motivation for selecting adamantyl as an alternative to cycloalkyl in a DP-IV inhibitor.

119. Given the disclosures of Ashworth and Villhauer, one of ordinary skill in the art would have been motivated in March 2000 to make the adamantyl substituted 2-cyano pyrrolidide (i.e., adamantyl substituted Ashworth compound **25**) because Villhauer discloses the adamantyl group attached to the amino moiety 2-cyano pyrrolidide compound.

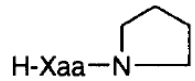
120. Ashworth provides motivation to position the adamantyl group of Villhauer at the 2-position of the aminoacyl pyrrolidide of Ashworth compound **25** given that the cyclohexyl moiety was also positioned at the 2-position. Thus one of ordinary skill in the art would easily surmise that the adamantyl-substituted Ashworth compound **25** (shown on the right-hand side below) is merely a logical extension of what was previously known at the time of filing (the compound on the left hand side below):



121. Accordingly, well before March 2000, it would have been obvious to one of ordinary skill in the art to substitute the cyclohexyl group at the 2-position of the Ashworth lead compound **25** with an adamantyl group. One of ordinary skill in the art would have expected the modification to improve the characteristics of the compound, and particularly, to increase the potency and stability of the compound.

122. In the context of the ’186 patent, one of ordinary skill in the art would only need to verify the readily predicted results of adding an adamantyl group and removing the cyclohexyl group. Such a modification requires less experimentation than is invited by the specification of the ’186 patent.

123. One of ordinary skill in the art would have been motivated to add a hydroxyl group at the 3-position of the adamantyl substituent of the modified Ashworth lead compound **25** in order to improve the compound’s characteristics. For example, addition of a hydroxyl moiety would have been expected to reduce the compound’s partition coefficient (thereby enhancing its solubility and permeability) and potentially increasing its metabolic stability. Specifically, one of ordinary skill in the art would have expected the hydroxyl group to increase compound solubility and possibly increase absorption of the compound without diminishing its activity.



Compound N°	Xaa	K_i (μM)[13]
5	Cyclohexylglycine [Chg]	0.064 ± 0.01
6	(R,S)-Cyclopentylglycine [Cpg]	0.21 ± 0.04
7	Ile	0.41 ± 0.01
8	*allo*-Ile	0.44 ± 0.04
9	Val	0.47 ± 0.02
10	Lys(Cbz)	0.52 ± 0.07
11	tert-Butylglycine [Tbg]	0.88 ± 0.20
12	Thr(Me)	0.90 ± 0.15
13	Orn(Cbz)	0.91 ± 0.20
14	2-Aminohexanoic acid [Aha]	1.20 ± 0.20
15	Glu	2.00 ± 0.40
16	Pro	2.10 ± 0.20
17	Cyclohexylalanine [Cha]	2.15 ± 0.50
18	Glu(OBn)	2.70 ± 0.30
19	Thr	4.90 ± 0.90
20	Phenylglycine [Phg]	5.30 ± 0.10
21	Ser(Bn)	6.00 ± 1.50
22	Ala	7.00 ± 1.00
23	Asp	14.50 ± 1.90

Ex. 1007, p. 1064.

124. Also, it would have been within the general knowledge of one of ordinary skill in the art—as evidenced by Lipinski (Ex. 1017), Hansch (Ex. 1018), Cates (Ex. 1019) and/or other references available to one of ordinary skill in the art—to incorporate a hydroxyl group in the adamantyl-modified Ashworth lead compound, e.g., to reduce the partition coefficient of the compound, and thus potentially increase the solubility in aqueous solution. Thus, the teachings of Ashworth in combination with such knowledge would have motivated one of ordinary skill in the art to make such a modification.

125. Raag provides additional motivation for incorporation of a hydroxyl group at a specific position on the adamantyl ring. Raag discloses a study of the metabolism of adamantane by cytochrome P-450_{CAM}. Ex. 1009, Abstract. Table III

of Raag, shows the substrates that are subject to hydroxylation, including adamantane and other substrates:

Table III: Various Substrate-Dependent Parameters[g]

	 camphor	 adamantanone	 adamantane	 thiocamphor	 camphor/Y96F	 norcamphor	 camphane
molec vol	315 Å^3	300 Å^3	293 Å^3	322 Å^3	315 Å^3	236 Å^3	309 Å^3
hydrogen bond to Y96	yes[a]	yes[b]	no	no	no	yes[b]	no
no. of iron ligands	5[a]	5[b]	6	6		6[b]	6
redox pot. Fe^{3+}/Fe^{2+}	−170 mV[c]	−175 mV[c]				−206 mV[c]	
high-spin %	94–97%[c–e]	96–98%[c,d]	99%[d]	65%[e]	59%[e]	46%[c]	46%[e]
regiospecif of substr hydroxylatn	5-exo (100%)[d–f]	5 (100%)[d]	1 (100%)[d]	5-exo (64%)[e] 6-exo (34%) 3-exo (2%)	5-exo (92%)[e,f] 4 (1%) 6-exo (2–4%) 3-exo (0–4%) 9 (<1%)	5-exo (45%)[f] 6-exo (47%) 3-exo (8%)	5-exo (90%)[e] 6-exo (10%)
substr temp factor (Fe^{3+})	16.2 Å^2[a]	16.5 Å^2[b]	24.7 Å^2	23.5 Å^2		33.5 Å^2[b]	30.1 Å^2
substr hydrophilic groups	yes	yes	no	yes	yes	yes	no
hydroxylatn "efficiency"	100%[e,f]			98%[e]	100%[e]	12%[f]	8%[e]
L6–substr dist	NA	NA	2.63 Å	2.35 Å (70%) 3.35 Å (30%)		3.0 Å[b]	2.88 Å
L6–iron dist	NA	NA	1.95 Å	1.35 Å		1.73 Å[b]	1.67 Å
L6 occupancy	NA	NA	1.00	0.90		0.97[b]	1.00
L6 temp factor	NA	NA	14.3 Å^2	19.6 Å^2		3.8 Å^2[b]	7.7 Å^2
cation occupancy	1.00[a]	1.00[b]	0.89	0.91		1.00[b]	0.72
cation temp factor	12.1 Å^2[a]	10.0 Å^2[b]	15.5 Å^2	14.2 Å^2		7.9 Å^2[b]	21.7 Å^2

[a] Poulos et al. (1985, 1987). [b] Raag and Poulos (1989a). [c] Fisher and Sligar (1985). [d] White et al. (1984). [e] Atkins and Sligar (1988b). [f] Atkins and Sligar (1989). [g] Carbon numbering for each substrate begins with C-1 at the top of the six-membered ring which is in the plane of the table. Numbering proceeds counterclockwise such that the carbonyl carbon is C-2 and C-5 is in the lower right-hand portion of the ring. Note that C-5 is a secondary carbon in some substances and a tertiary carbon in others.

Id. at 2678.

Column 7 of Table III describes the regiospecific hydroxylation of adamantane at a specific 1-position, i.e., at a tertiary carbon site (and not a secondary carbon site). *Id.* This position corresponds directly to the hydroxylation site (i.e., the 3-position on the adamantyl ring) in saxagliptin and the location of the hydroxyl group of the adamantyl-modified Ashworth compound **25**.

126. Raag also teaches that "[a]damantane is . . . metabolized to a single product despite having a relatively high active site mobility. The single product can be attributed to the existence of only two types of unique carbon atoms in

adamantane, together with the greater reactivity of tertiary versus secondary carbons." *Id.* As additional evidence for the teachings of Raag, Hoffman describes the antiviral drug rimantadine, which contains an adamantane moiety that was known to be metabolized to a hydroxylated derivative. Ex. 1016. Hoffman serves as further basis of what was generally known in the art regarding the tendency for adamantane to preferentially undergo hudroxylation at the 3-position.

127. Therefore, it was known long before March 2000 that 3-hydroxylated adamantyl groups were used in drugs and that adamantyl groups were subject to hydroxylation at the same site as a result of normal metabolism. Further, one of ordinary skill in the art, given the teaching of Raag (and as evidenced by Hoffman), would have been motivated to block metabolism of a substituted adamantyl ring at the 3-position by placing a group such as a hydroxyl group at that position. Blocking metabolism at the 3-position would result in greater metabolic stability.

128. Furthermore, at the time the application of the '186 patent was filed, it was also known that information on metabolites of candidate drugs "can guide structural modifications, thereby improving the activity and/or bioavailability." *See* Walter A. Korfmacher et al., *HPLC-API/MS/MS: a powerful tool for integrating drug metabolism into the drug discovery process*, 2 DRug Disc. Today 532 (1997) (hereinafter "Korfmacher," Ex. 1020). Korfmacher teaches the following advantages of metabolite identification:

> Metabolite identification in drug discovery provides early information that can lead to structural changes in the current lead compound,

> improving such pharmacokinetic parameters as oral bioavailability, half-life ($t_{1/2}$), or C_{max}. Often these parameters can be changed by improving the metabolic stability of the compound. In order to improve metabolic stability, it is very important to know how a compound is metabolized. The goal of drug discovery is to progress a lead compound into a final candidate drug that can be placed in the development stage. . . **Early metabolite identification can provide information on how to improve the metabolic stability of the lead structure. In this way, future lead compounds might be a metabolite identified from the previous lead drug or an analog of the previous drug designed to block the major route of metabolism.**

Id., at 534 (emphasis added).

129. Therefore, it was well known that metabolites (such as 3-hydroxy substituted adamantyl compounds) could provide improved metabolic stability to a compound.

130. Additionally, having a hydroxyl group at the 3-position would also improve the Lipinski parameters, such as reducing Log P and improving permeability as discussed below. The partition coefficient (P) is a ratio of concentrations of un-ionized compound between two liquid phases, and Log P is as a measure of compound lipophilicity. One of ordinary skill in the art would have been motivated to add a hydroxyl group at the 3-position of the adamantyl-substituted moiety of the modified Ashworth lead compound **25** because the use of hydroxyl groups on drugs increases the solubility of the drugs in water. This position is supported by the knowledge of one of ordinary skill in the art, as

evidenced by at least by the Lipinski, Hansch and/or Cates disclosures as discussed in details in ¶¶ 50-51 above.

131. One of ordinary skill in the art would have been motivated to improve characteristics or properties of the lead compound, e.g., the solubility thereof, particularly wherein the prior art indicates a potential problem with such a characteristic or property, e.g., very low solubility, as predicted by one of ordinary skill in the art, for example using information and teachings available, such as evidenced by Lipinski, Hansch and Cates.

132. Accordingly, before 2000, in view of the knowledge of one of ordinary skill in the art, as seen in the teachings of Lipinski, Hansch and Cates, it would have been obvious to one of ordinary skill in the art to add a hydroxy group at the 3-position of the adamantyl modified compound **25**. The person of ordinary skill in the art would have had reason to try such an addition with an expectation of success in preparing a DP-IV inhibitor with improved water solubility, as well as increased stability (as taught in Korfmacher), permeability and bioavailability.

133. As discussed above, one of ordinary skill in the art would have understood the significance of dipeptide conformation on the effective interaction between DP-IV and its substrates and inhibitors. For example, Lin reports that "[DP-IV] possesses a high conformational specificity for a trans amide bond" and notes "the importance of the trans conformation." Ex. 1015, p. 14020. As would have been appreciated by one of ordinary skill in the art, the orientation of certain functional groups in the ultimate compound (e.g., the free amine and 2-cyano moieties) would be controlled, at least in part, by selecting the trans versus cis

conformation. As discussed above, it was generally known in the art that the trans conformation would be favored over the cis conformation for a DP-IV inhibitor. *Id.* at 14020.

134. One of ordinary skill in the art also would have been motivated to optimize the interaction between the cyano functional group and the DP-IV enzyme. Specifically, a person of ordinary skill would have been motivated to optimize the interaction between DP-IV and the cyano group by exploring variations in the point of attachment on the pyrrolidine ring as well as the orientation of the cyano group on the pyrrolidine ring. One of ordinary skill in the art would have selected as a starting point the 2-cyano position found in both Ashworth compound **25** and Villhauer. The cyano moiety in saxagliptin shares the same pyrrolidine ring position described in these prior art references.

135. A person of ordinary skill would have also sought to modulate the orientation of the 2-cyano moiety on the pyrrolidine ring in order to optimize interaction with and inhibition of the DP-IV enzyme. The primary strategy in March 2000 for modulating the orientation of a ring-bound substituent would have been through fusion of the pyrrolidine ring with another ring. *See*, e.g., Ex. 1021, p. 243. Fusion between two rings results in significant changes in ring flexibility, including as discussed above, ring flattening. These changes in turn would be expected by one of ordinary skill in the art to affect the orientation of ring-bound substituents (e.g., the 2-cyano moiety of Ashworth, compound **25**). The smallest ring that can be used for fusion is a cyclopropyl ring. *Id.*

136. Cyclopropyl rings are one of the most commonly used ring fusion

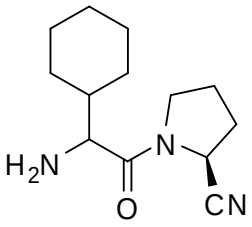
agents because: (i) addition of a cyclopropyl ring has a negligible effect on compound molecular weight, which can translate to better drug-like qualities; (ii) cyclopropane has an exceedingly small footprint, meaning it exerts a minimal steric effect on the rest of the compound to which it is attached and (iii) cyclopropane provides greater conformational restriction than larger ring fusions, resulting in fewer possible conformations. *See*, e.g., *id*.

137. One of ordinary skill in the art would have been motivated to select cyclopropyl fusion as a means for modulating the interaction between a DP-IV inhibitor and DP-IV. Chiou represents what was generally known in the art in March 2000 regarding the effects of cyclopropyl ring fusion. Specifically, Chiou explored the fusion of a cyclopropyl ring onto acetylcholine (ACh) in order to produce a compound that was "1) structurally as close to ACh as possible and 2) conformationally as rigid as possible." According to Chiou, cyclopropyl rings "are considered the smallest chemical structure . . . capable of conferring conformational rigidity." *Id.* at 243. Like Chiou, one of ordinary skill in the art would have been motivated to start with a compound having known activity (e.g., Ashworth compound **25**) and to optimize it by making small, incremental changes to its size and rigidity near the active 2-cyano group.

138. For the above reasons, cyclopropyl fusion to the pyrrolidine ring of Ashworth compound **25** would have been one of the first modifications a person of ordinary skill would have chosen for its optimization in March 2000. Moreover, the pool of compounds that would have been tried by a person of ordinary skill would have been quite small given the likelihood of selecting the cyclopropyl

fusion modification.

139. Selection of the point of attachment for the cyclopropyl ring would have been straightforward for one of ordinary skill in the art in March 2000. As can be seen in the pyrrolidine ring of Ashworth compound **25** below, there are only three possible cyclopropyl fusion sites at the pyrrolidine ring:

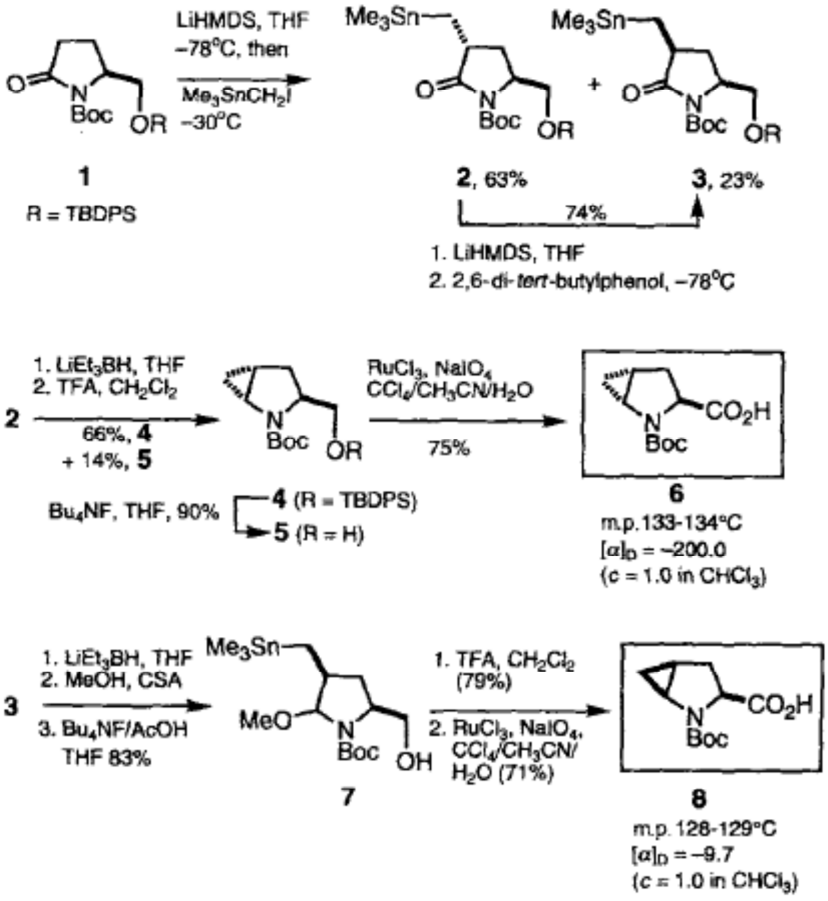


Ashworth Compound **25**

The resulting fusion would thus be one of: 1,2-methanopyrrolidine, 3,4-methanopyrrolidine or 4,5-methanopyrrolidine. One of ordinary skill in the art would have understood in March 2000 that two possible orientations of the fused cyclopropane ring could exist for each of the above three positions ring. *See*, e.g., Ex. 1010, p. 1882, compounds **6** and **8**.

140. One of ordinary skill in the art would have prioritized fusion of the cyclopropane ring at the two positions farthest from the carbon bearing the cyano moiety. Thus the skilled artisan would have conservatively started with the 4,5-methanopyrrolidine and 3,4-methanopyrrolidine fusions. Therefore, the 4,5-methanopyrrolidine, as present in saxagliptin, would have been one of only a small set of compounds that would have been investigated by one of ordinary skill in the art.

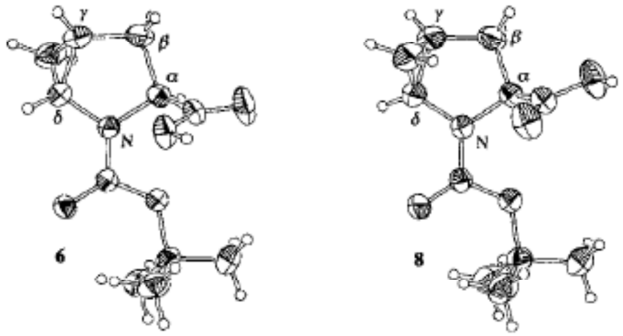
141. Hanessian provides motivation for producing a fused pyrrolidine-cyclopropyl ring system as found in saxagliptin. Specifically, Hanessian teaches that the use of conformationally constrained analogues of proline were well known in the peptidomimetic research area well before March 2000. Hanessian describes the "highly stereocontrolled syntheses of the diastereomeric 4,5-methano-L-prolines and 5,6-methano-L-pipecolic acids by a novel intramolecular cyclopropanation reaction of iminium ions . . ." Ex. 1010, p. 1882. One such example shown by Hanessian is compound **8**, which was synthesized according to Scheme 1 below:



Id.

142. The structure and conformation of compound **8** in the solid state were unambiguously confirmed by single X-ray analysis. *Id.* Further, Table 1 of Hanessian shows selected torsion angles for compound **8** where "considerable 'flattening' of the pyrrolidine ring is observed relative to *N*-Boc-L-proline." *Id*.

Table 1. Selected torsion angles and root-mean-square deviations from fitted atoms in a given plane of X-ray crystal structures, and ^{13}C NMR chemical shifts ($CDCl_3$).



	N-Boc-L-proline [20]	**6**	**8**
$\tau(NC_\alpha)$	−17	−5.6	−14.4
$\tau(C_\alpha C_\beta)$	+31	+4.8	+15.3
$\tau(C_\beta C_\gamma)$	−35	−2.6	−11.4
$\tau(C_\gamma C_\delta)$	+24	−0.7	+2.9
$\tau(C_\delta N)$	−4	+4.1	+7.6
$\tau(BocNC_\alpha CO_2H)$	−72	−64.0	−67.1
rms deviation of fitted atoms	0.018 C_α, N, C_δ, C_γ	0.003 C_β, C_γ, C_δ, N	0.013 C_β, C_γ, C_δ, N
	δ(cis/trans)	*δ(cis/trans)*	*δ(cis/trans)*
COOH	178.35/176.60	177.7/175.5	179.1/176.1
NC=O	153.95/155.39	157.1/154	155.7/154.1
C_α	58.8	60.8/60.1	59.5/59.1
C_β	30.75/29.53	32.0	31.5/29.1

Id. Hanessian confirms the "flattening" of the pyrrolidine ring by determining the root-mean-square values for the C_β and N atoms from the plane defined by C_β, C_γ, C_δ and N (*see* Table 1 above). It was determined that for compound **8**, the out-of-plane carbon was the carbon bearing the carboxyl group when compared to *N*-Boc proline. *Id*. Therefore, Hanessian taught that modification of a substituted proline

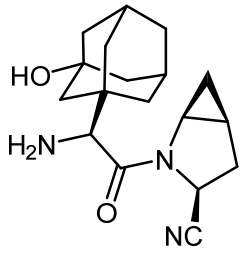
ring (such as a 2-carboxyl substituted proline) to a 4,5-methanoproline ring system "flattens" the ring. Ring flattening would also be expected to result in a modified orientation of the 2-cyano group. Modifying the orientation of the 2-cyano group in Ashworth compound **25** would likely result in a modified interaction with DP-IV and possibly cause it to resist intramolecular reaction with the free amine group found in DP-IV inhibitors (i.e., increased stability).

143. One of ordinary skill in the art would have had reason to modify the 2-cyano substituted proline portion of the Ashworth lead compound **25** to a 4,5-methanoproline ring system in order to enhance compound stability. For example, Ashworth teaches that, "[s]ubstrates and inhibitors of DP-IV require a free N-terminus, which means that potential dipeptide serine protease inhibitors (e.g., C-terminal aldehydes, boronic acids, α-ketoacids, trifluoromethylketones, or chloromethylketones) are inherently unstable at neutral pH due to intramolecular cyclisation." Ex. 1007, p. 1163. One of ordinary skill in the art would have had reason to try modifying the 2-cyano substituted proline portion of the Ashworth compound **25**, to produce a 4,5-methanoproline ring system in order to "flatten" the proline ring as taught in Hanessian, thereby adjusting the orientation of the cyano substituent to the proline ring and minimizing or preventing intramolecular cyclization, as taught by Ashworth.

144. Hanessian describes and teaches: (i) modification of a substituted proline ring (such as a 2-carboxyl substituted proline) (ii) to produce a 4,5-methano-modified substituted proline ring with the 2-substituent orientation modified with respect to the proline ring.

145. Accordingly, before 2000, it would have been obvious to one of ordinary skill in the art to modify the substituted proline ring of the Ashworth compound to a 4,5-methano-modified compound. Such chemist would have had reason to make such a modification with a reasonable expectation of success for improving the characteristics of the compound. For example, according to the teachings of Ashworth, one of ordinary skill in the art would have expected success in preparing the DP-IV inhibitor with improved stability properties.

146. By making these commonly known modifications at the positions indicated above, routine experimentation would have led to the following molecule:



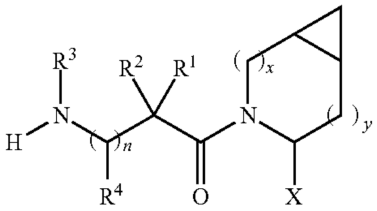
147. This molecule is identical to the compounds recited in claims 8 and 25 of the ’186 patent and encompassed by claims 1, 2, 4, 6, 7, 9-11, 26-28, 32-35, and 39-40 of the ’186 patent.

148. Taken together, the prior art provided reason: 1) to select the core structure of Ashworth compound **25** to form a DP-IV inhibitor; 2) to substitute the cyclohexyl group at the 2-position of the acetyl-pyrrolidine-2-carbonitrile of the lead compound with tricyclo[3.3.1.1]dec-1-yl group (adamantyl group); 3) to add a hydroxyl group at the 3-position of the adamantyl group and 4) to form a 4,5-methanoproline moiety of the lead compound. Thus, claims 8 and 25 of the ’186

patent are unpatentably obvious over Ashworth in view of the knowledge and motivation of one of ordinary skill in the art, as evidenced by prior art references (including Villhauer, Raag, and Hanessian).

Claim 1:

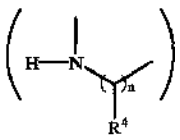
"A compound having the structure



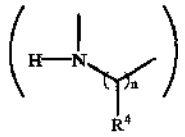
wherein x is 0 or 1 and y is 0 or 1, provided that
x=1 when y=0 and
x=0 when y=1; and wherein
n is 0 or 1;
X is H or CN;
R^1, R^2, R^3 and R^4 are the same or different and are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, alkylthioalkyl, arylalkylthioalkyl, cycloalkenyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl or cycloheteroalkylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3, 4 or 5 groups selected from hydrogen, halo, alkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, heteroarylamino, arylamino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol,

alkylthio, alkylcarbonyl, acyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, alkoxycarbonylamino, alkylsulfonyl, aminosulfonyl, aminosulfonyl, alkylsulfonyl, sulfonamido or sulfonyl;

and R^1 and R^3 may optionally be taken together to form $–(CR^5R^6)_m–$ where m is 2 to 6, and R^5 and R^6 are the same or different and are independently selected from hydroxy, alkoxy, H, alkyl, alkenyl, alkynyl, cycloalkyl, halo, amino, substituted amino, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or R^1 and R^4 may optionally be taken together to form $–(CR^7R^8)_p–$ wherein p is 2 to 6, and R^7 and R^8 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, halo, amino, substituted amino, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or optionally R^1 and R^3 together with



form a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO_2; or optionally R^1 and R^3 together with



form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

with the proviso that where x is 1 and y is 0, X is H, n is 0, and one of R^1 and R^2 is H and the other is alkyl, then R^3 is other than pyridyl or substituted pyridyl;

including all stereoisomers thereof;

or a pharmaceutically acceptable salt thereof, and all stereoisomers thereof."

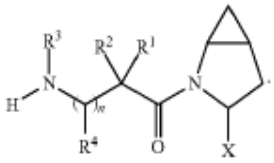
149. Claim 1 of the '186 patent discloses a genus of compounds encompassing saxagliptin. For example, saxagliptin is encompassed within claim 1 with the following R-group elections: x = 0, y = 1, n is 0, X is CN, R^1 is cycloalkyl, R^2 is hydrogen and R^3 is hydrogen. According to the '186 patent, "the term 'cycloalkyl' . . . includes . . . adamantyl . . . which . . . may be optionally substituted with 1 to 4 substituents such as . . . hydroxy." Ex. 1001, col. 9, l. 48 – col. 10 l. 21. Claim 1 further recites hydroxy as a possible substituent ("R^1 . . . [is] selected from . . . cycloalkyl . . . optionally substituted . . . [with] hydroxy"). Because it would have been obvious to one of ordinary skill in the art to modify compound **25** of Ashworth, as described above, the structures of claim 1 of the

’186 patent would have been obvious for at least the reasons set forth above with respect to claims 8 and 25.

150. The genus of compounds encompassed by claim 1 is extremely large, covering several orders of magnitude more compounds than are described in the ’186 patent. Moreover, DP-IV inhibition was explored broadly in the art by March 2000, as evidenced by the large pool of prior art references disclosing such inhibitors. *See,* e.g., Ex. 1007 and Ex. 1008. From within this large pool of available references, one of ordinary skill in the art in March 2000 could have relied on a number of possible combinations for a teaching of the elements of saxagliptin and to provide motivation to combine those references. For example, the mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound **25** (the lead compound) as taught by Hanessian would have led to a compound within the scope of claim 1 of the ’186 patent. Because this modification would have been obvious to one of ordinary skill in the art, for at least the reasons set forth above, claim 1 is obvious.

Claim 2:

“The compound as defined in claim 1 having the structure:



”

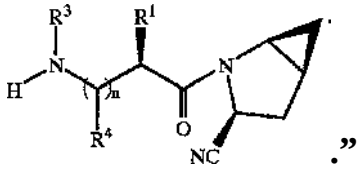
151. Claim 2 of the ’186 patent discloses a genus of compounds encompassing saxagliptin. For example, saxagliptin is encompassed within claim 1

with the following R-group elections: x = 0, y = 1, n is 0, X is CN, R^1 is hydroxytricycloalkyl, R^2 is hydrogen and R^3 is hydrogen. As would be appreciated by one of ordinary skill in the art, hydroxy adamantane is a type of hydroxytricycloalkyl. Because it would have been obvious to one of ordinary skill in the art to modify the Ashworth lead compound **25**, as described above, the structure of claim 2 of the '186 patent would have been obvious for at least the reasons set forth above with respect to claims 8 and 25.

152. Moreover, mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound **25** (the lead compound) as taught by Hanessian would have led to a compound within the scope of claim 2 of the '186 patent. Because this modification would have been obvious to one of ordinary skill in the art, for at least the reasons set forth above, claim 2 is obvious.

Claim 4:

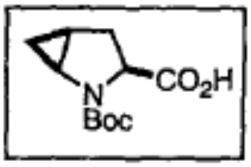
"The compound as defined in claim 1 having the structure:



."

153. Claim 4 of the '186 patent discloses a genus of compounds encompassing saxagliptin. For example, saxagliptin is encompassed within claim 4 with the following R-group elections: n is 0, R^1 is hydroxytricycloalkyl and R^3 is hydrogen. As would be appreciated by one of ordinary skill in the art, hydroxy adamantane is a type of hydroxytricycloalkyl.

154. Hanessian discloses the following compound **8**:



8

Ex. 1010, p. 1882. As seen above, the orientation of substituents on the pyrrolidine ring of compound **8** is the same as recited in claim 4. Thus Hanessian provides motivation for the pyrrolidine and cyano orientations of claim 4. Further, and as would be understood by one of ordinary skill in the art, there are two possible configurations for the R^1 group, i.e., into the plane and out of the plane. Because Hanessian teaches the orientation of pyrrolidine ring substituents and R^1 can adopt only two possible configurations, one of ordinary skill in the art would have found it routine to optimize the orientation of the R^1 group to yield the configuration of claim 4.

155. Because it would have been obvious to one of ordinary skill in the art to modify lead compound **25** of Ashworth, as described above, the structures of claim 4 of the ’186 patent would have been obvious for at least the reasons set forth above with respect to claims 8 and 25.

156. Moreover, mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound **25** (the lead compound) would have led to a compound within the scope of claim 4 of the ’186 patent. Because this modification would have been obvious to one of ordinary skill in the

art, for at least the reasons set forth above, claim 4 is obvious.

Claim 6:

"The compound as defined in claim 1 wherein:

R^3 is H, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl hydroxybicycloalkyl, or hydroxytricycloalkyl,

R^2 is H or alkyl, n is 0,

X is CN."

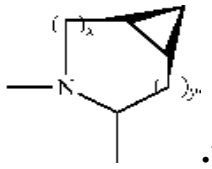
157. Claim 6 of the '186 patent discloses a genus of compounds encompassing saxagliptin. For example, saxagliptin is encompassed within claim 6 with the following R-group elections: R^1 is hydroxytricycloalkyl and R^2 is hydrogen. As would be appreciated by one of ordinary skill in the art, hydroxy adamantane is a type of hydroxytricycloalkyl. Because it would have been obvious to one of ordinary skill in the art to modify the lead compound **25** of Ashworth, as described above, the structures of claim 6 of the '186 patent would be held obvious for at least the reasons set forth above with respect to claims 8 and 25.

158. The genus of compounds encompassed by claim 6 is extremely large, covering several orders of magnitude more compounds than are described in the '186 patent. Moreover, DP-IV inhibition was explored broadly in the art by March 2000, as evidenced by the large pool of prior art references disclosing such inhibitors. *See,* e.g., Ex. 1007 and Ex. 1008. From within this large pool of available references, one of ordinary skill in the art in March 2000 could have relied on a number of possible combinations for a teaching of the elements of saxagliptin and to provide motivation to combine those references. For example,

the mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound **25** (the lead compound) as taught by Hanessian would have led to a compound within the scope of claim 6 of the ’186 patent. Because this modification would have been obvious to one of ordinary skill in the art, for at least the reasons set forth above, claim 6 is obvious.

Claim 7:

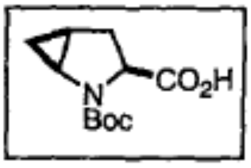
“The compound as defined in claim 1 wherein the cyclopropyl fused to the pyrrolidine has the configuration:



.”

159. Claim 7 of the ’186 patent discloses a genus of compounds encompassing saxagliptin. For example, saxagliptin is encompassed within claim 7 with the following R-group elections: x = 0 and y = 1. Because it would have been obvious to one of skill in the art to modify the Ashworth lead compound **25**, as described above, the structures of claim 7 of the ’186 patent would be held obvious for at least the reasons set forth above with respect to claims 8 and 25.

160. Hanessian discloses the following compound **8**:



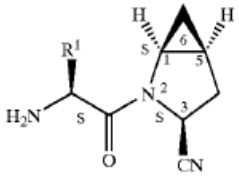
8

Ex. 1010, p. 1882. As seen above, the orientation of substituents on the pyrrolidine ring of compound **8** is the same as recited in claim 7. Thus Hanessian provides motivation for the pyrrolidine and cyano orientations of claim 7.

161. The genus of compounds encompassed by claim 7 is extremely large, covering several orders of magnitude more compounds than are described in the '186 patent. Moreover, DP-IV inhibition was explored broadly in the art by March 2000, as evidenced by the large pool of prior art references disclosing such inhibitors. *See*, e.g., Ex. 1007 and Ex. 1008. From within this large pool of available references, one of ordinary skill in the art in March 2000 could have relied on a number of possible combinations for a teaching of the elements of saxagliptin and to provide motivation to combine those references. For example, the mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound **25** (the lead compound) as taught by Hanessian would have led to a compound within the scope of claim 7 of the '186 patent. Because this modification would have been obvious to one of ordinary skill in the art, for at least the reasons set forth above, claim 7 is obvious.

Claim 10:

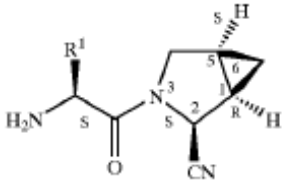
"A compound which is



(1S, 2 (2S), 3S, 5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

or

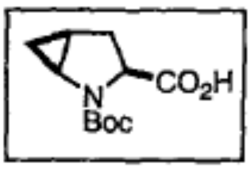


(1R, 2S, 3(2S), 5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl."

162. Claim 10 of the '186 patent discloses a genus of compounds encompassing saxagliptin. For example, saxagliptin is encompassed within claim 1 with the following R-group elections: R^1 is hydroxytricycloalkyl. As would be appreciated by one of ordinary skill in the art, hydroxy adamantane is a type of hydroxytricycloalkyl.

163. Hanessian discloses the following compound **8**:



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Ex. 1010, p. 1882. As seen above, the orientation of substituents on the pyrrolidine ring of compound **8** is the same as recited in claim 10. Thus Hanessian provides motivation for the pyrrolidine and cyano orientations of claim 10. In conjunction with these teachings, one of ordinary skill in the art would have found it routine to optimize the orientation of the R^1 group, especially considering the small number of possible orientations available.

164. Because it would have been obvious to one of skill in the art to modify lead compound **25** of Ashworth, as described above, the structures of claim 10 of the ’186 patent would be held obvious for at least the reasons set forth above with respect to claims 8 and 25.

165. The genus of compounds encompassed by claim 10 is extremely large, covering several orders of magnitude more compounds than are described in the ’186 patent. Moreover, DP-IV inhibition was explored broadly in the art by March 2000, as evidenced by the large pool of prior art references disclosing such inhibitors. *See*, e.g., Ex. 1007 and Ex. 1008. From within this large pool of available references, one of ordinary skill in the art in March 2000 could have relied on a number of possible combinations for a teaching of the elements of saxagliptin and to provide motivation to combine those references. For example, the mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound **25** (the lead compound) would have led to a compound within the scope of claim 10 of the ’186 patent. Because this modification would have been obvious to one of ordinary skill in the art, for at least the reasons set forth above, claim 10 is obvious.

Claim 9:

"The compound as defined in claim 8 wherein the pharmaceutically acceptable salt is the hydrochloride salt or the trifluoroacetic acid salt."

Claim 26:

"The compound as defined in claim 25, wherein the pharmaceutically acceptable salt is the hydrochloride salt."

Claim 33:

"The method of claim 32, wherein the pharmaceutically acceptable salt is the hydrochloride salt."

Claim 40:

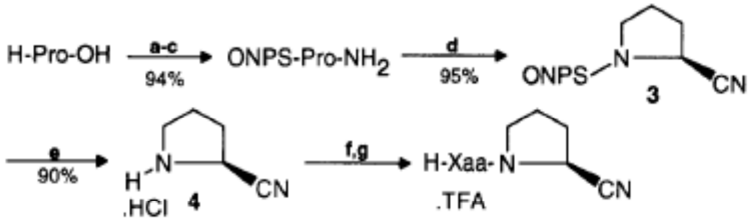
"The method of claim 39, wherein the pharmaceutically acceptable salt is the hydrochloride salt."

166. Claim 9 of the '186 patent recites the compound as defined in claim 8 and further claims the hydrochloride salt or the trifluoroacetic acid salt as the pharmaceutically acceptable salt. Claim 26 of the '186 patent recites the compound as defined in claim 25 and further claims the hydrochloride salt as the pharmaceutically acceptable salt. Claim 33 of the '186 patent recites the method of claim 32 wherein the pharmaceutically acceptable salt is the hydrochloride salt. Claim 40 of the '186 patent recites the method of claim 39 wherein the pharmaceutically acceptable salt is the hydrochloride salt. It would have been obvious to one of ordinary skill in the art to make and use the hydrochloride salt or the trifluoroacetic acid salt because it was previously disclosed in Ashworth. Further, making the salt would have been an ordinary exercise or task one of ordinary skill in the art would have performed at the time the application which led

to the ’186 patent was filed.

167. Ashworth teaches the formation of DP-IV pyrrolidides as both the hydrochloride salt and trifluoroacetic acid salt. For example, Ashworth describes the “subsequent acid catalyzed deprotection (4N HCl/dioxane) afforded the inhibitor as its **hydrochloride salt**.” Ex. 1007, p. 1165 (emphasis added). Ashworth also describes the preparation of dipeptide nitriles as shown in Scheme I, below.

Scheme I. *Preparation of dipeptide nitriles.*



Reagents: **a**.ONPS-Cl, 2N NaOH. **b**. HONSu, Water soluble carbodiimide. **c** conc. NH_4OH, dioxane. **d**. imidazole (2 equiv.), $POCl_3$ (4 equiv.), pyridine. **e**. 4N HCl/dioxane (3 equiv.), diethyl ether. **f**. Boc-Xaa-OH, pyBop, NEt_3, CH_2Cl_2. **g**. Trifluoroacetic acid.

Id.

168. Here, step g of Scheme I shows the formation of the trifluoroacetic acid salt. *Id.* Because it would have been obvious to one of skill in the art to modify the lead compound **25** of Ashworth, as described above, the hydrochloride salt or trifluoroacetic acid salt of claim 9 or the hydrochloride salt of claims 26, 33, and 40 of the ’186 patent would be held obvious for at least the reasons set forth above with respect to claims 8 and 25, given the disclosure that hydrochloride salts or trifluoroacetic acid salts were synthesized in Ashworth. Further, it would have been within the ordinary routine of one of skill in the art to make pharmaceutically

acceptable salts, such as hydrochloride salts or trifluoroacetic acid salts once the base compound was synthesized. Villhauer also teaches the use of pharmaceutically acceptable salt, including the hydrochloride salt.

> **Claim 11:**
>
> **"A pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor."**
>
> **Claim 27:**
>
> **"A pharmaceutical composition comprising the compound of claim 25 and a pharmaceutically acceptable carrier therefor."**
>
> **Claim 28:**
>
> **"A pharmaceutical composition comprising the compound of claim 26 and a pharmaceutically acceptable carrier therefor."**

169. Claim 11 of the '186 patent claims a pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier thereof. Claim 27 of the '186 patent claims a pharmaceutical composition comprising saxagliptin and a pharmaceutically acceptable carrier thereof. Claim 28 of the '186 patent claims a pharmaceutical composition comprising the compound of claim 26 and a pharmaceutically acceptable carrier thereof. It would have been obvious to one of ordinary skill in the art to make and use the pharmaceutical composition as claimed in claims 11, 27, and 28 because it was previously disclosed in Ashworth. Further, making the pharmaceutical composition would have been an ordinary exercise or task one of ordinary skill in the art would have performed at the time the application which led to the '186 patent was filed, given

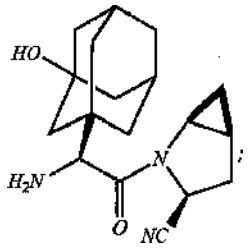
the purpose of testing the compounds for DP-IV inhibitory activity.

170. Ashworth teaches the use of a pharmaceutical composition of DP-IV pyrrolidides. For example, Ashworth notes that "[a]ll compounds were tested in vitro against pure human DP-IV . . . Inhibition was determined using the fluorogenic substrate, H-Ala-Pro-AFC at three concentrations per inhibitor. A typical assay (total volume 0.4 mL) comprised sodium HEPES 83.3 mM, EDTA 1.67 mM, BSA 0.5 mg mL^{-1}, pH 7.8, DP-IV 25 μU mL^{-1}, **inhibitor (in 10 mM acetate pH 4.0**)." Ex. 1007, p. 1166, FN 13 (emphasis added). Ashworth also describes the preparation of inhibitors "in buffered, aqueous solution (100 mM Tris pH 7.4)" *Id*. at 1166, FN 19. Here, Ashworth describes the use of acetate and/or Tris buffers as pharmaceutically acceptable carriers in the pharmaceutical composition of DP-IV pyrrolidides, such as the lead compound **25**. Because it would have been obvious to one of ordinary skill in the art to modify the lead compound **25** of Ashworth, as described above, the pharmaceutical composition of claims 11, 27, and 28 of the '186 patent would be held obvious for at least the reasons set forth above with respect to claims 8 and 25, given the use of acetate and/or Tris buffers as disclosed in Ashworth. Further, it would have been within the ordinary routine of one of skill in the art to make pharmaceutical compositions comprising a compound of claim 1 and a pharmaceutically acceptable carrier, given the desire to test the compounds for DP-IV inhibitory activity.

Claim 32:

"A method for treating diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, impaired glucose homeostasis,

or impaired glucose tolerance in a mammal comprising administering to the mammal a pharmaceutical composition comprising a compound that is



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor."

Claim 34:

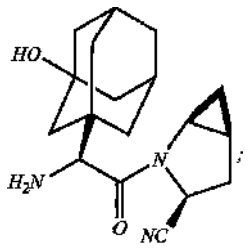
"The method of claim 32, for treating diabetes."

Claim 35:

"The method of claim 33, for treating diabetes."

Claim 39:

"A method for treating type II diabetes in a mammal comprising administering to the mammal a pharmaceutical composition comprising a compound that is



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor."

171. Claim 32 of the '186 patent recites a method for treating diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, impaired glucose homeostasis, or impaired glucose tolerance in a mammal comprising administering

to the mammal a pharmaceutical composition comprising saxagliptin. Claims 34 and 35 of the ’186 patent further recite treating diabetes. Claim 39 of the ’186 patent recites a method for treating type II diabetes in a mammal comprising administering to the mammal a pharmaceutical composition comprising saxagliptin.

172. Villhauer describes the use of DP-IV inhibitor compounds in treating conditions mediated by DP-IV. For example, Villhauer describes these inhibitors “useful in the treatment of **non-insulin-dependent diabetes mellitus**, arthritis, **obesity**, and osteoporosis such as calcitonin-osteoporosis.” Ex. 1008, p. 18 (emphasis added).

173. Accordingly, it would have been obvious to one of ordinary skill in the art to use a therapeutically effective amount of the compound of 25 or 26 in the treatment of at least one of the diseases recited in claims 32, 34-35, and 39, i.e., type II diabetes and/or diabetes.

EACH FEATURE OF CLAIMS 12, 13, 14, 15, 29, 30, 36, 37, 41 AND 42 IS DISCLOSED BY ASHWORTH, VILLHAUER, RAAG, HANESSIAN AND BACHOVCHIN

174. As discussed above, Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), Hanessian (Ex. 1010), and Bachovchin (Ex. 1011) can be considered prior art to the ’186 patent.

Claim 12:

“A pharmaceutical combination comprising a compound as defined in claim 1 and an antidiabetic agent other than a DP4

inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent."

Claim 13:

"The pharmaceutical combination as defined in claim 12 comprising said compound as defined in claim 1 and the antidiabetic agent other than a DP4 inhibitor."

Claim 14:

"The combination as defined in claim 13 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, an aP2 inhibitor, a glycogen phosphorylase inhibitor, an AGE inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1) or mimetic thereof, insulin and/or a meglitinide."

Claim 29:

"The composition of claim 27 or 28 further comprising an antidiabetic agent other than a DP4 inhibitor."

Claim 36:

"The method of any one of claims 32, 33, 34, or 35 wherein the pharmaceutical composition further comprises an antidiabetic agent other than a DP4 inhibitor."

Claim 41:

"The method of any one of claims 39 or 40, wherein the pharmaceutical composition further comprises an antidiabetic agent other than a DP4 inhibitor."

Claim 42:

"The method of claim 41, wherein the antidiabetic agent is metformin."

175. Claim 12 of the '186 patent recites a pharmaceutical combination

comprising a compound as defined in claim 1 and an antidiabetic agent other than a DP-IV inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent. Claim 13 which depends from claim 12 further limits the pharmaceutical combination to one including, an antidiabetic agent other than a DP-IV inhibitor. Claim 14 which depends from claim 13 further limits the antidiabetic agent to 1,2,3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, an aP2 inhibitor, a glycogen phosphorylase inhibitor, an AGE inhibitor, an insulin sensitizer, a glucogen-like peptide-1 (GLP-1) or mimetic thereof, insulin and/or a meglitinide. Claim 29 recites a composition comprising saxagliptin and an antidiabetic agent other than a DP-IV inhibitor. Claim 36 recites a method for treating diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, impaired glucose homeostatis, or impaired glucose tolerance in a mammal comprising administering saxagliptin and an antidiabetic agent other than a DP-IV inhibitor. Claim 41 recites a method for treating type II diabetes in a mammal comprising administering a pharmaceutical composition comprising saxagliptin and an antidiabetic agent other than a DP-IV inhibitor. Claim 42 depends from claim 41 and further claims where the antidiabetic agent is metformin.

176. Bachovchin discloses improved methods for reducing at least one of insulin resistance, hyperinsulinemia, and type 2 diabetes in animal subjects (including humans). Ex. 1011, p. 4, ll. 7-11. In particular, Bachovchin describes the use of DP-IV inhibitors in an amount effective to treat, among other indications, Type II diabetes. *Id.* at 6, ll. 16-22. Claim 4 of Bachovchin recites, “A

method for treating Type II diabetes, comprising administering to an animal a composition including one or more inhibitors of dipeptidylpeptidase IV [(DP-IV)].” *Id.* at claim 4. Moreover, various examples of DP-IV inhibitors are listed in Bachovchin. For example, a class of DP-IV inhibitors shown in Bachovchin are compounds based on the dipeptide (D)-Ala-(L)-Ala. Bachovchin also discloses the use of pharmaceutical compositions of DP-IV inhibitors, “another aspect of the present invention relates to pharmaceutical compositions of dipeptidylpeptidase inhibitors, particularly DPIV inhibitors.” *Id.* at 7, ll. 29-30. Thus, the use of DP-IV inhibitors for treating type 2 diabetes was well known at least one year before the application which led to the ’186 patent was filed.

177. Furthermore, Bachovchin also extensively describes treating type 2 diabetes by using DP-IV inhibitors in combination therapy with various antidiabetic agents other than DP-IV inhibitors:

The [DP-IV] inhibitors used according to the invention can also be used conjointly with agents acting on the ATP-dependent potassium channel of the β-cells, such as glibenclamide, **glipizide**, **gliclazide** and AG-EE 623 ZW. The [DP-IV] inhibitors may also advantageously be applied in combination with other oral agents such as **metformin** and related compounds or glucosidase inhibitors as, for example, **acarbose**.

Id. at 46, ll. 27-31 (emphasis added).

178. Because (i) it would have been obvious to synthesize the structure of claim 1 as a DP-IV inhibitor compound to treat type 2 diabetes, as discussed above, and (ii) Bachovchin explicitly teaches the use of a DP-IV inhibitor in

combination with an antidiabetic agent other than a DP-IV inhibitor (including metformin) for the treatment of type 2 diabetes, one of skill in the art would have known to use a compound of claim 1, as exemplified by the compound of claim 25, in combination with an antidiabetic agent to treat type 2 diabetes. Accordingly, it would have been obvious to a person of ordinary skill in the art to use the combination as recited in claims 12-14, 29, 36, 41, and 42 of the ’186 patent.

Claim 15:
“The combination as defined in claim 14 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, G1 -262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, Exendin-4, LY307161, NN2211, and/or LY315902.”

Claim 30:
“The composition of claim 29 wherein the antidiabetic agent is metformin.”

Claim 37:
“The method of claim 36, wherein the antidiabetic agent is metformin.”

Claim 42:
“The method of claim 41, wherein the antidiabetic agent is metformin.”

179. Claims 15, 30, 37, and 42 of the ’186 patent further provide the limitation of metformin as the antidiabetic agent. Claims 30, 37 and 42 require metformin as the antidiabetic agent. Claim 15 recites metformin in a list of antidiabetic agents. As described above, Bachovchin explicitly teaches the use of DP-IV inhibitors in combination with metformin: “The [DP-IV] inhibitors may also advantageously be applied in combination with other oral agents such as metformin . . .” *Id.* at 46. Because it would have been obvious to synthesize the structure of claim 1, as a DP-IV inhibitor compound to treat type 2 diabetes, as shown above, and Bachovchin explicitly teaches the use of DP-IV inhibitor compounds in combination with metformin, one of skill in the art would have known to use the combination as recited in claims 15, 30, 37, and 42 of the ’186 patent. Accordingly, claims 15, 30, 37, and 42 of the ’186 patent would have been found obvious.

EACH FEATURE OF CLAIMS 12, 17, 18 AND 22 IS DISCLOSED BY ASHWORTH, VILLHAUER, RAAG, HANESSIAN AND THE XENICAL LABEL

180. As discussed above, Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), Hanessian (Ex. 1010), and the Xenical Label (Ex. 1013) can be considered prior art to the ’186 patent.

Claim 12:

“A pharmaceutical combination comprising a compound as defined in claim 1 and an antidiabetic agent other than a DP4 inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent.”

Claim 17:

"The combination as defined in claim 12 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a thyroid receptor beta compound, an anorectic agent, and/or a fatty acid oxidation upregulator."

Claim 18:

"The combination as defined in claim 17 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, famoxin, and/or mazindol."

Claim 22:

"A pharmaceutical combination comprising a compound as defined in claim 1 and an agent for treating infertility, an agent for treating polycystic ovary syndrome, an agent for treating a growth disorder and/or frailty, an anti-arthritis agent, an agent for preventing or inhibiting allograft rejection in transplantation, an agent for treating autoimmune disease, an anti-AIDS agent, an agent for treating inflammatory bowel disease/syndrome, an agent for treating anorexia nervosa, an anti-osteoporosis agent and/or an anti-obesity agent."

181. Claims 12, 17, 18, and 22 of the '186 patent further provide the limitations of additional therapeutic agent compositions, which are combined with the claimed DP-IV inhibitors. Each of claims 12, 17, 18, and 22 recites an anti-obesity agent, among other aspects.

182. The Xenical Label discloses the FDA-approved uses of the anti-obesity agent, Xenical (i.e., orlistat), and supporting studies. In one such study,

patients with type 2 diabetes were treated with Xenical. The Xenical label reports that "XENICAL is indicated for **obesity management** . . . in the presence of other risk factors (e.g., . . . **diabetes**)." Ex. 1013, p. 0018 (emphasis added). Furthermore, the Xenical Label states "epidemiological studies have established a relationship between **obesity** and visceral fat and the risks for cardiovascular disease [and] **type 2 diabetes**." *Id.* at 0013 (emphasis added). According to the Xenical Label, Xenical (i.e., orlistat) "is a **lipase inhibitor**." *Id.* at 0011 (emphasis added).

183. Orlistat is one of the specific anti-obesity agents recited in claim 18, and thus falls within the scope of anti-obesity agents as recited in claims 12 and 22. Orlistat is also a lipase inhibitor, as recited in claim 17. *See,* e.g., Ex. 1013, p. 0011.

184. As was well known in the art as of March 2000, and as evidenced by the Xenical Label, the conditions of obesity and type 2 diabetes often coexisted in patients. Moreover, well in advance of March 2000, there was specific guidance for treating the two conditions simultaneously, such as described in the Xenical Label. Therefore, a person of ordinary skill in the art would have been motivated to combine the use of a known DP-IV inhibitor with an anti-obesity agent, such as orlistat.

EACH FEATURE OF CLAIMS 12, 19, 20 AND 21 IS DISCLOSED BY ASHWORTH, VILLHAUER, RAAG, HANESSIAN AND THE MEVACOR LABEL

185. As discussed above, Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), Hanessian (Ex. 1010), and the Mevacor Label (Ex. 1014) can be considered prior art to the '186 patent.

Claim 12:

"A pharmaceutical combination comprising a compound as defined in claim 1 and an antidiabetic agent other than a DP4 inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent."

Claim 19:

"The combination as defined in claim 12 wherein the lipid modulating agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, an ACAT inhibitor, a cholesteryl ester transfer protein inhibitor, or an ATP citrate lyase inhibitor."

Claim 20:

"The combination as defined in claim 19 wherein the lipid modulating agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, implitapide, CP-529,414, avasimibe, TS-962, MD-700, and/or LY295427."

186. Claims 12, 19, and 20 of the '186 patent further provide the limitations of additional therapeutic agent compositions, which are combined with the claimed DP-IV inhibitors. Each of claims 12, 19, and 20 recites a lipid-modulating agent, among other aspects.

187. The Mevacor Label discloses the FDA-approved uses of the lipid-modulating agent, Mevacor (i.e., lovastatin), and supporting studies. As indicated in the Mevacor label, "poorly controlled **diabetes** mellitus" was considered a

"secondary cause[ ] for **hypercholesterolemia** . . ." Ex. 1014, p. 0010. (emphasis added). According to the Mevacor Label, Mevacor (i.e., lovastatin) "is a specific inhibitor of **HMG-CoA reductase**." *Id.* at 0007 (emphasis added).

188. Mevacor is one of the specific lipid-modulating agents recited in claim 20, and thus falls within the scope of anti-obesity agents as recited in claims 12 and 21. Mevacor (i.e., lovastatin) is also a HMG-CoA reductase, as recited in claim 19.

189. As was well known in the art as of March 2000, and as evidenced by the Mevacor Label, the conditions of hypercholesterolemia and type 2 diabetes often coexisted in patients. Moreover, well in advance of March 2000, there was specific guidance for treating the two conditions simultaneously, such as described in the Mevacor Label. Therefore, a person of ordinary skill in the art would have been motivated to combine the use of a known DP-IV inhibitor with a lipid-modulating agent, such as lovastatin.

Claim 21:

> **"The combination as defined in claim 19 wherein the compound as defined in claim 1 is present in a weight ratio to the lipid-modulating agent within the range from about 0.01 to about 100:1."**

190. Claim 21 of the '186 patent further provides the limitation of a dosage range for the claimed DP-IV inhibitors in combination with a lipid-modulating agent.

191. The Mevacor Label provides dosages for Mevacor as follows: "[t]he recommended dosing range is 20-80 mg/day in a single or two divided doses; the maximum recommended dose is 80 mg/day." Ex. 1014, p. 0014.

192. The '186 patent provides the following guidance regarding dosages for the compounds of structure I:

> The dose for adults is preferably between 10 and 1,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

Ex. 1001, col. 21, l. 67 to col. 22, l. 3.

193. Villhauer discloses "for most larger primates, a daily dosage of from about 0.1 mg to about 250 mg, preferably from about 1 mg to about 100 mg" of the disclosed N-glycyl-2-cyanopyrrolidines. Ex. 1008, p. 19, ll. 18-19. This range overlaps with the '186 patent's disclosed adult dosage range of 10-1000 mg. Ex. 1001, col. 21, l. 67 to col. 22, l. 3. The Mevacor Label also provides dosages for Mevacor as follows: "[t]he recommended dosing range is 20-80 mg/day in a single or two divided doses; the maximum recommended dose is 80 mg/day." Ex. 1014, p. 0014.

194. Using the dosage ranges provided by Villhauer for the claimed DP-IV inhibitors (i.e., 0.1 mg to 250 mg/day) and the Mevacor Label (i.e., 20 to 80 mg/day), the weight ratio of the compound of the claimed DP-IV inhibitors to a lipid-modulating agent (e.g., lovastatin) would be 0.00125 to 12.5: 1. This dosage overlaps with the range recited in claim 21 of "from about 0.01 to about 100:1."

195. As discussed in detail above, the combined treatment of type 2 diabetes and hypercholesterolemia was well known in the art. Thus, a person of ordinary skill would have been motivated in March 2000 to administer a DP-IV inhibitor in combination with a lipid-modulating agent. A person of ordinary skill in the art in March 2000, also would have considered it routine to determine the weight ratio between the compounds of the ’186 patent of structure I and lipid-modulating agents (e.g., orlistat) and would have reasonably expected that dosage ratio to fall, at least in part, within the scope of the broad range recited in claim 21 (i.e., about 0.01 to about 100:1).

196. Notably, the ’186 patent does not provide any examples or specific guidance describing the dosages of the claimed DP-IV inhibitors of structure I, much less the ratio between those compounds and lipid-modulating agents. Instead, the ’186 patent recites generally accepted dosages for known lipid-modulating agents and a very broad dosage range for claimed DP-IV inhibitors. Further, there is no suggestion of any special effect, such as synergy, in combining the claimed DP-IV inhibitors with known lipid-modulating agents.

EACH FEATURE OF CLAIM 16 IS DISCLOSED BY ASHWORTH, VILLHAUER, RAAG, HANESSIAN AND THE GLUCOPHAGE LABEL

197. As discussed above, Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), Hanessian (Ex. 1010), and the Glucophage Label (Ex. 1012) can be considered prior art to the ’186 patent.

Claim 16:

"The combination as defined in claim 13 wherein the compound as defined in claim 1 is present in a weight ratio to the antidiabetic agent within the range from about 0.01 to about 100:1."

198. Claim 16 of the '186 patent further provides the limitation of a dosage range for the claimed DP-IV inhibitors in combination with another antidiabetic agent.

199. Villhauer discloses "for most larger primates, a daily dosage of from about 0.1 mg to about 250 mg, preferably from about 1 mg to about 100 mg" of the disclosed N-glycyl-2-cyanopyrrolidines. Ex. 1008, p. 19, ll. 18-19. This range overlaps with the '186 patent's disclosed adult dosage range of 10-1000 mg. Ex. 1001, col. 21, l. 67 to col. 22, l. 3. The Glucophage Label provides dosages for Glucophage (i.e., metformin) as follows: "[i]n general, clinically significant responses are not seen at doses below 1500 mg per day . . . [and] GLUCOPHAGE may be given to a maximum daily dose of 2550 mg per day." Ex. 1012, p. 0048.

200. Using the dosage ranges provided by Villhauer for the claimed DP-IV inhibitors (i.e., 0.1 mg to 250 mg/day) and the Glucophage Label (i.e., 1,500 to 2,550 mg/day), the weight ratio of the compound of structure I to the antidiabetic agent (e.g., metformin) would be 0.00004 to 0.17:1. This dosage range overlaps with the range recited in claim 16 of "from about 0.01 to about 100:1."

201. The Glucophage Label describes co-administration of a plurality of antidiabetic agents. For example, it describes a "study of GLUCOPHAGE and

glyburide, alone and in combination . . . in obese patients with type 2 diabetes," (Ex. 1012, p. 0017) where glyburide is also an antidiabetic agent for use in treating type 2 diabetes. Therefore, a person of ordinary skill would have been motivated to use a combination of antidiabetic agents for the treatment of type 2 diabetes, including in combination with a DP-IV inhibitor.

202. A person of ordinary skill in the art in March 2000, also would have considered it routine to determine the weight ratio between the DP-IV inhibitors of structure I in the '186 patent and a second antidiabetic agent (e.g., metformin) and would have reasonably expected that dosage ratio to fall, at least in part, within the scope of the broad range recited in claim 21 (i.e., about 0.01 to about 100:1). Indeed, the range is so broad that those of ordinary skill in the art would have considered it to be simply an invitation for further experimentation.

203. Notably, the '186 patent does not provide any examples or specific guidance describing the dosages of the claimed DP-IV inhibitors of structure I, much less the ratio between those compounds and other antidiabetic agents. Instead, the '186 patent recites generally accepted dosages for known antidiabetic agents and a very broad dosage range for claimed DP-IV inhibitors. Further, there is no suggestion of any special effect, such as synergy, in combining the claimed DP-IV inhibitors with other known antidiabetic agents.

X. CONCLUDING STATEMENTS

204. In signing this declaration, I understand that the declaration will be files as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be

subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

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

Dated: June 4, 2015

By: /David P. Rotella/
David P. Rotella, Ph.D.

XI. APPENDIX – LIST OF EXHIBITS

Exhibit	Description
1001	U.S. Reissue Patent 44,186 E to Robl et al. (reissued Apr. 30, 2013)
1002	U.S. Patent No. 6,395,767 to Robl et al. (issued May 28, 2002)
1004	*Curriculum Vitae* of David P. Rotella, Ph.D.
1005	File History of U.S. Patent No. 6,395,767 to Robl et al.
1006	File History of U.S. Reissue Patent 44,186 E to Robl et al.
1007	Doreen M. Ashworth et al., *2-cyanopyrrolidides as potent, stable inhibitors of dipeptidyl peptidase IV*, 6 BIOORG. & MED. CHEM. LTRS. 1163 (1996)
1008	WO Patent App. Pub. No. 98/19998 to Villhauer (pub'd May 14,1998)
1009	Reetta Raag & Thomas L. Poulos, *Crystal Structure of Cytochrome P-450$_{CAM}$ Complexed with Camphane, Thiocamphor, and Adamantane: Factors Controlling P-450 Substrate Hydroxylation*, 30 BIOCHEMISTRY 2674 (1991)
1010	Stephen Hanessian et al., *The Synthesis of Enantiopure ω-Methanoprolines and ω-Methanopipecolic Acids by a Novel Cyclopropanation Reaction: The "Flattening" of Proline*, 36 ANGEW. CHEM. ED. ENGL. 1881 (1997)
1011	WO Patent App. Pub. No. 99/38501 to Bachovchin et al. (pub'd Aug. 5, 1999)
1012	GLUCOPHAGE Label (available by FOIA Jan. 8, 1998)
1013	XENICAL Label (available by FOIA Aug. 9, 1999)
1014	MEVACOR Label (available by FOIA Sept. 15, 1994)

Exhibit	Description
1015	Jian Lin et al., *Inhibitin of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics*, 95 PROC. NATL. ACAD. SCI. USA 14020 (1998)
1016	Howared E. Hoffman et al., *Pharmacokinetics and Metabolism of Rimantadine Hydrochloride in Mice and Dogs*, 32(11) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 1699 (1988)
1017	Christopher A. Lipinski et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*, 23 ADV. DRUG DELIV. REV. 3 (1996)
1018	Hansch et al., *Cluster Analysis and the Design of Congener Sets, in* SUBSTITUENT CONSTANTS FOR CORRELATION ANALYSIS IN CHEMISTRY AND BIOLOGY 48 (John Wiley & Sons1979)
1019	Lindley A. Cates, *Calculation of Drug Solubilities by Pharmacy Students*, 45 Am. J. Pharm. Educ. 11 (1981)
1020	Walter A. Korfmacher et al., *HPLC-API/MS/MS: a powerful tool for integrating drug metabolism into the drug discovery process*, 2 DRug Disc. Today 532 (1997)
1021	C. Y. Chiou et al., *The Cholinergic Effects and Rates of Hydrolysis of Conformationally Rigid Analogs of Acetylcholine*, 166 *J. Pharm. Exp. Ther*. 243 (1969)
1022	Daniel E. Koshland, Jr., *The Key-Lock Theory and the Induced Fit Theory*, 33 ANGEW. CHEM. ED. ENGL. 2375 (1994)
1023	E.J. Ariëns & A. M. Simonis, *Optimalization of Pharmacokinetics – An Essential Aspect of Drug Development – by Metabolic Stabilization, Pharmacochem. Lib., in* 4 PHARMACOCHEM. LIB. 165 (1982)

Exhibit	Description
1024	R. Scott Obach, *Prediction of Human Clearance of Twenty-nine Drugs from Hepatic Microsomal Intrinsic Clearance Data: An Examination of In Vitro Half-life Approach and Nonspecific Binding to Microsomes*, 27 DRUG METAB. DISPOS. 1350 (1999)
1025	Yung-chi Cheng & William H. Prusoff, *Relationship Between the Inhibition Constant (K_I) and the Concentration of Inhibitor which Causes 50 Per Cent Inhibition (I_{50}) of an Enzymatic Reaction*, 22 Biochem. Pharmacol. 3099 (1973)
1026	Debnath Pal & Pinak Chakrabarti, *Cis Peptide Bonds in Proteins: Residues Involved, their Conformations, Interactions and Location*, 294 J. of Mol. Biol. 271 (1999)
1027	U.S. Provisional Patent Application No. 60/1888,555 to Robl