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(71) **Applicant** *(for all designated States except US)*: **CONCERT PHARMACEUTICALS, INC.** [US/US]; 99 Hayden Avenue, Suite 100, Lexington, MA (US).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only)*: **HARBESON, Scott, L.** [US/US]; 203 Pemberton Street, Unit 5, Cambridge, MA 02140 (US).

(74) **Agents**: **BARBOSA, Stephanie, A.** et al.; Woodcock Washburn, Llp, Cira Centre, 12th Floor, 2929 Arch Street, Philadelphia, PA 19104 (US).

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(54) **Title**: SUBSTITUTED CYANOPYRROLIDINE DERIVATIVES

(57) **Abstract**: This invention relates to novel substituted cyanopyrrolidines, their derivatives and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a dipeptidyl peptidase 4 (DPP-4) inhibitor.

SUBSTITUTED CYANOPYRROLIDINE DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATIONS

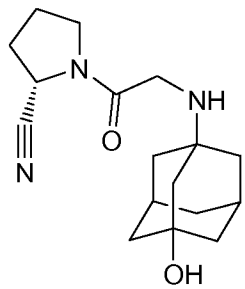
[0001] This application claims the benefit of U.S. Provisional Application No. 61/074,008, filed June 19, 2008, the entirety of which is incorporated herein.

TECHNICAL FIELD

[0002] This invention relates to novel substituted cyanopyrrolidines, their derivatives and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a dipeptidyl peptidase 4 (DPP-4) inhibitor.

BACKGROUND

[0003] Vildagliptin (1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile):



is currently approved for type 2 diabetes mellitus and acts as a selective and potent inhibitor of DPP-4. Vildagliptin administration results in rapid and complete DPP-4 inhibition and subsequent increased levels of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Increasing the levels of endogenous incretin hormones leads to improved β-cell function including enhanced sensitivity of the β-cells to glucose which in turn results in improved glucose-dependent insulin secretion. Additionally, increased levels of endogenous GLP-1 also enhances the sensitivity of pancreatic α-cells to

glucose which leads to improved regulation of glucagon secretion. The overall effect is an increase in the insulin/glucagon ratio during hyperglycemia leading to reduced glycemia. (*See* the EMEA's Summary of Product Characteristics for Galvus at http://www.emea.europa.eu/humandocs/PDFs/EPAR/galvus/H-771-PI-en.pdf).

[0004] The major elimination pathway of vildagliptin in humans is through metabolism. A total of 69% of the dose is metabolized, 51% of which is due to the major inactive metabolite, LAY 151, a product of nitrile hydrolysis. Further hydrolysis of the amide group of LAY151 accounts for an additional 4% of the dose. DPP-4 contributes partially to the hydrolysis of vildagliptin and CYP450 enzymes are not involved to any quantifiable extent. *In vitro* studies have demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. (*See* EMEA's Summary of Product Characteristics for Galvus). The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. Common adverse reactions include, but are not limited to, tremor, headache, dizziness, asthenia, weight increase, peripheral edema, and nausea. Rare cases of hepatic dysfunction (including hepatitis) have been reported. Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. (*See* EMEA's Summary of Product Characteristics for Galvus).

[0005] Despite the beneficial activities of vildagliptin, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Definitions

[0006] The terms "ameliorate" and "treat" are used interchangeably and include both therapeutic and prophylactic treatment. Both terms mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

[0007] "Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[0008] It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of vildagliptin will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E et al.,

Seikagaku, 1994, 66:15; Gannes, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

[0009] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[0010] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[0011] In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[0012] The term "isotopologue" refers to a species that differs from a specific compound of this invention only in the isotopic composition thereof.

[0013] The term "compound," when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues *in toto* will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

[0014] The invention also provides salts, of the compounds of the invention.

[0015] A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

[0016] The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[0017] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2- sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

[0018] The compounds of the present invention (e.g., compounds of Formula I), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or

otherwise. As such, compounds of this invention can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present invention may exist as either a racemic mixture or a scalemic mixture, or as individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers, or less than "X"% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[0019] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

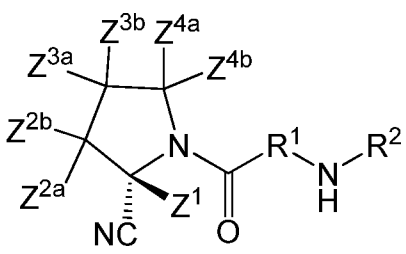
[0020] The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

[0021] "D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

[0022] Throughout this specification, a variable may be referred to generally (e.g.,"each R") or may be referred to specifically (e.g., R^1, R^2, R^3, etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

Therapeutic Compounds

[0023] The present invention provides compounds of Formula I:



(I)

wherein:

R^1 is selected from $-CH_2-$ and $-CD_2-$;

R^2 is 3-hydroxyadamantyl, wherein 1 to 14 hydrogen atoms in R^2 are optionally replaced with deuterium;

each Z is independently selected from hydrogen and deuterium; and

when each Z is hydrogen and R^2 does not comprise deuterium, R^1 is $-CD_2-$. Compounds of the present invention comprise at least one deuterium.

[0024] In other embodiments of Formula I:

each Z^2 is the same;

each Z^3 is the same;

each Z^4 is the same; and

R^2 is selected from 3-hydroxyadamantyl and 3-hydroxy-d_{14}-adamantyl (i.e., 3-hydroxyadamantyl wherein 14 hydrogen atoms are replaced with deuterium).

[0025] An additional embodiment of this invention provides a compound of Formula I wherein Z^{2a} and Z^{2b} are the same; Z^{3a}, Z^{3b}, Z^{4a} and Z^{4b} are the same; and R^2 is selected from 3-hydroxyadamantyl and 3-hydroxy-d_{14}-adamantyl (i.e., 3-hydroxyadamantyl wherein 14 hydrogen atoms are replaced with deuterium). In one aspect of this embodiment Z^{2a} and Z^{2b} are both hydrogen. In another aspect of this embodiment Z^{2a} and Z^{2b} are both deuterium. In an additional aspect Z^{3a}, Z^{3b}, Z^{4a} and Z^{4b} are all hydrogen. In yet another aspect Z^{3a}, Z^{3b}, Z^{4a} and Z^{4b} are all deuterium.

[0026] In yet another embodiment, the compound is selected from any one of the compounds (Cmpd) set forth in Table 1 (below):

Table 1: Exemplary Embodiments of Formula I

Cmpd	Z^1	Z^{2a}/ Z^{2b}	Z^{3a}/ Z^{3b}	Z^{4a}/ Z^{4b}	R^1	R^2
100	H	H	H	H	CD_2	3-hydroxyadamantyl
101	H	H	H	H	CH_2	3-hydroxy-d_{14}-adamantyl
102	H	H	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
103	D	H	H	H	CD_2	3-hydroxyadamantyl
104	D	H	H	H	CH_2	3-hydroxyadamantyl
105	D	H	H	H	CH_2	3-hydroxy-d_{14}-adamantyl
106	D	H	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
107	H	D	H	H	CD_2	3-hydroxyadamantyl
108	H	D	H	H	CH_2	3-hydroxyadamantyl
109	H	D	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
110	H	D	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
111	D	D	D	D	CD_2	3-hydroxyadamantyl
112	D	D	D	D	CH_2	3-hydroxyadamantyl
113	D	D	D	D	CD_2	3-hydroxy-d_{14}-adamantyl

Cmpd	Z^1	Z^{2a}/Z^{2b}	Z^{3a}/Z^{3b}	Z^{4a}/Z^{4b}	R^1	R^2
114	D	D	D	D	CD_2	3-hydroxy-d_{14}-adamantyl

[0027] In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

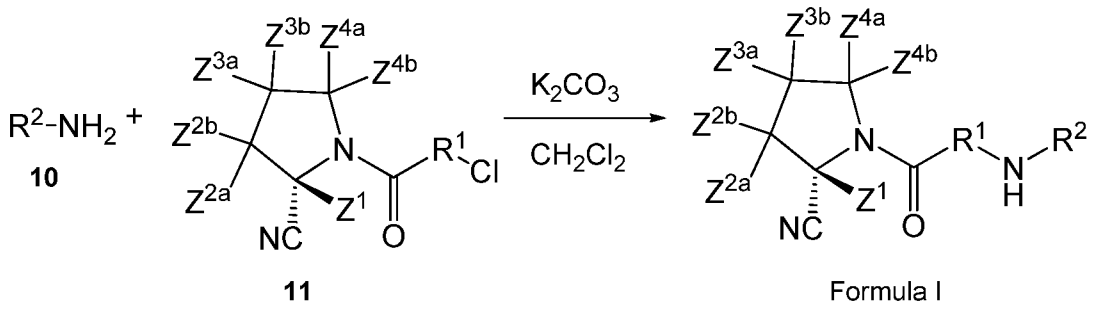
[0028] The synthesis of compounds of Formula I can be readily achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance in Villhauer, EB et al., J Med Chem, 2003, 46: 2774-2789 and PCT publication WO2000034241.

[0029] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Syntheses

[0030] A convenient method for synthesizing compounds of Formula I is depicted in Scheme 1.

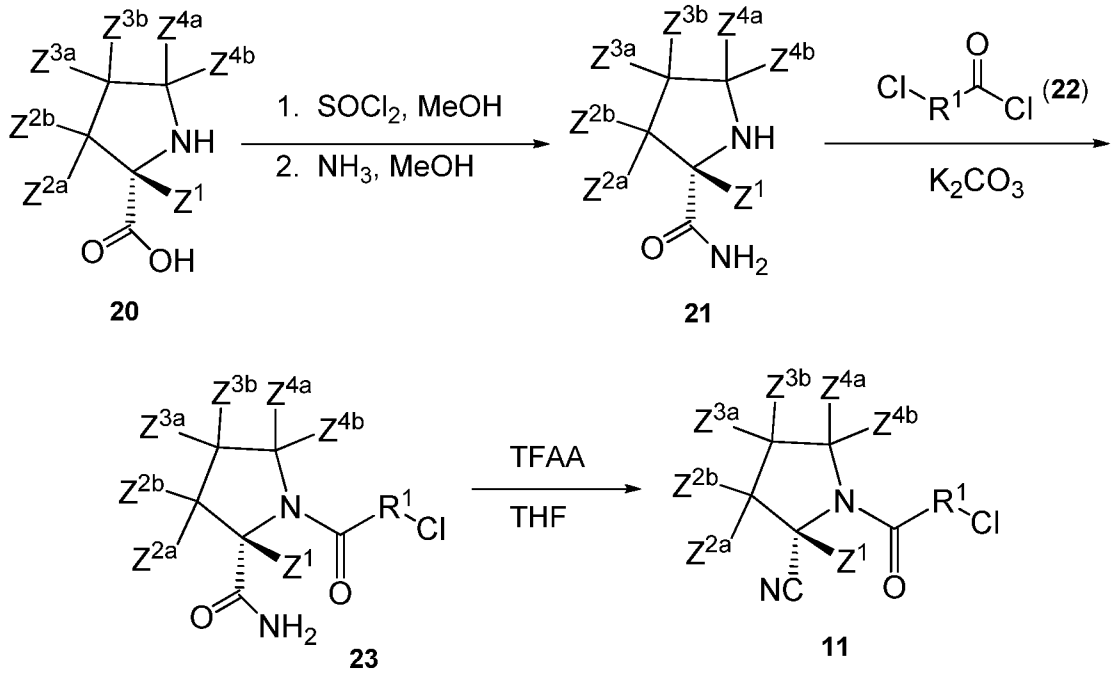
Scheme 1



[0031] According to Scheme 1, a compound of Formula I may be prepared as follows. To a cooled mixture of an appropriately deuterated chloroacetyl-2-cyanopyrolidine **11** and potassium carbonate in dichloromethane is added a solution of the appropriately deuterated 1-amino-3-hydroxy-adamantane **10** in dichloromethane. After stirring for 20 hours, the reaction mixture is filtered and the filtrate concentrated to dryness. Purification by chromatography provides a compound of Formula I.

[0032] An appropriately deuterated chloroacetyl-2-cyanopyrolidine **11** may be prepared according to Scheme 2.

Scheme 2

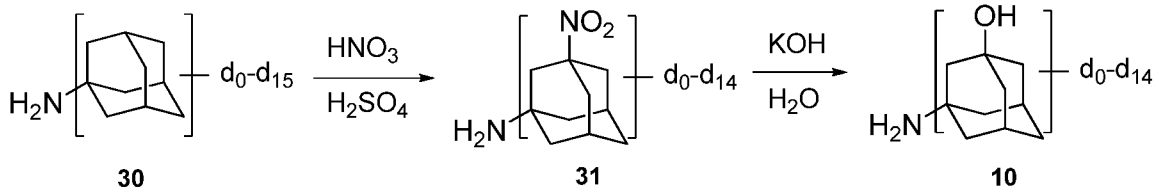


[0033] The appropriately deuterated proline **20** may be prepared according to the method of Herold, F et al., Tet Asym, 2007, 18: 091-2098. Treatment of the proline **20** with thionyl chloride in methanol to produce the methyl ester, is followed by conversion to the amide **21** upon treatment with ammonia in methanol. The proline amide **21** may be coupled with chloroacetyl chloride (or d2-chloroacetyl chloride) **22** in the presence of K_2CO_3. Filtration and solvent removal will provide the desired amide **23**. Conversion of the amide **23** to the nitrile **11** may be accomplished by treatment with trifluoroacetic anhydride in THF at room temperature.

[0034] The example of a deuterated proline **20**, where each Z is deuterium, is commercially available. Another example, where each Z^2 is deuterium; and Z^1, each Z^3 and each Z^4 is hydrogen may be prepared as described by Barraclough, P et al., Org Biomol Chem, 2006, 4: 1483-1491. An additional example of a deuterated proline **20** where Z^1 is deuterium; and each Z^2, Z^3, and Z^4 is hydrogen may be prepared as described by Seebach, D et al., JACS, 1983, 105: 5390-5398.

[0035] An appropriately deuterated 1-amino-3-hydroxyadamantane **10** may be prepared according to Scheme 3.

Scheme 3



As depicted in Scheme 3, intermediate **10** may be prepared as described in detail here. An appropriately deuterated aminoadamantane, added to a chilled solution of nitric acid in conc. sulfuric acid and stirred for several hours in an ice bath followed by stirring at room temperature for 30 hours, yields the corresponding 1-amino-3-nitro compound **31**. To a cooled solution of **31** is carefully added solid KOH. After work-up, compound **10** is obtained as a white solid.

[0036] Perdeuterated aminoadamantane (d15) is commercially available. Alternatively, the perdeuterated aminoadamantane may be obtained by the method described in Canadian Patent 873,873.

[0037] The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R^1, R^2, R^3, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

[0038] Additional methods of synthesizing compounds of Formula I and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[0039] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

Compositions

[0040] The invention also provides pyrogen-free pharmaceutical compositions comprising an effective amount of a compound of Formula I (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

[0041] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0042] If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

[0043] Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

[0044] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA (17th ed. 1985).

[0045] Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately

bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0046] In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[0047] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[0048] Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[0049] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[0050] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. 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 mannitol, 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. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

[0051] The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[0052] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

[0053] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

[0054] Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

[0055] Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

[0056] According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

[0057] According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

[0058] According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

[0059] According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

[0060] Where an organ or tissue is accessible because of removal from the patient, such organ or tissue may be bathed in a medium containing a composition of this invention, a

composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

[0061] In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as vildagliptin. Such agents include those indicated as being useful in combination with vildagliptin, including but not limited to, those described in WO 2006022428, WO 2006041976, WO 2003101448, WO 2002074042, WO 2006005613, WO 2001052825, WO 2005049088, WO 2006076231, WO 2007041368, WO 2007041833, WO 2007128801, WO 2004052362, WO 2005117861, WO 2003099279, WO 2007041053, WO 2005042003, WO 2005120474, WO 2006084757, WO 2006135693, WO 2007023754, and WO 2007006790 .

[0062] Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from diabetes particularly type 2 diabetes mellitus; cardiovascular disorders such as cardiac hypertrophy, cardiac remodeling after myocardial infarction, pulmonary congestion and cardiac fibrosis; renal damage or impairment; hyperlipidemia and conditions associated therewith, such as CHD, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia and post-prandial lipemia; a proliferative disease, especially a solid tumor disease; insulin resistance; impaired glucose metabolism; conditions of impaired glucose tolerance; conditions of impaired fasting plasma glucose; hypoglycemia; obesity; diabetic retinopathy; macular degeneration; cataracts; diabetic nephropathy; glomerulosclerosis; diabetic neuropathy; erectile dysfunction; premenstrual syndrome; coronary heart disease; hypertension; angina pectoris; skin and connective tissue disorders; foot ulcerations and ulcerative colitis; endothelial dysfunction and impaired vascular compliance; altered gastrointestinal motility; sensitivity and/or secretion disorder(s) which include, but are not limited to, heartburn, bloating, postoperative ileus, abdominal pain and discomfort, early satiety, epigastric pain, nausea, vomiting, burbulence, regurgitation, intestinal pseudoobstruction, anal incontinence, GERD, IBS, dyspepsia, chronic constipation or diarrhea, diabetic gastropathy, gastroparesis, e.g. diabetic gastroparesis, ulcerative colitis, Crohn's disease, ulcers and the visceral pain associated therewith; neurodegenerative disorders, cognitive disorders and for improving memory (both short term and long term) and learning ability; autoimmune diseases; graft rejection; disorders characterized by growth hormone deficiency,

including growth retardation and metabolic disorders as well as burns, wounds, trauma and convalescence following surgery; arthritis and osteoporosis .

[0063] In one embodiment, the second therapeutic agent is selected from metformin, a sulphonylurea, and a thiazolidinedione.

[0064] In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[0065] In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

[0066] The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., (1966) Cancer Chemother. Rep 50: 219. Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

[0067] In one embodiment, an effective amount of a compound of this invention can range from about 0.5 mg to about 1 g per treatment. In a more specific embodiment the range is from about 5 mg to 500 mg, or from about 10 mg to 200 mg, or most specifically from about 50 mg to about 100 mg per treatment. Treatment typically is administered one to two times daily .

[0068] Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for vildagliptin.

[0069] For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount

is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

[0070] It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

[0071] In another embodiment, the invention provides a method of blocking the activity of dipeptidylpeptidase-4 (DPP-4) in a cell, comprising contacting a cell with one or more compounds of Formula I herein.

[0072] According to another embodiment, the invention provides a method of treating a patient suffering from, or susceptible to, a disease that is beneficially treated by vildagliptin comprising the step of administering to said patient an effective amount of a compound or a composition of this invention. Such diseases are well known in the art and are disclosed in, but not limited to the following patents and published applications: WO 2000034241, WO 2005049022, WO 2003101448, WO 2002074042, WO 2006005613, WO 2005079795, WO 2007035665, WO 2007041368, WO 2004052362, WO 2003099279, WO 2005042003, and WO 2006135723. Such diseases include, but are not limited to, diabetes particularly type 2 diabetes mellitus; cardiovascular disorders such as cardiac hypertrophy, cardiac remodeling after myocardial infarction, pulmonary congestion and cardiac fibrosis; renal damage or impairment; hyperlipidemia and conditions associated therewith, such as CHD, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia and post-prandial lipemia; a proliferative disease, especially a solid tumor disease; insulin resistance; impaired glucose metabolism; conditions of impaired glucose tolerance; conditions of impaired fasting plasma glucose; hypoglycemia; obesity; diabetic retinopathy; macular degeneration; cataracts; diabetic nephropathy;

glomerulosclerosis; diabetic neuropathy; erectile dysfunction; premenstrual syndrome; coronary heart disease; hypertension; angina pectoris; skin and connective tissue disorders; foot ulcerations and ulcerative colitis; endothelial dysfunction and impaired vascular compliance; altered gastrointestinal motility; sensitivity and/or secretion disorder(s) which include, but are not limited to, heartburn, bloating, postoperative ileus, abdominal pain and discomfort, early satiety, epigastric pain, nausea, vomiting, burbulence, regurgitation, intestinal pseudoobstruction, anal incontinence, GERD, IBS, dyspepsia, chronic constipation or diarrhea, diabetic gastropathy, gastroparesis, e.g. diabetic gastroparesis, ulcerative colitis, Crohn's disease, ulcers and the visceral pain associated therewith; neurodegenerative disorders, cognitive disorders and for improving memory (both short term and long term) and learning ability; autoimmune diseases; graft rejection; disorders characterized by growth hormone deficiency, including growth retardation and metabolic disorders as well as burns, wounds, trauma and convalescence following surgery; arthritis and osteoporosis .

[0073] In another particular embodiment, the method of this invention is used to treat a patient suffering from or susceptible to a disease or condition selected from type 2 diabetes mellitus.

[0074] Methods delineated herein also include those wherein the patient is identified as in need of a particular stated treatment. Identifying a patient in need of such treatment can be in the judgment of a patient or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[0075] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to said patient one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with vildagliptin. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention and a second therapeutic agent.

[0076] In particular, the combination therapies of this invention include co-administering a compound of Formula I and a second therapeutic agent for treatment of the following conditions (with the particular second therapeutic agent indicated in parentheses following the indication: type 2 diabetes mellitus (metformin, a sulphonylurea, or a thiazolidinedione).

[0077] The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a patient does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said patient at another time during a course of treatment.

[0078] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[0079] In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[0080] In yet another aspect, the invention provides the use of a compound of Formula I alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a patient of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I for use in the treatment or prevention in a patient of a disease, disorder or symptom thereof delineated herein.

Pharmaceutical Kits

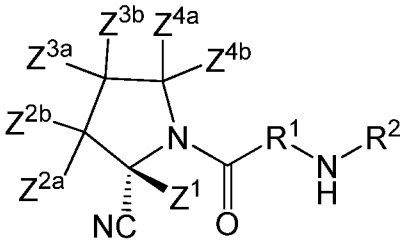
[0081] The present invention also provides kits for use to treat type 2 diabetes mellitus. These kits comprise (a) a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein said pharmaceutical composition is in a container; and (b) instructions describing a method of using the pharmaceutical composition to treat type 2 diabetes mellitus.

[0082] The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition. Examples include bottles, ampules, divided or multi-chambered holders bottles, wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. In one embodiment, the container is a blister pack.

[0083] The kits of this invention may also comprise a device to administer or to measure out a unit dose of the pharmaceutical composition. Such device may include an inhaler if said composition is an inhalable composition; a syringe and needle if said composition is an injectable composition; a syringe, spoon, pump, or a vessel with or without volume markings if said composition is an oral liquid composition; or any other measuring or delivery device appropriate to the dosage formulation of the composition present in the kit.

[0084] In certain embodiment, the kits of this invention may comprise in a separate vessel of container a pharmaceutical composition comprising a second therapeutic agent, such as one of those listed above for use for co-administration with a compound of this invention.

[0085] Certain embodiments of the invention include compounds of Formula I:



(I)

wherein:

R^1 is selected from $-CH_2-$ and $-CD_2-$;

R^2 is 3-hydroxyadamantyl, wherein 1 to 14 hydrogen atoms in R^2 are optionally replaced with deuterium;

each Z is independently selected from hydrogen and deuterium; and

when each Z is hydrogen and R^2 does not comprise deuterium, R^1 is $-CD_2-$.

[0086] Preferred compounds of Formula I include those wherein each Z^2 is the same. Other preferred compounds include those wherein each Z^3 is the same. Still other preferred compounds include those wherein each Z^4 is the same.

[0087] In other preferred compounds of Formula I, R^1 is selected from 3-hydroxyadamantyl and 3-hydroxy-d_{14}-adamantyl.

[0088] In other preferred compounds of Formula I, each Z^2 is the same; each Z^3 is the same; each Z^4 is the same; and the compound is selected from any one of the compounds set forth in the table below

Cmpd	Z^1	Each Z^2	Each Z^3	Each Z^4	R^1	R^2
100	H	H	H	H	CD_2	3-hydroxyadamantyl
101	H	H	H	H	CH_2	3-hydroxy-d_{14}-adamantyl
102	H	H	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
103	D	H	H	H	CD_2	3-hydroxyadamantyl
104	D	H	H	H	CH_2	3-hydroxyadamantyl
105	D	H	H	H	CH_2	3-hydroxy-d_{14}-adamantyl
106	D	H	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
107	H	D	H	H	CD_2	3-hydroxyadamantyl
108	H	D	H	H	CH_2	3-hydroxyadamantyl
109	H	D	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
110	H	D	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
111	D	D	D	D	CD_2	3-hydroxyadamantyl
112	D	D	D	D	CH_2	3-hydroxyadamantyl
113	D	D	D	D	CD_2	3-hydroxy-d_{14}-adamantyl
114	D	D	D	D	CD_2	3-hydroxy-d_{14}-adamantyl

[0089] In other preferred embodiments, any atom not designated as deuterium in a compound of Formula I is present at its natural isotopic abundance.

[0090] Other preferred embodiments include pyrogen-free compositions comprising a compound of Formula I and an acceptable carrier. Preferably, the carrier is a pharmaceutically acceptable carrier.

EXAMPLE 1. Evaluation of Metabolic Stability

[0091] ***Microsomal Assay:*** Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

[0092] ***Determination of Metabolic Stability:*** 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5 - 50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5 - 50 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25 - 1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37 °C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 °C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for vidagliptin and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

[0093] ***Data analysis:*** The *in vitro* $t_{1/2}$s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

in vitro $t_{1/2}$ = 0.693/k

k = -[slope of linear regression of % parent remaining(ln) vs incubation time]

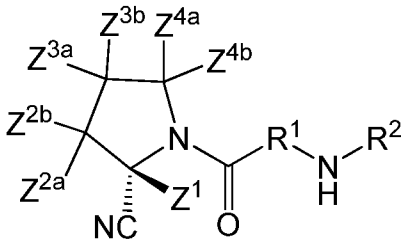
Data analysis is performed using Microsoft Excel Software.

[0094] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the

compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

What is Claimed:

1. A compound of Formula I:



(I)

wherein:

R^1 is selected from $-CH_2-$ and $-CD_2-$;

R^2 is 3-hydroxyadamantyl, wherein 1 to 14 hydrogen atoms in R^2 are optionally replaced with deuterium;

each Z is independently selected from hydrogen and deuterium; and

when each Z is hydrogen and R^2 does not comprise deuterium, R^1 is $-CD_2-$.

2. The compound of claim 1, wherein:

Z^{2a} and Z^{2b} are the same;

Z^{3a}, Z^{3b}, Z^{4a} and Z^{4b} are the same; and

R^2 is selected from 3-hydroxyadamantyl and 3-hydroxy-d_{14}-adamantyl.

3. The compound of claim 2, wherein Z^{2a} and Z^{2b} are hydrogen.

4. The compound of claim 2, wherein Z^{2a} and Z^{2b} are deuterium.

5. The compound of claim 2 or 3, wherein Z^{3a}, Z^{3b}, Z^{4a} and Z^{4b} are hydrogen.

6. The compound of claim 2 or 3, wherein Z^{3a}, Z^{3b}, Z^{4a} and Z^{4b} are deuterium.

7. The compound of claim 2, selected from any one of the compounds set forth in the table below

Cmpd	Z^1	Z^{2a}/ Z^{2b}	Z^{3a}/ Z^{3b}	Z^{4a}/ Z^{4b}	R^1	R^2
100	H	H	H	H	CD_2	3-hydroxyadamantyl
101	H	H	H	H	CH_2	3-hydroxy-d_{14}-adamantyl
102	H	H	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
103	D	H	H	H	CD_2	3-hydroxyadamantyl
104	D	H	H	H	CH_2	3-hydroxyadamantyl

Cmpd	Z^1	Z^{2a}/ Z^{2b}	Z^{3a}/ Z^{3b}	Z^{4a}/ Z^{4b}	R^1	R^2
105	D	H	H	H	CH_2	3-hydroxy-d_{14}-adamantyl
106	D	H	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
107	H	D	H	H	CD_2	3-hydroxyadamantyl
108	H	D	H	H	CH_2	3-hydroxyadamantyl
109	H	D	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
110	H	D	H	H	CD_2	3-hydroxy-d_{14}-adamantyl
111	D	D	D	D	CD_2	3-hydroxyadamantyl
112	D	D	D	D	CH_2	3-hydroxyadamantyl
113	D	D	D	D	CD_2	3-hydroxy-d_{14}-adamantyl
114	D	D	D	D	CD_2	3-hydroxy-d_{14}-adamantyl

8. The compound of any one of claims 1 to 7, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

9. A pyrogen-free pharmaceutical composition comprising a compound of any one of claims 1 to 8; and a pharmaceutically acceptable carrier.

10. The composition of claim 9 further comprising a second therapeutic agent selected from metformin, a sulphonylurea, and a thiazolidinedione.

11. The composition of claim 9 or 10 for use in the treatment of type 2 diabetes in a patient.

12. The composition of claim 11, wherein the patient is also being treated with a second therapeutic agent selected from metformin, a sulphonylurea, and a thiazolidinedione.

13. A method of treating type 2 diabetes comprising the step of administering to a patient in need thereof a composition of claim 9.

14. The method of claim 13, further comprising the step of co-administering to the patient in need thereof a second therapeutic agent selected from metformin, a sulphonylurea, and a thiazolidinedione.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/047596

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07B59/00 C07D207/16 A61K31/40 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07B C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/34241 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; VILLHAUER EDWIN B) 15 June 2000 (2000-06-15) the whole document	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 2009	21/09/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Diederen, Jeroen

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/047596

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0034241 A	15-06-2000	AT 307112 T	15-11-2005
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		CZ 20012028 A3	12-09-2001
		DE 69927844 T2	27-07-2006
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