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(71) Applicant *(for all designated States except US)*: **GLENMARK PHARMACEUTICALS S.A.** [CH/CH]; Chemin de la Combeta, 5, CH-2300 La Chaux-de-Fonds (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **THOMAS, Abraham** [IN/IN]; 303, Kavita Apartments, 3rd Floor, Equity Cooperative Housing Society, Plot No. 35, Sector 29, Vashi, Navi Mumbai 400 705 (IN). **LINGAM, V.S., Prasada Rao** [IN/IN]; Flat No 101, Enkay Square Co-operative Housing Society Ltd., Plot No. 21, Sector 6, Koparkharine, Navi Mumbai 400 709 (IN). **SHAH, Daisy, Manish** [IN/IN]; Padmashree Building, 1st Floor, Block 4, Anant Patil Marg, Dadar (W), Mumbai 400 028 (IN).

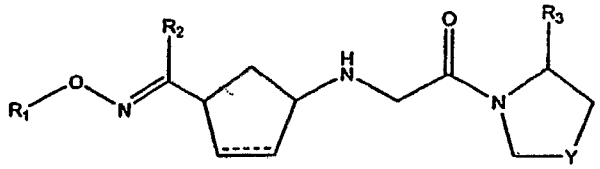
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(54) Title: DIPEPTIDYL PEPTIDASE IV INHIBITOR COMPOUNDS AND COMPOSITIONS



(1)

(57) Abstract: The present invention relates to dipeptidyl peptidase IV (DPP-IV) inhibitors of formula (1), pharmaceutical compositions containing them, processes for their preparation, and methods for treating disorders mediated by DPP-IV inhibition, such as diabetes, especially Type II diabetes, with them, wherein R_j is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl; R_2 is hydrogen or Q-β alkyl; Y is $-S(O)^m$, $-CH_2-$, -CHF or CF_2; R_3 is hydrogen, nitrile (-CN), COOH, or an isostere of a carboxylic acid.

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DIPEPTIDYL PEPTIDASE IV INHIBITOR COMPOUNDS AND COMPOSITIONS

Field of the Invention

The present invention relates to dipeptidyl peptidase IV (DPP-IV) inhibitors, pharmaceutical compositions containing them, processes for their preparation, and methods for treating disorders mediated by DPP-IV inhibition, such as diabetes, especially Type II diabetes, with them.

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. Patients with Type II 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.

There are two generally recognized forms of diabetes. In Type I diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In Type II 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. Therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

The available treatments for Type II 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 sulphonylureas or meglitinide becomes ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistance 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 II diabetes.

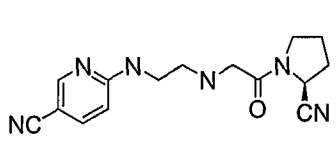
The glitazones (i.e., 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for ameliorating many symptoms of Type II diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of Type II diabetes 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 sensitization 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 PPAR agonists, such as troglitazone.

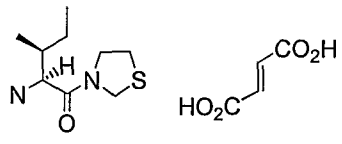
Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (e.g., acrabose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DPP-IV") enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly Type II diabetes. See, for example, WO 97/40832, WO 98/19998, U.S. Patent No. 5,939,560, *Bioorg. Med. Chem. Lett.*, 6(10), 1163-1166 (1996), and *Bioorg. Med.Chem. Lett.*, 6(22), 2745-2748 (1996). The usefulness of DPP-IV inhibitors in the treatment of Type II diabetes is based on the fact that DPP-IV 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-IV 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-IV 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-IV 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-IV 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-IV inhibitors may also have other therapeutic utilities, as discussed herein. DPP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DPP-IV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions.

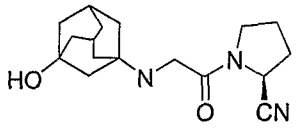
The compounds shown below are DPP-IV inhibitors which have reached advanced stages of human clinical trials:



A



B



C

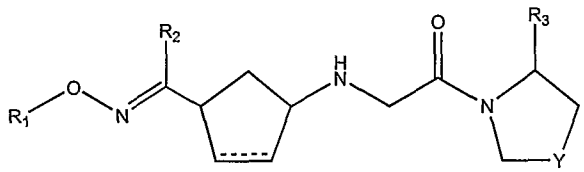
Novartis "NVP-DPP-728" which has the formula A, Probiodrug " P32/98 which has the formula B and Novartis "NVP-LAF-237" which has the formula C .

Other DPP-IV inhibitors are described in PCT Patent publication WO 03/084940, *JMC* (2003), 46(13), 2774-2789, PCT Patent publication WO 03/037327, EP Patent publication EP 1 354 882 A1, PCT Patent publication WO 98/19998, U.S. Patent No. 6,011,155.

Although a number of DPP-IV inhibitors have been described in the literature, all have limitations relating to potency, stability or toxicity, accordingly, it is clear that a great need exists for new DPP-IV inhibitors which are useful in treating conditions mediated by DPP-IV inhibition.

Summary of the Invention

The present invention relates to Dipeptidyl peptidase IV (DPP-IV) inhibitors of the formula **(I)**:



(1)

wherein

R_1 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl,

substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl;

R_2 is hydrogen or C_{1-6} alkyl;

Y is $-S(O)^m$, $-CH_2-$, -CHF or CF_2;

R_3 is hydrogen, nitrile (-CN), COOH, or an isostere of a carboxylic acid, such as SO_3H, CONOH, $B(OH)_2$, $PO_3R_4R_5$, $SO_2NR_4R_5$, a tetrazole, an amide, an ester or an acid anhydride;

R_4 and R_5 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, –C(O)- R_4, $-C(O)O-R_4$, $-C(O)NR_4R_5$, $-S(O)m-R_4$, $-S(O)m-NR_4R_5$, $-NR_4R_5$,$-OR_4$, or $-SR_4$;

the dotted line [----] in the carbocyclic ring represents an optional double bond; and

m is an integer from 0 to 3,

and analogs thereof, tautomers thereof, enantiomers thereof, diastereomers thereof, regioisomers thereof, stereoisomers thereof, polymorphs thereof, pharmaceutically acceptable salts thereof, N-oxides thereof, prodrugs thereof ,and pharmaceutically acceptable solvates thereof.

Preferred is a compound of formula (I), wherein R_1 is substituted or unsubstituted alkyl.

Further preferred is a compound of formula (I), wherein R_1 is cyanomethyl.

Further preferred is a compound of formula (I), wherein R_1 is ethyl.

Further preferred is a compound of formula (I), wherein R_1 is methoxyethyl.

Further preferred is a compound of formula (I), wherein R_1 is propyl.

Further preferred is a compound of formula (I), wherein R_1 is butyl.

Preferred is a compound of formula (I), wherein R_1 is cycloalkyl.

Further preferred is a compound of formula (I), wherein R_1 is cyclopentyl.

Further preferred is a compound of formula (I), wherein R_1 is adamantyl.

Preferred is a compound of formula (I), wherein R_1 is substituted or unsubstituted arylalkyl.

Further preferred is a compound of formula (I), wherein R_1 is benzyl.

Further preferred is a compound of formula (I), wherein R_1 is 4-cyano-benzyl.

Further preferred is a compound of formula (I), wherein R_1 is 4-halo-benzyl.

Further preferred is a compound of formula (I), wherein R_1 is 4-chloro-benzyl.

Further preferred is a compound of formula (I), wherein R_1 is 4-fluoro-benzyl.

Further preferred is a compound of formula (I), wherein R_1 is 4-trifluoro-benzyl.

Further preferred is a compound of formula (I), wherein R_1 is 4-tert-butylbenzyl.

Further preferred is a compound of formula (I), wherein R_1 is 4-tert-butylbenzyl.

Further preferred is a compound of formula (I), wherein R_1 is 3-propyl-phenyl.

Preferred is a compound of formula (I), wherein R_1 is substituted or unsubstituted

Heteroarylalkyl.

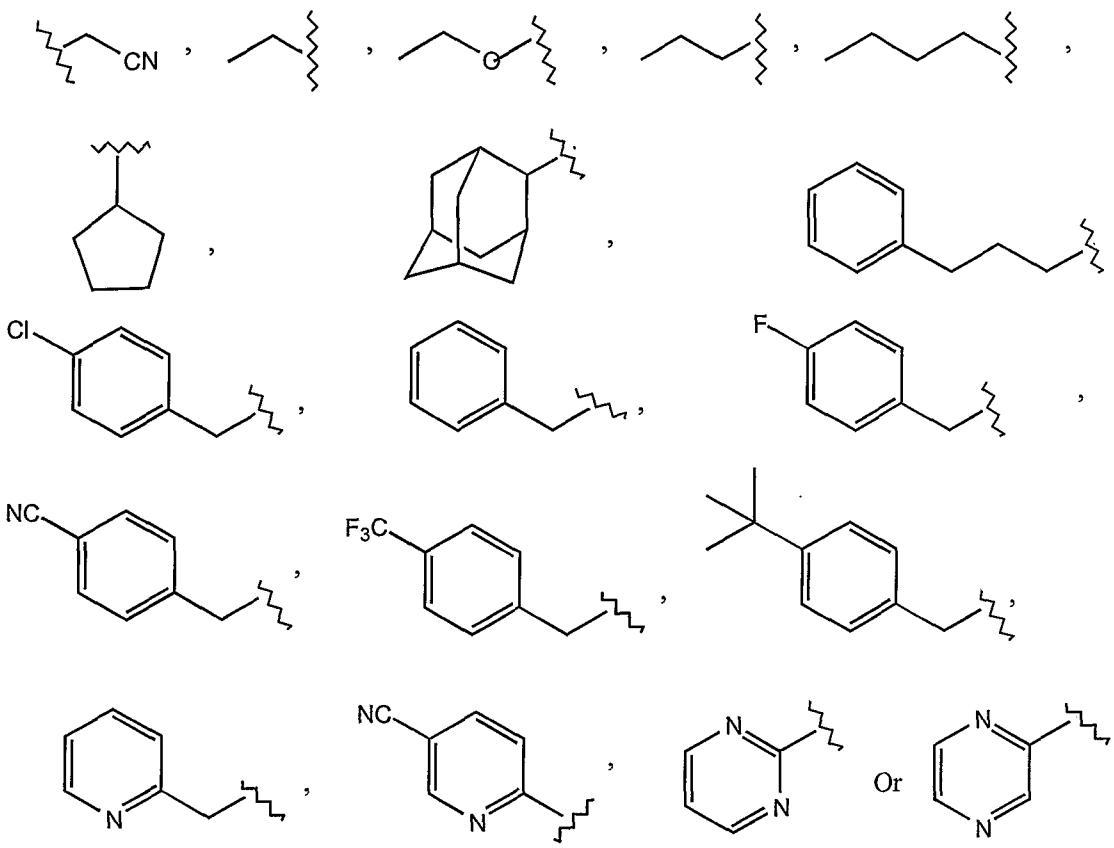
Further preferred is a compound of formula (I), wherein R_1 is 2-pyridyl-methyl.

Further preferred is a compound of formula (I), wherein R_1 is 5-cyano-2-pyridyl.

Further preferred is a compound of formula (I), wherein R_1 is 2-pyrimidinyl.

Further preferred is a compound of formula (I), wherein R_1 is 2-pyrazinyl.

More preferred is a compound of formula (I), wherein R_1 is



Preferred is a compound of formula (I), wherein R_2 is substituted or unsubstituted C_{1-6} alkyl.

Further preferred is a compound of formula (I), wherein R_2 is methyl.

Further preferred is a compound of formula (I), wherein R_2 is ethyl.

Preferred is a compound of formula (I), wherein R_3 is nitrile.

Preferred is a compound of formula (I), wherein Y is $-CH_2$.

Further preferred is a compound of formula (I), wherein Y is -CHF.

One of ordinary skill in the art of synthesis will recognize that a cyclopentane or cyclopentene ring bearing 1,3-substituents can fall into a *cis* or *trans* geometry. In principle, such substitution pattern, with two chiral centres, can lead up to 4 enantiomers. Therefore, the compounds of the present invention may be prepared as a mixture of enantiomers as well as single enantiomers. Mixtures as well as single enantiomers of the above mentioned isomers are within the scope of this invention. The optically active compounds of the present invention may be obtained by resolution, asymmetric synthesis or by other methods known to those skilled in the art.

Some representative compounds according to the present invention are specified below. The present invention should not be construed as limited to them:

1. (2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoro-pyrrolidine-2-carbonitrile;
2. (2*S*,4*S*)-1-{2-[(1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoro-pyrrolidine-2-carbonitrile;
3. (2*S*)-1-{2-[(3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentylamino]acetyl} pyrrolidine-2-carbonitrile;
4. (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-(1-Butyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoro-pyrrolidine-2-carbonitrile;
5. (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[(Cyclopentyloxyimino)ethyl]cyclopentylamino} acetyl) -4-fluoropyrrolidine-2-carbonitrile;
6. (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Adamantyloxyimino)ethyl]cyclopentylamino} acetyl)-pyrrolidine-2-carbonitrile;
7. (2*S*)-1-(2-{(3*S*,1*R*)-3-(1-(2-Methoxyethoxyimino) ethyl]cyclopentylamino} acetyl)-pyrrolidine-2-carbonitrile;
8. (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(Cyanomethoxyimino)ethyl]cyclopentylamino} acetyl)-4-fluoropyrrolidine-2-carbonitrile;
9. (2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1-Benzyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoro-pyrrolidine-2-carbonitrile;
10. (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyimino)ethyl]cyclopentylamino} acetyl)-pyrrolidine-2-carbonitrile;
11. (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyimino)ethyl]cyclopentylamino} -acetyl)-4-fluoropyrrolidine-2-carbonitrile;
12. (2*S*,4*S*)-4-Fluoro-1-(2-{(3*R*,1*S*)-3-(1-(4-trifluorobenzyloxyimino)ethyl] cyclopentyl-amino} acetyl)pyrrolidine-2-carbonitrile;
13. (2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(4-fluorobenzyloxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile;
14. (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyimino)propyl] cyclopentylamino}-acetyl)-4-fluoropyrrolidine-2-carbonitrile;

15. (2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(3-phenylpropyloxyimino)ethyl] cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile;
16. (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentylamino} acetyl)-pyrrolidine-2-carbonitrile;
17. (2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(2-pyridylmethoxyimino)ethyl] cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile;
18. (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentyl amino}-acetyl)pyrrolidine-2-carbonitrile;
19. (2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentyl amino}-acetyl)pyrrolidine-2-carbonitrile;
20. (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentylamino} acetyl)-pyrrolidine-2-carbonitrile; and
21. (2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile; and

pharmaceutically acceptable salts thereof. The invention also encompasses active metabolites of a compound of the invention.

Another embodiment is a pharmaceutical composition comprising at least one compound of the present invention and a pharmaceutically acceptable excipient such as a pharmaceutically acceptable carrier or diluent. Preferably, the pharmaceutical composition includes a therapeutically effective amount of the compound(s) of the present invention.

Yet another embodiment is a method of treating a condition that may be regulated or normalized through inhibition of DPP-IV, such as diabetes (especially type II diabetes) in a subject in need thereof by administering to the subject an effective amount of a compound of the present invention

Detailed Description of the Invention

Definitions:

The term "alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a

single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

The term "alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain having 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl and 2-butenyl.

The term "alkynyl" refers to a straight or branched chain hydrocarbyl radical having at least one carbon-carbon triple bond, and having in the range of 2 up to about 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred), e.g., ethynyl, propynyl, and butynyl.

The term "alkoxy" refers to an alkyl group as defined above attached via an oxygen linkage to the rest of the molecule. Non-limiting examples of such groups include $-OCH_3$ and $-OC_2H_5$.

The term "alkylcarbonyl" refers to an alkyl group as defined above attached via a carbonyl linkage to the rest of the molecule. Non-limiting examples of such groups include $-C(O)CH_3$ and $-C(O)C_2H_5$.

The term "alkoxycarbonyl" refers to an alkoxy group as defined above attached via a carbonyl linkage to the rest of the molecule. Non-limiting examples of such groups include $-C(O)-OCH_3$ and $-C(O)-OC_2H_5$.

The term "alkylcarbonyloxy" refers to an alkylcarbonyl group as defined above attached via an oxygen linkage to the rest of the molecule. Non-limiting examples of such groups include $-O-C(O)CH_3$ and $-O-C(O)C_2H_5$.

The term "alkylamino" refers to an alkyl group as defined above attached via an amino linkage to the rest of the molecule. Non-limiting examples of such groups include $-NH_2CH_3$, $-NH(CH_3)_2$, and $-N(CH_3)_3$.

The term "cycloalkyl" refers to a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Non-limiting examples of multicyclic cycloalkyl groups include perhydronapththyl, adamantyl and norbornyl groups, bridged cyclic groups and sprirobicyclic groups, e.g., sprio (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical containing in the range of 3 up to about 8 carbon atoms directly attached to an alkyl group which are then attached to the main structure at any carbon from the alkyl

group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl and cyclopentylethyl.

The term "cycloalkenyl" refers to a cyclic ring-containing radical containing in the range of 3 up to about 8 carbon atoms with at least one carbon-carbon double bond such as cyclopropenyl, cyclobutenyl and cyclopentenyl.

The term "cycloalkenylalkyl" refers to a cyclic ring-containing radical containing in the range of about 3 up to 8 carbon atoms with at least one carbon-carbon double bond directly attached to an alkyl group which is then attached to the main structure at any carbon from the alkyl group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropenylmethyl, cyclobutenylethyl and cyclopentenylethyl.

The term "aryl" refers to an aromatic radical having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl and biphenyl.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., $-CH_2C_6H_5$ and $-C_2H_5C_6H_5$.

The term "heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heteroaromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl,

decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofuranyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, and isochromanyl. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclyl" refers to a heterocylic ring radical as defined above. The heterocylcyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" refers to a heterocylic ring radical as defined above directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

The term "heteroaryl" refers to an aromatic heterocyclic ring radical. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to a heteroaryl ring radical as defined above directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from the alkyl group that results in the creation of a stable structure.

The term "cyclic ring" refers to a cyclic ring containing 3-10 carbon atoms.

The term "protecting group" or "PG" refers to a substituent that is employed to block or protect a particular functionality while other functional groups on the compound may remain reactive. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include, but are not limited to, acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include, but are not limited to, acetyl, benzyl, tetrahydropyranyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Suitable carboxy-protecting groups include, but are not limited to, $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-

toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)ethyl, 2-(diphenylphosphino)-ethyl, and nitroethyl. For a general description of protecting groups and their use, see, T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The term "halogen" refers to a radical of fluorine, chlorine, bromine or iodine.

Unless otherwise specified, the term "substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstiuted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, and $-ONO_2$, wherein R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclic ring. According to one embodiment, the substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" cannot be "substituted alkenyl".

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases (such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn), salts of organic bases (such as N,N'-diacetylethylenediamine, glucamine, triethylamine,

choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, thiamine, and the like), salts of chiral bases (such as alkylphenylamine, glycinol, phenyl glycinol and the like), salts of natural amino acids (such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, omithine, lysine, arginine, serine, and the like), salts of non-natural amino acids (such as D-isomers or substituted amino acids), salts of guanidine, salts of substituted guanidine (wherein the substituents are selected from nitro, amino, alkyl, alkenyl, or alkynyl), ammonium salts, substituted ammonium salts, and aluminum salts. Other pharmaceutically acceptable salts include acid addition salts (where appropriate) such as sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Yet other pharmaceutically acceptable salts include, but are not limited to, quaternary ammonium salts of the compounds of the present invention with alkyl halides or alkyl sulphates (such as MeI and $(Me)_2SO_4$). Pharmaceutically acceptable solvates may be hydrates or comprise other solvents of crystallization such as alcohols.

Pharmaceutically acceptable solvates include hydrates and other solvents of crystallization (such as alcohols). The compounds of the present invention may form solvates with low molecular weight solvents by methods known in the art.

The term "treating" or "treatment" of a state, disorder or condition includes:
(1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition;
(2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; or
(3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to a subject to be treated is either statistically significant or at least perceptible to the subject or to the physician.

The term "subject" includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife).

A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

The term "prodrug" refers to a compound that is transformed in vivo to yield a compound of Formula (A) or a pharmaceutically acceptable salt, hydrate or solvate thereof. The transformation may occur by various mechanisms, such as through hydrolysis in blood. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987; and "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Pharmaceutical Compositions

Another embodiment is a pharmaceutical composition comprising, as an active ingredient, at least one compound of the invention which inhibits the enzymatic activity of DPP-IV (or a pharmaceutically acceptable salt or prodrug or hydrate thereof) together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the invention of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy, 19th Supp. Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable basic addition salt or prodrug or hydrate thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material that

acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound of the invention which inhibits the enzymatic activity of DPP-IV to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that may be prepared by conventional tabletting techniques may contain: 1 Core: Active compound (as free compound or salt thereof) 250 mg Colloidal silicon dioxide (Aerosil®) 1.5 mg Cellulose, microcryst. (Avicel®) 70 mg Modified cellulose gum (Ac-Di-Sol®) 7.5 mg Magnesium stearate Ad. Coating: HPMC approx. 9 mg *Mywacett 9-40 T approx. 0.9 mg *Acylated monoglyceride used as plasticizer for film coating.

Methods of Treatment

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of a condition that may be regulated or normalized via inhibition of DPP-IV.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of metabolic disorders.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for blood glucose lowering.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of Type II diabetes.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of impaired glucose tolerance (IGT).

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of impaired fasting glucose (IFG).

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the prevention of hyperglycemia.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for delaying the progression of impaired glucose tolerance (IGT) to Type II diabetes.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for delaying the progression of non-insulin requiring Type II diabetes to insulin requiring Type II diabetes.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for increasing the number and/or the size of beta cells in a subject.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of beta cell degeneration, in particular apoptosis of beta cells.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of disorders of food intake.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of obesity.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for appetite regulation or induction of satiety.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of dyslipidemia.

A further aspect of the present invention is the use of a compound of the present invention as a pharmaceutical composition in a therapeutically effective amount for the treatment of functional dyspepsia, in particular irritable bowel syndrome.

The compounds of the invention may be administered to a subject, especially a human, in need of such treatment, prevention, elimination, alleviation or amelioration of the various diseases as mentioned above, e.g., Type II diabetes, IGT, IFG, obesity,

appetite regulation or as a blood glucose lowering agent, and especially Type II diabetes.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 1000 mg,

preferably from about 0.1 to about 500 mg, per day may be used. A more preferable dosage is about 0.5 mg to about 250 mg per day. In choosing a regimen for patients, it may frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed as a unit dosage form comprising from about 0.05 to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier or diluent.

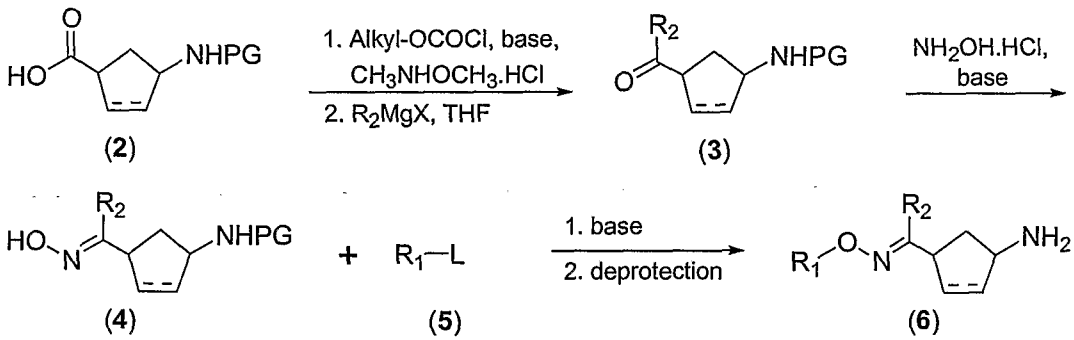
Generally, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.05 mg to about 1000 mg, preferably from about 0.5 mg to about 250 mg of the compound of the present invention admixed with a pharmaceutically acceptable carrier or diluent.

Methods of Preparation

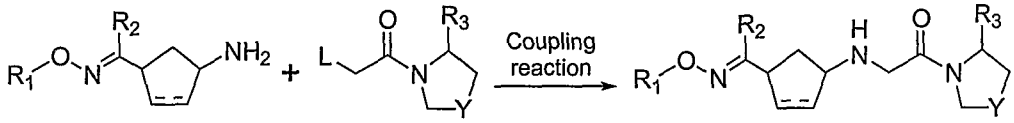
The compounds of formula **(1)** can be prepared using a variety of methods known in the literature and known to those skilled in the art. One such approach is given in the general synthetic scheme.

General Synthetic Scheme

Step 1:



Step 2:

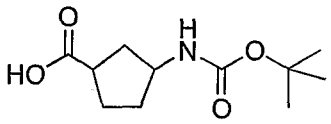


wherein PG is a protecting group, X is a halogen and each occurrence of L is independently a leaving group. The intermediate of formula **(2)** can be converted to the intemediate of formula **(3)**, by, for example, reacting the compound of formula **(2)** with N,O-dimethylhydroxylamine hydrochloride in presence of an alkylchloroformate and a base (such as triethylamine) which can then be treated with acompound of formula R_2MgX where X is halogen to give the intermediate of formula **(3)**. The compound of formula **(3)** ca be converted to a formula of formula **(4)** by reacting the compound of formula **(3)** with hydroxylamine hydrochloride, optionally in the presence of a base, to give the intermediate of formula **(4)**. The intermediate of formula **(4)** can be coupled with an intermediate of formula **(5)**, optionally in the presence of a base, and the coupled product can then be deprotected, for exapmple, with a suitable reagent such as EtOAc.HCl gas or trifluoroacetic acid, or by hydrogenation to yield the intermediate of formula **(6)**. The intermediate of formula **(7)** can be prepared by methods known in the art such as in *J. Med. Chem.*, 2003, 46, 2774-2789; International publication No. WO 03/002553. Desired compounds of formula **(1)** can be obtained by coupling of the intermediates of general formula **(6)** and **(7)** optionally in the presence of a base such as triethylamine or K_2CO_3. One of ordinary skill in the art will recognize that the coupling sequence of the fragments **(1)**-**(7)** can be altered and the compounds of formula **I** can be obtained by a variety of other methods known in the art.

Intermediates

Intermediate 1

***cis*-(±)-3-*N*-BOC-Aminocyclopentane-1-carboxylic acid**



Step 1: (±)-2-*N*-BOC-Azabicyclo[2.2.1]hept-5-ene-3-one: A solution of di-*tert*-butyl dicarbonate (144.0 g, 660.5 mmol) in THF (100 ml) was added (20 min) to a stirred

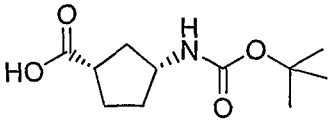
solution of (±)-2-Azabicyclo[2.2.1]hept-5-ene-3-one (60.0 g, 549.8 mmol), triethylamine (83.5 g, 824.6 mmol) and 4-dimethylaminopyridine (6.7 g, 54.8 mmol) in THF (500 ml) at room temperature. The reaction mixture was stirred for another 4 h at room temperature. The solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate (800 ml) and washed with water (3 x 500 ml) and brine (400 ml). The EtOAc extract was dried (Na_2SO_4) and evaporated under reduced pressure to give 115.0 g of the compound as a white solid; IR (KBr) 2979, 1755, 1705, 1455, 1331, 1305, 1149, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.13-2.16 (m, 1H), 2.33-2.37 (m, 1H), 3.38-3.40 (m, 1H), 4.94-4.96 (m, 1H), 6.64-6.66 (m, 1H), 6.88-6.90 (m, 1H).

Step 2: *cis*-(±)-4-*N*-BOC-Aminocyclopent-2-ene-1-carboxylic acid: To a stirred solution of Step 1 intermediate (30.0 g, 143.3 mmol) in THF (100 ml) was added 1N sodium hydroxide (300 ml) and the mixture was stirred at 40 °C for 20 h. The reaction mixture was cooled to 0 °C and acidified to pH 3.5 with 1N hydrochloric acid. The mixture was extracted with dichloromethane (3 x 200 ml) and the combined extracts were washed with water (2 x 300 ml), brine (300 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 31.5 g of the product as a white solid; IR (KBr) 3408, 3222, 2982, 1724, 1681, 1504, 1392 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.87-2.03 (m, 1H), 2.37-2.60 (m, 1H), 3.49 (brs, 1H), 4.60 (brs, 1H), 4.49 (brs, 1H), 5.90 (brs, 2H), 9.01 (brs, 1H).

Step 3: *cis*-(±)-3-*N*-BOC-Aminocyclopentane-1-carboxylic acid: To a solution of Step 2 intermediate (15.0 g, 66.0 mmol) in methanol (100 ml) was added 5 % Pd/C (1.0 g) and the mixture was maintained under hydrogen pressure (40 psi) for 2 h at room temperature. The catalyst was then filtered off and the filtrate was concentrated under reduced pressure to give 14.9 g of the product as a white solid; IR (KBr) 3304, 3249, 3098, 2978, 1705, 1646, 1403, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.53-2.20 (m, 5H), 2.11-2.35 (m, 1H), 2.73-3.01 (m, 1H), 4.05 (brs, 1H), 4.86 (brs, 1H).

Intermediate 2

(1*S*,3*R*)-(+)-3-*N*-BOC-Aminocyclopentane-1-carboxylic acid



Method A:

This intermediate was prepared by the optical resolution of Intermediate 1 using (*S*)-(-)-phenylethylamine in isopropyl alcohol. The desired product was isolated as a white solid; IR and ^{1}H NMR spectra were identical with that of the racemic intermediate. $[\alpha]_D$ +12.2 ° (c = 1.0, MeOH).

Method B:

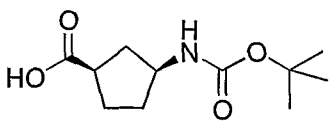
Step 1: (1*S*,4*R*)-(+)-2-*N*-BOC-Azabicyclo[2.2.1]hept-5-ene-3-one: This intermediate was synthesized from (1*S*,4*R*)-(+)-2-Azabicyclo[2.2.1]hept-5-ene-3-one (10.0 g, 91.74 mmol) and di-*tert*-butyl dicarbonate (26.0 g, 119.26 mmol) using triethylamine (13.92 g, 137.5 mmol) and 4-dimethylaminopyridine (1.1 g, 9.17 mmol) in THF (50 ml) as described in Intermediate 1, Step 1 to give 19.3 g of the compound as a white solid; IR and ^{1}H NMR spectra of the product were identical with that of the racemic product from Intermediate 1, Step 1.

Step 2: (1*R*,4*S*)-(+)-2-*N*-BOC-Azabicyclo[2.2.1]heptan-3-one: The Step 1 intermediate (9.0 g, 43.26 mmol) from Method B was hydrogenated using 5 % Pd/C (1.0 g) to give 9.0 g of the product as a white solid; IR (KBr) 2982, 1754, 1708, 1349, 1316, 1217, 1155, 1096, 921 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, *J* = 10.2 Hz, 1H), 1.52 (s, 9H), 1.73-1.96 (m, 5H), 2.86 (brs, 1H), 4.53 (brs, 1H).

Step 3: (1*S*,3*R*)-(+)-3-*N*-BOC-Aminocyclopentane-1-carboxylic acid: To a stirred solution of Step 2 intermediate (8.5 g, 40.26 mmol) in THF (40 ml) was added 1N sodium hydroxide (80 ml) and the mixture was stirred at 50 °C for 24 h. The reaction mixture was cooled to 0 °C and acidified to pH 3.5 with 1 N hydrochloric acid. The mixture was extracted with dichloromethane (3 x 100 ml) and the combined organic extracts were washed with water (2 x 100 ml), brine (100 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 8.0 g of the product as a white solid, which was identical in all respects with the product isolated by Method A.

Intermediate 3

(3*S*,1*R*)-(-)-3-*N*-BOC-Aminocyclopentane-1-carboxylic acid



Method A:

This intermediate was prepared by the optical resolution of Intermediate 1 using (*R*)-(+)-phenylethylamine in isopropyl alcohol. The desired product was isolated as a white solid; IR and ^{1}H NMR spectra were identical with that of the racemic intermediate. $[\alpha]_D$ - 12.2 ° (c = 1.0, MeOH).

Method B:

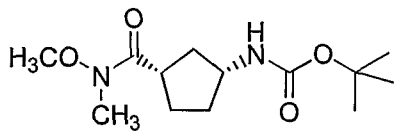
Step 1: (1*R*,4*S*)-(-)-2-*N*-BOC-Azabicyclo[2.2.1]hept-5-ene-3-one: This intermediate was synthesized from (1*R*,4*S*)-(-)-2-Azabicyclo[2.2.1]hept-5-ene-3-one (10.0 g, 91.74 mmol) and di-*tert*-butyl dicarbonate (23.9 g, 119.26 mol) in the presence of triethylamine (13.9 g, 137.3 mmol) and 4-dimethylaminopyridine (1.1 g, 9.0 mmol) in THF (50 ml) as described in Intermediate 1, Step 1 to give 19.1 g of the compound as a white solid; IR and ^{1}H NMR spectra of the product were identical with that of the racemic product from Intermediate 1, Step 1.

Step 2: (1*S*,4*R*)-(-)-2-*N*-BOC-Azabicyclo[2.2.1]heptan-3-one: The Step 1 intermediate (9.0 g, 43.26 mmol) from Method B was hydrogenated using 5 % Pd/C (1.0 g) to give 9.0 g of the product as a white solid; IR and ^{1}H NMR spectra of the product were identical with that of (1*R*,4*S*)-(+)-2-*N*-BOC-Azabicyclo[2.2.1]heptan-3-one (see Step 2, Method B, Intermediate 2).

Step 3: (1*R*,3*S*)-(-)-3-*N*-BOC-Aminocyclopentane-1-carboxylic acid: Hydrolytic cleavage of Step 2 intermediate (8.5 g, 40.26 mmol) using 1N sodium hydroxide (80 ml) in THF as described in Intermediate 1, Step 2 gave 8.0 g of the product as a white solid, which was identical in all respects with the product isolated by Method A.

Intermediate 4

N1-Methoxy-N1-methyl-(1S,3R)-3-N-BOC-aminocyclopentane-1-carboxamide

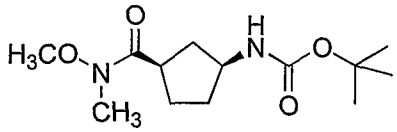


Ethyl chloroformate (3.08 g, 26.2 mmol) was added to a stirred and cooled (-10 °C) solution of Intermediate 2 (5.0 g, 21.83 mmol) and triethylamine (5.51 g, 54.59 mmol) in dry THF (15 ml) over 5 min under a nitrogen atmosphere. The reaction mixture was stirred for another 30 min at the same temperature and a solution of N,O-dimethylhydroxylamine hydrochloride (2.56 g, 26.64 mmol) in a mixture of THF (20 ml) and water (3 ml) was added over 5 min. The mixture was allowed to warm to room temperature and stirred for 12 h. The solvent was removed under reduced

pressure and the residual aqueous solution was basified with 1N NaOH to pH 10 and extracted with ethyl acetate (3 x 150) ml. The combined organic extracts were washed with 1N HCl, brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford 4.2 g of the product as a white solid; IR (KBr) 3379, 2969, 1682, 1665, 1520, 1170, 618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.71-1.79 (m, 2H), 1.81-1.98 (m, 3H), 2.05-2.11 (m, 1H), 3.21 (s, 3H), 3.27 (brs, 1H), 3.70 (s, 3H), 4.10 (brs, 1H), 5.51 (brs, 1H).

Intermediate 5

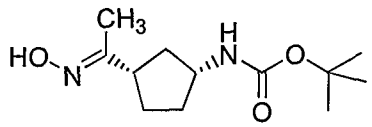
***N*1-Methoxy-*N*1-methyl-(3*S*,1*R*)-3-*N*-BOC-aminocyclopentane-1-carboxamide**



This compound was synthesized by the reaction of N,O-dimethylhydroxylamine hydrochloride (2.56 g, 26.64 mmol) with mixed anhydride prepared from Intermediate 3 (5.0 g, 21.83 mmol) and ethyl chloroformate (3.08 g, 26.2 mmol) as described in Intermediate 4 to afford 4.0 g of the product as a white solid; IR and ^1H NMR spectra of the product were identical with that of *N*1-Methoxy-*N*1-methyl-(1*S*,3*R*)-3-*N*-BOC-aminocyclopentane-1-carboxamide (Intermediate 4).

Intermediate 6

1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone oxime



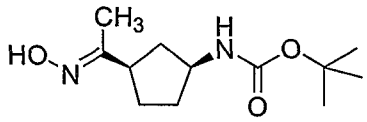
Step 1: 1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone: A solution of Intermediate 4 (2.0 g, 7.35 mmol) in dry ether (15 ml) was added to a 1 M solution of methyl magnesium iodide in ether (5.5 ml, 5.51 mmol). The resultant mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched with saturated aqueous NH_4Cl solution and the product was extracted into ethyl acetate (2 x 100 ml). The combined organic layers were washed with water (2 x 100 ml), brine (100), dried (Na_2SO_4) and concentrated to afford 1.3 g of the product as a white solid; IR (KBr) 3359, 2990, 1705, 1682, 1528, 1392, 1167 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.50-1.58 (m, 1H), 1.64-1.94 (m, 5H), 2.06-2.16 (m, 1H), 2.19 (s, 3H), 2.99-3.01 (m, 1H), 4.01 (brs, 1H), 4.86 (brs, 1H).

Step 2: 1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone oxime: Hydroxylamine hydrochloride (336 mg, 4.83 mmol) was added to a solution of Step 1 intermediate (1.0 g, 4.39 mmol) in water (10 ml), followed by the addition of saturated sodium carbonate solution (10 ml). The resultant solution was stirred at room temperature for 4 h. The product was extracted into ethyl acetate (200 ml), washed with water (2 x 100 ml), brine (100 ml), dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography using 10 % acetone in petroleum ether as eluent to afford 850 mg of the product as a white solid; IR (KBr) 3358, 2980, 2961, 1679, 1529, 1390, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.51-1.65 (m, 2H), 1.70-1.94 (m, 3H), 1.99 (s, 3H), 2.01-2.09 (m, 1H), 2.22-2.28 (m, 1H), 2.90-2.96 (m, 1H), 3.98-4.03 (m, 1H), 5.94 (brs, 1H).

Intermediate 7

1-[(3*S*,1*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone oxime

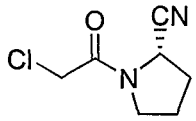


Step 1: 1-[(3*S*,1*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone: This compound was synthesized using Intermediate 5 (2.0 g, 7.35 mmol) and 1 M methylmagnesium iodide (5.5 ml, 5.51 mmol) in dry ether (15 ml) as described in Intermediate 6, Step 1 to afford 1.2 g of the product as a white solid; IR (KBr) 3359, 2973, 1705, 1683, 1527, 1367, 1253, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.50-1.72 (m, 2H), 1.82-1.94 (m, 3H), 2.06-2.16 (m, 1H), 2.19 (s, 3H), 2.99-3.03 (m, 1H), 4.02 (brs, 1H), 4.86 (brs, 1H).

Step 2: 1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone oxime: This compound was synthesized using the Step 1 intermediate (1.0 g, 4.39 mmol), hydroxylamine hydrochloride (336 mg, 4.83 mmol) and saturated aqueous sodium carbonate solution (10 ml) as described in Intermediate 6, Step 2 to afford 900 mg of the product as a white solid; IR (KBr) 3358, 3261, 2962, 1679, 1530, 1391, 1369, 1287, 1172, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.48-1.57 (m, 2H), 1.67-1.85 (m, 2H), 1.88 (s, 3H), 1.93-2.07 (m, 1H), 2.18 (brs, 1H), 2.65-2.73 (m, 1H), 4.02 (brs, 1H), 4.89 (brs, 1H), 7.39 (brs, 1H).

Intermediate 8

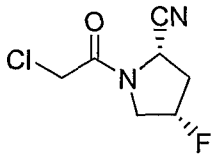
(2*S*)-1-(2-Chloroacetyl)-2-pyrrolidinecarbonitrile



This intermediate was prepared from L-(-)-proline using a literature procedure (*J. Med. Chem.*, **2003**, *46*, 2774-2789).

Intermediate 9

(2*S*,4*S*)-1-(2-Chloroacetyl)-4-fluoropyrrolidine-2-carbonitrile



Step 1: (2*S*,4*S*)-*N*-BOC-4-Fluoropyrrolidine-2-carboxamide: This intermediate was prepared in 5 steps from L-(-)-4-hydroxyproline using a literature procedure (WO 03/002553 A2)

Step 2: (2*S*,4*S*)-*N*-BOC-4-Fluoropyrrolidine-2-carbonitrile: To a stirred and cooled (0 °C) solution of Step 1 intermediate (10.0 g, 43.10 mmol) in dry THF (50 ml) was added triethylamine (13.93 g, 138 mmol) and trifluoroacetic anhydride (14.5 g, 69.05 mmol). The resulting clear solution was stirred at the same temperature for 1 h. The reaction was quenched with water (100 ml) and extracted with chloroform (2 x 100 ml). The combined organic extracts were washed with water (2 x 100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 9.0 g (97.6 %) of the product as an off-white solid; IR (KBr) 2979, 2243, 1387, 1240, 1168, 1123, 1072, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49-1.53 (m, rotomer, 9H), 2.25-2.47 (m, 1H), 2.64 (t, J = 14.7 Hz, 1H), 3.52 (dd, J = 9.6 and 3.6 Hz, rotomer, 0.5H), 3.64 (dd, J = 9.3, 3.3 Hz, rotomer, 0.5H), 3.73-3.94 (m, 1H), 4.64 (d, J = 8.7 Hz, rotomer, 0.6H), 4.76 (d, J = 8.7 Hz, rotomer, 0.4H), 5.31 (brd, J = 51.3 Hz, 1H).

Step 3: (2*S*,4*S*)-4-Fluoropyrrolidine-2-carbonitrile *p*-methylbenzenesulfonate: 4-Methyl-benzenesulfonic acid monohydrate (15.2 g, 79.91 mmol) was added to a solution of Step 2 intermediate (8.5 g, 39.72 mmol) in acetonitrile (170 ml) and the mixture was stirred at room temperature for 48 h. The solvent was then evaporated under reduced pressure to afford a brown residue which was taken up in dry diethyl

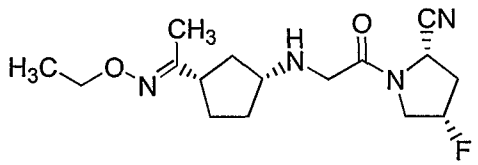
ether (200 ml) and stirred for 1 h. The white crystalline product separated out was collected by filtration and dried under vacuum to give 10.5 g (87 %) of the product as a pale pink solid; IR (KBr) 3304, 2927, 2249, 1393, 1167, 1123, 1034, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.37-2.65 (m, 2H), 3.76-3.87 (m, 2H), 5.10 (brs, 2H), 5.33 (brd, J = 51.6 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H).

Step 4: (2*S*,4*S*)-1-(2-Chloroacetyl)-4-fluoropyrrolidine-2-carbonitrile: A solution of step 3 intermediate (10.0g, 32.89 mmol) and triethylamine (4.32 g, 42.77 mmol) in dichloromethane (200 ml) was added dropwise to a stirred and cooled (0 °C) solution of chloroacetyl chloride (4.81 g, 32.95 mmol) in dichloromethane (50 ml) over a period of 10 min. The mixture was stirred at the same temperature for 2 h and diluted with dichloromethane (100 ml) and water (100 ml) under stirring. The layers were separated. The organic layer was washed with water (2 x 50 ml), brine (50 ml) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was triturated with diethyl ether to give 5.89 g (94 %) of the product as an off-white solid; IR (KBr) 2924, 2241, 1678, 1407, 1281, 1225, 1076, 1051, 958 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26-2.48 (m, 1H), 2.66-2.80 (m, 1H), 4.06 (s, 2H), 3.81-4.29 (m, 2H), 4.95 (d, J = 9.6 Hz, rotomer, 0.8H), 5.38 (brd, J = 51.3 Hz, rotomer, 0.2H), 5.46 (d, J = 9.0 Hz, rotomer, 0.2H), 5.46 (dt, J = 44.4 and 3.3 Hz, rotomer, 0.8H).

Examples

Example 1

(2*S*,4*S*)-1-{2-(3*S*,1*R*)-3-[(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoro-pyrrolidine-2-carbonitrile



Step 1: (3*S*,1*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-*N*-BOC-amine: To a stirred and cooled (-10 °C) suspension of 60 % sodium hydride (99 mg, 2.45 mmol) in *N,N*-dimethylacetamide (10 ml) was added Intermediate 6 (600 mg, 2.48 mmol) in dimethylacetamide (5 ml) and the mixture was stirred for 20 min at the same temperature. Ethyl bromide (540 mg, 4.95 mmol) was then added and the resultant mixture was stirred for 12 h under nitrogen atmosphere during which time the temperature increased to room temperature. The reaction mixture was quenched with

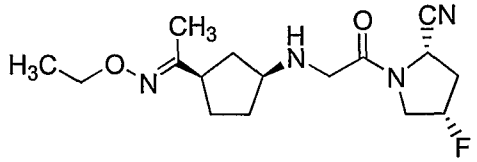
ice-cold water and the product was extracted into ethyl acetate (2 x 50 ml). The combined organic layers were washed with water (2 x 50 ml), brine (50 ml) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was purified by silica gel chromatography using 10 % ethyl acetate in petroleum ether as the eluent to afford 600 mg of the product as white solid; IR (KBr) 3373, 2923, 1680, 1525, 1493, 1367, 1295, 1180, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 6.9 Hz, 3H), 1.44 (s, 9H), 1.51-1.81 (m, 3H), 1.84 (s, 3H), 1.86-2.13 (m, 3H), 2.69-2.74 (m, 1H), 3.99 (brs, 1H), 4.08 (q, J = 6.9 Hz, 2H), 5.16 (brs, 1H).

Step 2: (3*S*,1*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-amine: To a stirred and cooled (0-10 °C) solution of Step 1 intermediate (590 mg, 2.18 mmol) in dichloromethane (3 ml) was added trifluoroacetic acid (3 ml) and the mixture was stirred for 1 h under nitrogen atmosphere. The mixture was evaporated under reduced pressure. The residue obtained was diluted with water (10 ml), basified to pH 12 using solid potassium carbonate and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 365 mg of the amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoropyrrolidine-2-carbonitrile: A solution of Intermediate 9 (207 mg, 1.08 mmol) in dry THF (10 ml) was added dropwise to a stirred and cooled (10 °C) mixture of the amine from Step 2 (365 mg, 2.14 mmol), K_2CO_3 (299 mg, 2.16 mmol) and NaI (163 mg, 1.08 mmol) in dry THF(15 ml) under nitrogen atmosphere. The temperature of the reaction mixture was slowly raised to room temperature and the mixture was stirred for 4 h under nitrogen atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 90 mg of the product as a white solid; IR (KBr) 3436, 3314, 2244, 1655, 1423, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.41-1.56 (m, 2H), 1.64-1.80 (m, 3H), 1.82 (s, 3H), 1.83-1.95 (m, 2H), 2.03-2.14 (m, 1H), 2.17-2.43 (m, 1H), 2.63-2.76 (m, 2H), 3.11-3.21 (m, 1H), 3.39 (d, J = 3.9 Hz, 2H), 3.48-3.96 (m, 1H), 4.05 (q, J = 7.2 Hz, 2H), 4.95 (d, J = 9.6 Hz, rotomer, 0.75H), 5.08 (d, J = 8.7 Hz, rotomer, 0.25H), 5.35 (dt, J = 51.0 and 3.6 Hz, rotomer, 0.25H), 5.43 (dt, J = 51.0 and 3.6 Hz, rotomer, 0.75H).

Example 2

(2*S*,4*S*)-1-{2-[(1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoro-pyrrolidine-2-carbonitrile



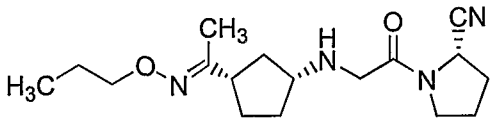
Step 1: (1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 7 (600 mg, 2.48 mmol) and ethyl bromide (540 mg, 4.95 mmol) using 60 % sodium hydride (99 mg, 2.45 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 600 mg of the product as white solid; IR (KBr) 3372, 2981, 2359, 1678, 1526, 1368, 1295, 1174, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 6.9 Hz, 3H), 1.44 (s, 9H), 1.50-1.81 (m, 3H), 1.83 (s, 3H), 1.85-2.13 (m, 3H), 2.68-2.73 (m, 1H), 4.01 (s, 1H), 4.06 (q, J = 7.2 Hz, 2H), 5.19 (brs, 1H).

Step 2: (1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-amine: This compound was prepared from Step 1 intermediate (590 mg, 2.18 mmol) using trifluoroacetic acid (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to give 366 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-1-{2-[(1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoropyrrolidine-2-carbonitrile: This product was prepared from Step 2 intermediate (366 mg, 2.14 mmol) and Intermediate 9 (207 mg, 1.08 mmol) using K_2CO_3 (299 mg, 2.16 mmol) and NaI (163 mg, 1.08 mmol) in dry THF (10 ml) as described in Example 1, Step 3 to give 100 mg of the product as a white solid; IR (KBr) 3436, 3315, 2934, 2244, 1655, 1423, 1360, 1231, 1127, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.41-1.56 (m, 2H),1.64-1.80 (m, 3H), 1.82 (s, 3H), 1.83-1.95 (m, 2H), 2.03-2.14 (m, 1H), 2.17-2.43 (m, 1H), 2.63-2.76 (m, 2H), 3.11-3.21 (m, 1H), 3.39 (d, J = 3.9Hz, 2H), 3.48-3.96 (m, 1H), 4.05 (q, J = 7.2 Hz, 2H), 4.95 (d, J = 9.6 Hz, rotomer, 0.75H), 5.08 (d, J = 8.7Hz, rotomer, 0.25H), 5.25 (dt, J = 3.6Hz, rotomer, 0.25H), 5.34 (dt, J = 3.6Hz, rotomer, 0.75H).

Example 3

(2*S*)-1-{2-[(3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentylamino]acetyl}pyrrolidine-2-carbonitrile



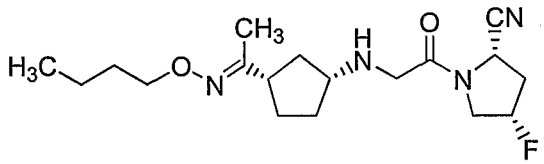
Step 1: (3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and *n*-propyl bromide (661 mg, 5.37 mmol) using 60 % NaH (247 mg, 6.16 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 750 mg of the product as a white solid; IR (KBr) 3428, 2962, 1660, 1422, 1317 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 1.50-1.81 (m, 5H), 1.83 (s, 3H), 1.87-2.13 (m, 3H), 2.68-2.73 (m, 1H), 3.96-4.00 (m, 3H), 5.17 (brs, 1H).

Step 2: (3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentan-1-amine: This compound was prepared from Step 1 intermediate (700 mg, 2.46 mmol) using TFA (4 ml) in dichloromethane (4 ml) as described in Example 1, Step 2 to afford 450 mg of the amine, which was used as such for the next step.

Step 3: (2*S*)-1-{2-[(3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentylamino]acetyl}-pyrrolidine-2-carbonitrile: This was prepared from Step 2 intermediate (450 mg, 2.44 mmol) and Intermediate 8 (212 mg, 1.23 mmol) using K_2CO_3 (339 mg, 2.45 mmol) and NaI (184 mg, 1.23 mmol) in dry THF (30 ml) as described in Example 1, Step 3 to give 90 mg of the product as a yellow semisolid; IR (neat) 3429, 2962, 2241, 1660, 1422, 1317 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.42-1.93 (m, 10H), 2.03-2.31 (m, 6H), 2.65-2.76 (m, 1H), 3.12-3.19 (m, 1H), 3.34-3.59 (m, 4H), 3.97 (t, J = 6.6Hz, 2H), 4.77 (d, J = 6.9 Hz, 1H).

Example 4

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[(1-Butyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoro-pyrrolidine-2-carbonitrile



Step 1: (3*S*,1*R*)-3-(1-Butyloxyiminoethyl)cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (750 mg, 3.09 mmol) and *n*-butyl bromide (510 mg, 3.72 mmol) using 60 % NaH (186 mg, 4.62 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 750 mg of the product as a white solid; IR (KBr) 3358, 2962, 1679, 1530, 1447, 1369, 1287 cm^{-1}; ^1H NMR (300 MHz,

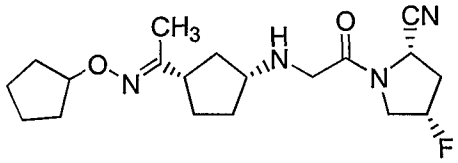
$CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.32-1.39 (m, 1H), 1.44 (s, 9H), 1.48-1.79 (m, 7H), 1.83 (s, 3H), 1.85-2.13 (m, 3H), 2.65-2.75 (m, 1H), 4.02 (t, J = 6.6 Hz, 2H), 5.14 (brs, 1H).

Step 2: (3*S*,1*R*)-3-(1-Butyloxyiminoethyl)cyclopentan-1-amine: This was prepared from Step 1 intermediate (700 mg, 2.35 mmol) using TFA (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 459 mg of the amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[(1-Butyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoropyrrolidine-2-carbonitrile: This was prepared from Step 2 intermediate (459 mg, 2.32 mmol) and Intermediate 9 (223 mg, 1.17 mmol) using K_2CO_3 (323 mg, 2.34 mmol) and NaI (175 mg, 1.16 mmol) in dry THF (30 ml) as described in Example 1, Step 3 to give 90 mg of the product as an oil, IR (neat) 3318, 2957, 2871, 2242, 1666, 1418, 1365, 1227, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.32-1.68 (m, 5H), 1.81 (t, J = 6.5 Hz 3H), 1.83-1.97 (m, 6H), 2.03-2.21 (m, 2H), 2.63-2.74 (m, 1H), 3.12-3.19 (m, 1H), 3.41 (s, 2H), 3.59-3.97 (m, 2H), 4.01 (t, J = 6.6 Hz, 2H), 4.96 (d, J = 9.6 Hz, rotomer, 0.75H), 5.09 (d, J = 9.3 Hz, rotomer, 0.25H), 5.36 (dt, J = 51.1 and 3.6 Hz, rotomer, 0.25H), 5.42 (dt, J = 51.1 and 3.6 Hz, rotomer, 0.75H).

Example 5

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[(Cyclopentyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoropyrrolidine-2-carbonitrile



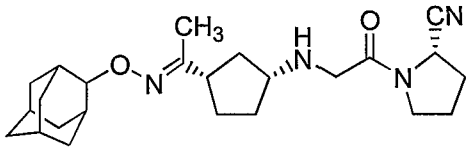
Step 1: (3*S*,1*R*)-3-(1-Cyclopentyloxyiminoethyl)cyclopentan-1-*N*-BOC-amine: This was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and cyclopentyl bromide (738 mg, 4.95 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 830 mg of the product as a white solid; IR (KBr) 3380, 2959, 2930, 1685, 1523, 1368, 1294, 1173, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.47-2.09 (m, 17H), 2.67-2.76 (m, 1H), 3.99 (s, 1H), 4.58-4.63 (m, 1H), 5.25 (s, 1H).

Step 2: (3*S*,1*R*)-3-(1-Cyclopentyloxyiminoethyl)cyclopentan-1-amine: This compound was prepared from Step 1 intermediate (830 mg, 2.67 mmol) using TFA (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 555 mg of the amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[(Cyclopentyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoropyrrolidine-2-carbonitrile: This product was prepared from Step 2 intermediate (555 mg, 2.63 mmol) and Intermediate 9 (255 mg, 1.34 mmol) using K_2CO_3 (369 mg, 2.67 mmol) and NaI (200 mg, 1.33 mmol) in dry THF (50 ml) as described in Example 1, Step 3 to give 150 mg of the product as a semisolid; IR (neat) 3434, 2956, 2870, 2243, 1663, 1423, 1364, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44-1.61 (m, 4H), 1.64-2.00 (m, 10H), 2.03-2.43 (m, 4H), 2.63-2.77 (m, 2H), 3.15-3.24 (m, 1H), 3.42 (s, 2H), 3.55-4.24 (m, 3H), 4.60-4.64 (m, 1H), 4.96 (d, J = 9.3 Hz, rotomer, 0.75H), 5.15 (d, J = 8.7 Hz, rotomer, 0.25H), 5.37 (dt, J = 51.2 and 3.6 Hz, rotomer, 0.25H), 5.42 (dt, J = 51.2 and 3.6 Hz, rotomer, 0.75H).

Example 6

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Adamantyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile



Step 1: (3*S*,1*R*)-3-[1-(2-Adamantyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This product was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and 2-bromoadamantane (1.3 g, 6.04 mmol) using 60 % NaH (246 mg, 6.16 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.2 g of the product as a white solid; IR (KBr) 3351, 2963, 1648, 1541, 1444, 1389, 1297, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.48-1.54 (m, 2H), 1.58-1.83 (m, 4H), 1.86 (m, 3H), 1.93-2.03 (m, 1H), 2.06-2.17 (m, 2H), 2.68-2.78 (m, 1H), 4.02 (brs, 1H), 5.02 (brs, 1H), 5.55 (s, 1H).

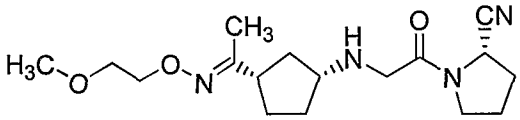
Step 2: (3*S*,1*R*)-3-[1-(2-Adamantyloxyimino)ethyl]cyclopentan-1-amine: This product was prepared from Step 1 intermediate (650 mg, 1.73 mmol) using TFA (3

ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 470 mg of the amine, which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Adamantyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile: This product was prepared from Step 2 intermediate (470 mg, 1.71 mmol) and Intermediate 8 (149 mg, 0.86 mmol) using K_2CO_3 (238 mg, 1.73 mmol) and NaI (129 mg, 0.86 mmol) in dry THF (40 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 2 % methanol in chloroform as the eluent to afford 90 mg of the product as a semisolid; IR (neat) 2909, 2856, 2239, 1661, 1410, 1274, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39-1.60 (m, 5H), 1.81-1.91 (m, 11H), 1.94 (s, 3H), 2.13-2.32 (m, 8H), 2.78-2.84 (m, 1H), 3.13-3.20 (m, 1H), 3.39 (s, 2H), 3.41-3.47 (m, 1H), 3.52-3.59 (m, 1H), 4.66 (brs, 1H), 4.77 (d, J = 4.5 Hz, 1H).

Example 7

(2*S*)-1-(2-{(3*S*,1*R*)-3-(1-(2-Methoxyethoxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile



Step 1: (3*S*,1*R*)-3-[1-(2-Methoxyethoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and 2-bromoethyl methyl ether (689 mg, 5.07 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 1.10 g of the product as a semisolid; IR (KBr) 3342, 2973, 2931, 1711, 1519, 1454, 1365, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.48-1.84 (m, 4H), 1.85 (s, 3H), 1.88-2.18 (m, 2H), 2.65-2.75 (m, 1H), 3.39 (s, 3H), 3.61-3.64 (m, 2H), 4.01 (s, 1H), 4.16-4.19 (m, 2H), 5.13 (s, 1H).

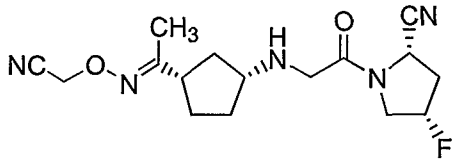
Step 2: (3*S*,1*R*)-3-[1-(2-Methoxyethoxyimino)ethyl]cyclopentan-1-amine: This compound was prepared from Step 1 intermediate (1.1 g, 3.66 mmol) using TFA (2.5 ml) in dichloromethane (2.5 ml) as described in Example 1, Step 2 to afford 483 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(3*S*,1*R*)-3-(1-(2-Methoxyethoxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile: This product was prepared from Step 2 (728 mg,

3.63 mmol) and Intermediate 8 (316 mg, 1.83 mmol) using K_2CO_3 (506 mg, 3.66 mmol) and NaI (275 mg, 1.83 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude product was purified by silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 250 mg of the product as a semisolid; IR (neat) 3317, 2947, 2877, 2240, 1660, 1416, 1363, 1315, 1194, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41-1.58 (m, 2H), 1.71-1.92 (m, 8H), 2.03-2.31 (m, 5H), 2.64-2.76 (m, 1H), 3.11-3.21 (m, 1H), 3.93 (s, 5H), 3.44-3.64 (m, 3H), 4.13-4.18 (m, 2H), 4.77 (d, J = 7.2 Hz, 1H).

Example 8

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(Cyanomethoxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoropyrrolidine-2-carbonitrile



Step 1: (3*S*,1*R*)-3-(1-Cyanomethoxyoxyiminoethyl)cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and bromoacetonitrile (743 mg, 6.19 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 800 mg of the product as a white solid; IR (KBr) 3340, 2967, 2116, 1681, 1536, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.49-1.64 (m, 3H), 1.71-1.84 (m, 1H), 1.86 (s, 3H), 1.88-2.21 (m, 2H), 2.69-2.74 (m, 1H), 4.01 (brs, 1H), 4.67 (s, 2H), 4.74 (brs, 1H).

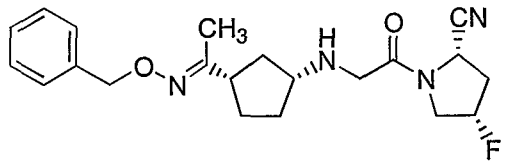
Step 2: (3*S*,1*R*)-3-(1-Cyanomethoxyoxyiminoethyl)cyclopentan-1-amine: This was prepared from Step 1 intermediate (750 mg, 2.67 mmol) using TFA (2.5 ml) in dichloromethane (2.5 ml) described in Example 1, Step 2 to afford 477 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(Cyanomethoxyimino)ethyl]cyclopentylamino}-acetyl)-4-fluoropyrrolidine-2-carbonitrile: This was prepared from Step 2 intermediate (477 mg, 2.63 mmol) and Intermediate 9 (254 mg, 1.33 mmol) using K_2CO_3 (368 mg, 3.66 mmol) and NaI (200 mg, 1.33 mmol) in dry THF (30 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 5 % methanol in chloroform as the eluent to afford 90 mg of the product as a semisolid; IR (neat) 3435, 2245, 1651, 1428, 1366, 1323, 1228, 1065

cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54-1.65 (m, 3H), 1.72-1.99 (m, 5H), 2.02-2.48 (m, 2H), 2.63-2.78 (m, 2H), 3.18-3.27 (m, 1H), 3.43 (s, 2H), 3.61-4.16 (m, 3H), 4.68 (s, 2H), 4.96 (d, J = 9.3 Hz, rotomer, 0.75H), 5.15 (d, J = 8.7 Hz, rotomer, 0.25H), 5.36 (dt, J = 51.1 and 3.0 Hz, rotomer, 0.25H), 5.42 (dt, J = 51.1 and 3.3 Hz, rotomer, 0.75H).

Example 9

(2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1-Benzyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoro-pyrrolidine-2-carbonitrile



Step 1: (3*S*,1*R*)-3-(1-Benzyloxyoxyiminoethyl)cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 3.90 mmol) and benzyl bromide (848 mg, 4.95 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to give 1.0 g of the product as a white solid; IR (KBr) 3372, 2980, 2874, 1682, 1527, 1454, 1390, 1273, 1171, 1068 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.47-1.53 (m, 1H), 1.57-1.83 (m, 2H), 1.86 (s, 3H), 1.89-1.99 (m, 2H), 2.04-2.13 (m, 1H), 2.65-2.75 (m, 1H), 4.01 (brs, 1H), 5.00 (brs, 1H), 5.07 (s, 2H), 7.26-7.38 (m, 5H).

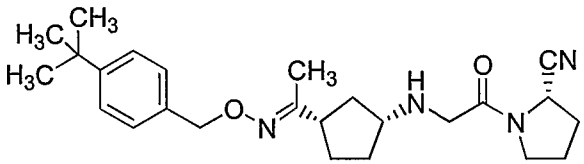
Step 2: (3*S*,1*R*)-3-(1-Benzyloxyoxyiminoethyl)cyclopentan-1-amine: This was prepared from Step 1 intermediate (1.1 g, 4.13 mmol) using TFA (2.5 ml) in dichloromethane (2.5 ml) as described in Example 1, Step 2 to afford 691 mg of the free amine which was used as such for the next step.

Step 3: (2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1-Benzyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoropyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (691 mg, 2.97 mmol) and Intermediate 9 (286 mg, 1.50 mmol) using K_2CO_3 (414 mg, 3.00 mmol) and NaI (225 mg, 1.50 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 5 % methanol in chloroform as the eluent to afford 150 mg of the product as a semisolid; IR (neat) 3325, 2953, 2242, 1666, 1419, 1365, 1318, 1226, 1051 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.56 (m, 2H), 1.64-1.82 (m, 5H), 1.86 (s, 3H), 2.02-2.11 (m, 1H), 2.19-2.41 (m, 1H), 2.63-2.77 (m, 2H), 3.11-3.20 (m, 1H),

3.37 (d, J = 3.0 Hz, 2H), 3.43-4.01 (m, 3H), 4.95 (d, J = 9.3 Hz, rotomer, 0.75H), 5.11 (d, J = 8.7 Hz, rotomer, 0.25H), 5.33 (dt, J = 51.0 and 3.0 Hz, rotomer, 0.25H), 5.43 (dt, J = 51.0 and 3.3Hz, rotomer, 0.75H), 7.19-7.36 (m, 5H).

Example 10

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile



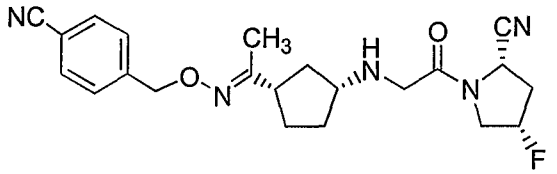
Step 1: (3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This product was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and *t*-butyl benzyl chloride (980 mg, 5.36 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.1 g of the product as a white solid; IR (KBr) 3363, 2966, 1686, 1531, 1444, 1364, 1289, 1176 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.44 (s, 9H), 1.60 (s, 3H), 1.65-1.83 (m, 2H), 1.85-1.99 (m, 3H), 2.04-2.14 (m, 1H), 2.65-2.73 (m, 1H), 4.00 (brs, 1H), 5.04 (s, 2H), 5.07 (brs, 1H), 7.30, (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H).

Step 2: (3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyoxyimino)ethyl]cyclopentan-1-amine: This compound was prepared from the Step 1 intermediate (1.0 g, 2.57 mmol) using TFA (2.5 ml) in dichloromethane (2.5 ml) as described in Example 1, Step 2 to afford 736 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile: This was prepared from Step 2 intermediate (736 mg, 2.55 mmol) and Intermediate 8 (222 mg, 1.29 mmol) using K_2CO_3 (355 mg, 2.57 mmol) and NaI (193 mg, 1.28 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude product was purified by silica gel column chromatography using 5 % methanol in chloroform as eluent to afford 150 mg of the product; IR (KBr) 3430, 2960, 2241, 1661, 1415, 1364, 1267 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.42-1.63 (m, 2H), 1.73-1.83 (m, 4H), 1.85 (s, 3H), 2.03-2.30 (m, 5H), 2.69-2.75 (m, 1H), 3.12-3.19 (m, 1H), 3.37-3.58 (m, 4H), 4.77 (d, J = 6.0 Hz, 1H), 5.03 (s, 2H), 7.23-7.38 (m, 4H).

Example 11

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyimino)ethyl]cyclopentylamino}-acetyl)-4-fluoropyrrolidine-2-carbonitrile



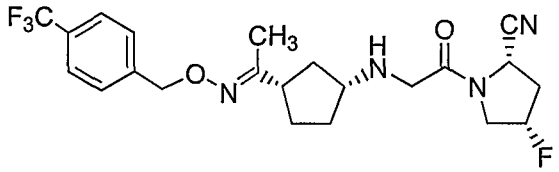
Step 1: (3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and 4-cyanobenzyl bromide (972 mg, 4.96 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 800 mg of the product; IR (KBr) 3839, 3351, 2970, 2932, 2231, 1672, 1526, 1366, 1167 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.48-1.61 (m, 2H), 1.68-1.85 (m, 1H), 1.88 (s, 3H), 1.94-2.00 (m, 1H), 2.06-2.19 (m, 2H), 2.67-2.72 (m, 1H), 4.01 (s, 1H), 4.88 (s, 1H), 5.11 (s, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H).

Step 2: (3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyimino)ethyl]cyclopentan-1-amine: This was prepared from Step 1 intermediate (780 mg, 2.18 mmol) using trifluoroacetic acid (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 554 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyimino)ethyl]cyclopentylamino}-acetyl)-4-fluoropyrrolidine-2-carbonitrile: This was prepared from Step 2 intermediate (554 mg, 2.15 mmol) and Intermediate 9 (208 mg, 1.09 mmol) using K_2CO_3 (301 mg, 2.18 mmol) and NaI (164 mg, 1.09 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 250 mg of the product as a semisolid; IR (neat) 3445, 2954, 2869, 2228, 1661, 1416, 1365, 1227, 1056 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.54 (m, 2H), 1.63-1.94 (m, 9H), 2.04-2.43 (m, 2H), 2.64-2.75 (m, 2H), 3.12-3.21 (m, 1H), 3.38 (s, 2H), 3.40-4.01 (m, 3H), 4.95 (d, J = 9.3 Hz, rotomer, 0.75H), 5.02 (d, J = 9.3 Hz, rotomer, 0.25H), 5.33 (dt, J = 51.1 and 3.0 Hz, rotomer, 0.25H), 5.42 (dt, J = 51.1 and 3.3 Hz, rotomer, 0.75Hz).

Example 12

(2*S*,4*S*)-4-Fluoro-1-(2-{(3*R*,1*S*)-3-[(1-(4-trifluorobenzyloxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile



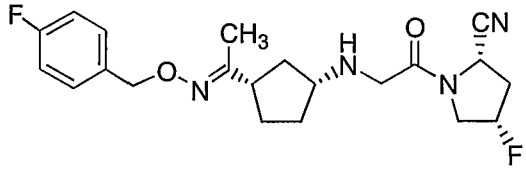
Step 1: (3*S*,1*R*)-3-[1-(4-Trifluorobenzyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and 4-(trifluoro methyl)benzyl bromide (1.18 g, 4.93 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.3 g of the product as a white solid; IR (KBr) 3377, 2982, 2872, 1680, 1515, 1417, 1325, 1162, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.47-1.76 (m, 3H), 1.78-1.85 (m, 1H), 1.88 (s, 3H), 1.91-2.15 (m, 2H), 2.65-2.75 (m, 1H), 4.01 (brs, 1H), 4.95 (brs, 1H), 5.11 (s, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H).

Step 2: (3*S*,1*R*)-3-[1-(4-Trifluorobenzyloxyoxyimino)ethyl]cyclopentan-1-amine: This was prepared from Step 1 intermediate (1.3 g, 3.25 mmol) using trifluoroacetic acid (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 970 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-4-Fluoro-1-(2-{(3*R*,1*S*)-3-[(1-(4-trifluorobenzyloxyimino)ethyl]cyclopentylamino}acetyl)pyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (970 mg, 3.22 mmol) and Intermediate 9 (309 mg, 1.62 mmol) using K_2CO_3 (448 mg, 3.24 mmol) and NaI (243 mg, 1.62 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude product was purified using silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 200 mg of the product as a semisolid; IR (KBr) 3444, 3020, 2958, 2401, 1667, 1417, 1326, 1216, 1166, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44-1.57 (m, 2H), 1.66-1.85 (m, 2H), 1.88 (s, 3H), 1.92-2.11 (m, 2H), 2.17-2.43 (m, 1H), 2.63-2.76 (m, 2H), 3.13-3.22 (m, 1H), 3.38 (s, 2H), 3.56-4.01 (m, 3H), 4.95 (d, *J* = 9.3 Hz, rotomer, 0.75H), 5.05 (d, *J* = 9.0 Hz, rotomer, 0.25H), 5.11 (s, 2H), 5.26 (t, *J* = 51.0 and 3.0 Hz, rotomer, 0.25H), 5.33 (dt, *J* = 51.0 and 3.0 Hz, rotomer, 0.75H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 2H).

Example 13

(2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(4-fluorobenzyloxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile



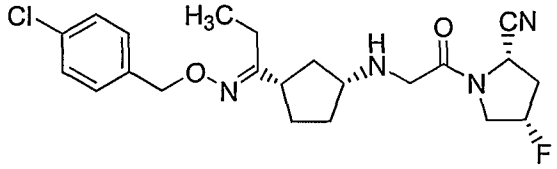
Step 1: (3*S*,1*R*)-3-[1-(4-Fluorobenzyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and 4-fluorobenzyl bromide (937 mg, 4.95 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.2 g of the product as a pale yellow solid; IR (KBr) 3346, 2970, 1682, 1513, 1217 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28-1.39 (m, 1H), 1.44 (s, 9H), 1.47-1.77 (m, 3H), 1.80-2.17 (m, 4H), 2.19-2.36 (m, 1H), 3.35-3.47 (m, 1H), 3.96 (brs, 1H), 4.52 (brs, 1H), 5.00 (d, J = 7.5 Hz, 2H), 6.99-7.06 (m, 2H), 7.28-7.36 (m, 2H).

Step 2: (3*S*,1*R*)-3-[1-(4-Fluorobenzyloxyoxyimino)ethyl]cyclopentan-1-amine: This was prepared from Step 1 intermediate (1.0 g, 2.85 mmol) using trifluoroacetic acid (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 707 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(4-fluorobenzyloxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (707 mg, 2.81 mmol) and Intermediate 9 (272 mg, 1.42 mmol) using K_2CO_3 (394 mg, 2.85 mmol) and NaI (214 mg, 1.42 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude material was purified using silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 150 mg of the product as a semisolid; IR (KBr) 3435, 2925, 2243, 1664, 1509, 1419, 1319, 1222 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.25 (m, 1H), 1.49-1.64 (m, 2H), 1.74-1.84 (m, 2H), 1.86 (s, 3H), 1.88-2.44 (m, 6H), 2.63-2.74 (m, 2H), 3.19-3.26 (m, 1H), 3.36-3.43 (m, 1H), 3.61-4.15 (m, 2H), 4.96 (d, J = 9.0 Hz, rotomer, 0.75H), 5.13 (d, J = 9.0 H, rotomer, 0.25H), 5.32 (dt, J = 51.0 and 3.6 Hz, rotomer, 0.25H), 5.42 (dt, J = 51.0 and 3.6 Hz, rotomer, 0.75H), 7.03 (t, J = 8.4 Hz, 2H), 7.31-7.35 (m, 2H).

Example 14

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyimino)propyl]cyclopentylamino}-acetyl)-4-fluoropyrrolidine-2-carbonitrile



Step 1: 1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-propanone: This compound was prepared by the reaction of Intermediate 4 (2.0 g, 7.35 mmol) with 3M ethereal solution of ethyl magnesium bromide (3.7 ml, 11.03 mmol) in dry ether (15 ml) as described in Intermediate 6, Step 1 to afford 1.2 g of the product as a white solid; IR (KBr) 3365, 2970, 1706, 1685, 1528, 1459, 1365, 1170, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, J = 7.2 Hz, 3H), 1.43 (s, 9H), 1.50-1.72 (m, 2H), 1.74-1.93 (m, 2H), 2.04-2.20 (m, 2H), 2.41-2.58 (2H), 3.03 (t, J = 7.2 Hz, 1H), 3.99 (brs, 1H), 5.00 (brs, 1H).

Step 2: 1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-propanone oxime: This was prepared from Step 1 intermediate (1.1 g, 4.56 mmol), hydroxylamine hydrochloride (380 mg, 5.47 mmol) and saturated Na_2CO_3 solution (10 ml) as described in Intermediate 6, Step 2 to afford 650 mg of the product as a white solid; IR (KBr) 3388, 2969, 2942, 1687, 1522, 1365, 1242, 1175, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, J = 15.0 Hz, 3H), 1.44 (s, 9H), 1.48-1.57 (m, 2H), 1.65-1.88 (m, 3H), 1.95-2.06 (m, 1H), 2.16-2.44 (m, 3H), 2.67-2.75 (m, 1H), 4.01 (brs, 1H), 4.99 (brs, 1H).

Step 3: (3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyoxyimino)propyl]cyclopentan-1-*N*-BOC-amine:

This was prepared from Step 2 intermediate (600 mg, 2.34 mmol) and 4-chlorobenzyl bromide (578 mg, 2.81mmol) using 60 % NaH (140 mg, 3.51 mmol) in dry DMA (15 ml) as described in Example 1, Step 1 to afford 860 mg of the product as an off white solid; IR (KBr) 3354, 2970, 2930, 1677, 1526, 1491, 1251, 1169, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03-1.09 (m, 3H), 1.44 (s, 9H), 1.48-1.73 (m, 6H), 1.81-1.96 (m, 2H), 2.17-2.26 (m, 1H), 2.35-2.42 (m, 1H), 2.70-2.75 (m, 1H), 4.02 (brs, 1H), 5.01 (s, 2H), 5.17 (brs, 1H), 7.24-7.33 (m, 4H).

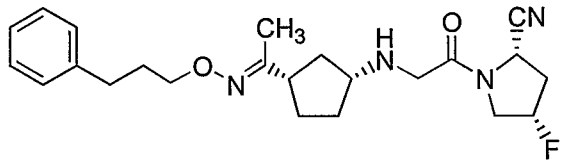
Step 4: (3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyimino)propyl]cyclopentan-1-amine: This was prepared from the Step 3 intermediate (850 mg, 2.23 mmol) using trifluoroacetic

acid (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 620 mg of the free amine, which was used as such for the next step.

Step 5: (2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyimino)propyl]cyclopentylamino}-acetyl)-4-fluoropyrrolidine-2-carbonitrile: This compound was prepared from Step 4 intermediate (620 mg, 2.20 mmol) and Intermediate 9 (212 mg, 1.11mmol) using K_2CO_3 (307 mg, 2.22 mmol) and NaI (167 mg, 1.11 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 120 mg of the product as a semisolid; IR (neat) 3319, 2933, 2242, 1667, 1599, 1491, 1409, 1361, 1226, 1014 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, J = 7.8 Hz, 3H), 1.46-1.60 (m, 2H), 1.69-2.11 (m, 7H), 2.17-2.43 (m, 3H), 2.63-2.73 (m, 2H), 3.13-3.28 (m, 1H), 3.38 (s, 2H), 3.57-3.95 (m, 2H), 4.95 (d, J = 9.3 Hz, rotomer, 0.75H, 5.12 (d, J = 9.0 Hz, rotomer, 0.25H), 5.01 (s, 2H), 5.33 (dt, J = 51.0 and 3.0 Hz, rotomer, 0.25H), 5.43 (dt, J = 51.0 and 3.3 Hz, rotomer, 0.75H), 7.19-7.33 (m, 4H).

Example 15

(2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(3-phenylpropyloxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile



Step 1: (3*S*,1*R*)-3-[1-(3-Phenylpropyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This was prepared from Intermediate 6 (1.0 g, 3.90 mmol) and 1-bromo-3-phenylpropane (933 mg, 4.68 mmol) using 60 % NaH (146 mg, 6.08 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 830 mg of the product as a semisolid; IR (neat) 3338, 2960, 1680, 1530, 1190, 1020 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) 0.84-0.96 (m, 1H), 1.43 (s, 9H), 1.49-1.79 (m, 2H), 1.83 (s, 3H), 1.87-2.14 (m, 6H), 2.67-2.76 (m, 2H), 3.98 (brs, 1H), 4.06 (t, J = 6.6 Hz, 2H), 5.09 (brs, 1H), 7.16-7.36 (m, 5H).

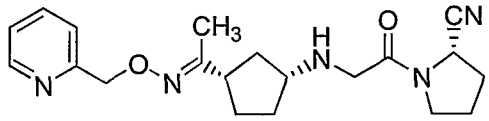
Step 2: (3*S*,1*R*)-3-[1-(3-Phenylpropyloxyimino)ethyl]cyclopentan-1-amine: This was prepared from Step 1 intermediate (800 mg, 2.14 mmol) using trifluoroacetic acid (2.5

ml) in dichloromethane (2.5 ml) as described in Example 1, Step 2 to afford 586 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(3-phenylpropyloxyimino)ethyl]cyclopentylamino}acetyl)pyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (579 mg, 2.11 mmol) and Intermediate 9 (203 mg, 1.06 mmol) using K_2CO_3 (294 mg, 2.13 mmol) and NaI (160 mg, 1.06 mmol) in dry THF (40 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 150 mg of the product as a semisolid; IR (neat) 3434, 2088, 1652, 1427, 1324, 1227, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25-1.59 (m, 2H), 1.69-1.89 (m, 8H), 1.92-2.01 (m, 5H), 2.63-2.77 (m, 3H), 3.13-3.20 (m, 1H), 3.40 (s, 2H), 3.47-3.95 (m, 2H), 4.04 (t, J = 6.3 Hz, 2H), 4.94 (d, J = 9.0 Hz, rotomer, 0.75H), 5.09 (d, J = 8.7 Hz, rotomer, 0.25H), 5.33 (dt, J = 51.0 and 3.0 Hz, rotomer, 0.25H), 5.42 (dt, J = 51.0 and 3.3 Hz, rotomer, 0.75H), 7.15-7.30 (m, 5H).

Example 16

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile



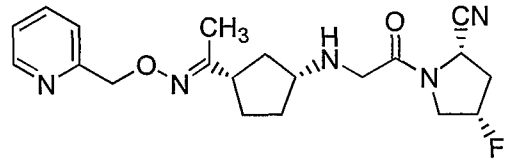
Step 1: (3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.5 g, 6.19 mmol) and 2-picolylchloride hydrochloride (1.2 g, 4.68 mmol) using 60 % NaH (372 mg, 9.29 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 2.0 g of the product as a colourless liquid; IR (neat) 3337, 2973, 1708, 1520, 1437, 1365, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.47-1.89 (m, 5H), 1.92 (s, 3H), 1.96-2.32 (m, 1H), 2.66-2.73 (m, 1H), 3.99 (brs, 1H), 4.90 (brs, 1H), 5.20 (m, 2H), 7.16-7.23 (m, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.66-7.72 (m, 1H), 8.56 (d, J = 4.8 Hz, 1H).

Step 2: (3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentan-1-amine: This compound was prepared from Step 1 intermediate (1.0 g, 3.00 mmol) using TFA (4 ml) in dichloromethane (4 ml) as described in Example 1, Step 2 to afford 691 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (691 mg, 2.96 mmol) and Intermediate 8 (255 mg, 1.98 mmol) using K_2CO_3 (408 mg, 2.95 mmol) and NaI (221 mg, 1.47 mmol) in dry THF (50 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 170 mg of the product as a semisolid; IR (neat) 3429, 2956, 2242, 1657, 1594, 1436, 1317, 1065 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47-1.56 (m, 2H), 1.73-1.89 (m, 1H), 1.91 (s, 3H), 2.01-2.30 (m, 9H), 2.69-2.74 (m, 1H), 3.16-3.20 (m, 1H), 3.38-3.58 (m, 4H), 4.77 (d, J = 5.7 Hz, 1H), 5.18 (d, J = 4.8 Hz, 2H), 7.15-7.19 (m, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.65-7.70 (m, 1H), 8.55 (d, J = 4.8 Hz, 1H).

Example 17

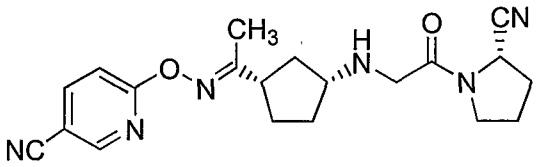
(2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(2-pyridylmethoxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile



This compound was prepared by the coupling reaction of Step 2 intermediate, Example 16 (690 mg, 2.95 mmol) and Intermediate 9 (285 mg, 1.49 mmol) using K_2CO_3 (413 mg, 2.99 mmol) and NaI (224 mg, 1.49 mmol) in dry THF (40 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 170 mg of the product as a semisolid; IR (neat) 3429, 2955, 2244, 1661, 1595, 1428, 1364, 1228, 1057 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44-1.57 (m, 2H), 1.68-1.89 (m, 4H), 1.92 (s, 3H), 1.98-2.39 (m, 3H), 2.63-2.73 (m, 2H), 3.12-3.19 (m, 1H), 3.39 (s, 1H), 3.48 (s, 2H), 3.50-3.99 (m, 2H), 4.95 (d, J = 9.0 Hz, rotomer, 0.75H), 5.12 (d, J = 8.7 Hz, rotomer, 0.25H), 5.35 (dt, J = 51.0 and 3.0 Hz, rotomer, 0.25H), 5.43 (dt, J = 51.0 and 3.3 Hz, rotomer, 0.75H), 7.16-7.23 (m, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.65-7.71 (m, 1H), 8.55 (d, J = 3.3 Hz, 1H).

Example 18

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile



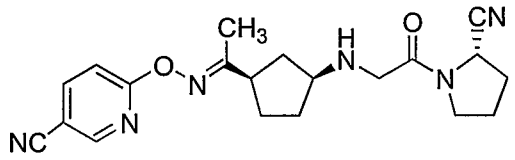
Step 1: (3*S*,1*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and 6-chloronicotinonitrile (686 mg, 4.95 mmol) using 60 % NaH (248 mg, 6.16 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.2 g of the product as a white solid; IR (KBr) 3341, 2929, 2226, 1678, 1592, 1470, 1385, 1291 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.49-2.11 (m, 5H), 2.12 (s, 3H), 2.22-2.31 (m, 1H), 2.84-2.92 (m, 1H), 4.11 (brs, 1H), 5.18 (brs, 1H), 7.26-7.30 (m, 1H), 7.89-7.93 (dd, J = 9.0 and 2.7 Hz, 1H), 5.88 (d, J = 1.8 Hz, 1H).

Step 2: (3*S*,1*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-amine: This was prepared from Step 1 intermediate (1.0 g, 2.90 mmol) using TFA (4 ml) in dichloromethane (4 ml) as described in Example 1, Step 2 to afford 701 mg of the free amine which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile: This compound was prepared using Step 2 intermediate (701 mg, 2.85 mmol) and Intermediate 8 (250 mg, 1.46 mmol) using K_2CO_3 (400 mg, 2.89 mmol) and NaI (217 mg, 1.46 mmol) in dry THF (40 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 5 % methanol in chloroform as the eluent to afford 90 mg of the product as a semisolid; IR (neat) 3434, 2958, 2231, 1654, 1593, 1472, 1383, 1290, 1135 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25-2.06 (m, 6H), 2.13 (s, 3H), 2.16-2.32 (m, 3H), 2.88-2.94 (m, 1H), 3.23-3.27 (m, 1H), 3.38-3.63 (m, 6H), 4.77 (d, J = 6.3 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.90-7.93 (dd, J = 9.0 and 2.7 Hz, 1H), 8.56 (d, J = 1.5 Hz, 1H).

Example 19

(2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile



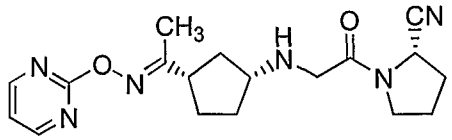
Step 1: (1*S*,3*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 7 (800 mg, 3.30 mmol) and 6-chloronicotinonitrile (687 mg, 4.96 mmol) using 60 % NaH (198 mg, 4.95 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.0 g of the product as a pale yellow solid; IR (KBr) 3341, 2968, 2226, 1680, 1592, 1470, 1385, 1291 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.50-1.62 (m, 2H), 1.70-2.07 (m, 3H), 2.13 (s, 3H), 2.22-2.29 (m, 1H), 2.87-2.92 (m, 1H), 4.12 (brs, 1H), 5.18 (brs, 1H), 7.24-7.31 (m, 1H), 7.90-7.94 (dd, J = 6.6 and 2.1 Hz, 1H), 8.59 (t, J = 1.5 Hz, 1H).

Step 2: (1*S*,3*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-amine: This was prepared from Step 1 intermediate (800 mg, 2.32 mmol) using TFA (4 ml) in dichloromethane (4 ml) as described in Example 1, Step 1 to afford 561 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (561 mg, 2.29 mmol) and Intermediate 8 (200 mg, 1.16 mmol) using K_2CO_3 (320 mg, 2.32 mmol) and NaI (174 mg, 1.16 mmol) in dry THF (40 ml) as described in Example 1, Step 3. The crude material was purified using silica gel column chromatography using 3 % methanol in chloroform as the eluent to afford 130 mg of the product as a semisolid; IR (neat) 3316, 2956, 2230, 1660, 1592, 1471, 1289 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-1.66 (m, 2H), 1.85-1.98 (m, 4H), 2.14 (s, 3H), 2.16-2.33 (m, 4H), 2.86-2.97 (m, 1H), 3.23-3.28 (m, 1H), 3.43 (s, 3H), 3.49-3.71 (m, 2H), 4.73 (d, J = 6.0 Hz, rotomer 0.2H), 4.78 (d, J = 6.6 Hz, rotomer, 0.8H), 7.36 (d, J = 6.6 Hz, 1H), 7.91-7.94 (m, 1H) 8.56 (t, J = 1.8 Hz, 1H)

Example 20

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile



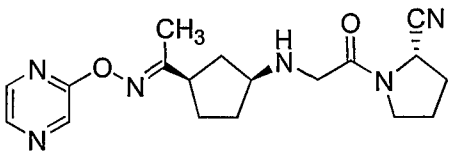
Step 1: (3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 6 (1.0 g, 4.13 mmol) and 2-chloropyrimidine (710 mg, 6.19 mmol) using 60 % NaH (246 mg, 6.16 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.1 g of the product as a white solid; IR (KBr) 3297, 2870, 1698, 1573, 1520, 1408, 1365, 1285 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.49-1.67 (m, 2H), 1.81-1.92 (m, 3H), 2.14 (s, 3H), 2.16-2.21 (m, 2H), 2.90-2.96 (m, 1H), 4.24 (brs, 1H), 7.02 (t, J = 4.8 Hz, 1H), 8.64 (d, J = 4.8 Hz, 2H).

Step 2: (3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentan-1-amine: This was prepared from Step 1 intermediate (800 mg, 2.50 mmol) using TFA (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 1 to afford 544 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (544 mg, 2.47 mmol) and Intermediate 8 (215 mg, 1.24 mmol) using K_2CO_3 (344 mg, 2.49 mmol) and NaI (187 mg, 1.24 mmol) in dry THF (40 ml) as described in Example 1, Step 3. The crude material was purified by silica gel chromatography using 5 % methanol in chloroform as the eluent to afford 100 mg of the product as a semisolid; IR (neat) 3400, 2930, 2253, 1667, 1574, 1409, 1328 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64-1.77 (m, 2H), 1.85-1.94 (m, 2H), 1.99-2.08 (m, 1H), 2.16 (s, 3H), 2.18-2.31 (m, 6H), 3.06-3.12 (m, 1H), 3.42-3.67 (m, 5H), 4.77 (d, J = 6.9 Hz, 1H), 7.04 (t, J = 4.5 Hz, 1H), 8.62 (d, J = 5.7 Hz, 2H).

Example 21

(2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile



Step 1: (1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine: This compound was prepared from Intermediate 7 (1.0 g, 4.13 mmol) and chloropyrazine (709 mg, 6.18 mmol) using 60 % NaH (246 mg, 6.16 mmol) in dry DMA (20 ml) as described in Example 1, Step 1 to afford 1.0 g of the product as a white solid; IR (KBr) 3343, 2955, 2339, 1676, 1533, 1406, 1369, 1274 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.51-2.09 (m, 5H), 2.13 (s, 3H), 2.19-2.32 (m, 1H), 2.86-2.93 (m, 1H), 4.12 (brs, 1H), 5.24 (brs, 1H), 8.23-8.27 (m, 2H), 8.58 (d, J = 1.2 Hz, 1H).

Step 2: (1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentan-1-amine: This compound was prepared from Step 1 Intermediate (600 mg, 1.87 mmol) using TFA (3 ml) in dichloromethane (3 ml) as described in Example 1, Step 2 to afford 406 mg of the free amine, which was used as such for the next step.

Step 3: (2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile: This compound was prepared from Step 2 intermediate (406 mg, 1.83 mmol) and Intermediate 8 (161 mg, 0.93 mmol) using K_2CO_3 (257 mg, 1.86 mmol) and NaI (140 mg, 0.93 mmol) in dry THF (30 ml) as described in Example 1, Step 3. The crude material was purified by silica gel column chromatography using 5 % methanol in chloroform as the eluent to afford 100 mg of the product as a semisolid; IR (neat) 3317, 2958, 2241, 1660, 1531, 1406, 1371, 1282 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53-1.67 (m, 2H), 1.86-1.93 (m, 6H), 2.13 (s, 3H), 2.14-2.35 (m, 5H), 2.91-2.97 (m, 1H), 3.21-3.27 (m, 1H), 3.43 (s, 2H), 3.56-3.64 (m, 1H), 4.78 (d, J = 6.3 Hz, 1H), 8.19-8.27 (m, 2H), 8.62 (d, J = 1.5 Hz, 1H).

Protocol for in-vitro DPP-IV assay

DPP-IV activity was determined by the cleavage rate of 7-amino-4-methyl coumarin (AMC) from synthetic substrate Glycyl-Prolyl-AMC. In brief, the assay was conducted by adding 10 ng of human recombinant Dipeptidyl peptidase IV enzyme (DPPIV, available commercially from R & D Systems, Inc of Minneappolis,MN 55413, USA) in 50 µl of the assay buffer (25 mM Tris, pH 7.4, 140 mM NaCl, 10 mM KCl, 1% BSA) to 96 well black flat bottom microtiter plates. The reaction was initiated by adding 50 µl of 100 µM substrate Gly-Pro-AMC. The incubation was carried out in the kinetic mode at 30 °C for 30 minutes. Fluorescence

was measured using Fluorostar at excitation filter of 380 nm and emission filter of 460 nm). Test compounds and solvent controls were added as 1 µl additions. A standard curve of free amino methyl coumarin (AMC) was generated using 0-100 µM AMC in the assay buffer. The curve generated, which was linear was used for the interpolation of catalytic activity.

TESTS FOR IC_{50} STUDIES:

Test compounds dissolved in DMSO at 5-6 concentrations were tested in duplicate along with the solvent control and blank samples. Percent inhibition was calculated at each concentration with respect to the solvent control sample (no test compound added). IC_{50} values were calculated from 3 experiments using the prism software.

Table 1: DPP-IV inhibition using human recombinant DPP-IV enzyme (n = 2)

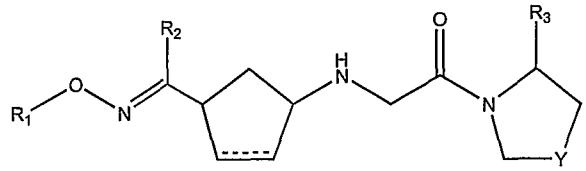
Example	IC_{50} (nM)	Example	IC_{50} (nM)
Example 1	13.98 nM	Example 11	23.76 nM
Example 2	8.51 nM	Example 12	59.61 nM
Example 3	148 nM	Example 13	49.84 nM
Example 4	26.49 nM	Example 14	56% at 300 nM
Example 5	12.73 nM	Example 15	49.69 nM
Example 6	20% at 300 nM	Example 16	95.86 nM
Example 7	137.4 nM	Example 17	12.21 nM
Example 8	15.56 nM	Example 18	41.05 nM
Example 9	33.96 nM	Example 19	22.54 nM
Example 10	43% at 300 nM	Example 21	51.86

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.

All patents, patent applications and non-patent publications are herein incorporated by reference to the same extent as if each individual patent, patent application or publication was specifically and individually indicated to be incorporated herein by reference.

We Claim

1. A Compound of Formula (1)



(1)

wherein

R_1 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl;

R_2 is hydrogen or C_{1-6} alkyl;

Y is $-S(O)^m$, $-CH_2-$, -CHF or CF_2;

R_3 is hydrogen, nitrile (-CN), COOH, or an isostere of a carboxylic acid;

R_4 and R_5 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R_4$, $-C(O)O-R_4$, $-C(O)NR_4R_5$, $-S(O)m-R_4$, $-S(O)m-NR_4R_5$, $-NR_4R_5$,$-OR_4$, or $-SR_4$;

the dotted line [----] in the carbocyclic ring represents an optional double bond; and

m is an integer from 0 to 3,

or an analog thereof, tautomer thereof, enantiomer thereof, diastereomer thereof, regioisomer thereof, stereoisomer thereof, polymorph thereof, pharmaceutically

acceptable salt thereof, N-oxide thereof, prodrug thereof, or pharmaceutically acceptable solvate thereof.

2. A compound of claim 1, wherein R_1 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl or substituted or unsubstituted heteroarylalkyl.

3. A compound of claim 1 or 2, wherein R_1 is ethyl, propyl, cyanomethyl methoxyethyl, cyclopentyl, adamantyl, benzyl, 4-cyano-benzyl, 4-chloro-benzyl, 4-fluoro-benzyl, 4-trifluoro-benzyl, 4-tert-butylbenzyl, 4-tert-butylbenzyl, 3-phenylpropyl, 2-pyridylmethyl, 5-cyano-2-pyridyl, 2-pyrimidinyl, or 2-pyrazinyl.

4. A compound of claim 1 wherein R_2 is substituted or unsubstituted C_{1-6} alkyl.

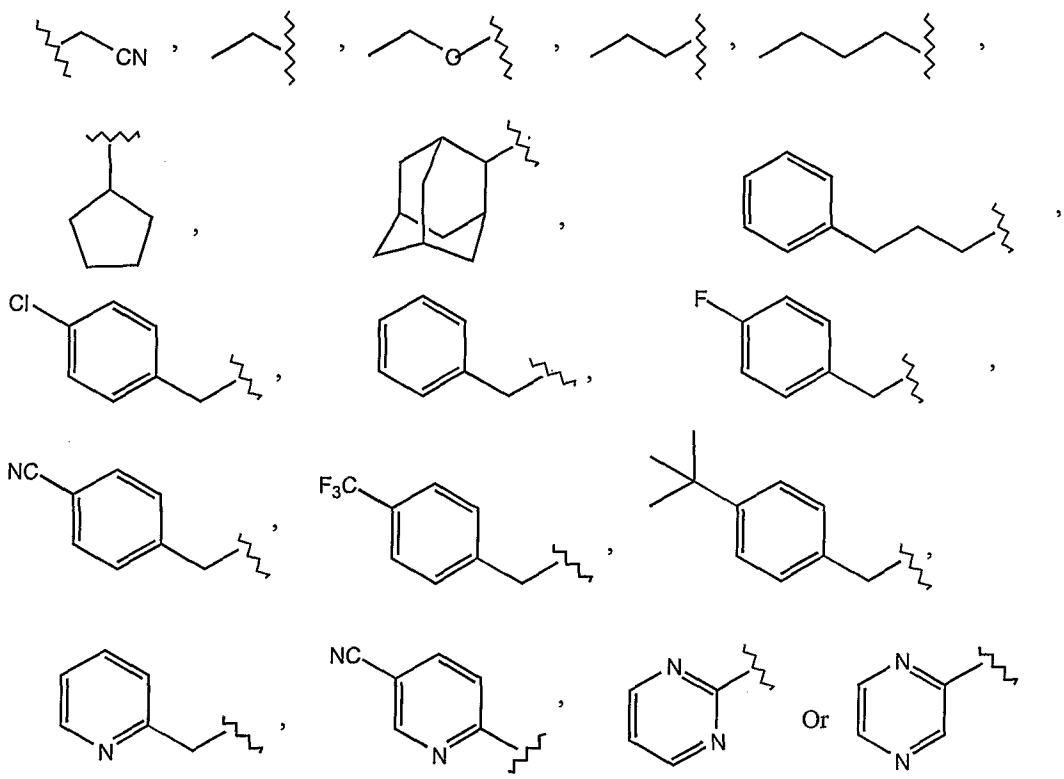
5. A compound of claim 4 wherein R_2 is methyl or ethyl.

6 A compound of claim 1 wherein the isostere of a carboxylic acid is SO_3H, CONOH, $B(OH)_2$, $PO_3R_4R_5$,SO_2N R_4R_5, a tetrazole, an amide, an ester or an acid anhydride.

7 A compound of claim 6, wherein R_3 is nitrile.

8. A compound of claim 1, wherein Y is -CH_2- or –CHF.

9. A compound of claim 1, wherein R_1 is selected from



10. A compound which is:

(2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoro-pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-1-{2-[(1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentylamino]acetyl}-4-fluoro-pyrrolidine-2-carbonitrile;

(2*S*)-1-{2-[(3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentylamino]acetyl}pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-(1-Butyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoro-pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[(Cyclopentyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoropyrrolidine-2-carbonitrile;

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Adamantyloxyimino)ethyl]cyclopentylaminoacetyl)-pyrrolidine-2-carbonitrile;

(2*S*)-1-(2-{(3*S*,1*R*)-3-(1-(2-Methoxyethoxyimino) ethyl]cyclopentylamino} acetyl)-pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(Cyanomethoxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoropyrrolidine-2-carbonitrile;

(2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1-Benzyloxyimino)ethyl]cyclopentylamino}acetyl)-4-fluoro-pyrrolidine-2-carbonitrile;

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyimino)ethyl]cyclopentylamino} -acetyl)-4-fluoropyrrolidine-2-carbonitrile;

(2*S*,4*S*)-4-Fluoro-1-(2-{(3*R*,1*S*)-3-(1-(4-trifluorobenzyloxyimino)ethyl] cyclopentyl-amino} acetyl)pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(4-fluorobenzyloxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-1-(2-{(3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyimino)propyl]cyclopentylamino}-acetyl)-4-fluoropyrrolidine-2-carbonitrile;

(2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(3-phenylpropyloxyimino)ethyl]cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile;

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile;

(2*S*,4*S*)-4-Fluoro-1-(2-{(3*S*,1*R*)-3-[1-(2-pyridylmethoxyimino)ethyl] cyclopentyl-amino}acetyl)pyrrolidine-2-carbonitrile;

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile;

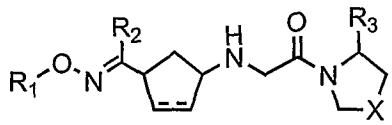
(2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentylamino}-acetyl)pyrrolidine-2-carbonitrile;

(2*S*)-1-(2-{(3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile;

(2*S*)-1-(2-{(1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentylamino}acetyl)-pyrrolidine-2-carbonitrile; or

a pharmaceutically acceptable salt thereof.

11. A method of preparing a compound of formula (1)



(1)

wherein

R_1 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl;

R_2 is hydrogen or C_{1-6} alkyl;

Y is $-S(O)^m$, $-CH_2-$, -CHF or CF_2;

R_3 is hydrogen, nitrile (-CN), COOH, or an isostere of a carboxylic acid;

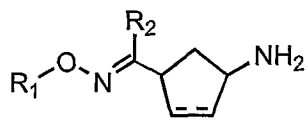
R_4 and R_5 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, –C(O)- R_4, $-C(O)O-R_4$, $-C(O)NR_4R_5$, $-S(O)m-R_4$, $-S(O)m-NR_4R_5$, $-NR_4R_5$,$-OR_4$, or $-SR_4$;

the dotted line [----] in the carbocyclic ring represents an optional double bond; and

m is an integer from 0 to 3,

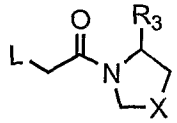
comprising the step of:

coupling a compound of formula (6)



(6)

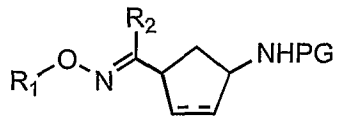
with a compound of formula (7)



(7)

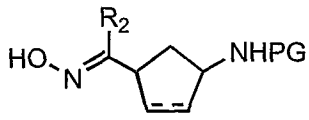
to provide a compound of formula (1).

12. The method of claim 11, wherein the compound of formula (6) is prepared by deprotecting a compound of formula (6a)



(6a)

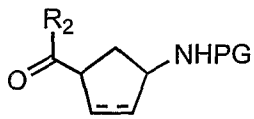
13. The method of claim 12, wherein the compound of formula (6a) is prepared by coupling a compound of formula (4)



(4)

with a compound of the formula R_1L, where L is a leaving group, in the presence of a base.

14. The method of claim 13, wherein the compound of formula (4) is prepared by treating a compound of formula (3)

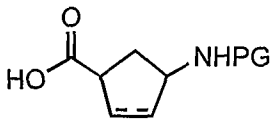


(3)

with a hydroxylamine or a salt thereof.

15. The method of claim 14, wherein the salt of the hydroxylamine is hydroxylamine hydrochloride.

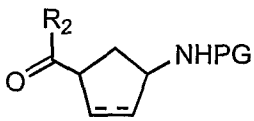
16. The method of claim 14 or 15, wherein the compound of formula (3) is prepared by activating the carboxyl group of a compound of formyla 2



(2)

with an activating agent, and further reacting the compound with R_2MgX, where X is a halogen.

17. A compound of formula (3)



(3)

wherein

R_2 is selected from hydrogen and substituted or unsubstituted C_{1-6} alkyl;

PG is a protecting group; and

the dotted line represents an optional double bond.

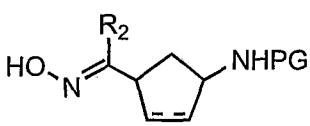
18. A compound of claim 17 which is:

1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone;

1-[(3*S*,1*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone; or

1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-propanone.

19. A compound of Formula (4)



(4)

. wherein

R_2 is selected from hydrogen and substitttuted or unsubstituted C_{1-6} alkyl;

PG is protecting group; and

the dotted line represents an optional double bond.

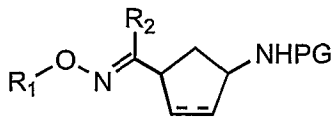
20. A compound of claim 19 which is:

1-[(1*S*,3R)-3-*N*-BOC-aminocyclopentyl]-1-ethanone oxime;

1-[(3*S*,1*R*)-3-*N*-BOC-aminocyclopentyl]-1-ethanone oxime; or

1-[(1*S*,3*R*)-3-*N*-BOC-aminocyclopentyl]-1-propanone oxime.

21. A compound of formula (6a)



(6a)

wherein:

R_1 is substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted cycloalkyl, substituted or unsubstituted cyclyalkylalkyl; substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl or substituted or unsubstituted heteroarylalkyl;

R_2 is selected from hydrogen and C_{1-6} alkyl; and

PG is protecting group; and

the dotted line represents an optional double bond.

22. A compound of claim 21 which is:

(3*S*,1*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-*N*-BOC-amine;

(1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-*N*-BOC-amine;

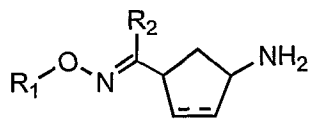
(3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentan-1-*N*-BOC-amine;

(3*S*,1*R*)-3-(1-Butyloxyiminoethyl)cyclopentan-1-*N*-BOC-amine;

(3*S*,1*R*)-3-(1-Cyclopentyloxyiminoethyl)cyclopentan-1-*N*-BOC-amine;

(3*S*,1*R*)-3-[1-(2-(Adamantyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(2-Methoxyethoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-(1-Cyanomethoxyoxyiminoethyl)cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-(1-Benzyloxyoxyiminoethyl)cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(4-Trifluorobenzyloxyoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(4-Fluorobenzyloxyoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyoxyimino)propyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(3-Phenylpropyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(1*S*,3*R*)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine;
(3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine; or
(1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentan-1-*N*-BOC-amine.

23. A compound of formula (6)



(6)

wherein:

R_1 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloaklylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl or substituted or unsubstituted heteroarylalkyl;

R_2 is selected from hydrogen and C_{1-6} alkyl; and

the dotted line represents an optional double bond.

24. A compounds of claim 23 which is:
(3*S*,1*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-amine;
(1*S*,3*R*)-3-(1-Ethoxyiminoethyl)cyclopentan-1-amine;
(3*S*,1*R*)-3-(1-Propyloxyiminoethyl)cyclopentan-1-amine;
(3*S*,1*R*)-3-(1-Butyloxyiminoethyl)cyclopentan-1-amine;
(3*S*,1*R*)-3-(1-Cyclopentyloxyiminoethyl)cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(2-Adamantyloxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(2-Methoxyethoxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-(1-Cyanomethoxyoxyiminoethyl)cyclopentan-1-amine;
(3*S*,1*R*)-3-(1-Benzyloxyoxyiminoethyl)cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(4-*tert*-butylbenzyloxyoxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(4-Cyanobenzyloxyoxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(4-Trifluorobenzyloxyoxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(4-Fluorobenzyloxyoxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(4-Chlorobenzyloxyoxyimino)propyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(3-Phenylpropyloxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(2-Pyridylmethoxyimino)ethyl]cyclopentan-1-amine;
(3S,1R)-3-[1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-amine;
(1S,3R)-3- [1-(5-Cyano-2-pyridyloxyimino)ethyl]cyclopentan-1-amine;
(3*S*,1*R*)-3-[1-(2-Pyrimidinyloxyimino)ethyl]cyclopentan-1-amine; or
(1*S*,3*R*)-3-[1-(2-Pyrazinyloxyimino)ethyl]cyclopentan-1-amine.

25. A method of treating a condition that is regulated or normalized via inhibition of DPP-IV in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-10.

26. A method for treating a metabolic disorder, Type II diabetes, impaired glucose tolerance, impaired fasting glucose (IFG), food intake disorders, obesity, dyslipidemia, or functional dyspepsia in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-10.

27. A method for treating Type II diabetes in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-10.

28. A method for (i) lowering blood glucose, (ii) preventing or treating hyperglycemia, (iii) delaying the progression of impaired glucose tolerance to Type II diabetes, (iv) delaying the progression of non-insulin requiring Type II diabetes to insulin requiring Type II diabetes, (v) increasing the number and/or the size of beta cells, (vi) preventing or treating beta cell degeneration, or (vii) regulating appetite or inducing satiety in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-10.

29. A method of treatment and/or prophylaxis of a disease selected from diabetes, non-insulin dependent diabetes mellitus, impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, railty, arthritis, allograft rejection in transplantation, autoimmune diseases, AIDS, allergic disorders, intestinal diseases, inflammatory bowel disease, obesity, anorexia nervosa, osteoporosis, hyperglycemia, syndrome X, diabetic complications, hyperinsulinemia, atherosclerosis or a related disease, immunomodulatory diseases, or metabolic syndrome in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-10.

30. A method of treating insulin resistant non-impaired glucose tolerance in order to prevent or delay the onset of non-insulin dependent diabetes mellitus in a subject comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-10.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000442

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D207/16 A61K31/401 A61K31/4025 C07D401/12 C07D403/12
C07C251/42 C07C251/52 C07C251/54 C07C251/58 C07C271/24
C07D213/30 C07D213/85 C07D239/34 C07D241/18

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)
C07D C07C A61K

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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/11103 A (ASTRA AB [SE]; BERGSTRAND HAAKAN [SE]; KARABELAS KOSTAS [SE]; LINDEN M) 19 March 1998 (1998-03-19) page 37 - page 38; example 20b)	17,18
X	US 2003/125389 A1 (RAJU BORE G [US] ET AL) 3 July 2003 (2003-07-03) page 21; example 8, column 1, step 2	17

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
7 December 2006	19/12/2006

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, Dieter

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000442

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAGATA H ET AL: "A convenient enantioselective synthesis of natural (1R,3S)-amidinomycin" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 8, no. 16, 28 August 1997 (1997-08-28), pages 2679-2681, XP004090350 ISSN: 0957-4166 page 2680; scheme 2, compound 7	17
A	WO 2006/011035 A (GLENMARK PHARMACEUTICALS LTD [IN]; THOMAS ABRAHAM [IN]; BALASUBRAMANIA) 2 February 2006 (2006-02-02) the whole document	1-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000442

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 25-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/000442

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811103 A	19-03-1998	AU 4143397 A ZA 9707809 A	02-04-1998 10-03-1998
US 2003125389 A1	03-07-2003	NONE	
WO 2006011035 A	02-02-2006	NONE	