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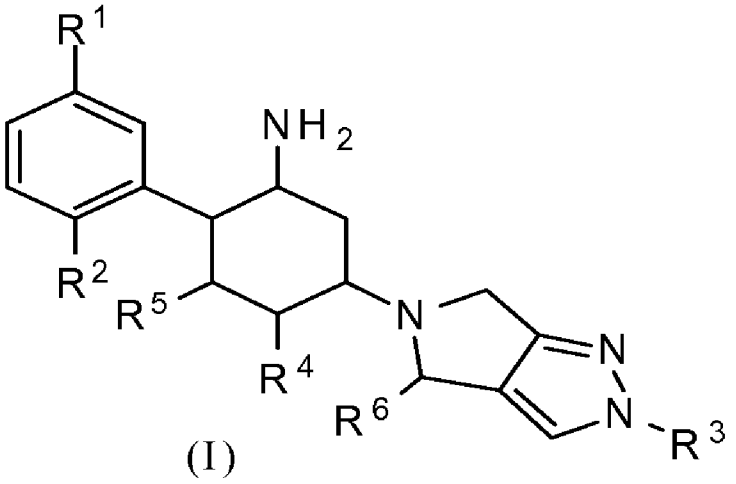
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(54) **Title**: TREATING DIABETES WITH DIPEPTIDYL PEPTIDASE-IV INHIBITORS



(I)

(57) **Abstract**: The present invention is directed to novel substituted dihydropyrrolopyrazoles of structural Formula I which are inhibitors of the dipeptidyl peptidase-N enzyme and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly Type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase IV enzyme is involved.

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TREATING DIABETES WITH DIPEPTIDYL PEPTIDASE-IV INHIBITORS

FIELD OF THE INVENTION

The present invention relates to substituted dihydropyrrolopyrazoles which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DPP-4 inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly Type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In Type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DPP-4") enzyme have also been found useful for the treatment of diabetes, particularly Type 2 diabetes [See WO 97/40832; WO 98/19998; U.S. Patent No. 5,939,560; U.S. Patent No. 6,303,661; U.S. Patent No. 6,699,871; U.S. Patent No. 6,166,063; Bioorg. Med. Chem. Lett., 6: 1163-1166 (1996); Bioorg. Med. Chem. Lett., 6: 2745-2748 (1996); D.J. Drucker in Exp. Opin. Invest. Drugs, 12: 87-100 (2003); K. Augustyns, et al., Exp. Opin. Ther. Patents, 13: 499-510 (2003); Ann E. Weber, J. Med. Chem., 47: 4135-4141 (2004); J.J. Holst, Exp. Opin. Emerg. Drugs, 9: 155-166 (2004); D. Kim, et al., J. Med. Chem., 48: 141-151 (2005); K. Augustyns, Exp. Opin. Ther. Patents, 15: 1387-1407 (2005); H.-U. Demuth in Biochim. Biophys. Acta, 1751: 33-44 (2005); and R. Mentlein, Exp. Opin. Invest. Drugs, 14: 57-64 (2005).

Additional patent publications that disclose DPP-4 inhibitors useful for the treatment of diabetes are the following: WO 2006/009886 (26 January 2006); WO 2006/039325 (13 April 2006); WO 2006/058064 (1 June 2006); WO 2006/127530 (30 November 2006); WO 2007/024993 (1 March 2007); WO 2007/070434 (21 June 2007); WO 2007/087231 (2 August 2007); WO 07/097931 (30 August 2007); WO 07/126745 (8 November 2007); WO 07/136603 (29 November 2007); WO 08/060488 (22 May 2008); WO2009025784; WO2010056708; WO2011037793; WO2011028455 and WO2011146358.

The usefulness of DPP-4 inhibitors in the treatment of Type 2 diabetes is based on the fact that DPP-4 *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DPP-4 leads to decreased inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DPP-4 inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DPP-4 inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DPP-4 is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

DPP-4 inhibitors also have other therapeutic utilities, as discussed herein. New compounds are needed so that improved DPP-4 inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions. In particular, there is a need for DPP-4 inhibitors that are selective over other members of the family of serine peptidases that includes quiescent cell proline dipeptidase (QPP), DPP8, and DPP9 [see G. Lankas, et al., "Dipeptidyl Peptidase-IV Inhibition for the Treatment of Type 2 Diabetes: Potential Importance of Selectivity Over Dipeptidyl Peptidases 8 and 9," Diabetes, 54: 2988-2994 (2005); N.S. Kang, et al., "Docking-based 3D-QSAR study for selectivity of DPP4, DPP8, and DPP9 inhibitors," Bioorg. Med. Chem. Lett., 17: 3716-3721 (2007)].

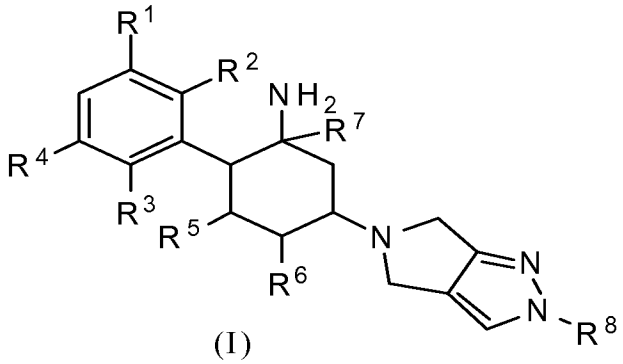
The therapeutic potential of DPP-4 inhibitors for the treatment of Type 2 diabetes is discussed by (i) D.J. Drucker, Exp. Opin. Invest. Drugs, 12: 87-100 (2003); (ii) K. Augustyns, et al., Exp. Opin. Ther. Patents, 13: 499-510 (2003); (iii) J.J. Holst, Exp. Opin. Emerg. Drugs, 9: 155-166 (2004); (iv) H.-U. Demuth, et al., Biochim. Biophys. Acta, 1751: 33-44 (2005); (v) R. Mentlein, Exp. Opin. Invest. Drugs, 14: 57-64 (2005); (vi) K. Augustyns, "Inhibitors of proline-specific dipeptidyl peptidases: DPP IV inhibitors as a novel approach for the treatment of Type 2 diabetes," Exp. Opin. Ther. Patents, 15: 1387-1407 (2005); (vii) D.J. Drucker and M.A. Nauck, "The incretin system: GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in Type 2 diabetes," The Lancet, 368: 1696-1705 (2006); (viii) T.W. von Geldern and J.M. Trevillyan, ""The Next Big Thing" in Diabetes: Clinical Progress on DPP-IV Inhibitors," Drug Dev. Res., 67: 627-642 (2006); (ix) B.D. Green et al., "Inhibition of dipeptidyl peptidase IV activity as a therapy of Type 2 diabetes," Exp. Opin. Emerging Drugs, 11: 525-539 (2006); (x) J.J. Holst and C.F. Deacon, "New Horizons in Diabetes Therapy," Immun., Endoc. & Metab. Agents in Med. Chem., 7: 49-55 (2007); (xi) R.K. Campbell, "Rationale for Dipeptidyl Peptidase 4 Inhibitors: a New Class of Oral Agents for the Treatment of Type 2 Diabetes Mellitus," Ann. Pharmacother., 41: 51-60 (2007); (xii) Z. Pei, "From the bench to the bedside: Dipeptidyl peptidase IV inhibitors, a new class of oral antihyperglycemic agents," Curr. Opin. Drug Discovery Development, 11: 512-532 (2008); and (xiii) J.J. Holst, et al., "Glucagon-like peptide-1, glucose homeostasis, and diabetes, Trends in Molecular Medicine, 14: 161-168 (2008). Specific DPP-4 inhibitors either already approved or under clinical investigation for the treatment of Type 2 diabetes include sitagliptin, vildagliptin, saxagliptin, alogliptin, carmegliptin, melogliptin, and dutogliptin.

SUMMARY OF THE INVENTION

The present invention is directed to substituted dihydropyrrolopyrazoles which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DPP-4 inhibitors") and which may be useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly Type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to substituted dihydropyrrolopyrazoles that are useful as inhibitors of dipeptidyl peptidase-IV. Compounds of the present invention are described by structural Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein

R^1, R^2 and R^4 are independently selected from the group consisting of C_{1-6}alkyl, halogen and hydrogen;

R^3 is hydrogen or halogen or, taken together with R^5, form a C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy;

R^5 is hydrogen, halogen, heterocycle, C_{3-7}cycloalkyl or, taken together with the carbon R^5 is attached, form a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or, taken together with R^3, form a C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or, taken together with R^6, form an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy;

R^6 is hydrogen, heterocycle, C_{3-7}cycloalkyl or, together with the carbon R^6 is attached, form a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or taken together with R^5 form an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of –OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy;

R^7 is selected from the group consisting of hydrogen C_{1-6}alkyl, C_{1-6}alkylOH and C_{1-6}alkoxy; wherein R^5, R^6, and R^7 cannot be simultaneously hydrogen; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}alkyl, SO_2C_{1-6}alkyl, and SO_2C_{3-6}cycloalkyl.

With regard to the compounds described herein, R^1, R^2 and R^4 are independently selected from the group consisting of C_{1-6}alkyl, halogen and hydrogen. In certain embodiments, R^1 is selected from the group consisting of C_{1-6}alkyl, halogen and hydrogen. In other

embodiments, R^2 is selected from the group consisting of C_{1-6}alkyl, halogen and hydrogen. In still other embodiments, R^4 is selected from the group consisting of C_{1-6}alkyl, halogen and hydrogen.

In one embodiment, R^1 is hydrogen. In another embodiment, R^1 is halogen. Suitable halogens include but are not limited to, fluorine, chlorine, bromine and iodine. In still another embodiment, R^1 is C_{1-6}alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl.

In one embodiment, R^2 is hydrogen. In another embodiment, R^2 is halogen. Suitable halogens include but are not limited to, fluorine, chlorine, bromine and iodine. In still another embodiment, R^2 is C_{1-6}alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl.

In one embodiment, R^4 is hydrogen. In another embodiment, R^4 is halogen. Suitable halogens include but are not limited to, fluorine, chlorine, bromine and iodine. In still another embodiment, R^4 is C_{1-6}alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl.

In certain embodiments of the compounds described herein, R^1 and R^3 are fluorine. In other embodiments, R^2 and R^4 are fluorine.

With regard to the compounds described herein, R^3 is hydrogen or halogen or, taken together with R^5, form a C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, R^3 is hydrogen. In another embodiment, R^3 is halogen. Suitable halogens include but are not limited to, fluorine, chlorine, bromine and iodine.

In yet another embodiment, R^3 is taken together with R^5 and forms a C_{5-7}cycloalkyl. Suitable, cycloalkyls include but are not limited to, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl can be unsubstituted. Alternatively the cycloalkyl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In another embodiment, R^3 is taken together with R^5 and forms a 5-7 membered heterocycle. Suitable heterocycles include but are not limited to, tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone.

The heterocycle can be unsubstituted. Alternatively the heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In certain embodiments, R^3 is taken together with R^5 to form a cyclohexyl or tetrahydropyran, wherein the cyclohexyl is unsubstituted or substituted with 1-3 substituents selected from the group consisting of C_{1-6}alkyl, halogen and C_{1-6}alkoxy.

In regard to the compounds described herein, R^5 is hydrogen, halogen, heterocycle, C_{3-7}cycloalkyl or, taken together with the carbon R^5 is attached, form a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or, taken together with R^3, form a C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or, taken together with R^6, form an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy.

In one embodiment, R^5 is hydrogen. In another embodiment, R^5 is halogen. Suitable halogens include but are not limited to, fluorine, chlorine, bromine and iodine. In another embodiment, R^5 is a heterocycle. Suitable heterocycles include, but are not limited to, Suitable heterocycles include but are not limited to, tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone. The heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In yet another embodiment, R^5 is C_{3-7}cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl can be unsubstituted. Alternatively, the cycloalkyl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted

with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In still other embodiments, R^5 is taken together with the carbon to which R^5 is attached, and forms a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, R^5 is taken together with the carbon to which R^5 is attached, and forms a C_{3-7}cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Alternatively, the cycloalkyl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In another embodiment, R^5 is taken together with the carbon to which R^5 is attached, and forms a 4-7 membered heterocycle. Suitable heterocycles include but are not limited to, tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone. The heterocycle can be unsubstituted. Alternatively the heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In yet another embodiment, R^3 is taken together with R^5 and forms a C_{5-7}cycloalkyl. Suitable, cycloalkyls include but are not limited to, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl can be unsubstituted. Alternatively the cycloalkyl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In another embodiment, R^5 is taken together with R^3 and forms a 5-7 membered heterocycle. Suitable heterocycles include but are not limited to, tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane,

dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone.

The heterocycle can be unsubstituted. Alternatively the heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In certain embodiments, R^5 is taken together with R^3 to form a cyclohexyl or tetrahydropyran, wherein the cyclohexyl is unsubstituted or substituted with 1-3 substituents selected from the group consisting of C_{1-6}alkyl, halogen and C_{1-6}alkoxy.

In certain embodiments of the compounds described herein, R^5 is taken together with R^6 and forms an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In certain embodiments, R^5 is taken together with R^6 and forms an aryl. Suitable aryls include, but are not limited to, phenyl and naphthyl. The aryl can be unsubstituted. Alternatively, the aryl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the aryl is substituted with one substituent. In one embodiment, the aryl is substituted with two substituents. In one embodiment, the aryl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In other embodiments, R^5 is taken together with R^6 and forms a C_{5-7}cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl can be unsubstituted. Alternatively, the cycloalkyl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In certain embodiments, R^5 is taken together with R^6 and forms a 5-7 membered heterocycle. Suitable heterocycles include but are not limited to, tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone.

The heterocycle can be unsubstituted. Alternatively the heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen

and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In regard to the compounds described herein, R^6 is hydrogen, heterocycle, C_{3-7}cycloalkyl or, together with the carbon R^6 is attached, form a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or taken together with R^5 form an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of –OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy.

In one embodiment, R^6 is hydrogen. In another embodiment, R^6 is a heterocycle. Suitable heterocycles include, but are not limited to, Suitable heterocycles include but are not limited to, tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone. The heterocycle can be unsubstituted. Alternatively the heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In yet another embodiment, R^6 is C_{3-7}cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl can be unsubstituted. Alternatively the cycloalkyl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In still other embodiments, R^6 is taken together with the carbon R^6 is attached, and forms a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, R^6 is taken together with the carbon R^6 is attached, and forms a C_{3-7}cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl can be unsubstituted. Alternatively the cycloalkyl can be substituted with 1-3 substituents selected from

the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In another embodiment, R^6 is taken together with the carbon R^6 is attached, and forms a 4-7 membered heterocycle. Suitable heterocycles include but are not limited to, tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone. The heterocycle can be unsubstituted. Alternatively the heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In certain embodiments of the compounds described herein, R^6 is taken together with R^5 and forms an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In certain embodiments, R^5 is taken together with R^6 and forms an aryl. Suitable aryls include, but are not limited to, phenyl and naphthyl. The aryl can be unsubstituted. Alternatively the aryl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the aryl is substituted with one substituent. In one embodiment, the aryl is substituted with two substituents. In one embodiment, the aryl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In other embodiments, R^6 is taken together with R^5 and forms a C_{5-7}cycloalkyl. Suitable cycloalkyls include, but are not limited to, Suitable cycloalkyls include, but are not limited to, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl can be unsubstituted. Alternatively, the cycloalkyl can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the cycloalkyl is substituted with one substituent. In one embodiment, the cycloalkyl is substituted with two substituents. In one embodiment, the cycloalkyl is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

In certain embodiments, R^6 is taken together with R^5 and forms a 5-7 membered heterocycle. Suitable heterocycles include but are not limited to, tetrahydrofuran (THF),

dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one and pyridone.

The heterocycle can be unsubstituted. Alternatively the heterocycle can be substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy. In one embodiment, the heterocycle is substituted with one substituent. In one embodiment, the heterocycle is substituted with two substituents. In one embodiment, the heterocycle is substituted with three substituents. Suitable substituents include but are not limited to, -OH, methyl, ethyl, fluorine, chlorine and methoxy.

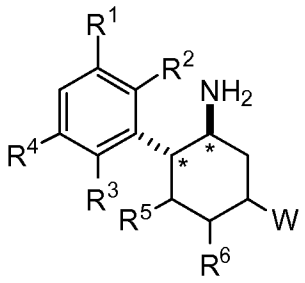
In one embodiment, R^6 is taken with the carbon it is attached to and forms a C_{1-6}alkyl, wherein the C_{1-6}alkyl is unsubstituted or substituted with 1-3 substituents selected from the group consisting of –OH and flourine. In another embodiment, R^6 is heterocycle, wherein the heterocycle is furan. In yet another embodiment, R^6 is taken with R^5 and forms a C_{5-7}cycloalkyl or phenyl.

In regard to the compounds described herein, R^7 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}alkylOH and C_{1-6}alkoxy. In certain embodiments, R^7 is hydrogen. In other embodiments, R^7 is C_{1-6}alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl. In still other embodiments, R^7 is C_{1-6}alkylOH. Suitable alcohols include, but are not limited to, methanol and ethanol. In yet other embodiments, R^7 is C_{1-6}alkoxy. Suitable alkoxies include, but are not limited to, methoxy, ethoxy and isopropoxy.

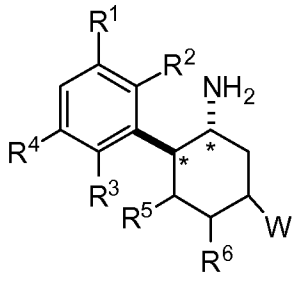
In certain embodiments of the compounds described herein, R^5, R^6, and R^7 are not simultaneously hydrogen.

With regard to the compounds described herein, R^8 is selected from the group consisting of hydrogen, C_{1-6}alkyl, SO_2C_{1-6}alkyl, and SO_2C_{3-6}cycloalkyl. In certain embodiments, R^8 is hydrogen. In other embodiments, R^8 is C_{1-6}alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl. In still other embodiments, R^8 is SO_2C_{1-6}alkyl. Suitable alkylsulfonyls include, but are not limited to, methylsulfonyl ($MeSO_2$-), ethylsulfonyl and isopropylsulfonyl. In other embodiments, R^8 is SO_2C_{3-6}cycloalkyl. Suitable cylcoalkylsulfonyls include, but are not limited to, cyclopropylsulfonyl. In one embodiment, R^8 is selected from the group consisting of hydrogen, SO_2CH_3, and SO_2cyclopropyl.

Also described herein are compounds of Formula Ia and Ib having the indicated stereochemical configuration at the two stereogenic carbon atoms marked with an *:

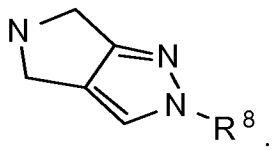


(Ia)

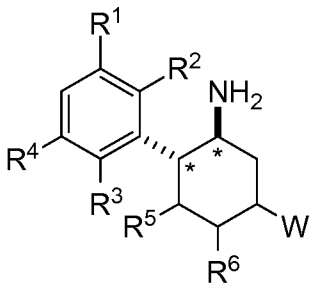


(Ib)

wherein W is

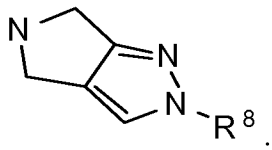


In one embodiment, compounds described herein have a Formula Ia having the indicated absolute stereochemical configuration at the two stereogenic carbon atoms marked with an *:

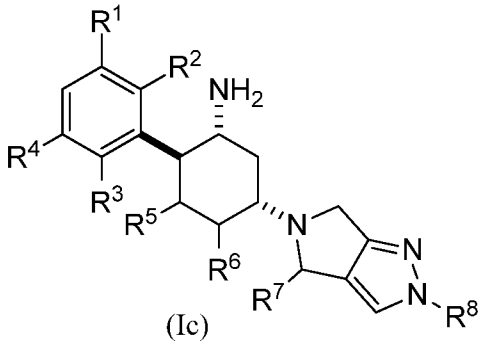


(Ia)

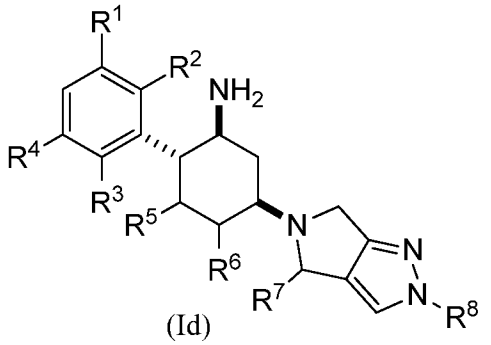
wherein W is



Also described herein are compounds of Formulae Ic or Id having the indicated stereochemical configuration at the three stereogenic carbon atoms marked with an *:

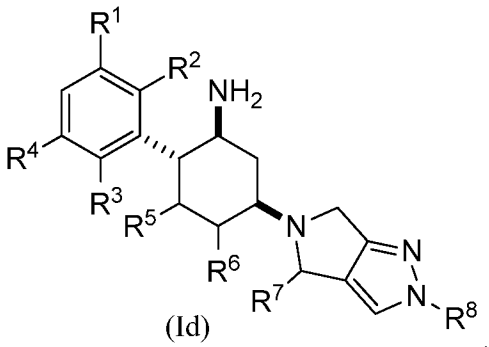


(Ic)



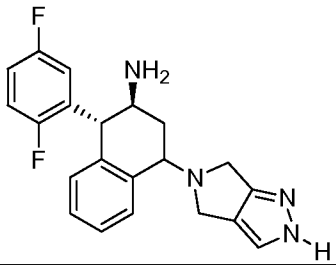
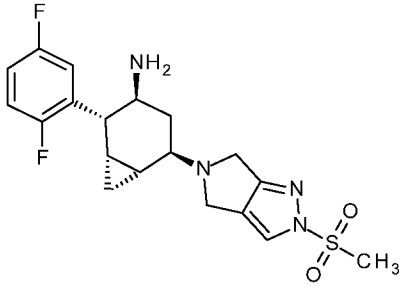
(Id)

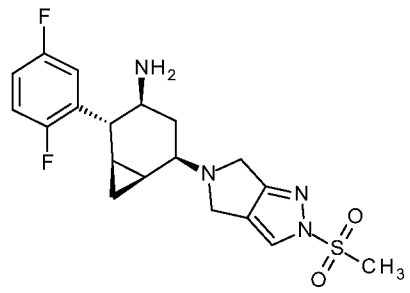
In one embodiment, compounds described herein have a Formula Id having the indicated absolute stereochemical configuration at the three stereogenic carbon atoms marked with an *:



(Id)

Non-limiting examples of compounds of the present invention that are useful as dipeptidyl peptidase-IV inhibitors include:

Structure	Example	IC50 (nM)
	1	>1,000
	2	9.0

	3	5.4

or a pharmaceutically acceptable salt thereof.

Also described herein are pharmaceutical compositions which comprise a compound described herein and a pharmaceutically acceptable carrier.

Also described herein are methods of treating a condition selected from the group consisting of insulin resistance, hyperglycemia, Type 2 diabetes in a mammal in need thereof comprising administering at least one of the compounds described herein to a mammal in need thereof.

Also described herein is the use of a compound described herein in the manufacture of a medicament for use in treating a condition selected from the group consisting of insulin resistance, hyperglycemia, Type 2 diabetes in a mammal in need thereof.

As used herein the following definitions are applicable.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy and alkanoyl, means carbon chains which may be linear or branched, and combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like. Where the specified number of carbon atoms permits, e.g., from C_{3-10}, the term alkyl also includes cycloalkyl groups, and combinations of linear or branched alkyl chains combined with cycloalkyl structures. When no number of carbon atoms is specified, C_{1-6} is intended.

"Cycloalkyl" is a subset of alkyl and means a saturated carbocyclic ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. A cycloalkyl group generally is monocyclic unless stated otherwise. Cycloalkyl groups are saturated unless otherwise defined.

The term “alkoxy” refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C_{1-10} alkoxy), or any number within this range [i.e., methoxy (MeO-), ethoxy, isopropoxy, etc].

The term “alkylsulfonyl” refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e.g., C_{1-6} alkylsulfonyl), or any number within this range [i.e., methylsulfonyl ($MeSO_2$-), ethylsulfonyl, isopropylsulfonyl, etc.].

The term "alkyloxycarbonyl" refers to straight or branched chain esters of a carboxylic acid derivative of the present invention of the number of carbon atoms specified (e.g., C_{1-6} alkyloxycarbonyl), or any number within this range [i.e., methyloxycarbonyl (MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl].

"Aryl" means a mono- or polycyclic aromatic ring system containing carbon ring atoms. The preferred aryls are monocyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls. The most preferred aryl is phenyl.

The term "heterocyclyl" refers to saturated or unsaturated non-aromatic rings or ring systems containing at least one heteroatom selected from O, S and N, further including the oxidized forms of sulfur, namely SO and SO_2. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, pyrrolidinone, oxazolidin-2-one, imidazolidine-2-one, pyridone, and the like.

"Heteroaryl" means an aromatic or partially aromatic heterocycle that contains at least one ring heteroatom selected from O, S and N. Heteroaryls also include heteroaryls fused to other kinds of rings, such as aryls, cycloalkyls and heterocycles that are not aromatic. Examples of heteroaryl groups include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridinyl, 2-oxo-(1*H*)-pyridinyl (2-hydroxy-pyridinyl), oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidinyl, pyrazinyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, dihydrobenzofuranyl, indolinyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, carbazolyl, benzodioxolyl, quinoxalinyl, purinyl, furazanyl, isobenzylfuranyl, benzimidazolyl, benzofuranyl, benzothienyl, quinolyl, indolyl, isoquinolyl, dibenzofuranyl, imidazo[1,2-*a*]pyridinyl, [1,2,4-triazolo][4,3-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4-triazolo][1,5-*a*]pyridinyl, 2-oxo-1,3-benzoxazolyl, 4-oxo-3*H*-quinazolinyl, 3-oxo-[1,2,4]-triazolo[4,3-*a*]-2*H*-pyridinyl, 5-oxo-[1,2,4]-4*H*-oxadiazolyl, 2-oxo-[1,3,4]-3*H*-oxadiazolyl, 2-oxo-1,3-dihydro-2*H*-imidazolyl, 3-oxo-2,4-dihydro-3*H*-1,2,4-triazolyl, and the like. For heterocyclyl and heteroaryl groups, rings and ring systems containing from 3-15 atoms are included, forming 1-3 rings.

"Halogen" refers to fluorine, chlorine, bromine and iodine. Chlorine and fluorine are generally preferred. Fluorine is most preferred when the halogens are substituted on an alkyl or alkoxy group (e.g. CF_3O and CF_3CH_2O).

The compounds of the present invention contain one or more asymmetric centers and can thus occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures, and individual diastereomers. In particular the compounds of the present invention have an asymmetric center at the stereogenic carbon atoms marked with an * in formulae Ia, Ib, Ic and Id. Additional asymmetric centers may be present depending upon the nature of the various

substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

Formula I shows the structure of the class of compounds without preferred stereochemistry. Formulae Ia and Ib show the preferred stereochemistry at the stereogenic carbon atoms to which are attached the NH_2 and W groups on the ring. Formulae Ic and Id show the preferred stereochemistry at the stereogenic carbon atoms to which are attached the NH_2, W, and dihydropyrrolopyrazole on the ring.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

In the compounds of generic Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to

include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

It will be understood that, as used herein, references to the compounds of structural formula I are meant to also include the pharmaceutically acceptable salts, and also salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine,

histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present invention, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as *O*-acetyl, *O*-pivaloyl, *O*-benzoyl, and *O*-aminoacyl, can be employed. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

Solvates, and in particular, the hydrates of the compounds of structural formula I are included in the present invention as well.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

The subject compounds are useful in a method of inhibiting the dipeptidyl peptidase-IV enzyme in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as inhibitors of dipeptidyl peptidase-IV enzyme activity.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

The present invention is further directed to a method for the manufacture of a medicament for inhibiting dipeptidyl peptidase-IV enzyme activity in humans and animals comprising combining a compound of the present invention with a pharmaceutically acceptable carrier or diluent. More particularly, the present invention is directed to the use of a compound of structural formula I in the manufacture of a medicament for use in treating a condition selected from the group consisting of hyperglycemia, Type 2 diabetes, obesity, and a lipid disorder in a mammal, wherein the lipid disorder is selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom inhibition of dipeptidyl peptidase-IV enzyme activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which

results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as inhibitors of dipeptidyl peptidase-IV enzyme activity may be demonstrated by methodology known in the art. Inhibition constants are determined as follows. A continuous fluorometric assay is employed with the substrate Gly-Pro-AMC, which is cleaved by DPP-4 to release the fluorescent AMC leaving group. The kinetic parameters that describe this reaction are as follows: K_m = 50 μM; k_{cat} = 75 s^{-1}; k_{cat}/K_m = 1.5 x 10^6 $M^{-1}s^{-1}$. A typical reaction contains approximately 50 pM enzyme, 50 μM Gly-Pro-AMC, and buffer (100 mM HEPES, pH 7.5, 0.1 mg/ml BSA) in a total reaction volume of 100 μL. Liberation of AMC is monitored continuously in a 96-well plate fluorometer using an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Under these conditions, approximately 0.8 μM AMC is produced in 30 minutes at 25 degrees C. The enzyme used in these studies was soluble (transmembrane domain and cytoplasmic extension excluded) human protein produced in a baculovirus expression system (Bac-To-Bac, Gibco BRL). The kinetic constants for hydrolysis of Gly-Pro-AMC and GLP-1 were found to be in accord with literature values for the native enzyme. To measure the dissociation constants for compounds, solutions of inhibitor in DMSO were added to reactions containing enzyme and substrate (final DMSO concentration is 1%). All experiments were conducted at room temperature using the standard reaction conditions described above. To determine the dissociation constants (K_i), reaction rates were fit by non-linear regression to the Michaelis-Menton equation for competitive inhibition. The errors in reproducing the dissociation constants are typically less than two-fold.

The compounds of structural formula (I), particularly the compounds of Examples 1-3 shown below, had activity in inhibiting the dipeptidyl peptidase-IV enzyme in the aforementioned assays, generally with an IC_{50} of less than about 1 μM, and more typically of

less than 0.1 μM. Such results are indicative of the intrinsic activity of the compounds of the present invention for use as inhibitors the dipeptidyl peptidase-IV enzyme activity.

Dipeptidyl peptidase-IV enzyme (DPP-4) is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DPP-4 is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes in humans or other species.

Accordingly, the subject compounds are useful in a method for the prevention or treatment of the following diseases, disorders and conditions.

Type II Diabetes and Related Disorders: It is well established that the incretins GLP-1 and GIP are rapidly inactivated *in vivo* by DPP-4. Studies with DPP-$4^{(-/-)}$-deficient mice and preliminary clinical trials indicate that DPP-4 inhibition increases the steady state concentrations of GLP-1 and GIP, resulting in improved glucose tolerance. By analogy to GLP-1 and GIP, it is likely that other glucagon family peptides involved in glucose regulation are also inactivated by DPP-4 (eg. PACAP). Inactivation of these peptides by DPP-4 may also play a role in glucose homeostasis. The DPP-4 inhibitors of the present invention therefore have utility in the treatment of type II diabetes and in the treatment and prevention of the numerous conditions that often accompany Type II diabetes, including Syndrome X (also known as Metabolic Syndrome), reactive hypoglycemia, and diabetic dyslipidemia. Obesity, discussed below, is another condition that is often found with Type II diabetes that may respond to treatment with the compounds of this invention.

The following diseases, disorders and conditions are related to Type 2 diabetes, and therefore may be treated, controlled or in some cases prevented, by treatment with the compounds of this invention: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component. In Syndrome X, also known as Metabolic Syndrome, obesity is thought to promote insulin resistance, diabetes, dyslipidemia, hypertension, and increased cardiovascular risk. Therefore, DPP-4 inhibitors may also be useful to treat hypertension associated with this condition.

Obesity: DPP-4 inhibitors may be useful for the treatment of obesity. This is based on the observed inhibitory effects on food intake and gastric emptying of GLP-1 and GLP-2. Exogenous administration of GLP-1 in humans significantly decreases food intake and slows gastric emptying (Am. J. Physiol., 277: R910-R916 (1999)). ICV administration of GLP-1 in rats and mice also has profound effects on food intake (Nature Medicine, 2: 1254-1258 (1996)). This inhibition of feeding is not observed in GLP-1R$^{(-/-)}$ mice, indicating that these effects are mediated through brain GLP-1 receptors. By analogy to GLP-1, it is likely that GLP-2 is also regulated by DPP-4. ICV administration of GLP-2 also inhibits food intake, analogous to the effects observed with GLP-1 (Nature Medicine, 6: 802-807 (2000)). In addition, studies with DPP-4 deficient mice suggest that these animals are resistant to diet-induced obesity and associated pathology (e.g. hyperinsulinonemia).

Cardiovascular Disease: GLP-1 has been shown to be beneficial when administered to patients following acute myocardial infarction, leading to improved left ventricular function and reduced mortality after primary angioplasty (Circulation, 109: 962-965 (2004)). GLP-1 administration is also useful for the treatment of left ventricular systolic dysfunction in dogs with dilated cardiomyopathy and ischemic induced left ventricular dysfunction, and thus may prove useful for the treatment of patients with heart failure (US2004/0097411). DPP-4 inhibitors are expected to show similar effects through their ability to stabilize endogenous GLP-1.

Growth Hormone Deficiency: DPP-4 inhibition may be useful for the treatment of growth hormone deficiency, based on the hypothesis that growth-hormone releasing factor (GRF), a peptide that stimulates release of growth hormone from the anterior pituitary, is cleaved by the DPP-4 enzyme *in vivo* (WO 00/56297). The following data provide evidence that GRF is an endogenous substrate: (1) GRF is efficiently cleaved *in vitro* to generate the inactive product GRF[3-44] (BBA 1122: 147-153 (1992)); (2) GRF is rapidly degraded in plasma to GRF[3-44]; this is prevented by the DPP-4 inhibitor diprotin A; and (3) GRF[3-44] is found in the plasma of a human GRF transgenic pig (J. Clin. Invest., 83: 1533-1540 (1989)). Thus DPP-4 inhibitors may be useful for the same spectrum of indications which have been considered for growth hormone secretagogues.

Intestinal Injury: The potential for using DPP-4 inhibitors for the treatment of intestinal injury is suggested by the results of studies indicating that glucagon-like peptide-2 (GLP-2), a likely endogenous substrate for DPP-4, may exhibit trophic effects on the intestinal epithelium (Regulatory Peptides, 90: 27-32 (2000)). Administration of GLP-2 results in increased small bowel mass in rodents and attenuates intestinal injury in rodent models of colitis and enteritis.

Immunosuppression: DPP-4 inhibition may be useful for modulation of the immune response, based upon studies implicating the DPP-4 enzyme in T cell activation and in chemokine processing, and efficacy of DPP-4 inhibitors in *in vivo* models of disease. DPP-4 has been shown to be identical to CD26, a cell surface marker for activated immune cells. The expression of CD26 is regulated by the differentiation and activation status of immune cells. It is generally

accepted that CD26 functions as a co-stimulatory molecule in *in vitro* models of T cell activation. A number of chemokines contain proline in the penultimate position, presumably to protect them from degradation by non-specific aminopeptidases. Many of these have been shown to be processed *in vitro* by DPP-4. In several cases (RANTES, LD78-beta, MDC, eotaxin, SDF-1alpha), cleavage results in an altered activity in chemotaxis and signaling assays. Receptor selectivity also appears to be modified in some cases (RANTES). Multiple N-terminally truncated forms of a number of chemokines have been identified in *in vitro* cell culture systems, including the predicted products of DPP-4 hydrolysis.

DPP-4 inhibitors have been shown to be efficacious immunosuppressants in animal models of transplantation and arthritis. Prodipine (Pro-Pro-diphenyl-phosphonate), an irreversible inhibitor of DPP-4, was shown to double cardiac allograft survival in rats from day 7 to day 14 (Transplantation, 63: 1495-1500 (1997)). DPP-4 inhibitors have been tested in collagen and alkyldiamine-induced arthritis in rats and showed a statistically significant attenuation of hind paw swelling in this model [Int. J. Immunopharmacology, 19:15-24 (1997) and Immunopharmacology, 40: 21-26 (1998)]. DPP-4 is upregulated in a number of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, Graves' disease, and Hashimoto's thyroiditis (Immunology Today, 20: 367-375 (1999)).

HIV Infection: DPP-4 inhibition may be useful for the treatment or prevention of HIV infection or AIDS because a number of chemokines which inhibit HIV cell entry are potential substrates for DPP-4 (Immunology Today 20: 367-375 (1999)). In the case of SDF-1alpha, cleavage decreases antiviral activity (PNAS, 95: 6331-6 (1998)). Thus, stabilization of SDF-1alpha through inhibition of DPP-4 would be expected to decrease HIV infectivity.

Hematopoiesis: DPP-4 inhibition may be useful for the treatment or prevention of hematopiesis because DPP-4 may be involved in hematopoiesis. A DPP-4 inhibitor, Val-Boro-Pro, stimulated hematopoiesis in a mouse model of cyclophosphamide-induced neutropenia (WO 99/56753).

Neuronal Disorders: DPP-4 inhibition may be useful for the treatment or prevention of various neuronal or psychiatric disorders because a number of peptides implicated in a variety of neuronal processes are cleaved *in vitro* by DPP-4. A DPP-4 inhibitor thus may have a therapeutic benefit in the treatment of neuronal disorders. Endomorphin-2, beta-casomorphin, and substance P have all been shown to be *in vitro* substrates for DPP-4. In all cases, *in vitro* cleavage is highly efficient, with k_{cat}/K_m about 10^6 $M^{-1}s^{-1}$ or greater. In an electric shock jump test model of analgesia in rats, a DPP-4 inhibitor showed a significant effect that was independent of the presence of exogenous endomorphin-2 (Brain Research, 815: 278-286 (1999)). Neuroprotective and neuroregenerative effects of DPP-4 inhibitors were also evidenced by the inhibitors' ability to protect motor neurons from excitotoxic cell death, to protect striatal innervation of dopaminergic neurons when administered concurrently with MPTP, and to promote recovery of striatal innervation density when given in a therapeutic manner following MPTP treatment [see Yong-Q. Wu, et al., "Neuroprotective Effects of Inhibitors of Dipeptidyl

peptidase-IV In Vitro and In Vivo," Int. Conf. On Dipeptidyl Aminopeptidases: Basic Science and Clinical Applications, September 26-29, 2002 (Berlin, Germany)].

Anxiety: Rats naturally deficient in DPP-4 have an anxiolytic phenotype (WO 02/34243; Karl *et al.*, Physiol. Behav. 2003). DPP-4 deficient mice also have an anxiolytic phenotype using the porsolt and light/dark models. Thus DPP-4 inhibitors may prove useful for treating anxiety and related disorders.

Memory and Cognition: GLP-1 agonists are active in models of learning (passive avoidance, Morris water maze) and neuronal injury (kainate-induced neuronal apoptosis) as demonstrated by During *et al.* (Nature Med. 9: 1173-1179 (2003)). The results suggest a physiological role for GLP-1 in learning and neuroprotection. Stabilization of GLP-1 by DPP-4 inhibitors are expected to show similar effects

Myocardial Infarction: GLP-1 has been shown to be beneficial when administered to patients following acute myocardial infarction (Circulation, 109: 962-965 (2004)). DPP-4 inhibitors are expected to show similar effects through their ability to stabilize endogenous GLP-1.

Tumor Invasion and Metastasis: DPP-4 inhibition may be useful for the treatment or prevention of tumor invasion and metastasis because an increase or decrease in expression of several ectopeptidases including DPP-4 has been observed during the transformation of normal cells to a malignant phenotype (J. Exp. Med., 190: 301-305 (1999)). Up- or down-regulation of these proteins appears to be tissue and cell-type specific. For example, increased CD26/DPP-4 expression has been observed on T cell lymphoma, T cell acute lymphoblastic leukemia, cell-derived thyroid carcinomas, basal cell carcinomas, and breast carcinomas. Thus, DPP-4 inhibitors may have utility in the treatment of such carcinomas.

Benign Prostatic Hypertrophy: DPP-4 inhibition may be useful for the treatment of benign prostatic hypertrophy because increased DPP-4 activity was noted in prostate tissue from patients with BPH (Eur. J. Clin. Chem. Clin. Biochem., 30: 333-338 (1992)).

Sperm motility/male contraception: DPP-4 inhibition may be useful for the altering sperm motility and for male contraception because in seminal fluid, prostatosomes, prostate derived organelles important for sperm motility, possess very high levels of DPP-4 activity (Eur. J. Clin. Chem. Clin. Biochem., 30: 333-338 (1992)).

Gingivitis: DPP-4 inhibition may be useful for the treatment of gingivitis because DPP-4 activity was found in gingival crevicular fluid and in some studies correlated with periodontal disease severity (Arch. Oral Biol., 37: 167-173 (1992)).

Osteoporosis: DPP-4 inhibition may be useful for the treatment or prevention of osteoporosis because GIP receptors are present in osteoblasts.

Stem Cell Transplantation: Inhibition of DPP-4 on donor stem cells has been shown to lead to an enhancement of their bone marrow homing efficiency and engraftment, and an increase in survival in mice (Christopherson, et al., Science, 305:1000-1003 (2004)). Thus DPP-4 inhibitors may be useful in bone marrow transplantation.

The compounds of the present invention have utility in treating or preventing one or more of the following conditions or diseases: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type 2 diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, (35) anxiety, (36) memory deficit, (37) cognition deficit, (38) stroke, (39) Alzheimer's disease, and other conditions that may be treated or prevented by inhibition of DPP-4.

The compounds of the present invention are further useful in methods for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other therapeutic agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, suppression or amelioration of diseases or conditions for whicl compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also include therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be administered separately or in the same pharmaceutical composition in combination with a compound of the formulas described herein include, but are not limited to:

(1) other dipeptidyl peptidase-IV (DPP-4) inhibitors (e.g., sitagliptin, alogliptin, linagliptin, vildagliptin, saxagliptin, omarigliptin);

(2) insulin sensitizers, including (i) PPARγ agonists, such as the glitazones (e.g. pioglitazone, AMG 131, MBX2044, mitoglitazone, lobeglitazone, IDR-105, rosiglitazone, and balaglitazone), and other PPAR ligands, including (1) PPARα/γ dual agonists (e.g., ZYH2,

ZYH1, GFT505, chiglitazar, muraglitazar, aleglitazar, sodelglitazar, and naveglitazar); (2) PPARα agonists such as fenofibric acid derivatives (e.g., gemfibrozil, clofibrate, ciprofibrate, fenofibrate, bezafibrate), (3) selective PPARγ modulators (SPPARγM's), (e.g., such as those disclosed in WO 02/060388, WO 02/08188, WO 2004/019869, WO 2004/020409, WO 2004/020408, and WO 2004/066963); and (4) PPARγ partial agonists; (ii) biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin hydrochloride, and extended-release formulations thereof, such as Glumetza™, Fortamet™, and GlucophageXR™; and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors (e.g., ISIS-113715 and TTP814);

(3) insulin or insulin analogs (e.g., insulin detemir, insulin glulisine, insulin degludec, insulin glargine, insulin lispro and inhalable formulations of each);

(4) leptin and leptin derivatives and agonists;

(5) amylin and amylin analogs (e.g., pramlintide);

(6) sulfonylurea and non-sulfonylurea insulin secretagogues (e.g., tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, meglitinides, nateglinide and repaglinide);

(7) α-glucosidase inhibitors (e.g., acarbose, voglibose and miglitol);

(8) glucagon receptor antagonists (e.g., such as those disclosed in WO 98/04528, WO 99/01423, WO 00/39088, and WO 00/69810);

(9) incretin mimetics, such as GLP-1, GLP-1 analogs, derivatives, and mimetics; and GLP-1 receptor agonists (e.g., dulaglutide, semaglutide, albiglutide, exenatide, liraglutide, lixisenatide, taspoglutide, CJC-1131, and BIM-51077, including intranasal, transdermal, and once-weekly formulations thereof);

(10) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (e.g., simvastatin, lovastatin, pravastatin, crivastatin, fluvastatin, atorvastatin, pitavastatin and rosuvastatin), (ii) bile acid sequestering agents (e.g., colestilan, colestimide, colesevalam hydrochloride, colestipol, cholestyramine, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) inhibitors of cholesterol absorption, (e.g., ezetimibe), and (iv) acyl CoA:cholesterol acyltransferase inhibitors, (e.g., avasimibe);

(11) HDL-raising drugs, (e.g., niacin and nicotinic acid receptor agonists, and extended-release versions thereof; MK-524A, which is a combination of niacin extended-release and the DP-1 antagonist MK-524);

(12) antiobesity compounds;

(13) agents intended for use in inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs or NSAIDs, glucocorticoids, and selective cyclooxygenase-2 or COX-2 inhibitors;

(14) antihypertensive agents, such as ACE inhibitors (e.g.,lisinopril, enalapril, ramipril, captopril, quinapril, and tandolapril), A-II receptor blockers (e.g., losartan, candesartan, irbesartan, olmesartan medoxomil, valsartan, telmisartan, and eprosartan), renin inhibitors (e.g., aliskiren), beta blockers, and calcium channel blockers;

(15) glucokinase activators (GKAs) (e.g., AZD6370);

(16) inhibitors of 11β-hydroxysteroid dehydrogenase type 1, (e.g., such as those disclosed in U.S. Patent No. 6,730,690, and LY-2523199);

(17) CETP inhibitors (e.g., anacetrapib, and torcetrapib);

(18) inhibitors of fructose 1,6-bisphosphatase, (e.g., such as those disclosed in U.S. Patent Nos. 6,054,587; 6,110,903; 6,284,748; 6,399,782; and 6,489,476);

(19) inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2);

(20) AMP-activated Protein Kinase (AMPK) activators;

(21) other agonists of the G-protein-coupled receptors: (i) GPR-109, (ii) GPR-119 (e.g., MBX2982 and PSN821), and (iii) GPR-40 (e.g., TAK875, 5-[4-[[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2-methylpyridine-3-yl]-2,3-dihydro-1H-indene-1-yl]oxy]phenyl]isothiazole-3-ol 1-oxide, 5-(4-((3-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)phenyl)methoxy)phenyl)iso, 5-(4-((3-(2-methyl-6-(3-hydroxypropoxy)pyridine-3-yl)-2-methylphenyl)methoxy)phenyl)isothiazole-3-ol 1-oxide, and 5-[4-[[3-[4-(3-aminopropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]isothiazole-3-ol 1-oxide);

(22) SSTR3 antagonists (e.g., such as those disclosed in WO 2009/001836);

(23) neuromedin U receptor agonists (e.g., such as those disclosed in WO 2009/042053, including, but not limited to, neuromedin S (NMS));

(24) SCD inhibitors;

(25) GPR-105 antagonists (e.g., such as those disclosed in WO 2009/000087);

(26) SGLT inhibitors (e.g., ASP1941, SGLT-3, empagliflozin, dapagliflozin, canagliflozin, BI-10773, PF-04971729, remogloflozin, TS-071, tofogliflozin, ipragliflozin, and LX-4211);

(27) inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2);

(28) inhibitors of fatty acid synthase;

(29) inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2);

(30) agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19, GPR131, and M-BAR);

(31) ileal bile acid transporter inhibitors;

(32) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;

(33) PPAR agonists;

(34) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(35) IL-1b antibodies, (e.g., XOMA052 and canakinumab); and

(36) bromocriptine mesylate and rapid-release formulations thereof.

Of particular interest are metformin hydrochloride, pioglitazone, rosiglitazone, simvastatin, atorvastatin, or a sulfonylurea.

Antiobesity compounds that can be combined with compounds of Formula I include topiramate; zonisamide; naltrexone; phentermine; bupropion; the combination of bupropion and naltrexone; the combination of bupropion and zonisamide; the combination of topiramate and phentermine; fenfluramine; dexfenfluramine; sibutramine; lipase inhibitors, such as orlistat and cetilistat; melanocortin receptor agonists, in particular, melanocortin-4 receptor agonists; CCK-1 agonists; melanin-concentrating hormone (MCH) receptor antagonists; neuropeptide Y_1 or Y_5 antagonists (such as MK-0557); CB1 receptor inverse agonists and antagonists (such as rimonabant and taranabant); β_3 adrenergic receptor agonists; ghrelin antagonists; bombesin receptor agonists (such as bombesin receptor subtype-3 agonists); and 5-hydroxytryptamine-2c (5-HT2c) agonists, such as lorcaserin. For a review of anti-obesity compounds that can be combined with compounds of the present invention, see S. Chaki et al., "Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity," Expert Opin. Ther. Patents, 11: 1677-1692 (2001); D. Spanswick and K. Lee, "Emerging antiobesity drugs," Expert Opin. Emerging Drugs, 8: 217-237 (2003); J.A. Fernandez-Lopez, et al., "Pharmacological Approaches for the Treatment of Obesity," Drugs, 62: 915-944 (2002); and K.M. Gadde, et al., "Combination pharmaceutical therapies for obesity Exp. Opin. Pharmacother., 10: 921-925 (2009).

In another aspect of the invention, a pharmaceutical composition is disclosed which comprises one or more of the following agents:

(a) a compound of structural Formula I;

(b) one or more compounds selected from the group consisting of:

(1) other dipeptidyl peptidase-IV (DPP-4) inhibitors;

(2) insulin sensitizers, including (i) PPARγ agonists, such as the glitazones (e.g. AMG 131, MBX2044, mitoglitazone, lobeglitazone, IDR-105, pioglitazone, rosiglitazone, and balaglitazone) and other PPAR ligands, including (1) PPARα/γ dual agonists, such as ZYH1, YYH2, chiglitazar, GFT505, muraglitazar, aleglitazar, sodelglitazar, and naveglitazar, (2) PPARα agonists, such as fenofibric acid derivatives (e.g., gemfibrozil, clofibrate, ciprofibrate, fenofibrate and bezafibrate), (3) selective PPARγ modulators (SPPARγM's), and (4) PPARγ partial agonists; (ii) biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin hydrochloride, and extended-release formulations thereof, such as Glumetza®, Fortamet®, and GlucophageXR®; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, such as ISI-113715, and TTP814;

(3) sulfonylurea and non-sulfonylurea insulin secretagogues, (e.g., tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, and meglitinides, such as nateglinide and repaglinide);

(4) α-glucosidase inhibitors (e.g., acarbose, voglibose and miglitol);

(5) glucagon receptor antagonists;

(6) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (e.g., lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, pitavastatin, and

rosuvastatin), (ii) bile acid sequestering agents (e.g., colestilan, cholestyramine, colestimide, colesevelam hydrochloride, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (ii inhibitors of cholesterol absorption, (e.g., ezetimibe), and (iv) acyl CoA:cholesterol acyltransferase inhibitors (e.g., avasimibe);

(7) HDL-raising drugs, such as niacin or a salt thereof and extended-release versions thereof; MK-524A, which is a combination of niacin extended-release and the DP-1 antagonis MK-524; and nicotinic acid receptor agonists;

(8) antiobesity compounds;

(9) agents intended for use in inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and selective cyclooxygenase-2 (COX-2) inhibitors;

(10) antihypertensive agents, such as ACE inhibitors (e.g., enalapril, lisinopril, ramipril, captopril, quinapril, and tandolapril), A-II receptor blockers (e.g., losartan, candesartan, irbesartan, olmesartan medoxomil, valsartan, telmisartan, and eprosartan), renin inhibitors (e.g., aliskiren), beta blockers (e.g., calcium channel blockers);

(11) glucokinase activators (GKAs) (e.g., AZD6370);

(12) inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (e.g., such as those disclosed in U.S. Patent No. 6,730,690; WO 03/104207; and WO 04/058741);

(13) inhibitors of cholesteryl ester transfer protein (CETP), (e.g., torcetrapib and MK-0859);

(14) inhibitors of fructose 1,6-bisphosphatase (e.g., such as those disclosed in U.S. Patent Nos. 6,054,587; 6,110,903; 6,284,748; 6,399,782; and 6,489,476);

(15) inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2);

(16) AMP-activated Protein Kinase (AMPK) activators;

(17) agonists of the G-protein-coupled receptors: (i) GPR-109, (ii) GPR-119 (e.g MBX2982, and PSN821), and (iii) GPR-40 (e.g., TAK875, 5-[4-[[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2-methylpyridine-3-yl]-2,3-dihydro-1H-indene-1-yl]oxy]phenyl]isothiazole-3-ol 1-oxide, 5-(4-((3-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)phenyl)methoxy)phenyl)iso, 5-(4-((3-(2-methyl-6-(3-hydroxypropoxy)pyridine-3-yl)-2-methylphenyl)methoxy)phenyl)isothiazole-3-ol 1 oxide, and 5-[4-[[3-[4-(3-aminopropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]isothiazole-3-ol 1-oxide);

(18) SSTR3 antagonists (e.g., such as those disclosed in WO 2009/011836);

(19) neuromedin U receptor agonists (e.g., such as those disclosed in WO2009/042053, including, but not limited to, neuromedin S (NMS));

(20) inhibitors of stearoyl-coenzyme A delta-9 desaturase (SCD);

(21) GPR-105 antagonists (e.g., such as those disclosed in WO 2009/000087);

(22) inhibitors of glucose uptake, such as sodium-glucose transporter (SGLT) inhibitors and its various isoforms, such as SGLT-1; SGLT-2 (e.g., ASP1941, TS071, BI10773, tofogliflozin, LX4211, canagliflozin, dapagliflozin and remogliflozin; and SGLT-3);

(23) inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2);

(24) inhibitors of fatty acid synthase;

(25) inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2);

(26) agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19, GPR131, and M-BAR);

(28) bromocriptine mesylate and rapid-release formulations thereof, and

(29) IL-1b antibodies (e.g., XOMA052, and canakinumab); and

(c) a pharmaceutically acceptable carrier.

When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compoun of the present invention.

The weight ratio of the compound of the present invention to the second active ingredier may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also b within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting

agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in

1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment or prevention of conditions which require inhibition of dipeptidyl peptidase-IV enzyme activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 mg of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 mg to about 1000 mg, preferably from about 1 mg to about 50 mg. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 350 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Synthetic methods for preparing the compounds of the present invention are illustrated in the following Schemes and Examples. Starting materials are commercially available or may be made according to procedures known in the art or as illustrated herein.

The compounds of structural Formula I of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The Examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts, such as those described previously hereinabove. The free amine bases corresponding to the isolated salts can be generated by neutralization with a suitable base, such as aqueous sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, and potassium hydroxide, and extraction of the liberated amine free base into an organic solvent followed by evaporation. The amine free base isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate acid and subsequent evaporation, precipitation, or crystallization. All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electron-spray ion-mass spectroscopy.

Synthetic methods for preparing the compounds of the present invention are illustrated in the following Schemes and Examples. Starting materials are commercially available or may be made according to procedures known in the art or as illustrated herein.

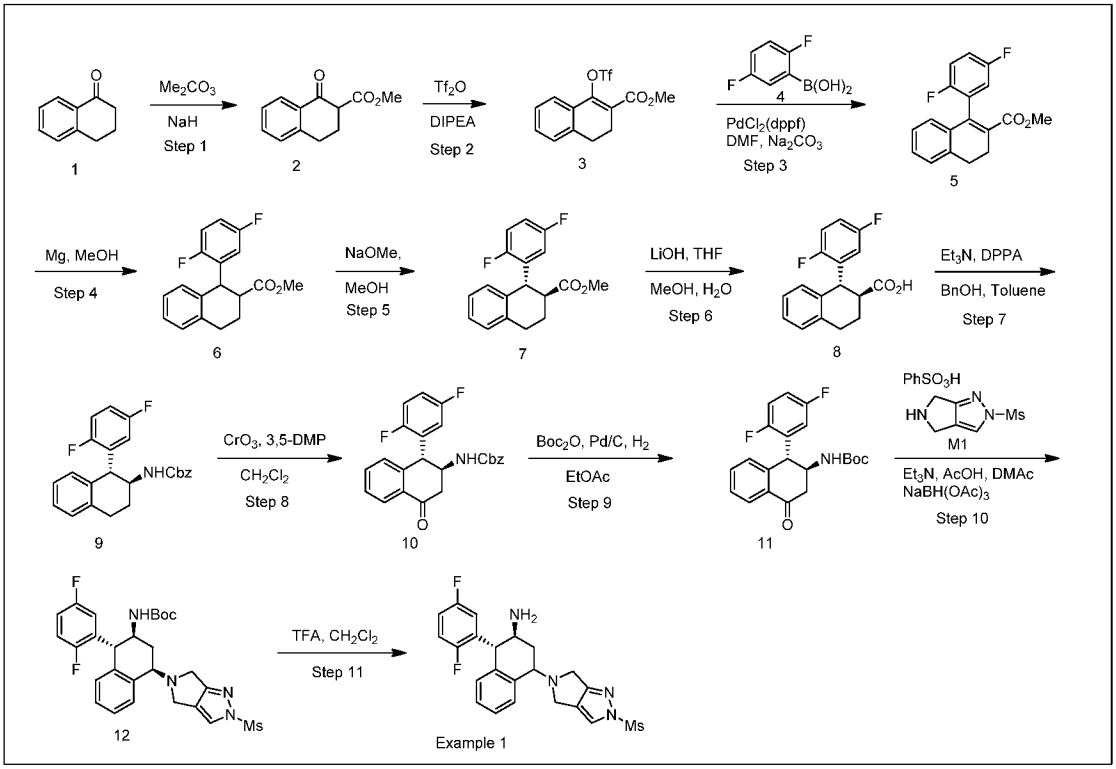
The following is a list of abbreviations that may be helpful when reading the description of the synthesis of the Intermediates and Examples shown below.

List of Abbreviations:

Alk	=	alkyl
Ar	=	aryl
Boc	=	*tert*-butoxycarbonyl
br	=	broad
CH_2Cl_2	=	dichloromethane

	d	=	doublet
	DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
	DEAD	=	diethyl azodicarboxylate
	DMA	=	*N,N*-dimethylacetamide
5	DMF	=	dimethylformamide
	DMSO	=	dimethyl sulfoxide
	ESI	=	electrospray ionization
	EtOAc	=	ethyl acetate
	HATU	=	*O*-(7-azabenzotriazol-1-yl)-*N,N,N,N'*-
10			tetramethyluronium hexafluorophosphate
	HOAc	=	acetic acid
	LC-MS	=	liquid chromatography-mass spectroscopy
	LiOH	=	lithium hydroxide
	m	=	multiplet
15	MeOH	=	methyl alcohol
	$MgSO_4$	=	magnesium sulfate
	MS	=	mass spectroscopy
	NaOH	=	sodium hydroxide
	Na_2SO_4	=	sodium sulfate
20	NMR	=	nuclear magnetic resonance spectroscopy
	PG	=	protecting group
	Ph	=	phenyl
	Rt or RT	=	room temperature
	s	=	singlet
25	t	=	triplet
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran

SCHEME 1



Example 1

Synthesis of 2: (Step 1)

To a solution of α-tetralone (10.0 g, 68.4 mmol) in dimethyl carbonate (64 mL) at room temperature was added NaH (3.28 g, 82 mmol) and stirred for 30 minutes. Toluene (213 mL) was added to the reaction mixture and heated at 80 °C for 2 hours. TLC shows incomplete reaction. Reaction was further continued for 30 minutes and allowed to come to room temperature. Reaction mixture was quenched with water (5.0 mL). Organic layer was separated, washed with water and brine, dried (Na_2SO_4), filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **2** as amorphous solid. Molecular Formula: $C_{12}H_{12}O_3$; LCMS purity: 52%; Expected: 204.1; Observed: 205.2 (M+1).

Synthesis of 3: (Step 2)

To a solution of **2** (1.0 g, 4.9 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added DIPEA (4.13 mL, 23.9 mmol) followed by trifluoromethanesulfonic anhydride (0.97 mL, 5.88 mmol). The reaction mixture was allowed to come to room temperature and continued the stirring for overnight. The reaction was quenched by addition of water. The organic layer was washed with citric acid solution and brine, dried (Na_2SO_4), filtered and concentrated under vacuum afforded triflate **3** which was used in the next step without further purification.

Synthesis of 5: (Step 3)

To a solution of triflate **3** (16.5 g, 49 mmol) and boronic acid **4** (11.40 g, 73.5 mmol) in DMF (490 mL) was added a solution of Na_2CO_3 (2M, 61.25 mL) and degassed with N_2 for 10 minutes. $PdCl_2(dppf).CH_2Cl_2$ (4.0 g, 4.9 mmol) was added to the reaction mixture under N_2 atmosphere and continued the stirring for 12 hours at room temperature. The reaction mixture was filtered through celite and concentrated under vacuum. The crude mass was dissolved in EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **5** as amorphous solid.
^1H NMR (400 MHz, $CDCl_3$): δ 7.21 - 7.30 (m, 2H), 7.02 - 7.17 (m, 3H), 6.86 (ddd, J = 3.05, 5.57, 8.47 Hz, 1H), 6.76 (d, J = 7.93 Hz, 1H), 3.60 (s, 3H), 2.92 - 3.00 (m, 2H), 2.75 - 2.83 (m, 2H).; Molecular Formula: $C_{18}H_{14}F_2O_2$; LCMS purity: 95.9%; Expected: 300.1; Observed: 301.2 (M+1).

Synthesis of 6: (Step 4)

To a stirred solution of **5** (2.0 g, 6.6 mmol) in methanol (51 mL) was added magnesium (1.94 g, 79.8 mmol) and the mixture was refluxed overnight under nitrogen atmosphere. The white precipitate formed was filtered over celite and the filtrate was evaporated under vacuum. The crude mass was purified through silica gel chromatography to afford **6**.
Molecular Formula: $C_{18}H_{16}F_2O_2$; GCMS Expected mass: 302; Observed: 302. ^1H NMR was not clean.

Synthesis of 7: (Step 5)

To a stirred solution of **6** (10.5 g, 34.7 mmol) in methanol (300 mL) was added 30% methanolic solution of NaOMe (7.5 mL g, 41.7 mmol) and the mixture was refluxed overnight under nitrogen atmosphere. The solvent evaporated under vacuum. The crude mass was purified through silica gel chromatography to afford **7**.
^1H NMR (400 MHz, $CDCl_3$): δ 7.11 - 7.18 (m, 2H), 6.96 - 7.11 (m, 2H), 6.86 - 6.96 (m, 1H), 6.79 (d, J = 7.74 Hz, 1H), 6.72 (ddd, J = 3.07, 5.67, 8.87 Hz, 1H), 4.70 (d, J = 8.80 Hz, 1H), 3.63 (s, 3H), 2.87 - 3.06 (m, 3H), 2.18 (dtd, J = 3.47, 5.22, 13.30 Hz, 1H), 2.01 - 2.12 (m, 1H).

Synthesis of 8: (Step 6)

To a solution of **7** (0.25 g, 0.82 mmol) in THF (1.64 mL) and MeOH (3.28 mL) was added a solution of $LiOH.H_2O$ (1M H_2O, 2.78 mL) at room temperature and stirred for 30 minutes. Reaction mixture was quenched with citric acid solution (pH 3 ~ 4) and extracted with EtOAc. Solvents were dried (Na_2SO_4), filtered, concentrated and purified through column to get acid **8**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 - 7.21 (m, 2H), 7.05 - 7.12 (m, 1H), 7.01 (dt, *J* = 4.54, 9.20 Hz, 1H), 6.87 - 6.96 (m, 1H), 6.81 (d, *J* = 7.74 Hz, 1H), 6.69 (ddd, *J* = 3.20, 5.67, 8.74 Hz, 1H), 4.71 (d, *J* = 8.00 Hz, 1H), 2.90 - 3.10 (m, 3H), 2.15 - 2.26 (m, 1H), 2.07 - 2.14 (m, 1H).; Molecular Formula: $C_{17}H_{14}F_2O_2$; GCMS Expected mass: 288.1; Observed: 288.1.

Synthesis of 9: (Step 7)

To a degassed solution of acid **8** (115 mg, 0.39 mmol) and benzyl alcohol (0.10 mL, 0.99 mmol) in toluene (6.2 mL) was added Et_3N (0.07 mL, 0.48 mmol) and DPPA (0.11 mL, 0.48 mmol) under nitrogen. The reaction mixture was heated at 100 °C for overnight. Solvents were removed under vacuum. Crude mixture was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **9** as viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 - 7.43 (m, 5H), 7.15 - 7.24 (m, 2H), 7.06 - 7.15 (m, 1H), 6.97 - 7.06 (m, 1H), 6.85 - 6.96 (m, 1H), 6.81 (d, *J* = 7.74 Hz, 1H), 6.51 - 6.60 (m, 1H), 4.99 - 5.09 (m, 2H), 4.92 (d, *J* = 7.47 Hz, 1H), 4.34 (d, *J* = 6.67 Hz, 1H), 4.16 (d, *J* = 8.00 Hz, 1H), 3.00 - 3.13 (m, 1H), 2.87 - 2.99 (m, 1H), 2.10 - 2.21 (m, 1H), 1.87 (dd, *J* = 5.87, 13.07 Hz, 1H).; Molecular Formula: $C_{24}H_{21}F_2NO_2$; LCMS purity: 87.2%; Expected: 393.2; Observed: 394.2 (M+1).

Synthesis of 10: (Step 8)

To a solution of **9** (1.40 g, 3.56 mmol) in CH_2Cl_2 (45 mL) at 0 °C was added 3,5-DMP (6.84 g, 71.2 mmol), followed by CrO_3 (7.12 g, 71.2 mmol) and continued for 2 hours. The reaction mixture was quenched with water and extracted with CH_2Cl_2. Combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **10** as viscous liquid.

^{1}H NMR (400 MHz, CD_3OD): δ 8.07 (d, *J* = 7.78 Hz, 1H), 7.53 (t, *J* = 7.53 Hz, 1H), 7.42 (t, *J* = 7.53 Hz, 1H), 7.23 - 7.39 (m, 3H), 7.04 - 7.21 (m, 4H), 6.92 (d, *J* = 8.03 Hz, 2H), 4.87 – 5.03 (m, 2H), 4.56 - 4.66 (m, 1H), 4.45 - 4.56 (m, 1H), 2.88 - 2.95 (m, 2H).; Molecular Formula: $C_{24}H_{19}F_2NO_3$; LCMS purity: 83.3%; Expected: 407.1; Observed: 408.2 (M+1).

Synthesis of 11: (Step 9)

To a solution of **10** (650 mg, 1.59 mmol) and Boc_2O (0.73 mL, 3.94 mmol) in EtOAc (10 mL) was added 10% Pd/C (130 mg). The reaction mixture was stirred under hydrogen atmosphere for overnight. The reaction mixture was filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **11** as viscous liquid.

^{1}H NMR (300 MHz, CD_3OD): δ 8.05 (d, *J* = 7.67 Hz, 1H), 7.51 (t, *J* = 7.45 Hz, 1H), 7.40 (t, *J* = 7.45 Hz, 1H), 6.99 - 7.23 (m, 2H), 6.91 (d, *J* = 7.45 Hz, 2H), 4.47 - 4.57 (m, 1H), 4.39 (d, *J* =

5.48 Hz, 1H), 2.77 - 2.94 (m, 2H), 1.27 (s, 9H).; Molecular Formula: $C_{21}H_{21}F_2NO_3$; LCMS purity: 94.5%; Expected: 373.2; Observed: 274.2 (M-99).

Synthesis of 12: (Step 10)

To a solution of **11** (260 mg, 0.69 mmol) in DMAc (1 mL) was added **M1** (288 mg, 0.84 mmol) followed by Et_3N (0.15 mL, 1.04 mmol) and stirred it for 5 minutes. AcOH (0.10 mL, 1.74 mmol) was added to the reaction mixture and continued the stirring for 30 minutes. $NaBH(OAc)_3$ (0.44 g, 2.09 mmol) was added to the reaction mixture and continued the stirring for 2 days. The reaction mixture was quenched with NH_4OH and extracted with EtOAc. Combined organics were concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **12**.

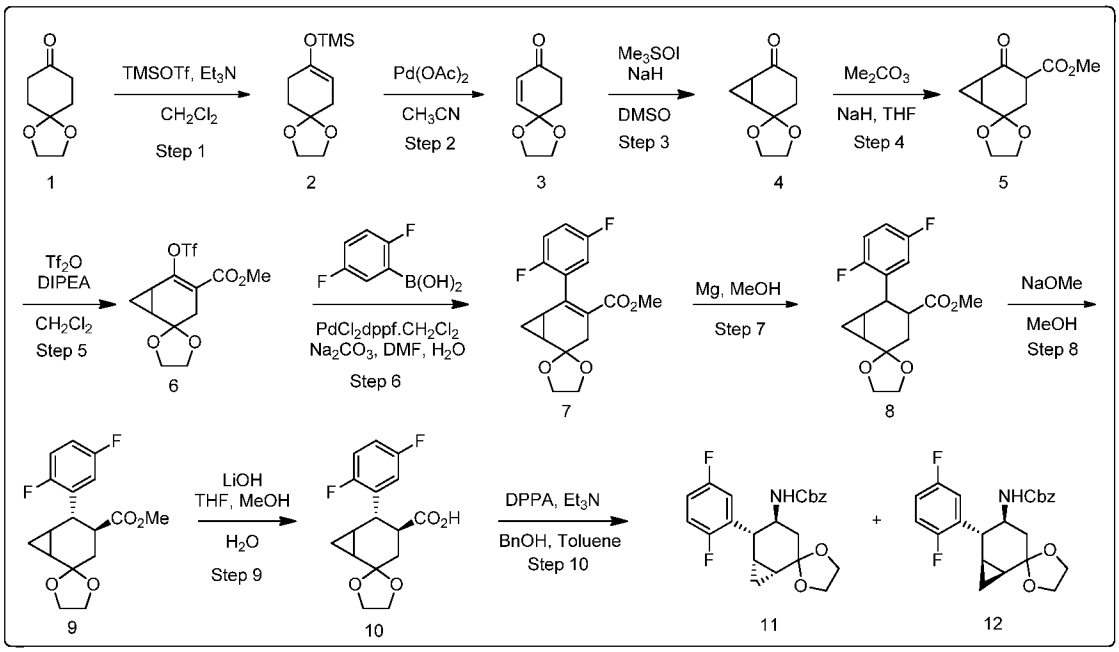
^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (br. s., 1H), 7.36 - 7.48 (m, 1H), 7.17 - 7.30 (m, 2H), 7.05 (dt, J = 4.40, 8.80 Hz, 1H), 6.91 (d, J = 7.04 Hz, 2H), 6.69 (ddd, J = 3.08, 5.50, 8.73 Hz, 1H), 4.65 (br. s., 1H), 4.55 (br. s., 1H), 4.29 (d, J = 8.22 Hz, 1H), 4.04 (br. s., 2H), 3.59 - 3.82 (m, 2H), 3.30 (s, 3H), 2.47 (br. s., 1H), 1.93 - 2.05 (m, 1H), 1.39 (s, 9H).; Molecular Formula: $C_{27}H_{30}F_2N_4O_4S$; LCMS purity: 84.2%; Expected: 544.2; Observed: 545.2 (M+1).

Synthesis of Example 1: (Step 11)

To a solution of **12** (20 mg, 0.036 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was was added TFA (0.1 mL) and continued the stirring for 30 minutes. Solvent was removed under vacuum and the crude mass was washed with n-hexane followed by Et_2O afforded **Example 1** as di-TFA salt.

^1H NMR (400 MHz, CD_3OD): δ 7.91 (s, 1H), 7.51 - 7.57 (m, 1H), 7.31 - 7.37 (m, 2H), 7.22 - 7.31 (m, 1H), 7.08 - 7.17 (m, 1H), 6.95 - 7.02 (m, 1H), 6.88 - 6.95 (m, 1H), 4.57 (d, J = 9.03 Hz, 1H), 4.19 - 4.38 (m, 4H), 3.76 - 3.89 (m, 2H), 3.37 (s, 3H), 2.71 (d, J = 13.55 Hz, 1H), 2.14 - 2.27 (m, 1H).; Molecular Formula: $C_{22}H_{22}F_2N_4O_2S$; HPLC purity: 99.4%; LCMS mass Expected: 444.1; Observed: 445.2 (M+1).

SCHEME 2



Example 2 and Example 3

Synthesis of 2 (Step 1):

A solution of trimethylsilyl trifluoromethanesulfonate (8.73 ml, 48 mmol) in dichloromethane (100 ml) was added over a 10 min period to a stirred solution of **1** (5.0 g, 32 mmol) and triethylamine (17.8 ml, 128 mmol) in dichloromethane (350 ml) at -5°C. The mixture was stirred for 15 min before the reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, dried, and evaporated under reduced pressure to leave a crude residue, which was filtered through a pad of silica using 1:1 EtOAc and petroleum ether as the eluent. The filtrate was evaporated under reduced pressure to give **2** as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76 - 4.68 (m, 1 H), 4.01 - 3.95 (m, 4 H), 2.29 - 2.25 (m, 2 H), 2.22 (ddd, J = 1.3, 5.9, 7.4 Hz, 2 H), 1.81 (t, J = 6.5 Hz, 2 H), 0.19 (s, 9 H).

Synthesis of 3 (Step 2):

Palladium(II) acetate (8.86 g, 39.4 mmol) was added to a solution of **2** (6.0 g, 26.3 mmol) in acetonitrile (250 ml) and the mixture was stirred for overnight at room temperature. The solvent was then evaporated under reduced pressure and the black residue was filtered through a pad of silica using EtOAc as the eluent. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution to remove traces of acetic acid. The organic phase was dried and evaporated under reduced pressure to give **3** a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 6.62 (dd, J = 0.8, 10.1 Hz, 1 H), 6.01 (d, J = 10.4 Hz, 1 H), 4.09 - 4.02 (m, 4 H), 2.64 (t, J = 6.5 Hz, 2 H), 2.25 - 2.17 (m, 2 H).

Synthesis of 4 (Step 3):

To a suspension of sodium hydride (142 mg, 3.56 mmol) in DMSO (4.0 mL) was added trimethylsulfoxonium iodide (783 mg, 3.56 mmol). After 20 min, a solution of enone (0.5 g, 3.24 mmol) in DMSO (4.0 mL) was added dropwise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic phases were combined, dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography afforded **4** as a viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 4.15 - 3.93 (m, 4 H), 2.46 - 2.27 (m, 2 H), 1.97 - 1.80 (m, 2 H), 1.80 - 1.70 (m, 2 H), 1.33 - 1.20 (m, 2 H).; Molecular Formula: $C_9H_{12}O_3$.; GCMS Expected: 168.1; Observed: 168.1 (M).

Synthesis of 5 (Step 4):

To a solution of **4** (1.20 g, 7.14 mmol) in dimethyl carbonate (6.6 mL) at room temperature was added NaH (342 mg, 8.57 mmol) and stirred at 80 °C for overnight. TLC shows complete conversion. Reaction mixture was quenched with ice water and extracted with EtOAc. Organic layer was separated, washed with water and brine, dried (Na_2SO_4), filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **5** as amorphous solid.

Molecular Formula: $C_{11}H_{14}O_5$; LCMS Expected: 226.1; Observed: 227.0 (M+1).

Synthesis of 6 (Step 5):

To a solution of **5** (1.52 g, 6.7 mmol) in CH_2Cl_2 (15 mL) at -78 °C was added DIPEA (5.64 mL, 33 mmol) followed by trifluoromethanesulfonic anhydride (1.32 mL, 8.0 mmol). The reaction mixture was allowed to come to room temperature and continued the stirring for overnight. TLC shows incomplete reaction. Trifluoromethanesulfonic anhydride (1.32 mL, 8.0 mmol) was added to the reaction mixture and continued for another 2 hours. The reaction was quenched by addition of aqueous citric acid solution. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under vacuum afforded triflate **6** which was used in the next step without further purification.

Synthesis of 7 (Step 6):

To a solution of triflate **6** (2.0 g, 6.6 mmol) and boronic acid (1.56 g, 9.9 mmol) in DMF (67 mL) was added a solution of Na_2CO_3 (2M, 8.25 mL) and degassed with N_2 for 10 minutes. $PdCl_2(dppf).CH_2Cl_2$ (0.53 g, 0.66 mmol) was added to the reaction mixture under N_2 atmosphere and continued the stirring for 12 hours at room temperature. Solvent was removed under vacuum. The crude mass was filtered through celite using EtOAc as eluent. The organic

layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **7** as amorphous solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 - 6.91 (m, 3 H), 4.17 - 4.02 (m, 4 H), 3.51 (s, 3 H), 2.87 (dd, J = 2.6, 17.7 Hz, 1 H), 2.37 (d, J = 17.6 Hz, 1 H), 1.76 - 1.69 (m, 1 H), 1.33 (dt, J = 5.3, 8.4 Hz, 1 H), 1.30 - 1.24 (m, 1 H), 1.23 - 1.16 (m, 1 H).; Molecular Formula: $C_{17}H_{16}F_2O_4$; LCMS purity: 65.4%; Expected: 322.1; Observed: 323.0 (M+1).

Synthesis of 8 (Step 7):

To a stirred solution of **7** (100 mg, 0.31 mmol) in methanol (5 mL) was added magnesium (75 mg, 3.1 mmol) and the mixture was refluxed overnight under nitrogen atmosphere. The white precipitate formed was filtered over celite and the filtrate was evaporated under vacuum. The crude mass was purified through silica gel chromatography to afford **8**. Molecular Formula: $C_{17}H_{18}F_2O_4$; LCMS purity: 93.4%; Expected: 324.1; Observed: 325.0 (M+1). ^{1}H NMR was not clean.

Synthesis of 9 (Step 8):

To a stirred solution of **8** (75 mg, 0.23 mmol) in methanol (2 mL) was added 25% methanolic solution of NaOMe (0.05 mL g, 0.28 mmol) and the mixture was refluxed overnight under nitrogen atmosphere. The solvents were evaporated under vacuum. The crude mass was dissolved in EtOAc and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under vacuum to afford **9** which was taken to the next step without further purification.

Synthesis of 10 (Step 9):

To a solution of **9** (1.0 g, 3.08 mmol) in THF (10 mL) and MeOH (1.0 mL) was added a solution of $LiOH.H_2O$ (0.26 g, 6.2 mmol) in H_2O (10 mL) at room temperature and stirred for 1 hour. TLC shows incomplete reaction. $LiOH.H_2O$ (0.26 g, 6.2 mmol) was added to the reaction mixture and continued for another 2 hours. The solvents were evaporated under vacuum. The crude mass was dissolved in water and washed with EtOAc. Aqueous layer was acidified with citric acid solution (pH 3 ~ 4) and extracted with EtOAc. Solvents were dried (Na_2SO_4), filtered, concentrated under vacuum to get acid **10**.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 - 6.94 (m, 2 H), 6.94 - 6.84 (m, 1 H), 4.11 - 3.94 (m, 4 H), 3.80 - 3.72 (m, 1 H), 2.69 (dt, J = 2.9, 11.9 Hz, 1 H), 2.10 - 1.97 (m, 1 H), 1.94 - 1.83 (m, 1 H), 1.50 - 1.35 (m, 2 H), 0.72 (q, J = 5.9 Hz, 1 H), 0.64 (dt, J = 5.9, 9.1 Hz, 1 H).; Molecular Formula: $C_{16}H_{16}F_2O_4$; LCMS purity: 96.31%; Expected: 310.1; Observed: 311.0 (M+1).

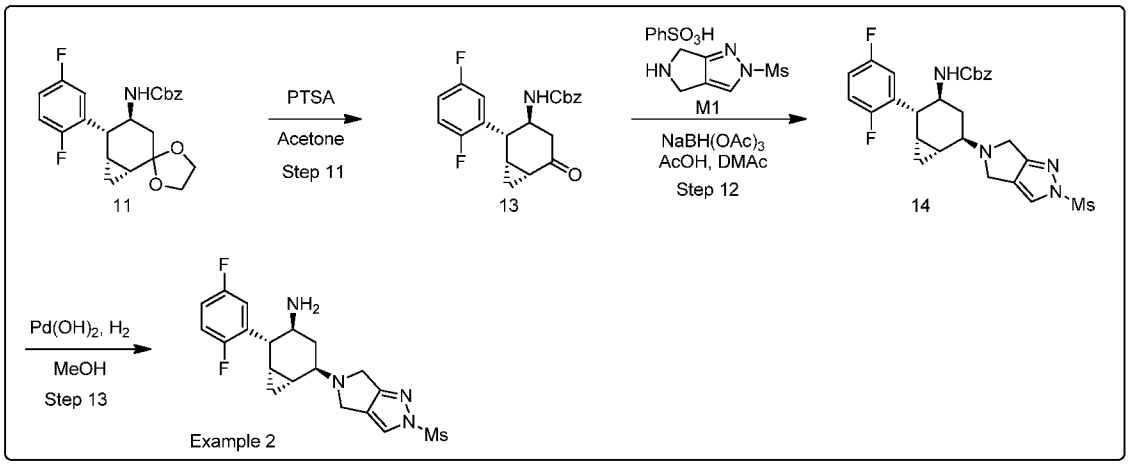
Synthesis of 11 and 12 (Step 10):

To a degassed solution of acid **10** (100 mg, 0.32 mmol) and benzyl alcohol (0.08 mL, 0.81 mmol) in toluene (4.2 mL) was added Et_3N (0.05 mL, 0.38 mmol) and DPPA (0.09 mL, 0.38 mmol) under nitrogen. The reaction mixture was heated at 80 °C for overnight. Solvents were removed under vacuum. Crude mixture was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered and concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **11** and **12**.

11: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 - 7.22 (m, 5 H), 7.19 - 7.07 (m, 1 H), 7.01 - 6.85 (m, 2 H), 4.99 (s, 2 H), 4.10 - 3.97 (m, 4 H), 3.92 - 3.78 (m, 1 H), 3.50 - 3.38 (m, 1 H), 2.17 - 2.07 (m, 1 H), 1.72 (dd, J = 10.2, 13.4 Hz, 1 H), 1.53 - 1.44 (m, 1 H), 1.39 (dt, J = 5.4, 8.8 Hz, 1 H), 0.83 - 0.70 (m, 2 H).; Molecular Formula: $C_{23}H_{23}F_2NO_4$; LCMS Expected: 415.2; Observed: 416.2 (M+1).

12: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 - 7.19 (m, 5 H), 7.15 (ddd, J = 3.1, 5.6, 8.8 Hz, 1 H), 7.06 - 6.85 (m, 2 H), 4.97 (d, J = 5.8 Hz, 2 H), 4.19 - 3.89 (m, 5 H), 3.08 - 3.00 (m, 1 H), 2.05 - 1.95 (m, 1 H), 1.58 - 1.46 (m, 1 H), 1.40 - 1.31 (m, 1 H), 1.25 - 1.16 (m, 1 H), 1.02 - 0.83 (m, 2 H).; Molecular Formula: $C_{23}H_{23}F_2NO_4$; LCMS Expected: 415.2; Observed: 416.4 (M+1).

SCHEME 3



Synthesis of 13 (Step 11):

To a stirred solution of **11** (65 mg, 0.15 mmol) in acetone (1 mL) was added PTSA (20 mg) and the mixture was stirred at 0 °C for 2 hours. The reaction mixture was basified with aq $NaHCO_3$ solution. Solvents were evaporated under vacuum. The crude mass was dissolved in EtOAc and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, concentrated and purified through column afforded **13**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.31 (m, 3 H), 7.27 - 7.16 (m, 3 H), 7.06 - 6.90 (m, 2 H), 4.96 (s, 2 H), 4.68 (d, J = 8.5 Hz, 1 H), 4.19 - 4.02 (m, 1 H), 3.56 (d, J = 11.4 Hz, 1 H), 2.94 (dd,

J = 5.6, 18.5 Hz, 1 H), 2.18 (dd, *J* = 11.3, 18.6 Hz, 1 H), 2.04 - 1.95 (m, 1 H), 1.86 (d, *J* = 7.6 Hz, 1 H), 1.61 - 1.55 (m, 1 H), 1.39 - 1.25 (m, 1 H).

Synthesis of 14 (Step 12):

To a solution of **13** (100 mg, 0.26 mmol) in DMAc (1 mL) was added **M1** (278 mg, 0.80 mmol) followed by Et_3N (0.11 mL, 0.80 mmol) and stirred it for 10 minutes. AcOH (0.07 mL, 1.3 mmol) was added to the reaction mixture and continued the stirring for 10 minutes. $NaBH(OAc)_3$ (171 mg, 0.80 mmol) was added to the reaction mixture and continued the stirring for over night. The reaction mixture was quenched with NH_4OH and extracted with EtOAc. Combined organics were concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **14**.

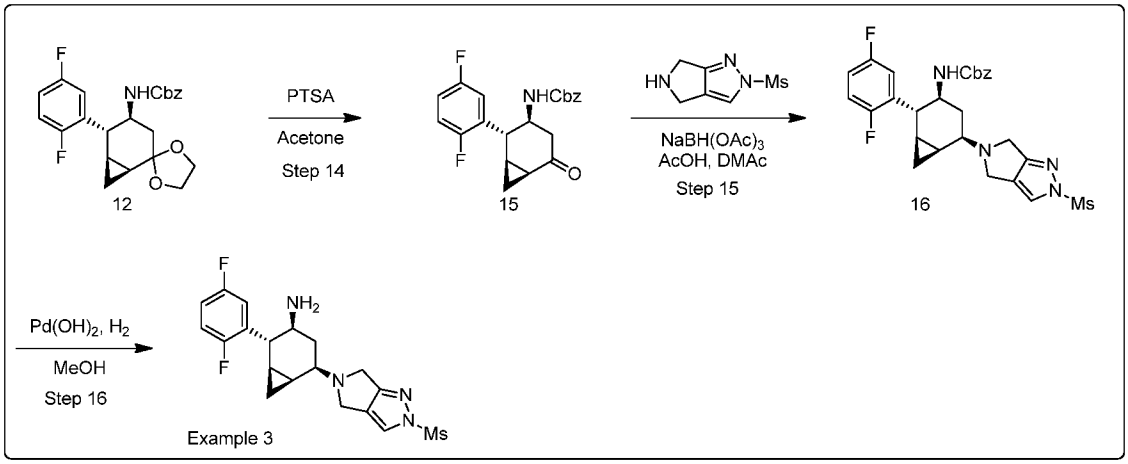
^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.39 - 7.21 (m, 5 H), 7.15 (br. s., 1 H), 7.00 (dt, *J* = 4.4, 9.2 Hz, 1 H), 6.96 - 6.87 (m, 1 H), 5.00 (s, 1 H), 4.76 - 4.67 (m, 1 H), 4.21 - 3.96 (m, 4 H), 3.73 - 3.58 (m, 1 H), 3.44 (dd, *J* = 4.4, 11.2 Hz, 1 H), 3.36 - 3.23 (m, 4 H), 2.31 - 2.15 (m, 1 H), 1.59 – 1.45 (m, 2 H), 1.20 (d, *J* = 5.3 Hz, 1 H), 0.92 - 0.81 (m, 1 H), 0.52 (d, *J* = 5.3 Hz, 1 H).; Molecular Formula: $C_{27}H_{28}F_2N_4O_4S$; LCMS purity: 94.50%; Expected: 542.2; Observed: 543.0 (M+1).

Synthesis of Example 2 (Step 13):

To a solution of **14** (40 mg, 0.07 mmol) in MeOH (5 mL) was added 10% $Pd(OH)_2$ (30 mg). The reaction mixture was stirred under hydrogen atmosphere for 2 hours. The reaction mixture was filtered and concentrated under vacuum. Crude mixture was purified by reversed phase HPLC afforded **Example 2** as di-TFA salt.

^1H NMR (400 MHz, CD_3OD): δ 8.13 (s, 1 H), 7.35 (ddd, *J* = 3.1, 5.7, 9.0 Hz, 1 H), 7.30 - 7.21 (m, 1 H), 7.21 - 7.12 (m, 1 H), 4.80 - 4.62 (m, 4 H), 3.99 - 3.90 (m, 1 H), 3.72 (dd, *J* = 5.0, 11.5 Hz, 1 H), 3.62 - 3.52 (m, 1 H), 3.74 (s, 3 H), 2.46 - 2.36 (m, 1 H), 1.87 (q, *J* = 11.9 Hz, 1 H), 1.69 - 1.57 (m, 1 H), 1.51 - 1.41 (m, 1 H), 1.00 (dt, *J* = 5.9, 9.3 Hz, 1 H), 0.80 (q, *J* = 5.7 Hz, 1 H).; Molecular Formula: $C_{19}H_{22}F_2N_4O_2S$; HPLC purity: 99.57%; LCMS mass Expected: 408.1; Observed: 409.2 (M+1).

SCHEME 4



Synthesis of 15 (Step 14):

To a stirred solution of **11** (300 mg, 0.72 mmol) in acetone (10 mL) was added PTSA (60 mg) and the mixture was stirred at 0 °C for 2 hours. The reaction mixture was basified with aq $NaHCO_3$ solution. Solvents were evaporated under vacuum. The crude mass was dissolved in EtOAc and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, concentrated and purified through column afforded **15**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 - 7.17 (m, 5 H), 7.10 - 6.87 (m, 3 H), 5.03 - 4.89 (m, 2 H), 4.13 - 3.93 (m, 1 H), 3.39 - 3.19 (m, 1 H), 2.55 (d, *J* = 6.8 Hz, 2 H), 2.02 - 1.91 (m, 1 H), 1.70 (d, *J* = 7.3 Hz, 1 H), 1.44 (dt, *J* = 5.5, 9.3 Hz, 1 H), 1.08 (d, *J* = 5.3 Hz, 1 H).; Molecular Formula: $C_{21}H_{19}F_2NO_3$; LCMS purity: 86.87%; Expected: 371.1; Observed: 238.0 (M-133).

Synthesis of 16 (Step 15):

To a solution of **15** (200 mg, 0.53 mmol) in DMAc (2 mL) was added **M1** (555 mg, 1.6 mmol) followed by Et_3N (0.22 mL, 1.6 mmol) and stirred it for 20 minutes. AcOH (0.15 mL, 2.7 mmol) was added to the reaction mixture and continued the stirring for 20 minutes. $NaBH(OAc)_3$ (341 mg, 1.6 mmol) was added to the reaction mixture and continued the stirring for over night. The reaction mixture was quenched with NH_4OH and extracted with EtOAc. Combined organics were concentrated under vacuum. Crude mixture was purified by silica gel chromatography afforded **16**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.38 - 7.18 (m, 5 H), 7.09 - 6.95 (m, 2 H), 6.91 (br. s., 1 H), 5.03 - 4.90 (m, 2 H), 4.71 - 4.60 (m, 1H), 4.20 - 3.90 (m, 4 H), 3.78 - 3.57 (m, 2 H), 3.30 (s, 3 H), 2.94 - 2.84 (m, 1 H), 2.16 (br. s., 1 H), 1.59 - 1.41 (m, 3 H), 1.00 - 0.85 (m, 2 H).; Molecular Formula: $C_{27}H_{28}F_2N_4O_4S$; LCMS purity: 96.47%; Expected: 542.2; Observed: 543.0 (M+1).

Synthesis of Example 3 (Step 16):

To a solution of **14** (100 mg, 0.18 mmol) in MeOH (5 mL) was added 10% $Pd(OH)_2$ (60 mg). The reaction mixture was stirred under hydrogen atmosphere for 2 hours. The reaction mixture was filtered and concentrated under vacuum. Crude mixture was purified by reversed phase HPLC afforded **Example 3** as di-TFA salt.

^{1}H NMR (400 MHz, CD_3OD): δ 8.17 (s, 1 H), 7.34 - 7.22 (m, 2 H), 7.22 - 7.14 (m, 1 H), 4.83 (d, *J* = 17.9 Hz, 4 H), 4.61 - 4.51 (m, 1 H), 3.59 - 3.50 (m, 1 H), 3.48 (s, 3 H), 3.16 (d, *J* = 11.1 Hz, 1 H), 2.51 - 2.41 (m, 1 H), 1.84 - 1.67 (m, 2 H), 1.52 - 1.41 (m, 1 H), 1.20 (dt, *J* = 5.8, 8.8 Hz, 1 H), 0.95 - 0.83 (m, 1 H).; Molecular Formula: $C_{19}H_{22}F_2N_4O_2S$; HPLC purity: 98.94%; LCMS mass Expected: 408.1; Observed: 409.2 (M+1).

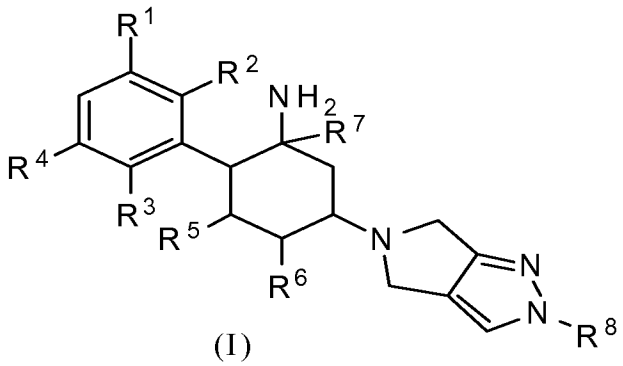
EXAMPLE OF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral pharmaceutical composition, a 100 mg potency tablet is composed of 100 mg of any one of the Examples, 268 mg microcrystalline cellulose, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active, microcrystalline cellulose, and croscarmellose are blended first. The mixture is then lubricated by magnesium stearate and pressed into tablets.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. The specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of structural Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein

R^1, R^2 and R^4 are independently selected from the group consisting of C_{1-6}alkyl, halogen and hydrogen;

R^3 is hydrogen or halogen or, taken together with R^5, form a C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy;

R^5 is hydrogen, halogen, heterocycle, C_{3-7}cycloalkyl or, taken together with the carbon R^5 is attached, form a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or, taken together with R^3, form a C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or, taken together with R^6, form an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy;

R^6 is hydrogen, heterocycle, C_{3-7}cycloalkyl or, together with the carbon R^6 is attached, form a C_{3-7}cycloalkyl or 4-7 membered heterocycle wherein the cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of -OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy or taken together with R^5 form an aryl, C_{5-7}cycloalkyl or 5-7 membered heterocycle wherein the aryl, cycloalkyl or heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of –OH, C_{1-6}alkyl, halogen and C_{1-6}alkoxy;

R^7 is selected from the group consisting of hydrogen C_{1-6}alkyl, C_{1-6}alkylOH and C_{1-6}alkoxy;

wherein R^5, R^6, and R^7 cannot be simultaneously hydrogen; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}alkyl, SO_2C_{1-6}alkyl, and SO_2C_{3-6}cycloalkyl.

2. The compound of Claim 1 wherein R^1 and R^3 are fluorine.

3. The compound of Claim 1 or 2 wherein R^2 and R^4 are fluorine.

4. The compound of Claim 1 or 3 wherein R^3 is taken together with R^5 to form a cyclohexyl and tetrahydropyran, wherein the cyclohexyl is unsubstituted or substituted with 1-3 substituents selected from the group consisting of C_{1-6}alkyl, halogen and C_{1-6}alkoxy.

5. The compound of any one of Claims 1 to 4 wherein the R^8 is selected from the group consisting of hydrogen, SO_2CH_3, and SO_2cyclopropyl.

6. The compound of any one of Claims 1 to 3 or 5 wherein R^6 is taken with the carbon it is attached to and forms a C_{3-7}cycloalkyl, wherein the C_{3-7}cycloalkyl is unsubstituted or substituted with 1-3 substituents selected from the group consisting of –OH and flourine.

7. The compound of any one of Claims 1 to 3 or 5 wherein R^6 is heterocycle, wherein the heterocycle is furan.

8. The compound of any one of Claims 1 to 3 or 5 wherein R^6 is taken with R^5 and forms a C_{5-7}cycloalkyl or phenyl.

9. The compound of any one of Claims 1 to 3 or 5 wherein R^5 is taken with the carbon it is attached to and forms a hetrocycle.

10. The compound of any one of Claims 1 to 3 or 5 wherein R^6 is taken with R^5 and forms a heterocycle.

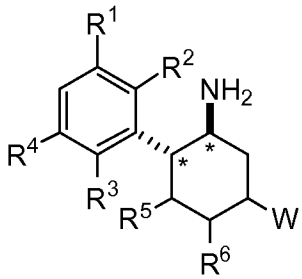
11. The compound of any one of Claims 1 to 3 or 5 wherein R^6 is taken with the carbon it is attached to and forms a heterocycle, wherein the heterocycle is imidazolidine-2,4-dione.

12. The compound of any one of Claims 1 to 3 or 5 to 7 wherein R^5 is hydrogen.

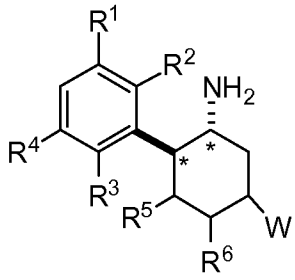
13. The compound of any one of Claims 1 to 3, 5, 9 or 11 wherein R^6 is hydrogen.

14. The compound of any one of Claims 1 to 3 or 5 wherein R^6 is taken together with R^7 to form a 5-7 membered heterocycle wherein the heterocycle is unsubstituted or substituted with 1-3 substituents selected from the group consisting of C_{1-6}alkyl, halogen and C_{1-6}alkoxy.

15. The compound of Claim 1 of structural Formula Ia or Ib having the indicated stereochemical configuration at the two stereogenic carbon atoms marked with an *:

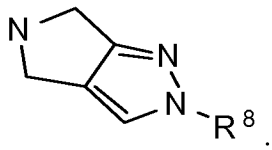


(Ia)

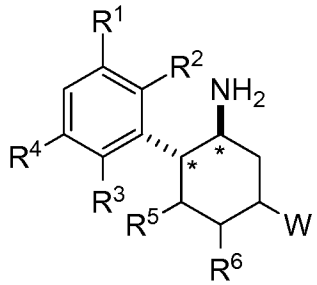


(Ib)

wherein W is

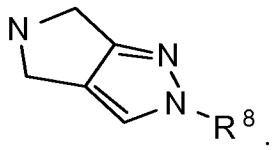


16. The compound of Claim 14 of structural Formula Ia having the indicated absolute stereochemical configuration at the two stereogenic carbon atoms marked with an *:

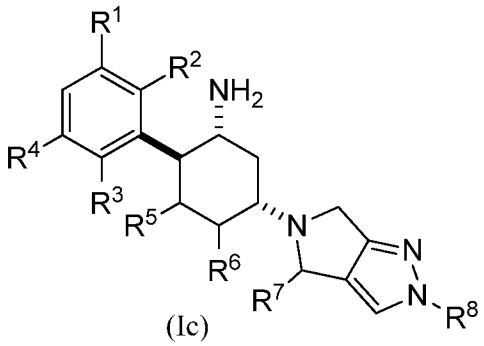


(Ia)

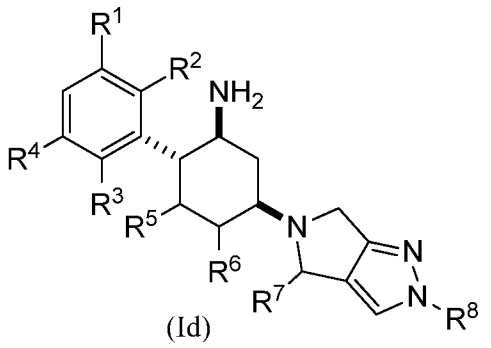
wherein W is



17. The compound of Claim 1 of structural formulae Ic or Id having the indicated stereochemical configuration at the three stereogenic carbon atoms marked with an *:

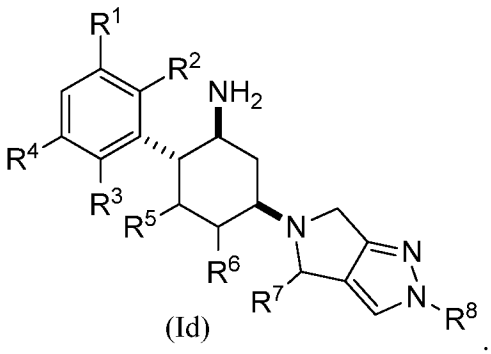


(Ic)



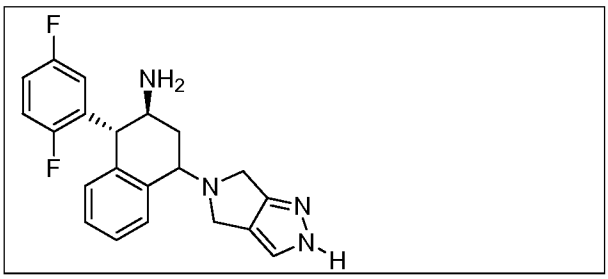
(Id)

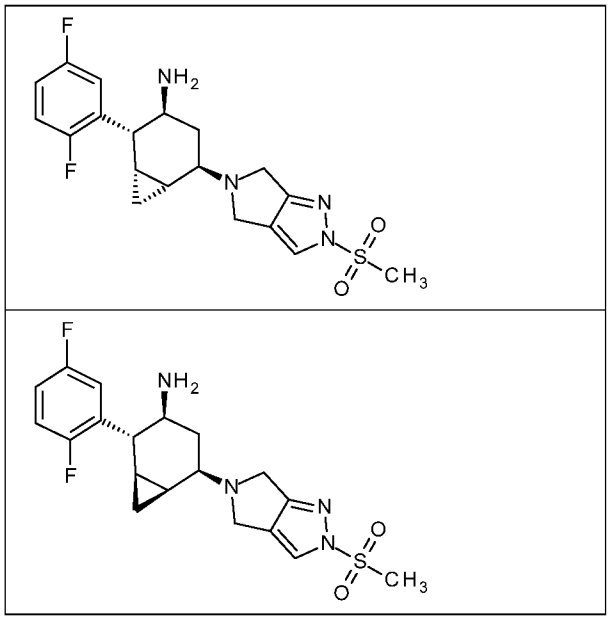
18. The compound of Claim 16 of structural Formula Id having the indicated absolute stereochemical configuration at the three stereogenic carbon atoms marked with an *:



(Id)

19. A compound selected from the group consisting of:





or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition which comprises a compound of any one of Claims 1 to 18 and a pharmaceutically acceptable carrier.

21. Use of a compound in accordance with Claim 1 in the manufacture of a medicament for use in treating a condition selected from the group consisting of insulin resistance, hyperglycemia, Type 2 diabetes in a mammal in need thereof.

22. Use of a compound of Claim 1 in therapy.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/50979

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 487/04; A61K 31/4162 (2013.01)
USPC - 514/406, 407, 412; 548/360.5, 453
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07D 487/04, A61K 31/4162 (2013.01)
USPC: 514/406, 407, 412, 548/360.5, 453

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; IP.com; Google/Google Scholar; SureChem.com; KEYWORDS: Dihydropyrrolopyrazole*, Aminocyclohexane*, dipeptide* ADJ peptid*, adeno* ADJ deamin*, DPP*, peptidas*, diabet*, aryl*, amino*cyclo*1hex*, *pyrazo*, *pyrrol*, *cyclo*1hex*, benz*, phenyl*, amino*1cyclo*1hexan*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7,750,034 B2 (BIFTU, T et al.) 06 July 2010; claims 1, 4, 6	1-2, 3/1-2, 15, 17, 19, 21-22
A	US 2007/0254865 A1 (BIFTU, T et al.) 01 November 2007; claims 1, 6, 8	1-2, 3/1-2, 15, 17, 19, 21-22
A	US 2011/0224195 A1 (BIFTU, T et al.) 15 September 2011; claim 1	1-2, 3/1-2, 15, 17, 19, 21-22
A	US 7,326,728 B2 (YANG, BV) 05 February 2008; preparation 4a	1-2, 3/1-2, 15, 17, 19, 21-22
A	US 4,987,153 A (KAY, DP et al.) 22 January 1991; claim 1	1-2, 3/1-2, 15, 17, 19, 21-22
A	WO 2002/076450 A1 (ASHTON, WT et al.) 03 October 2002; entire document	1-2, 3/1-2, 15, 17, 19, 21-22
A	US 2009/0105210 A1 (ASHTON, WT et al.) 23 April 2009; entire document	1-2, 3/1-2, 15, 17, 19, 21-22
A	US 7,253,172 B2 (BROCKUNIER, L et al.) 07 August 2007; entire document	1-2, 3/1-2, 15, 17, 19, 21-22

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 December 2013 (03.12.2013)	12 DEC 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/50979

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-14, 16, 18 and 20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.