TITLE OF THE INVENTION

AMINOTETRAHYDROPYRANS AS DIPEPTIDYL PEPTIDASE-IV INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

FIELD OF THE INVENTION

The present invention relates to novel substituted aminotetrahydropyrans 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.

The available treatments for Type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor

because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance due to the even higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for ameliorating many symptoms of Type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of Type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensititization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type II diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (e.g. acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DPP-4") enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and 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); Ann E. Weber, J. Med. Chem., 47: 4135-4141 (2004); D. Kim, et al., J. Med. Chem., 48: 141-151 (2005); and K. Augustyns, Exp. Opin. Ther. Patents, 15: 1387-1407 (2005). 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.

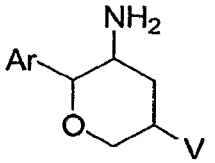
DPP-4 inhibitors also have other therapeutic utilities, as discussed herein. DPP-4 inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DPP-4 inhibitors can be found for the treatment of diabetes and potentially 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," Diabetes, 54: 2988-2994 (2005). The therapeutic potential of DPP-4 inhibitors for the treatment of Type 2 diabetes is discussed by D.J. Drucker in Exp. Opin. Invest. Drugs, 12: 87-100 (2003); by K. Augustyns, et al., in Exp. Opin. Ther. Patents, 13: 499-510 (2003); by J.J. Holst, Exp. Opin. Emerg. Drugs, 9: 155-166 (2004); by H.-U. Demuth in Biochim. Biophys. Acta, 1751: 33-44 (2005); by R. Mentlein, Exp. Opin. Invest. Drugs, 14: 57-64 (2005)

SUMMARY OF THE INVENTION

The present invention is directed to novel substituted 3-aminotetrahydropyrans 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.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel substituted 3-aminotetrahydropyrans that are useful as inhibitors of dipeptidyl peptidase-IV. Compounds of the present invention are described by structural formula I:



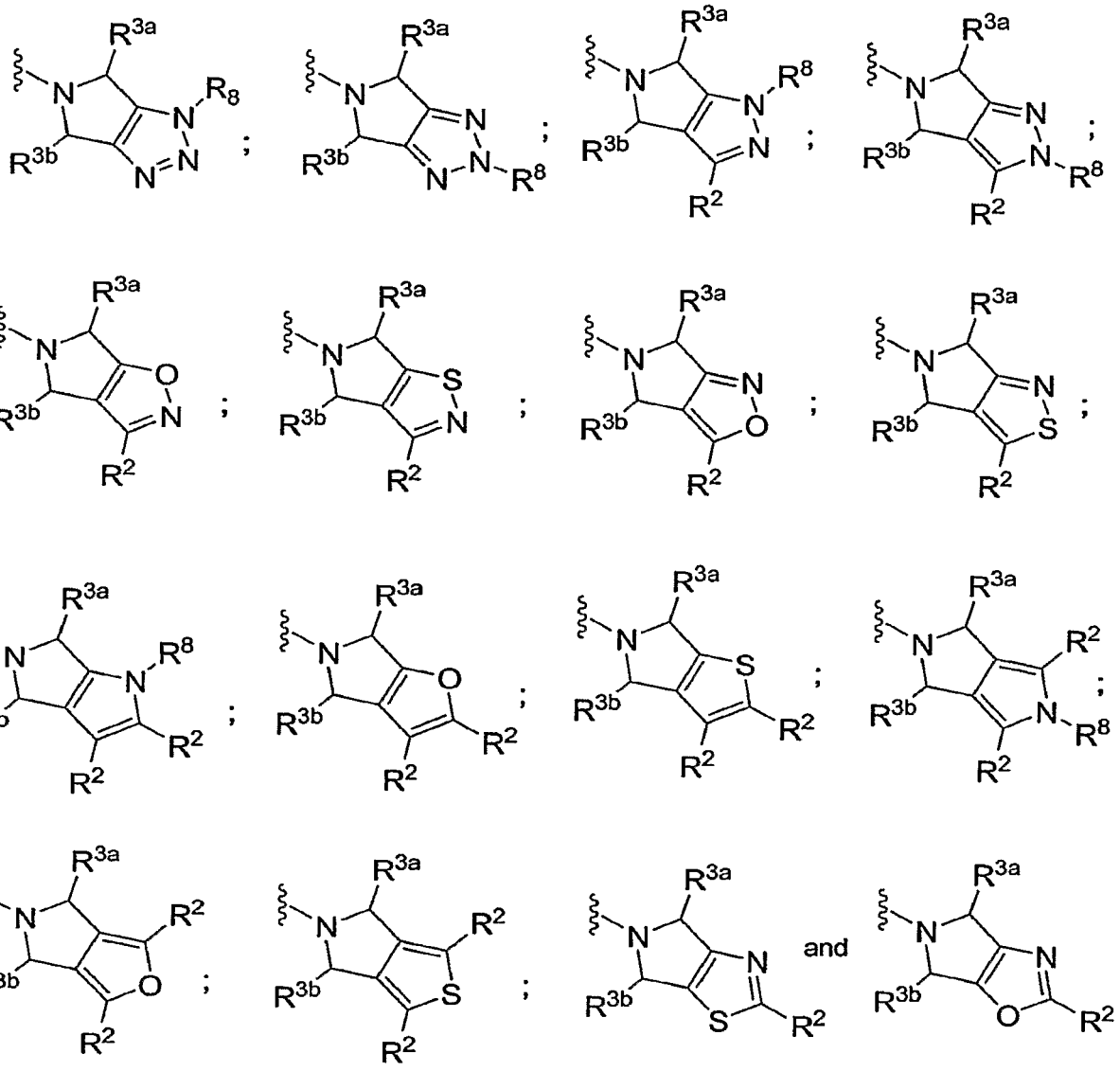
(I)

and pharmaceutically acceptable salts thereof; wherein
each n is independently 0, 1, 2 or 3;

each m is independently 0, 1, or 2;

each p is independently 0 or 1;

V is selected from the group consisting of:



Ar is phenyl optionally substituted with one to five R^1 substituents;

each R^1 is independently selected from the group consisting of

halogen,

cyano,

hydroxy,

C_{1-6} alkyl, optionally substituted with one to five fluorines,

C_{1-6} alkoxy, optionally substituted with one to five fluorines;

each R^2 is independently selected from the group consisting of

hydrogen,
hydroxy,
halogen,
cyano,
C_{1-10} alkoxy, wherein alkoxy is optionally substituted with one to five substituents independently selected from fluorine and hydroxy,
C_{1-10} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy,
C_{2-10} alkenyl, wherein alkenyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy,
$(CH_2)_n$-aryl, wherein aryl is optionally substituted with one to five substituents independently selected hydroxy, halogen, cyano, nitro, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,
$(CH_2)_n$-heteroaryl, wherein heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy, halogen, cyano, nitro, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,
$(CH_2)_n$-heterocyclyl, wherein heterocyclyl is optionally substituted with one to three substituents independently selected from oxo, hydroxy, halogen, cyano, nitro, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,
$(CH_2)_n$-C_{3-6} cycloalkyl, wherein cycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, cyano, nitro, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,
$(CH_2)_n$-COOH,
$(CH_2)_n$-$COOC_{1-6}$ alkyl,
$(CH_2)_n$-NR^4R^5,
$(CH_2)_n$-$CONR^4R^5$,
$(CH_2)_n$-$OCONR^4R^5$,
$(CH_2)_n$-$SO_2NR^4R^5$,
$(CH_2)_n$-SO_2R^6,
$(CH_2)_n$-$NR^7SO_2R^6$,
$(CH_2)_n$-$NR^7CONR^4R^5$,
$(CH_2)_n$-NR^7COR^7, and
$(CH_2)_n$-$NR^7CO_2R^6$;

wherein any individual methylene (CH_2) carbon atom in $(CH_2)_n$ is optionally substituted with one to two substituents independently selected from fluorine, hydroxy, C_{1-4} alkyl, and C_{1-4} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

R^{3a} and R^{3b} are each independently hydrogen or C_{1-4} alkyl optionally substituted with one to five fluorines;

R^4 and R^5 are each independently selected from the group consisting of

hydrogen,

$(CH_2)_m$-phenyl,

$(CH_2)_m$-C_{3-6} cycloalkyl, and

C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy and wherein phenyl and cycloalkyl are optionally substituted with one to five substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

each R^6 is independently C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxyl;

R^7 is hydrogen or R^6; and

R^8 is selected from the group consisting of

hydrogen,

$(CH_2)_p$-phenyl,

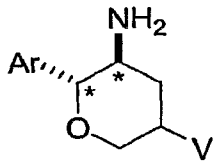
$(CH_2)_p$-C_{3-6} cycloalkyl, and

C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy and wherein phenyl and cycloalkyl are optionally substituted with one to five substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines.

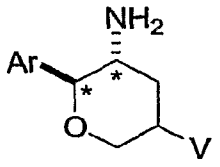
In one embodiment of the compounds of the present invention, each R^1 is independently selected from the group consisting of fluorine, chlorine, bromine, methyl, trifluoromethyl, and trifluoromethoxy.

In a second embodiment of the compounds of the present invention, R^{3a} and R^{3b} are both hydrogen.

In a third embodiment of the compounds of the present invention, there are provided compounds of structural formulae Ia and Ib of the indicated stereochemical configuration having a *trans* orientation of the Ar and NH_2 substituents on the two stereogenic tetrahydropyran carbon atoms marked with an *:



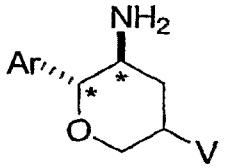
(Ia)



(Ib)

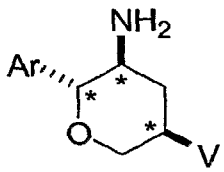
wherein Ar and V are as described above.

In a class of this third embodiment, there are provided compounds of structural formula Ia of the indicated absolute stereochemical configuration having a *trans* orientation of the Ar and NH_2 substituents on the two stereogenic tetrahydropyran carbon atoms marked with an *:

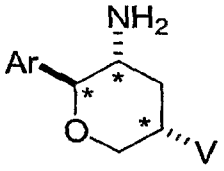


(Ia)

In a second class of this third embodiment, there are provided compounds of structural formulae Ic and Id of the indicated stereochemical configuration having a *trans* orientation of the Ar and NH_2 substituents, a *trans* orientation of the Ar and V substituents and a *cis* orientation of the NH_2 and V substituents on the three stereogenic tetrahydropyran carbon atoms marked with an *:



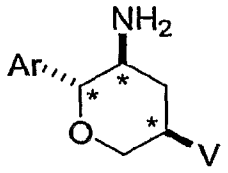
(Ic)



(Id)

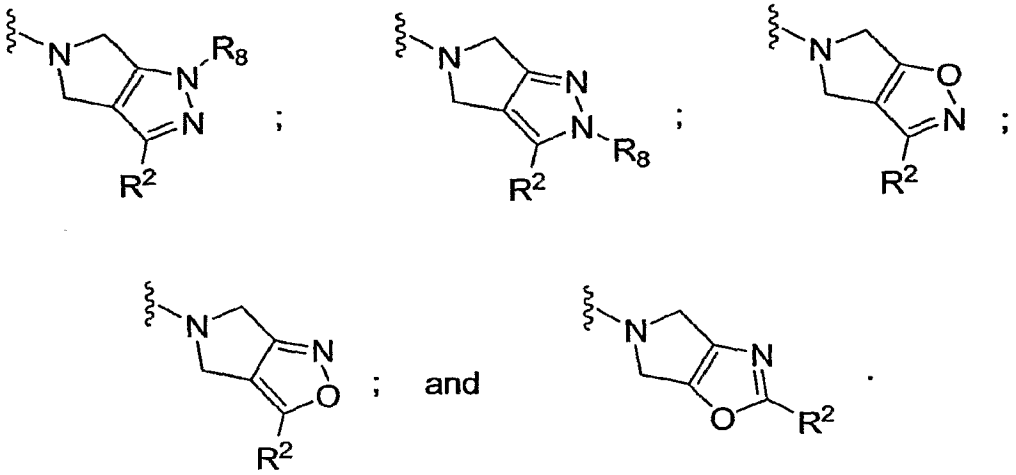
In a subclass of this class, there are provided compounds of structural formula Ic of the indicated absolute stereochemical configuration having a *trans* orientation of the Ar and NH_2

substituents, a *trans* orientation of the Ar and V substituents and a *cis* orientation of the NH_2 and V substituents on the three stereogenic tetrahydropyran carbon atoms marked with an *:



(Ic)

In a subclass of this subclass, V is selected from the group consisting of:



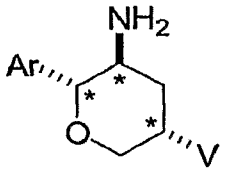
wherein R^2 and R^8 are as defined above.

In a third class of this third embodiment, there are provided compounds of structural formulae Ie and If of the indicated stereochemical configuration having a *trans* orientation of the Ar and NH_2 substituents, a *cis* orientation of the Ar and V substituents and a *trans* orientation of the NH_2 and V substituents on the three stereogenic tetrahydropyran carbon atoms marked with an *:



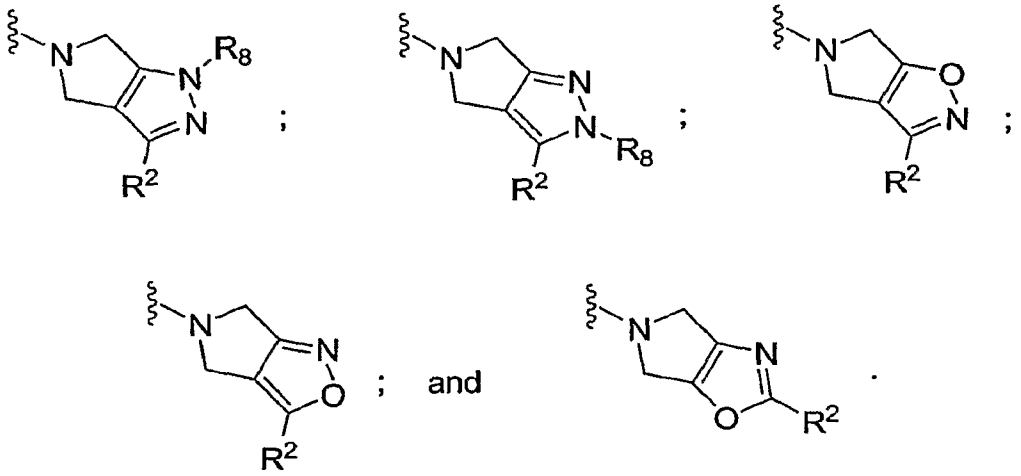
(Ie) (If)

In a subclass of this class, there are provided compounds of structural formula Ie of the indicated absolute stereochemical configuration having a *trans* orientation of the Ar and NH_2 substituents, a *cis* orientation of the Ar and V substituents and a *trans* orientation of the NH_2 and V substituents on the three stereogenic tetrahydropyran carbon atoms marked with an *:



(Ie)

In a subclass of this subclass, V is selected from the group consisting of:



wherein R^2 and R^8 are as defined above.

In a fourth embodiment of the compounds of the present invention, R^2 and R^8 are each independently selected from the group consisting of

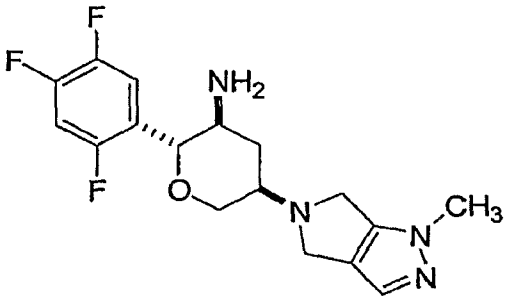
hydrogen,

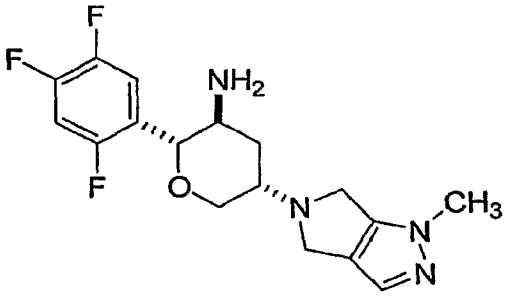
C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five fluorines, and

C_{3-6} cycloalkyl, wherein cycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkyl, and C_{1-4} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines.

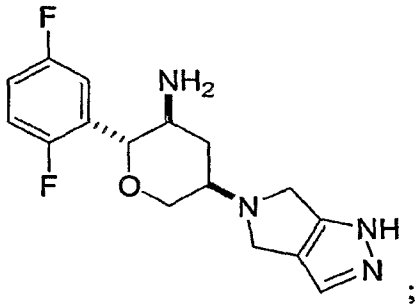
In a class of this fourth embodiment of the compounds of the present invention, R^2 and R^8 are each independently selected from the group consisting of hydrogen, C_{1-3} alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, and cyclopropyl.

Nonlimiting examples of compounds of the present invention that are useful as dipeptidyl peptidase-IV inhibitors are the following structures having the indicated absolute stereochemical configurations at the three stereogenic tetrahydropyran carbon atoms:





and



;

and pharmaceutically acceptable salts 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 "alkylthio" refers to straight or branched chain alkylsulfides of the number of carbon atoms specified (e.g., C_{1-10} alkylthio), or any number within this range [i.e., methylthio (MeS-), ethylthio, isopropylthio, etc.].

The term "alkylamino" refers to straight or branched alkylamines of the number of carbon atoms specified (e.g., C_{1-6} alkylamino), or any number within this range [i.e., methylamino, ethylamino, isopropylamino, t-butylamino, 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*-

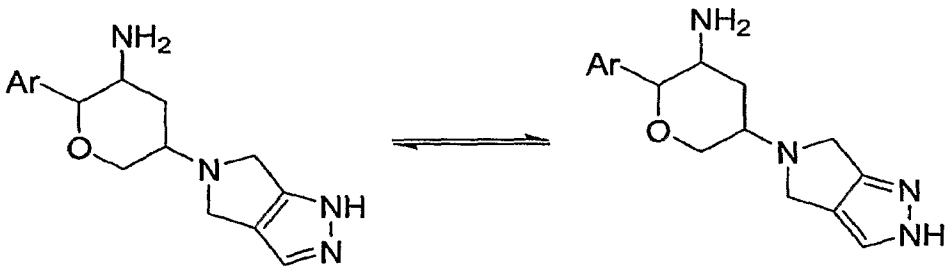
oxadiazolyl, 2-oxo-[1,3,4]-3*H*-oxadiazolyl, 2-oxo-1,3-dihydro-2*H*-imidazolyl, 3-oxo-2,4-dihydro-3*H*-1,2,4-triazolyl, and the like. For heterocyclyl and heteroaryl groups, rings and ring systems containing from 3-15 atoms are included, forming 1-3 rings.

"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, Id, Ie, and If. 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. An example of tautomers which are intended to be encompassed within the compounds of the present invention is illustrated below:



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 Ar groups on the tetrahydropyran ring. Formulae Ic and Id show the preferred stereochemistry at the stereogenic carbon atoms to which are attached the NH_2, Ar, and V groups on the tetrahydropyran 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.

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}; $k_{cat}/K_m = 1.5 \times 10^6$ $M^{-1}s^{-1}$. 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.

In particular, the compounds of the following examples had activity in inhibiting the dipeptidyl peptidase-IV enzyme in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in 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 subject compounds are further useful in a method for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other 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 which 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 therefor, 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 in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

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

(b) insulin sensitizers including (i) PPARγ agonists, such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, balaglitazone, and the like) and other PPAR ligands, including PPARα/γ dual agonists, such as KRP-297, muraglitazar, naveglitazar, tesaglitazar, TAK-559, PPARα agonists, such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), and selective PPARγ modulators (SPPARγM's), such as disclosed in WO 02/060388, WO 02/08188, WO 2004/019869, WO 2004/020409, WO 2004/020408, and WO 2004/066963; (ii) biguanides such as metformin and phenformin, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(c) insulin or insulin mimetics;

(d) sulfonylureas and other insulin secretagogues, such as tolbutamide, glyburide, glipizide, glimepiride, and meglitinides, such as nateglinide and repaglinide;

(e) α-glucosidase inhibitors (such as acarbose and miglitol);

(f) glucagon receptor antagonists, such as those disclosed in WO 97/16442; WO 98/04528, WO 98/21957; WO 98/22108; WO 98/22109; WO 99/01423, WO 00/39088, and WO 00/69810; WO 2004/050039; and WO 2004/069158;

(g) GLP-1, GLP-1 analogues or mimetics, and GLP-1 receptor agonists, such as exendin-4 (exenatide), liraglutide (NN-2211), CJC-1131, LY-307161, and those disclosed in WO 00/42026 and WO 00/59887;

(h) GIP and GIP mimetics, such as those disclosed in WO 00/58360, and GIP receptor agonists;

(i) PACAP, PACAP mimetics, and PACAP receptor agonists such as those disclosed in WO 01/23420;

(j) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, itavastatin, and rosuvastatin, and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPARα agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) PPARα/γ dual agonists, such as naveglitazar and muraglitazar, (vi) inhibitors of cholesterol absorption, such as beta-sitosterol and ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as avasimibe, and (viii) antioxidants, such as probucol;

(k) PPARδ agonists, such as those disclosed in WO 97/28149;

(l) antiobesity compounds, such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y_1 or Y_5 antagonists, CB1 receptor inverse agonists and antagonists, β_3 adrenergic receptor agonists, melanocortin-receptor agonists, in particular melanocortin-4 receptor agonists, ghrelin antagonists, bombesin receptor agonists (such as bombesin receptor subtype-3 agonists), cholecystokinin 1 (CCK-1) receptor agonists, and melanin-concentrating hormone (MCH) receptor antagonists;

(m) ileal bile acid transporter inhibitors;

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

(o) antihypertensive agents, such as ACE inhibitors (enalapril, lisinopril, captopril, quinapril, tandolapril), A-II receptor blockers (losartan, candesartan, irbesartan, valsartan, telmisartan, and eprosartan), beta blockers and calcium channel blockers;

(p) glucokinase activators (GKAs), such as those disclosed in WO 03/015774; WO 04/076420; and WO 04/081001;

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

(r) inhibitors of cholesteryl ester transfer protein (CETP), such as torcetrapib; and

(s) inhibitors of fructose 1,6-bisphosphatase, 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.

Dipeptidyl peptidase-IV inhibitors that can be combined with compounds of structural formula I include those disclosed in US Patent No. 6,699,871; WO 02/076450 (3 October 2002); WO 03/004498 (16 January 2003); WO 03/004496 (16 January 2003); EP 1 258 476 (20 November 2002); WO 02/083128 (24 October 2002); WO 02/062764 (15 August 2002); WO 03/000250 (3 January 2003); WO 03/002530 (9 January 2003); WO 03/002531 (9 January 2003); WO 03/002553 (9 January 2003);

WO 03/002593 (9 January 2003); WO 03/000180 (3 January 2003); WO 03/082817 (9 October 2003); WO 03/000181 (3 January 2003); WO 04/007468 (22 January 2004); WO 04/032836 (24 April 2004); WO 04/037169 (6 May 2004); and WO 04/043940 (27 May 2004). Specific DPP-4 inhibitor compounds include isoleucine thiazolidide (P32/98); NVP-DPP-728; vildagliptin (LAF 237); P93/01; and saxagliptin (BMS 477118).

Antiobesity compounds that can be combined with compounds of structural formula I include fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y_1 or Y_5 antagonists, cannabinoid CB1 receptor antagonists or inverse agonists, melanocortin receptor agonists, in particular, melanocortin-4 receptor agonists, ghrelin antagonists, bombesin receptor agonists, and melanin-concentrating hormone (MCH) receptor antagonists. For a review of anti-obesity compounds that can be combined with compounds of structural formula I, 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); and J.A. Fernandez-Lopez, et al., "Pharmacological Approaches for the Treatment of Obesity," Drugs, 62: 915-944 (2002).

Neuropeptide Y5 antagonists that can be combined with compounds of structural formula I include those disclosed in U.S. Patent No. 6,335,345 (1 January 2002) and WO 01/14376 (1 March 2001); and specific compounds identified as GW 59884A; GW 569180A; LY366377; and CGP-71683A.

Cannabinoid CB1 receptor antagonists that can be combined with compounds of formula I include those disclosed in PCT Publication WO 03/007887; U.S. Patent No. 5,624,941, such as rimonabant; PCT Publication WO 02/076949, such as SLV-319; U.S. Patent No. 6,028,084; PCT Publication WO 98/41519; PCT Publication WO 00/10968; PCT Publication WO 99/02499; U.S. Patent No. 5,532,237; U.S. Patent No. 5,292,736; PCT Publication WO 05/000809; PCT Publication WO 03/086288; PCT Publication WO 03/087037; PCT Publication WO 04/048317; PCT Publication WO 03/007887; PCT Publication WO 03/063781; PCT Publication WO 03/075660; PCT Publication WO 03/077847; PCT Publication WO 03/082190; PCT Publication WO 03/082191; PCT Publication WO 03/087037; PCT Publication WO 03/086288; PCT Publication WO 04/012671; PCT Publication WO 04/029204; PCT Publication WO 04/040040; PCT Publication WO 01/64632; PCT Publication WO 01/64633; and PCT Publication WO 01/64634.

Melanocortin-4 receptor (MC4R) agonists useful in the present invention include, but are not limited to, those disclosed in US 6,294,534, US 6,350,760, 6,376,509, 6,410,548, 6,458,790, US 6,472,398, US 5837521, US 6699873, which are hereby incorporated by reference in their entirety; in US Patent Application Publication Nos. US 2002/0004512, US2002/0019523, US2002/0137664, US2003/0236262, US2003/0225060, US2003/0092732, US2003/109556, US 2002/0177151, US 2002/187932, US 2003/0113263, which are hereby incorporated by reference in their entirety; and in WO 99/64002, WO 00/74679, WO 02/15909, WO 01/70708, WO 01/70337, WO 01/91752, WO 02/068387, WO 02/068388, WO 02/067869, WO 03/007949, WO 2004/024720, WO 2004/089307, WO

2004/078716, WO 2004/078717, WO 2004/037797, WO 01/58891, WO 02/070511, WO 02/079146, WO 03/009847, WO 03/057671, WO 03/068738, WO 03/092690, WO 02/059095, WO 02/059107, WO 02/059108, WO 02/059117, WO 02/085925, WO 03/004480, WO 03/009850, WO 03/013571, WO 03/031410, WO 03/053927, WO 03/061660, WO 03/066597, WO 03/094918, WO 03/099818, WO 04/037797, WO 04/048345, WO 02/018327, WO 02/080896, WO 02/081443, WO 03/066587, WO 03/066597, WO 03/099818, WO 02/062766, WO 03/000663, WO 03/000666, WO 03/003977, WO 03/040107, WO 03/040117, WO 03/040118, WO 03/013509, WO 03/057671, WO 02/079753, WO 02//092566, WO 03/-093234, WO 03/095474, and WO 03/104761.

The potential utility of safe and effective activators of glucokinase (GKAs) for the treatment of diabetes is discussed in J. Grimsby et al., "Allosteric Activators of Glucokinase: Potential Role in Diabetes Therapy," Science, 301: 370-373 (2003).

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 compound of the present invention.

The weight ratio of the compound of the present invention to the second active ingredient 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 be 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.

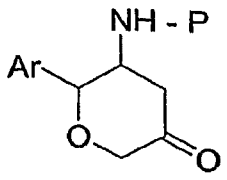
In the treatment or prevention of conditions which require inhibition of dipeptidyl peptidase-IV enzyme activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will 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 the present invention can be prepared from intermediates such as those of formula II and III using standard reductive amination conditions followed by deprotection,



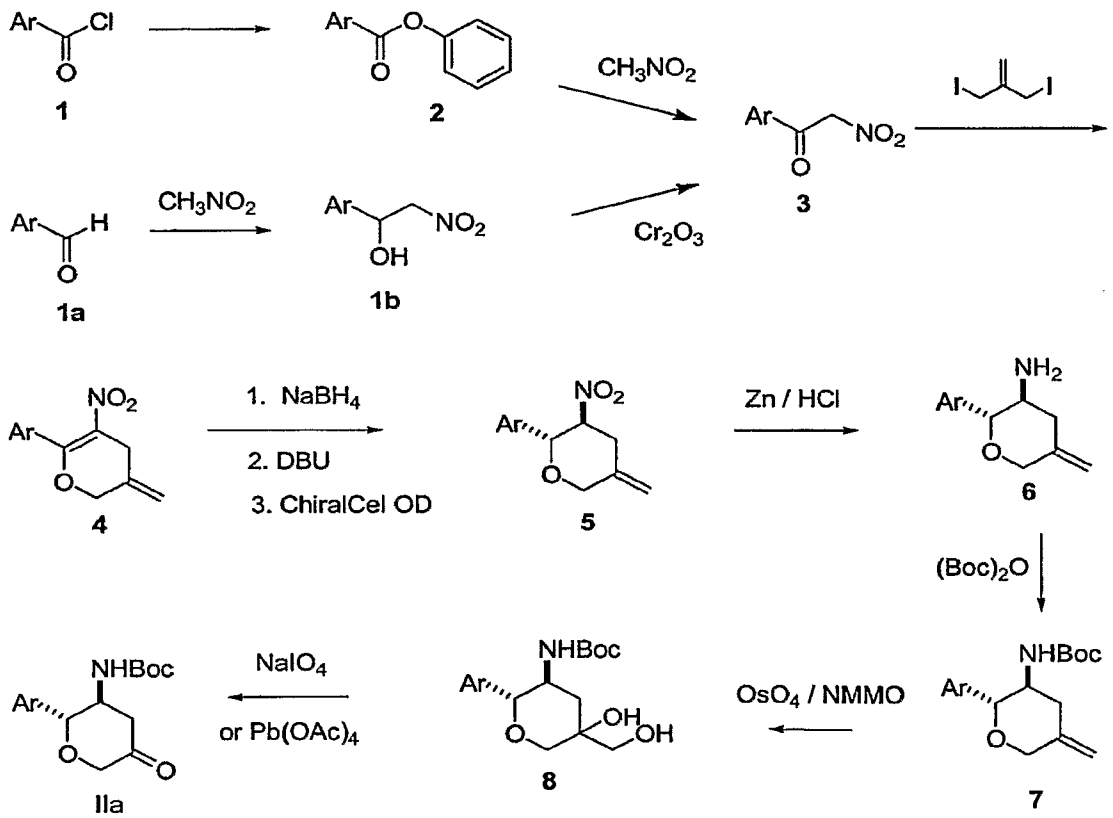
II



III

where Ar and V are as defined above and P is a suitable nitrogen protecting group such as tert-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), or 9-fluorenylmethoxycarbonyl (Fmoc). The preparation of these intermediates is described in the following Schemes.

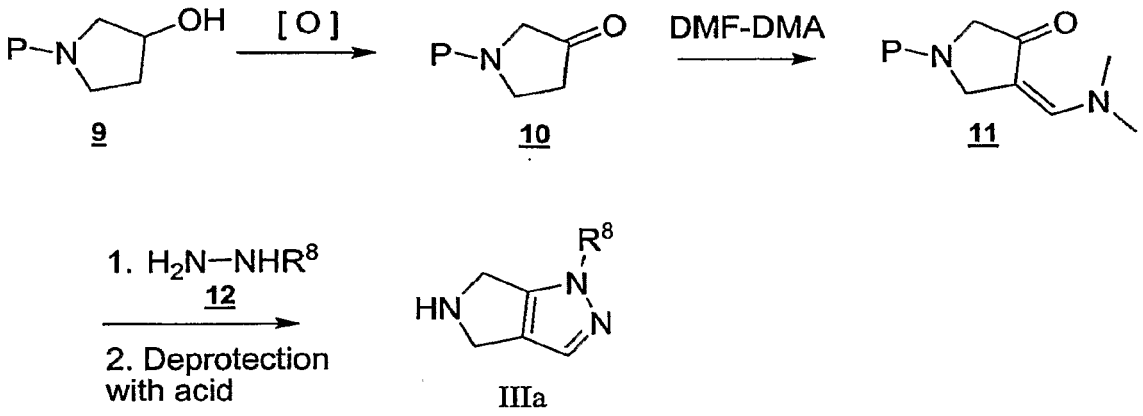
SCHEME 1



Intermediates of formula II are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Substituted benzoyl halide 1 is treated with phenol in the presence of a base such as *N,N*-diisopropylethylamine to form the ester 2. Treatment of 2 with the anion generated from nitromethane using sodium hydride gives the nitroketone 3. Alternatively, the nitroketone 3 can be made by reacting aldehyde 1a with nitromethane in the presence of a base and oxidizing the resulting nitroalcohol 1b with

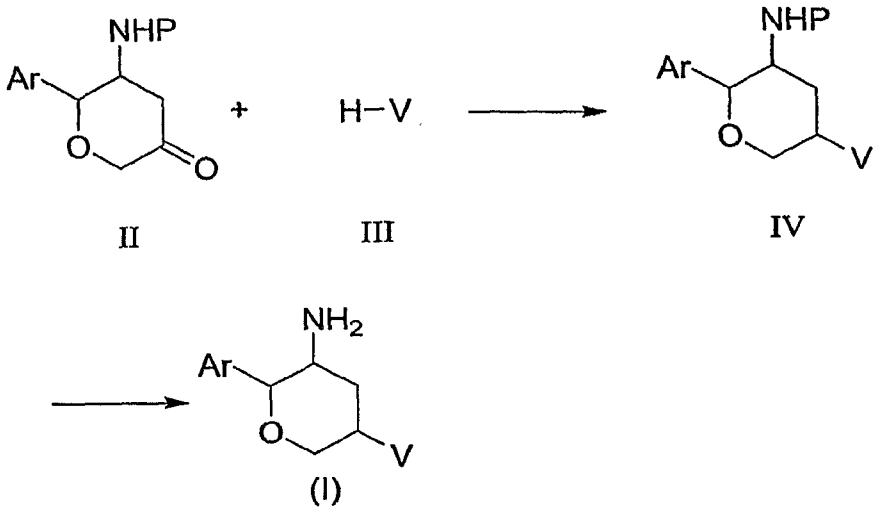
an oxidizing agent such as Jones reagent. Heating the nitroketone 3 with 3-iodo-2-(iodomethyl)prop-1-ene gives the pyran 4, which, when reduced with sodium borohydride and isomerized with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), provides the *trans* pyran 5. The enantiomers of 5 may be separated at this stage by a variety of methods known to those skilled in the art. Conveniently, the racemate may be resolved by HPLC using a chiral column. The nitro-substituted pyran 5 is then reduced, for example, using zinc and an acid, such as hydrochloric acid, and the resulting amine 6 protected, for example, as its BOC derivative, by treatment with di-*tert*-butyl dicarbonate to give 7. Treatment of 7 with osmium tetroxide and *N*-methylmorpholine *N*-oxide forms the diol 8 which upon treatment with sodium periodate gives intermediate pyranone IIa.

SCHEME 2



Intermediates of formula III are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route to prepare tetrahydropyrrolopyrazole IIIa is illustrated in Scheme 2. Trityl- or Boc-protected pyrrolidinol 9 may be oxidized by a variety of methods, such as the Swern procedure, commonly known to those in the art, to give the ketone 10, which upon treatment and heating with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) gives 11. The desired intermediate IIIa may then be readily obtained by heating a solution of 11 with hydrazine 12 in a suitable solvent such as ethanol optionally in the presence of a base such as sodium ethoxide followed by removal of the protecting group with acid.

SCHEME 3

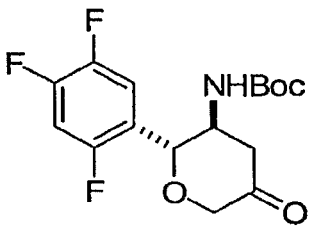


As illustrated in Scheme 3, the compounds of the present invention structural formula (I) may be prepared by reductive amination of Intermediate II in the presence of Intermediate III using reagents such as sodium cyanoborohydride, decaborane, or sodium triacetoxyborohydride in solvents such as dichloromethane, tetrahydrofuran, or methanol to provide Intermediate IV. The reaction is conducted optionally in the presence of a Lewis acid such as titanium tetrachloride or titanium tetraisopropoxide. The reaction may also be facilitated by adding an acid such as acetic acid. In some cases, Intermediate III may be a salt, such as a hydrochloric acid or trifluoroacetic acid salt, and in these cases it is convenient to add a base, generally *N,N*-diisopropylethylamine, to the reaction mixture. The protecting group is then removed with, for example, trifluoroacetic acid or methanolic hydrogen chloride in the case of Boc, or palladium-on-carbon and hydrogen gas in the case of Cbz to give the desired amine I. The product is purified, if necessary, by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel, such as with a Biotage® apparatus, or HPLC. Compounds that are purified by HPLC may be isolated as the corresponding salt.

In some cases the product I or synthetic intermediates illustrated in the above schemes may be further modified, for example, by manipulation of substituents on Ar or V. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions that are commonly known to those skilled in the art.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1



tert-Butyl [(2*R*,3*S*)-5-oxo-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

Step A: Phenyl 2,4,5-trifluorobenzoate

A solution of phenol (13.3 g, 141 mmol) in dry dichloromethane (370 mL) was cooled in ice bath and treated with *N,N*-diisopropylethylamine (34 mL, 193 mmol) followed by dropwise addition of 2,4,5-trifluorobenzoyl chloride (25g, 129 mmol) over a period of 15 minutes. The ice bath was removed, stirring was continued for two hours at room temperature and the solution was then transferred to a separatory funnel and the organic layer was washed successively with hydrochloric acid solution (2*N*, 150 mL), saturated aqueous sodium bicarbonate solution (150 mL), and brine (150 mL), dried over anhydrous sodium sulfate, filtered, evaporated and the resulting solid product was purified on silica in portions by eluting successively with hexane, and then 0-5% ether in hexane in a gradient fashion to yield phenyl 2,4,5-trifluorobenzoate as white solid.

Step B: 2-Nitro-1-(2,4,5-trifluorophenyl)ethanone

Sodium hydride (12 g, 60% in oil, 297 mmol) was rinsed with hexane (4 x 100 mL), flushed with anhydrous nitrogen, suspended in *N,N*-dimethylformamide (350 mL) and then treated with nitromethane (44 mL, 81 mmol). The resultant mixture was stirred at room temperature for 2.5 hours, cooled to 0 °C and then treated with a solution of phenyl 2,4,5-trifluorobenzoate (22.8 g, 90.0 mmol) in *N,N*-dimethylformamide (180 mL) over a period of two hours. The reaction mixture was kept at the same temperature overnight and stirring continued for an additional hour at room temperature. The mixture was poured into ice (400 g) with conc. hydrochloric acid (48 mL). The aqueous mixture was extracted with ethyl acetate (3 x 250 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was dissolved in ether – hexane (1:1, 240 mL) and water (200 mL). The organic layer was separated, and the crystals which formed upon standing and cooling in the freezer were recovered by filtration and dried to yield 2-nitro-1-(2,4,5-trifluorophenyl)ethanone as an off-white solid.

Step C: 3-Methylene-5-nitro-6-(2,4,5-trifluorophenyl)-3,4-dihydro-2*H*-pyran

A mixture of 3-chloro-2-(chloromethyl)prop-1-ene (1.0 g, 8 mmol) and sodium iodide (6.6 g, 44 mmol) in acetone (60 mL) was stirred at room temperature for 20 hours, evaporated under reduced pressure and dissolved in dichloromethane (150 mL) and water (50 mL). The organic layer was

dried over sodium sulfate, filtered and evaporated to yield 3-iodo-2-(iodomethyl)prop-1-ene as a reddish oil (2.45 g). *N,N*-diisopropylethylamine (0.20 mL) was added to a solution of 2-nitro-1-(2,4,5-trifluorophenyl)ethanone (110 mg, 0.5 mmol) in *N,N*-dimethylformamide (3 mL) and 3-iodo-2-(iodomethyl)prop-1-ene (170 mg, 0.55 mmol) and the mixture was heated at 60 °C for 2.5 hours, evaporated and purified by chromatography on a Biotage Horizon® system (silica, gradient 0-30% dichloromethane in hexane) to yield 3-methylene-5-nitro-6-(2,4,5-trifluorophenyl)-3,4-dihydro-2*H*-pyran.

Step D: (2*R*,3*S*)-5-Methylene-3-nitro-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran

To a solution of 3-methylene-5-nitro-6-(2,4,5-trifluorophenyl)-3,4-dihydro-2*H*-pyran (798 mg, 2.94 mmol) in chloroform (42 mL) and isopropyl alcohol (7.8 mL) was added silica gel (5.1 g), and sodium borohydride (420 mg, 11.1 mmol), and the reaction mixture stirred for 30 minutes at room temperature. The reaction mixture was then quenched by dropwise addition of hydrochloric acid (6 mL, 2*N*) and filtered. The resulting solid residue was washed with ethyl acetate (100 mL). The combined filtrate was washed successively with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, and evaporated. The resultant amber oil (802 mg) was dissolved in tetrahydrofuran (15 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 40 μL) was added. The solution was stirred for 105 minutes and then transferred to a separatory funnel containing ethyl acetate (100 mL) and 1*N* hydrochloric acid (50 mL). The organic layer was washed with brine and the aqueous layer extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to yield a crude product which was purified by flash chromatography (silica, 8-10% ether in hexane) to yield *trans*-5-methylene-3-nitro-2-(2,4,5 trifluorophenyl)tetrahydro-2*H*-pyran. A portion of this product (388 mg) was resolved by HPLC (ChiralCel OD, 1.5 % isopropyl alcohol in heptane) to yield the slower-moving enantiomer, (2*R*,3*S*)-5-methylene-3-nitro-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran.

Step E: (2*R*,3*S*)-5-Methylene-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine

To a vigorously stirred suspension of (2*R*,3*S*)-5-methylene-3-nitro-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran (200 mg, 0.73 mmol) and zinc powder (561 mg, 8.59 mmol) in ethanol (7 mL) was added 6*N* hydrochloric acid (2.3 mL, 14 mmol). After one hour, the mixture was treated with ether (100 mL) and aqueous sodium hydroxide solution (2.5*N*, 40 mL). The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and evaporated to yield (2*R*,3*S*)-5-methylene-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine which was used in the next step without further purification.

Step F: *tert*-Butyl [(2*R*,3*S*)-5-methylene-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

To a solution of (2*R*,3*S*)-5-methylene-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine (177 mg, 0.73 mmole) in dichloromethane (5 mL) was added di-*tert*-butyl dicarbonate (239 mg,

1.1 mmol) and the mixture stirred for 2.5 hours at room temperature. The solution was evaporated under reduced pressure to give *tert*-butyl [(2*R*, 3*S*)-5-methylene-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate as a white solid. It was used in the next step without further purification.

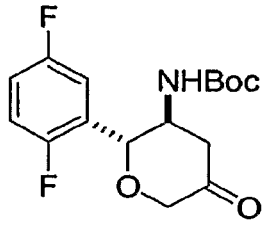
Step G: *tert*-Butyl [(2*R*,3*S*)-5-hydroxy-5-(hydroxymethyl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

To a solution of *tert*-butyl [(2*R*,3*S*)-5-methylene-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate (203 mg, 0.59 mmol) in *tert*-butyl alcohol (6 mL), acetone (3 mL) and water (1.5 mL) was added osmium tetroxide (0.113 mL of 2.5% solution in *tert*-butyl alcohol, 0.009 mmol). The resultant mixture was stirred at room temperature for 10 minutes and then treated with *N*-methylmorpholine *N*-oxide (92 mg, 0.79 mmol) and stirred for two days. After two days, the reaction mixture was treated with aqueous sodium bisulfite solution (5 mL, 2.0*N*) followed after 10 min by ethyl acetate. The organic layer was washed successively with 2*N* hydrochloric acid and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and evaporated to yield *tert*-butyl [(2*R*,3*S*)-5-hydroxy-5-(hydroxymethyl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate which was used in the next step without further purification.

Step H: *tert*-Butyl [(2*R*,3*S*)-5-oxo-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

To a solution of *tert*-butyl [(2*R*,3*S*)-5-hydroxy-5-(hydroxymethyl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate (223 mg, 0.59 mmol) in tetrahydrofuran (4 mL) was added a solution of sodium periodate (143 mg, 0.67 mmol) in water (1.3 mL) and the mixture stirred for 3 hours. The mixture was concentrated and purified by flash chromatography (silica, gradient 5-20% ethyl acetate in chloroform) to yield *tert*-butyl [(2*R*,3*S*)-5-oxo-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate as white solid.

INTERMEDIATE 2



tert-Butyl [(2*R*,3*S*)-5-oxo-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

Step A: 1-(2,5-Difluorophenyl)-2-nitroethanol

To sodium hydroxide (1N, 3L) and methanol (1500 mL) at 5 °C was added a solution of 2,5-difluorobenzaldehyde (350 g, 2.46 mol) and nitromethane (157 mL, 2.9 mol) in methanol (350 mL) dropwise over a period of 1 h. The reaction mixture was then neutralized with glacial acetic acid (165 mL). Aqueous workup gave the desired nitroalcohol.

Step B: 2-Nitro-1-(2,5-difluorophenyl)ethanone

A solution of Dess-Martin periodinane (125 g) in dichloromethane (600 mL) was added to a solution of the nitroalcohol made in Step A (46.3 g) at 10 °C over a period of 30 min. Stirring was continued for 2 h, and the reaction mixture was then poured onto a mixture of sodium bicarbonate (300 g) and sodium thiosulfate (333 g) in water (3 L). The desired product was extracted with methyl *t*-butyl ether (MTBE) (2 L). The aqueous layer was neutralized with HCl (2N, 1.5 L) and extracted with MTBE (3 L). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, evaporated and the residue was purified by chromatography (silica gel, eluting with dichloromethane) to yield the desired nitroketone.

Step C: 3-Iodo-2-(iodomethyl)prop-1-ene

A mixture of 3-chloro-2-(chloromethyl)prop-1-ene (1.0 g, 8 mmol) and sodium iodide (6.6 g, 44 mmol) in acetone (60 mL) was stirred at room temperature for 20 h, evaporated under reduced pressure and partitioned between dichloromethane (150 mL) and water (50 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to yield 3-iodo-2-(iodomethyl)prop-1-ene as a reddish oil.

Step D: 3-Methylene-5-nitro-6-(2,5-difluorophenyl)-3,4-dihydro-2*H*-pyran

N,N-diisopropylethylamine (184 mL) was added to a solution of 2-nitro-1-(2,5-difluorophenyl)ethanone (92.7 g, 461 mmol) in *N,N*-dimethylformamide (1000 mL) and 3-iodo-2-(iodomethyl)prop-1-ene (156 g, 507 mmol). The mixture was heated at 60 °C for 2 h, evaporated and purified by chromatography (silica gel, gradient 0-30% dichloromethane in hexane) to yield 3-methylene-5-nitro-6-(2,5-difluorophenyl)-3,4-dihydro-2*H*-pyran.

Step E: (2*R*,3*S*)-5-Methylene-3-nitro-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran

This compound was made by following the same method described in Intermediate 1, Step D.

Step F: (2*R*,3*S*)-5-Methylene-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran-3-amine

This compound was made by following the same method described in Intermediate 1, Step E.

Step G: *tert*-Butyl [(2*R*,3*S*)-5-methylene-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

This compound was made by following the same method described in Intermediate 1, Step F.

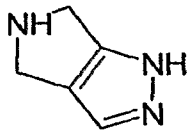
Step H: *tert*-Butyl [(2*R*,3*S*)-5-hydroxy-5-(hydroxymethyl)-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

This compound was made by following the same method described in Intermediate 1, Step G.

Step I: *tert*-Butyl [(2*R*,3*S*)-5-oxo-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate

To a solution of *tert*-butyl [(2*R*,3*S*)-5-hydroxy-5-(hydroxymethyl)-2-(2,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate (10.5 g) in methanol (100 mL) at 0 °C was added pyridine (7.8 mL) and lead tetraacetate (21.7 g). The reaction mixture was stirred for 20 min. Aqueous work-up with ethyl acetate gave crude product which was purified by chromatography (silica, 0-50% ethyl acetate/heptane) to yield *tert*-butyl [(2*R*,3*S*)-5-oxo-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate as white solid.

INTERMEDIATE 3



Step A: *tert*-Butyl (3*Z*)-3-[(dimethylamino)methylene]-4-oxopyrrolidine-1-carboxylate

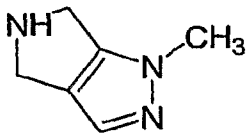
A solution of *tert*-butyl 3-oxopyrrolidine-1-carboxylate (40 g, 216 mmol) was treated with DMF-DMA (267 g, 2241 mmol) and heated at 105 °C for 40 min. The solution was cooled and evaporated under reduced pressure and the resulting orange solid was treated with hexane (200 mL) and cooled in the refrigerator over the weekend. The resulting brownish-yellow solid was collected by filtration, dried and used in the next setp without further purification.

Step B: 1,4,5,6-Tetrahydropyrrolo[3,4-*c*]pyrazole

A solution of hydrazine (3 mL) and *tert*-butyl (3*Z*)-3-[(dimethylamino)methylene]-4-oxopyrrolidine-1-carboxylate (19.22 g) in ethanol (40 mL) was heated at 85 °C in a sealed tube for 4 h. Solvent was removed under reduced pressure, and the residue was triturated with dichloromethane (160 mL) and ethyl acetate (15 mL). The resulting solid was filtered. The filtrate was concentrated and the resulting solid was triturated again and filtered. The combined solids were treated with 4*N* hydrochloric acid (250 mL) in methanol and stirred for 6 h. The reaction mixture was concentrated and dried. The resulting solid was treated again for 6 h with 4*N* hydrochloric acid (250 mL) in methanol. After concentration and drying, the resulting hydrochloride salt was treated with ammonia in methanol (2N, 300 mL) and ammonium hydroxide solution in water (28%, 30 mL) and concentrated to dryness. The solid obtained was treated with methanol (70 mL) and water (5 mL) and purified in three batches on Biotage Horizon® system (silica, gradient 5-17% methanol containing 10% concentrated ammonium hydroxide in ethyl acetate) to yield 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole.

^{1}H NMR (500 MHz, CD_3OD): δ 4.04 (d, 4H), 7.39(s, 1H).

INTERMEDIATE 4



1-Methyl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole

Step A: 1-Methyl-5-trityl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole

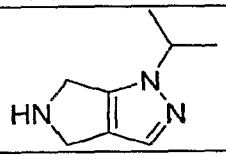
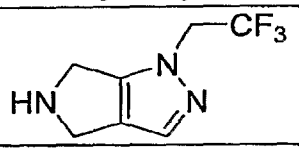
A solution of methyl hydrazine (0.11 mL) and (4*Z*)-4-[(dimethylamino)methylene]-1-tritylpyrrolidin-3-one (678 mg) in ethanol (5 mL) was heated at 84 °C in a sealed tube for 3 h. Solvent was removed under reduced pressure and the residue was purified on a Biotage Horizon® system (silica, 5% methanol/0.5% concentrated ammonium hydroxide/94.5% dichloromethane) to yield 1-methyl-5-trityl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole.

Step B: 1-Methyl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole

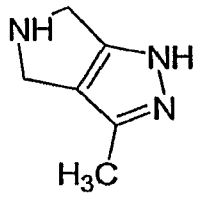
1-Methyl-5-trityl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole (670 mg) obtained in Step A above was treated with 4*N* hydrochloric acid (4 mL). After 1.5 h, the reaction mixture was concentrated. The residue was purified on a Biotage Horizon® system (silica, gradient 10-19% methanol containing 10% concentrated ammonium hydroxide in dichloromethane) to yield 1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole. LC-MS 124.1 (M+1).

The tetrahydropyrrolopyrazoles shown in Table 1 were made essentially following the methods described to make Intermediate 4.

TABLE 1

INTERMEDIATE	STRUCTURE	LC-MS (M+1)
5		152.1
6		192.0

INTERMEDIATE 7



3-Methyl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole

Step A: *tert*-Butyl 3-acetyl-4-oxopyrrolidine-1-carboxylate

To a solution of *tert*-butyl 3-oxopyrrolidine-1-carboxylate (370 mg) in tetrahydrofuran (20 mL) at –78 °C was added sodium bis(trimethylsilyl)amide (4.18 mL, 1.0*M* in tetrahydrofuran). The reaction mixture was stirred for 1.5 h, then treated with acetic anhydride (0.21 mL) and stirred at room temperature for 20 min. The reaction mixture was quenched by the dropwise addition of water and concentrated under vacuum. To the basic residue, ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate solution (30 mL) with an equal volume of water were added. The aqueous layer was separated, acidified by careful addition of hydrochloric acid to pH 3 and extracted with ethyl acetate (75 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to yield desired product which was used in the next step without further purification.

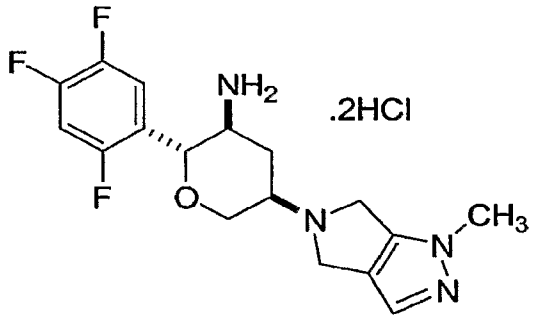
Step B: *tert*-Butyl 3-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5(1*H*)-carboxylate

This step was conducted by essentially following the method described to make the product from Intermediate 2, Step A.

Step C: 3-Methyl-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole

This step was conducted by essentially following the method described to make the product from Intermediate 2, Step B. LC-MS 124.2 (M+1).

EXAMPLE 1



(2*R*,3*S*,5*R*)-5-(1-Methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine, dihydrochloride salt

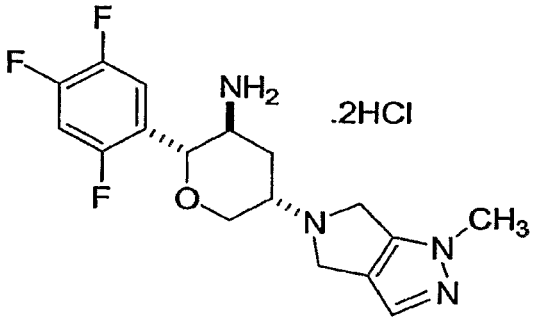
Step A: *tert*-Butyl [(2*R*,3*S*,5*R*)-5-(1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl carbamate

To a stirred solution of Intermediate 1 (50 mg, 0.145 mmol) and Intermediate 4 (29 mg, 0.235 mmol) in methanol (1.0 mL) was added decaborane (6 mg, 0.048 mmol), and the mixture was stirred for 15 h and evaporated under reduced pressure. The product (TLC less-mobile diastereoisomer) was purified by preparative thin layer chromatography with 5% methanol in dichloromethane to give *tert*-butyl [(2*R*,3*S*,5*S*)-5-(1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl carbamate. LC-MS 453.17 (M+1).

Step B: (2*R*,3*S*,5*R*)-5-(1-Methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine dihydrochloride salt

tert-Butyl [(2*R*,3*S*,5*S*)-5-(1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl carbamate from Step A was dissolved in a solution of hydrogen chloride (1 mL, 3*N* in ethyl acetate) and evaporated after two h to yield (2*R*,3*S*,5*S*)-5-(1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine dihydrochloride salt. ^{1}H NMR (500 MHz, CD_3OD): δ 7.57-7.50 (m, 1H); 7.39(s, 1H); 7.34-7.27(m, 1H); 4.91-4.80(m, 2H); 4.75(d, 1H, J=10 Hz); 4.72-4.62(m, 1H); 4.52-4.46(m, 1H); 4.2-4.12 (m, 1H); 3.92 (t, 1H, J = 12 Hz); 3.88 (s, 3H); 3.68(td, 1H, J = 12, 4 Hz); 3.33-3.29(m, 1H); 2.89-2.82(m, 1H); 2.24(q, 1H, J = 12Hz); LC-MS 353.17 (M+1).

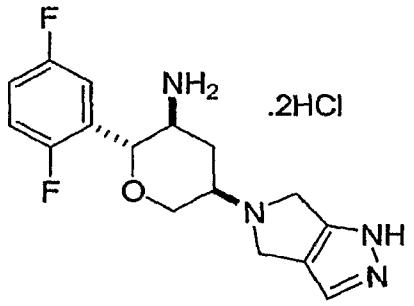
EXAMPLE 2



(2*R*,3*S*,5*R*)-5-(1-Methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine, dihydrochloride salt

This compound was prepared in a similar manner as Example 1, Step B, but using *tert*-butyl [(2*R*,3*S*,5*R*)-5-(1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-yl carbamate obtained as the TLC more-mobile diastereoisomer from Step A of Example 1. ^{1}H NMR (500 MHz, CD_3OD): δ 8.14-8.05 (m, 1H); 7.41(s, 1H); 7.31-7.24(m, 1H); 4.96-4.82(m, 4H); 4.52(d, 1H, J =16 Hz); 4.20(s, 1H); 4.14-4.04(m, 2H); 3.90(s, 3H); 3.33-3.28 (m, 1H); 2.83(d, 1H, J = 16Hz); 2.41(t, 1H, J = 16 Hz); LC-MS 353.17 (M+1).

EXAMPLE 3



(2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)tetrahydro)-5-(4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl) tetrahydro-2*H*-pyran-3-amine, dihydrochloride salt

Step A: *tert*-Butyl [(2*R*,3*S*,5*R*)-2-(2,5-difluorophenyl)-5-(4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-)tetrahydro-2*H*-pyran-3-yl carbamate

A solution of Intermediate 2 (6.03 g, 18.4 mmol) and Intermediate 3 (2.61 g, 23.94 mmol) in methanol (135 mL) was stirred for 30 min and then treated with decaborane (674 mg, 5.53 mmol). The mixture was stirred overnight and evaporated under reduced pressure. The residue was purified on Horizon® (silica, successive elution with ethyl acetate (6 L), 5-6% ethanol containing 10% ammonium hydroxide in ethyl acetate (2 L), 8-12% ethanol containing 10% ammonium hydroxide in ethyl acetate (3 L) to yield the title compound as the less-mobile diastereoisomer (silica, TLC 6% methanol containing 10% ammonia in dichloromethane). ^{1}H NMR (500 MHz, CD_3OD): δ 1.18-1.24 (m, 9H), 1.59-1.65 (q, 1H), 2.4 (m, 1H), 3.06 (m, 1H), 338 (m, 1H), 3.75 (m, 1H), 3.86 (m, 4H), 4.30 (m, 1H), 4.35 (d, 1H, J = 10 Hz), 7.02 (m, 2H), 7.20 (m, 1H), 7.38 (s, 1H).

Step B: (2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)tetrahydro)-5-(4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl) tetrahydro-2*H*-pyran-3-amine, dihydrochloride salt

tert-Butyl [(2*R*,3*S*,5*R*)-2-(2,5-difluorophenyl)-5-(4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-)tetrahydro-2*H*-pyran-3-yl carbamate (5 g) from Step A was dissolved in a solution of hydrogen chloride (300 mL, 3*N* in ethyl acetate) and stirred for 3 h. The solution was evaporated, redissolved in 200 mL methanol and evaporated again to remove traces of residual hydrogen chloride. The residue was triturated with ethanol (50 mL) and methanol (4 mL) to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 2.27 (dd, 1H, J = 11.7, 23.6 Hz), 2.90-2.92 (m, 1H), 3.67-3.70 (m, 1H), 3.94 (t, 1H, J = 11Hz), 4.15-4.19 (m, 1H), 4.54 (m, 1H), 4.72 (br, 4H), 4.78 (d, 1H, J = 10.3 Hz), 7.24 (m, 2H), 7.34 (m, 1H), 7.63 (s, 1H); LC-MS 321.3 (M+1).

EXAMPLE OF A PHARMACEUTICAL FORMULATION

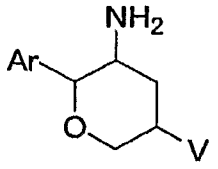
As a specific embodiment of an oral pharmaceutical composition, a 100 mg potency tablet is composed of 100 mg of any one of Examples 1-3, 268 mg microcrystalline cellulose, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active, microcrystalline cellulose, and

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.

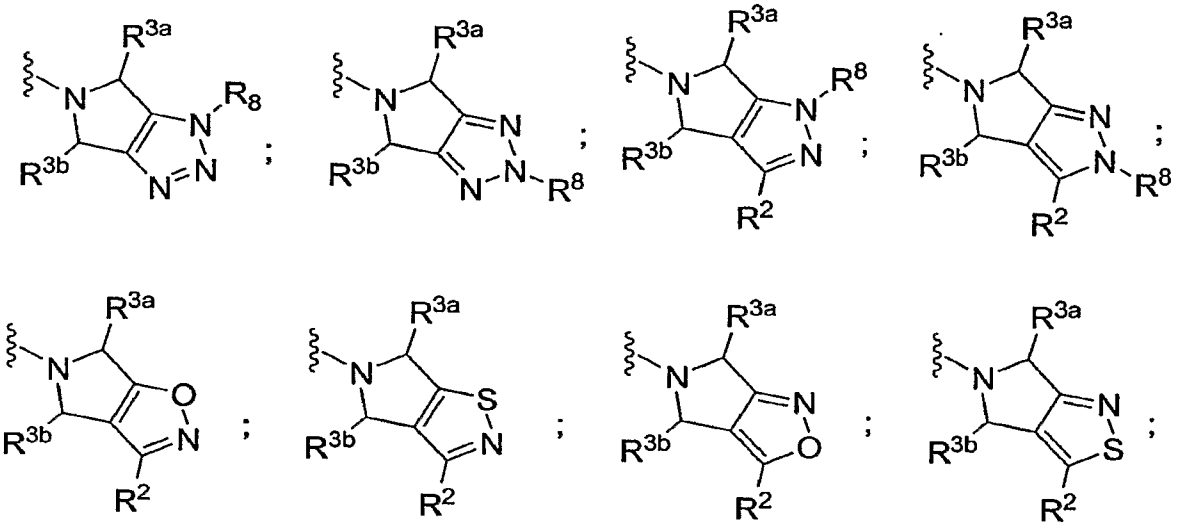
WHAT IS CLAIMED IS:

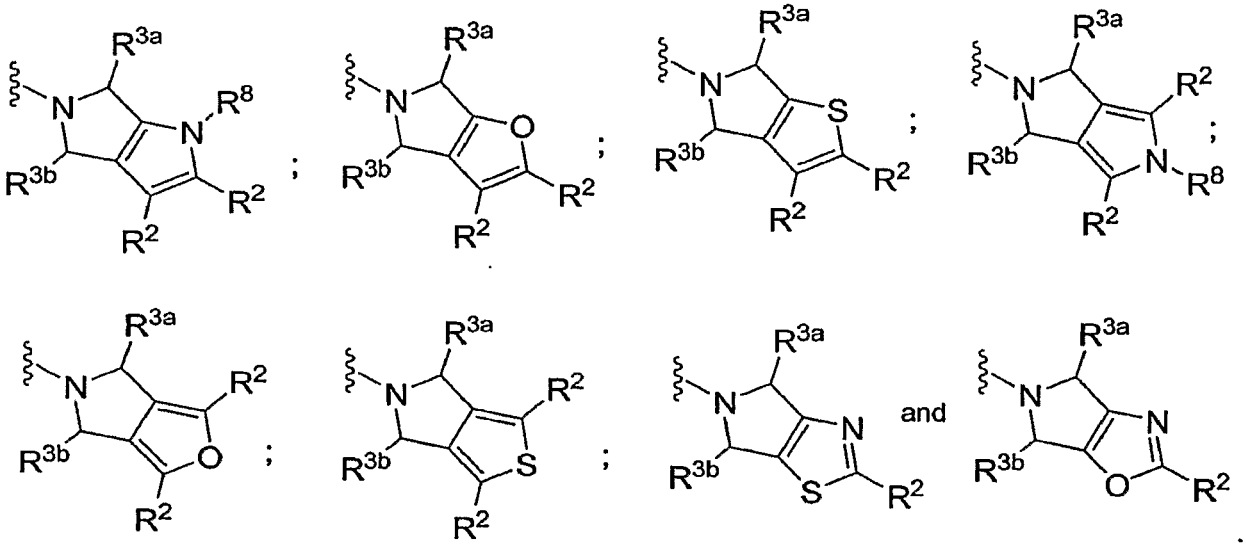
1. A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein
each n is independently 0, 1, 2 or 3;
each m is independently 0, 1, or 2;
each p is independently 0 or 1;
V is selected from the group consisting of:





Ar is phenyl optionally substituted with one to five R^1 substituents;

each R^1 is independently selected from the group consisting of

halogen,

cyano,

hydroxy,

C_{1-6} alkyl, optionally substituted with one to five fluorines,

C_{1-6} alkoxy, optionally substituted with one to five fluorines;

each R^2 is independently selected from the group consisting of

hydrogen,

hydroxy,

halogen,

cyano,

C_{1-10} alkoxy, wherein alkoxy is optionally substituted with one to five substituents independently selected from fluorine and hydroxy,

C_{1-10} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy,

C_{2-10} alkenyl, wherein alkenyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy,

$(CH_2)_n$-aryl, wherein aryl is optionally substituted with one to five substituents independently selected hydroxy, halogen, cyano, nitro, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,

$(CH_2)_n$-heteroaryl, wherein heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy, halogen, cyano, nitro, CO_2H, C_{1-6}

alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,

$(CH_2)_n$-heterocyclyl, wherein heterocyclyl is optionally substituted with one to three substituents independently selected from oxo, hydroxy, halogen, cyano, nitro, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,

$(CH_2)_n$-C_{3-6} cycloalkyl, wherein cycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, cyano, nitro, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines,

$(CH_2)_n$-COOH,

$(CH_2)_n$-$COOC_{1-6}$ alkyl,

$(CH_2)_n$-NR^4R^5,

$(CH_2)_n$-$CONR^4R^5$,

$(CH_2)_n$-$OCONR^4R^5$,

$(CH_2)_n$-$SO_2NR^4R^5$,

$(CH_2)_n$-SO_2R^6,

$(CH_2)_n$-$NR^7SO_2R^6$,

$(CH_2)_n$-$NR^7CONR^4R^5$,

$(CH_2)_n$-NR^7COR^7, and

$(CH_2)_n$-$NR^7CO_2R^6$;

wherein any individual methylene (CH_2) carbon atom in $(CH_2)_n$ is optionally substituted with one to two substituents independently selected from fluorine, hydroxy, C_{1-4} alkyl, and C_{1-4} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

R^{3a} and R^{3b} are each independently hydrogen or C_{1-4} alkyl optionally substituted with one to five fluorines;

R^4 and R^5 are each independently selected from the group consisting of

hydrogen,

$(CH_2)_m$-phenyl,

$(CH_2)_m$-C_{3-6} cycloalkyl, and

C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy and wherein phenyl and cycloalkyl are optionally substituted with one to five substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said

heterocyclic ring is optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

each R^6 is independently C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxyl;

R^7 is hydrogen or R^6; and

R^8 is selected from the group consisting of

hydrogen,

$(CH_2)_p$-phenyl,

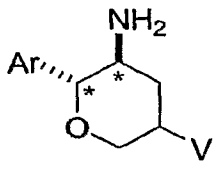
$(CH_2)_p$-C_{3-6} cycloalkyl, and

C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy and wherein phenyl and cycloalkyl are optionally substituted with one to five substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines.

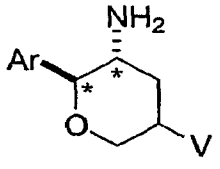
2. The compound of Claim 1 wherein each R^1 is independently selected from the group consisting of fluorine, chlorine, bromine, methyl, trifluoromethyl, and trifluoromethoxy.

3. The compound of Claim 1 wherein R^{3a} and R^{3b} are both hydrogen.

4. 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 *:

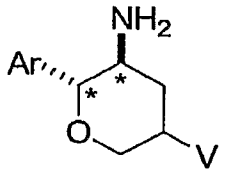


(Ia)



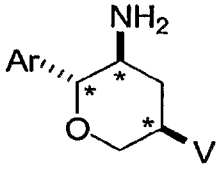
(Ib)

5. The compound of Claim 4 of structural formula Ia having the indicated absolute stereochemical configuration at the two stereogenic carbon atoms marked with an *:

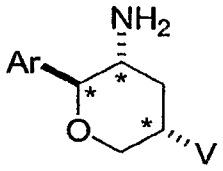


(Ia)

6. The compound of Claim 4 of structural formulae Ic and Id having the indicated stereochemical configuration at the three stereogenic carbon atoms marked with an *:

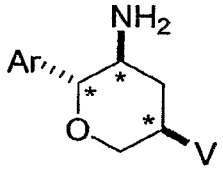


(Ic)



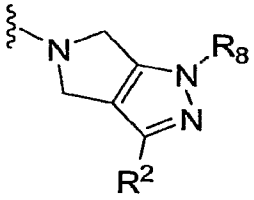
(Id)

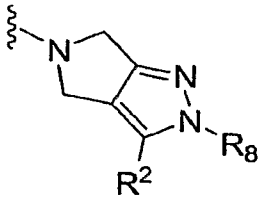
7. The compound of Claim 6 of structural formula Ic having the indicated absolute stereochemical configuration at the three stereogenic carbon atoms marked with an *:

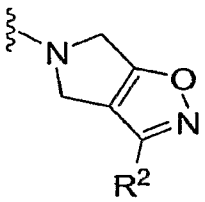


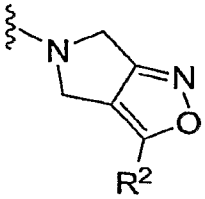
(Ic)

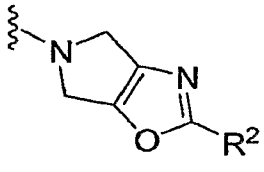
8. The compound of Claim 7 wherein V is selected from the group consisting of:

 ;

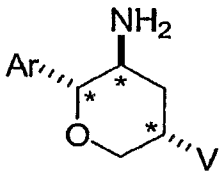
 ;

 ;

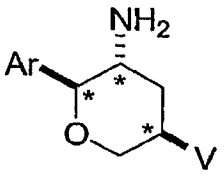
 ; and



9. The compound of Claim 4 of structural formulae Ie and If having the indicated stereochemical configuration at the three stereogenic carbon atoms marked with an *:

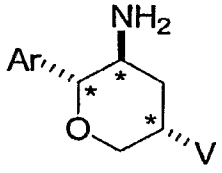


(Ie)



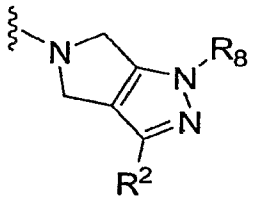
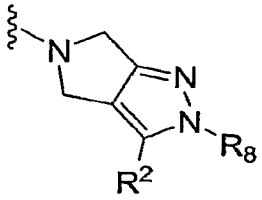
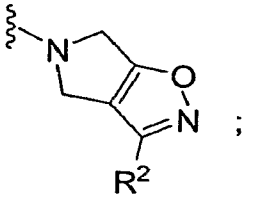
(If)

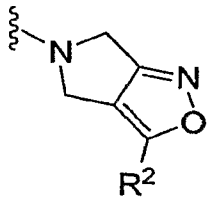
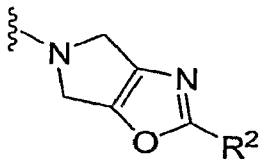
10. The compound of Claim 9 of structural formula Ie having the indicated absolute stereochemical configuration at the three stereogenic carbon atoms marked with an *:



(Ie)

11. The compound of Claim 10 wherein V is selected from the group consisting of:


;

;

;


; and

.

12. The compound of Claim 1 wherein R^2 and R^8 are each independently selected from the group consisting of

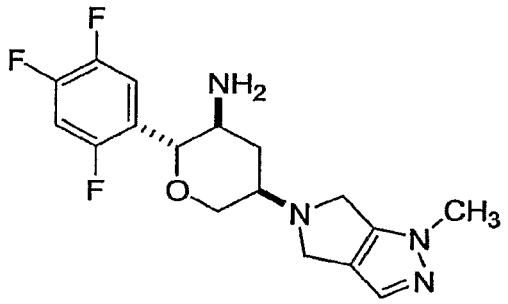
hydrogen,

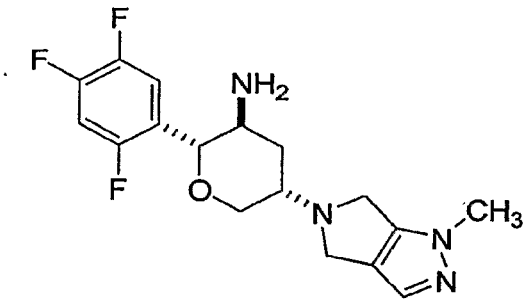
C_{1-6} alkyl, wherein alkyl is optionally substituted with one to five fluorines, and

C_{3-6} cycloalkyl, wherein cycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkyl, and C_{1-4} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines.

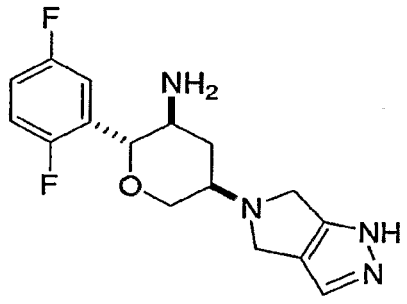
13. The compound of Claim 12 wherein R^2 and R^8 are each independently selected from the group consisting of hydrogen, C_{1-3} alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, and cyclopropyl.

14. A compound which is selected from the group consisting of:





and



;

or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

16. 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.

17. The pharmaceutical composition of Claim 15 additionally comprising metformin.