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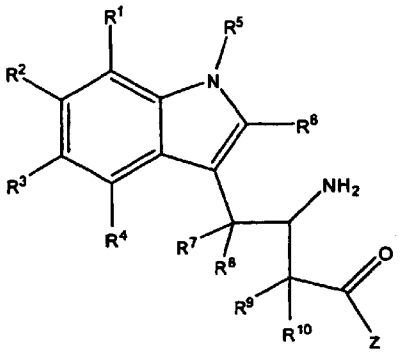

(I)

(57) Abstract: The present invention relates to indole derivatives useful as dipeptidyl peptidase IV (DPP-IV) inhibitors. Formula (I).

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INDOLES FOR USE AS DPP-IV INHIBITORS

Field of the Invention

This present invention relates to compounds useful as dipeptidyl peptidase IV (DPP-IV) inhibitors.

Background to 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 2 diabetes mellitus are, therefore, at increased risk of macro-vascular and micro-vascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. For this reason, the therapeutic control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

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

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

glucose production and secretion in the liver.

The available treatments for Type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic ß-cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissue. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance due to the even higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (i.e., 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for ameliorating many symptoms of Type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models or Type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycaemia. The glitazones that are currently marketed are agonists of the peroxisome proliferators 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 glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the glitazones, such as troglitazone.

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

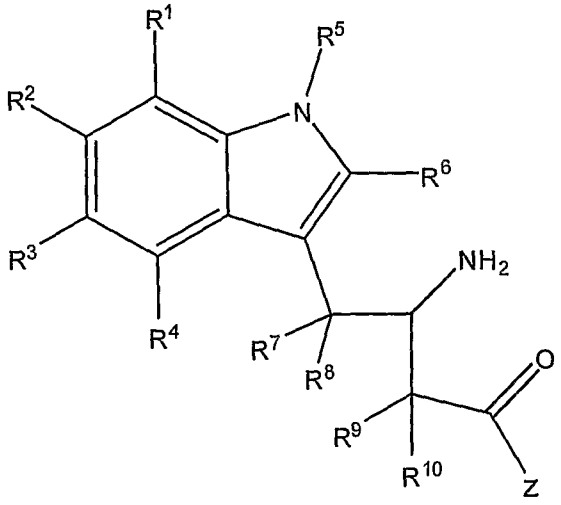
Compounds that are inhibitors of the dipeptidyl peptidase-IV enzyme (DPPIV) are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly Type 2 diabetes, see for example WO 97/40832 and WO 98/19998. The usefulness of DPPIV inhibitors in the treatment of Type 2 diabetes is based on the fact that DPPIV in vivo readily inactivates glucagons 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 DPPIV leads to decreased inactivation of the incretins and this in turn results in increased effectiveness of the incretins in stimulating insulin production by the pancreas. DPPIV inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DPPIV 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 (hypoglycaemia). Inhibition of DPPIV is therefore expected to increase insulin without increasing the risk of hypoglycaemia, which is a dangerous side effect associated with the use of insulin secretagogues.

DPPIV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DPPIV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions.

The present inventor(s) have identified indole derivatives that have DPPIV inhibitory activity.

Statements of the Invention

According to a first aspect of the present invention there is provided a compound of Formula I:



(I)

wherein

R^1, R^2, R^3 and R^4 are each independently selected from hydrogen, R^{12}, hydrocarbyl optionally substituted with R^{12}, and -$(CH_2)_k$-heterocyclyl optionally substituted with R^{12}, wherein each R^{12} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR^{13}, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$S(O)_lR^{13}$, -$N(R^{13})R^{14}$, -$C(O)N(R^{13})R^{14}$, -$SO_2N(R^{13})R^{14}$ and R^{15} and including the proviso that R^3 is not F;

wherein R^{13} and R^{14} are each independently selected from hydrogen or R^{15};

wherein R^{15} is selected from hydrocarbyl and -$(CH_2)_m$-heterocyclyl, and each R^{15} is optionally and independently substituted with one or more of halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6;

l is 0, 1 or 2;

m is 0, 1, 2, 3, 4, 5 or 6;

or one or more R^1 and R^2, R^2 and R^3, R^3 and R^4 taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12};

R^5 is independently selected from hydrogen and hydrocarbyl and each R^5 is optionally and independently substituted with one or more of halogen, cyano, amino, hydroxyl, and hydrocarbyl wherein each optional hydrocarbyl substituent is optionally and independently substituted with one or more of halogen, hydroxyl and hydrocarbyl optionally and independently substituted with one or more halogen;

R^6 is hydrogen or R^{15};

R^7 and R^8 are each independently selected from hydrogen or R^{12}; or R^7 and R^8 taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12}; or R^7 or R^8 together with R^9 or R^{10}, together with the atoms to which they are attached, form a carbocycle (e.g. 6-membered ring) or a heterocycle, optionally substituted with one or more R^{12};

R^9 and R^{10} are independently selected from hydrogen or R^{12}; or R^9 and R^{10} taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12};

Z is selected from the group consisting of hydrocarbyl optionally substituted with R^{12}, and $-(CH_2)_k$-heterocyclyl optionally substituted with R^{12}, wherein each R^{12} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^{13}$, $-OR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-S(O)_lR^{13}$, $-N(R^{13})R^{14}$, $-C(O)N(R^{13})R^{14}$, $-SO_2N(R^{13})R^{14}$ and R^{15}; or a salt thereof.

The compounds of the invention can exist in different forms, such as free acids, free bases, esters and other prodrugs, salts and tautomers, for example, and the invention includes all variant forms of the compounds.

Hydrocarbyl

The term "hydrocarbyl" as used herein includes reference to moieties consisting exclusively of hydrogen and carbon atoms; such a moiety may comprise an aliphatic and/or an aromatic moiety. The moiety may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Examples of hydrocarbyl groups include

C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl); C_{1-6} alkyl substituted by aryl (e.g. benzyl) or by cycloalkyl (e.g cyclopropylmethyl); cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl); alkenyl (e.g. 2-butenyl); alkynyl (e.g. 2-butynyl); aryl (e.g. phenyl, naphthyl or fluorenyl) and the like.

Alkyl

The terms "alkyl" and "C_{1-6} alkyl" as used herein include reference to a straight or branched chain alkyl moiety having 1, 2, 3, 4, 5 or 6 carbon atoms. This term includes reference to groups such as methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, sec-butyl or tert-butyl), pentyl, hexyl and the like. In particular, alkyl may have 1, 2, 3 or 4 carbon atoms.

Alkenyl

The terms "alkenyl" and "C_{2-6} alkenyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one double bond, of either E or Z stereochemistry where applicable. This term includes reference to groups such as ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl and 3-hexenyl and the like.

Alkynyl

The terms "alkynyl" and "C_{2-6} alkynyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one triple bond. This term includes reference to groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl and 3-hexynyl and the like.

Alkoxy

The terms "alkoxy" and "C_{1-6} alkoxy" as used herein include reference to -O-alkyl, wherein alkyl is straight or branched chain and comprises 1, 2, 3, 4, 5 or 6 carbon atoms. In one class of embodiments, alkoxy has 1, 2, 3 or 4 carbon atoms. This term includes reference to groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like.

Cycloalkyl

The term "cycloalkyl" as used herein includes reference to an alicyclic moiety having 3, 4, 5, 6, 7 or 8 carbon atoms. The group may be a bridged or polycyclic ring system. More often cycloalkyl groups are monocyclic. This term includes reference to groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl and the like.

Aryl

The term "aryl" as used herein includes reference to an aromatic ring system comprising 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring carbon atoms. Aryl is often phenyl but may be a polycyclic ring system, having two or more rings, at least one of which is aromatic. This term includes reference to groups such as phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

Carbocyclyl

The term "carbocyclyl" as used herein includes reference to a saturated (e.g. cycloalkyl) or unsaturated (e.g. aryl) ring moiety having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 carbon ring atoms. In particular, carbocyclyl includes a 3- to 10-membered ring or ring system and, in particular, a 5- or 6-membered ring, which may be saturated or unsaturated. A carbocyclic moiety is, for example, selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl, phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

Heterocyclyl

The term "heterocyclyl" as used herein includes reference to a saturated (e.g. heterocycloalkyl) or unsaturated (e.g. heteroaryl) heterocyclic ring moiety having from 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen, phosphorus, silicon and sulphur. In particular, heterocyclyl includes a 3- to 10-membered ring or ring system and more particularly a 5- or 6-or 7-membered ring, which may be saturated or unsaturated.

A heterocyclic moiety is, for example, selected from oxiranyl, azirinyl, 1,2-oxathiolanyl,

imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, especially thiomorpholino, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl, chromanyl and the like.

Heterocycloalkyl

The term "heterocycloalkyl" as used herein includes reference to a saturated heterocyclic moiety having 3, 4, 5, 6 or 7 ring carbon atoms and 1, 2, 3, 4 or 5 ring heteroatoms selected from nitrogen, oxygen, phosphorus and sulphur. The group may be a polycyclic ring system but more often is monocyclic. This term includes reference to groups such as azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxiranyl, pyrazolidinyl, imidazolyl, indolizidinyl, piperazinyl, thiazolidinyl, morpholinyl, thiomorpholinyl, quinolinidinyl and the like.

Heteroaryl

The term "heteroaryl" as used herein includes reference to an aromatic heterocyclic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen and sulphur. The group may be a polycyclic ring system, having two or more rings, at least one of which is aromatic, but is more often monocyclic. This term includes reference to groups such as pyrimidinyl, furanyl, benzo[b]thiophenyl, thiophenyl, pyrrolyl, imidazolyl, pyrrolidinyl, pyridinyl, benzo[b]furanyl, pyrazinyl, purinyl, indolyl, benzimidazolyl, quinolinyl, phenothiazinyl, triazinyl, phthalazinyl, 2H-chromenyl, oxazolyl, isoxazolyl, thiazolyl, isoindolyl, indazolyl, purinyl, isoquinolinyl, quinazolinyl, pteridinyl and the like.

Halogen

The term "halogen" as used herein includes reference to F, Cl, Br or I. In particular, halogen may be F or Cl.

Substituted

The term "substituted" as used herein in reference to a moiety means that one or more, especially up to 5, more especially 1, 2 or 3, of the hydrogen atoms in said moiety are replaced independently of each other by the corresponding number of the described substituents. The term "optionally substituted" as used herein means substituted or unsubstituted.

It will, of course, be understood that substituents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort whether a particular substitution is possible. For example, amino or hydroxy groups with free hydrogen may be unstable if bound to carbon atoms with unsaturated (e.g. olefinic) bonds. Additionally, it will of course be understood that the substituents described herein may themselves be substituted by any substituent, subject to the aforementioned restriction to appropriate substitutions as recognised by the skilled man.

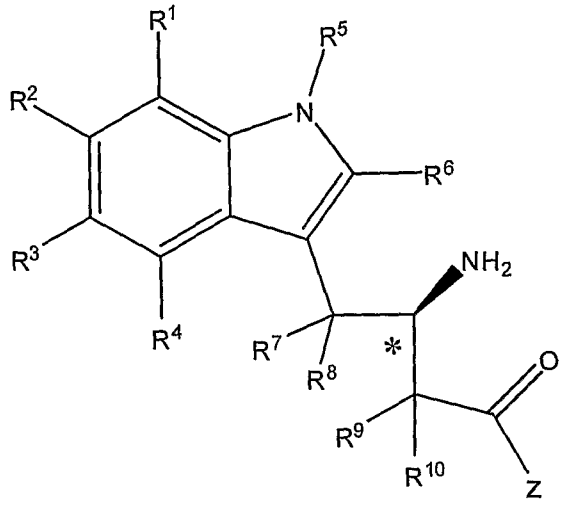
Independently

Where two or more moieties are described as being "each independently" selected from a list of atoms or groups, this means that the moieties may be the same or different. The identity of each moiety is therefore independent of the identities of the one or more other moieties.

The present invention further provides a compound according to the invention which comprises the racemate, the *S* or the *R* enantiomer or a mixture thereof, of a compound according to the invention. Preferably, the compound is the *S*-enantiomer or the *R*-enantiomer.

In one embodiment of the compounds of the present invention, the carbon atom marked with an * has the *R* configuration (according to the Cahn Ingold Prelog convention) as

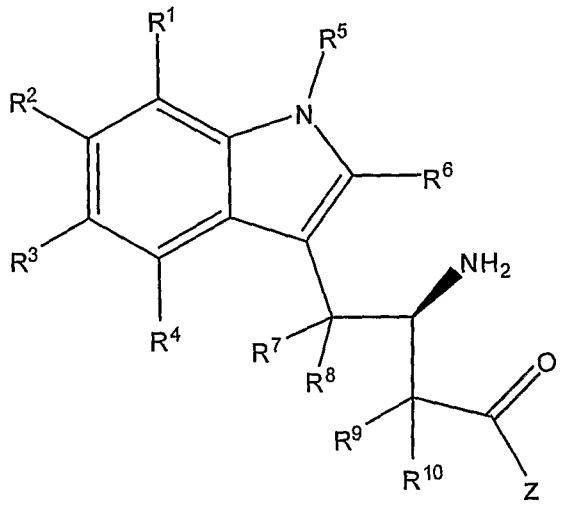
depicted in Formula Ia



(Ia)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and Z are as defined herein. For example R^7, R^8, R^9 and R^{10} are H.

Thus in a preferred aspect the invention provides a compound of Formula Ib



(Ib)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and Z are as defined herein.

$R^1$and R^2 are preferably each independently selected from hydrogen, halogen, cyano, OH, C_{1-6} alkyl and -O(C_{1-6} alkyl) wherein C_{1-6} alkyl and -O(C_{1-6} alkyl) are each optionally and independently substituted by one or more halogen.

More preferably R^1 and R^2 are each independently selected from hydrogen and F.

In one embodiment of the invention R^1 is F and R^2 is hydrogen.

In a further embodiment of the invention R^1 is hydrogen and R^2 is F.

In a yet further embodiment of the invention R^1 is F and R^2 is F.

Preferably R^1, R^2, and R^4 are each independently selected from hydrogen and F.

In one embodiment of the invention at least two of R^1, R^2 and R^4 are F, for example R^1 and R^4 are F.

In one embodiment of the invention R^1, R^2 and R^4 are F.

R^3 and R^4 are preferably each independently selected from hydrogen, halogen, cyano, OH, C_{1-6} alkyl and -O(C_{1-6} alkyl) wherein C_{1-6} alkyl and -O(C_{1-6} alkyl) are each optionally and independently substituted by one or more halogen and including the proviso that where R^3 is halogen R^3 is not F.

Preferably R^3 and R^4 are each independently hydrogen.

R^5 is preferably independently selected from hydrogen, C_{1-6} alkyl and carbocyclyl optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and OC_{1-6} alkyl or carbocyclyl (e.g aryl); wherein each optional C_{1-6} alkyl and OC_{1-6} alkyl substituent is optionally and independently substituted with one or more halogen; and wherein each optional carbocyclyl substituent is optionally and independently substituted with one or more halogen, hydroxyl, C_{1-6} alkyl optionally substituted with one or more halogen, or OC_{1-6} alkyl optionally substituted with one or more halogen.

Preferably R^5 is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl and phenyl optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and OC_{1-6} alkyl or phenyl; wherein each optional C_{1-6} alkyl and OC_{1-6} alkyl substituent is optionally and independently substituted with one or more halogen; and wherein each optional phenyl substituent is optionally and independently substituted with one or more halogen, hydroxyl, C_{1-6} alkyl optionally substituted with one or more halogen, or OC_{1-6} alkyl optionally substituted with one or more halogen.

More preferably R^5 is hydrogen or C1-6 alkyl optionally substituted as described herein.

Preferably still R^5 is hydrogen.

Preferably still R^6 is hydrogen.

R^7 and R^8 are preferably each independently selected from hydrogen, hydroxyl, halogen and C_{1-6} alkyl wherein C_{1-6} alkyl is optionally and independently substituted with one or more halogen; or R^7 and R^8 taken together with the atoms to which they are attached form C_{3-6} cycloalkyl optionally and independently substituted with one or more halogen.

More preferably R^7 and R^8 are each independently hydrogen.

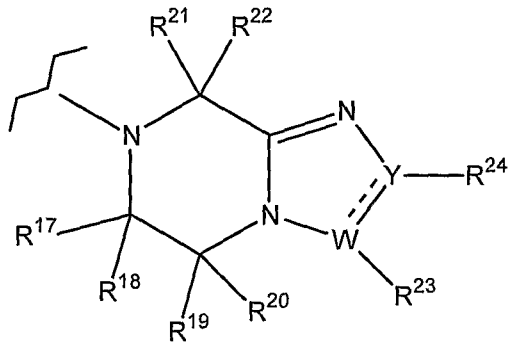
R^9 and R^{10} are preferably each independently selected from hydrogen, hydroxyl, halogen and C_{1-6} alkyl wherein C_{1-6} alkyl is optionally and independently substituted with one or more halogen; or R^9 and R^{10} taken together with the atoms to which they are attached form C_{3-6} cycloalkyl optionally and independently substituted with one or more halogen.

More preferably R^9 and R^{10} are each independently hydrogen.

Z is preferably a heterocyclic group, for example a 5, 6 or 7 membered monocyclic or polycyclic heterocyclic ring or ring system.

Preferably Z is a nitrogen-containing heterocyclic group. For example Z may be selected from the group consisting of imidazolyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrrolizidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, azepane, azepanone, diazepanone and azocane. Preferably Z is diazepanone.

Preferably Z is a group of Formula (II)



(II)

wherein

R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from hydrogen, R^{12}, hydrocarbyl optionally and independently substituted with R^{12}, and $-(CH_2)_k$-heterocyclyl optionally substituted with R^{12};

W and Y are independently selected from N, C, O and S;

R^{23} and R^{24}, which may be absent, are each independently selected from hydrogen, R^{12}, hydrocarbyl optionally and independently substituted with R^{12}, and $-(CH_2)_k$-heterocyclyl optionally substituted with R^{12}; or R^{23} and R^{24} taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12}.

R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are preferably each independently selected from hydrogen, halogen, hydroxyl, cyano, CO_2H, $CONH_2$, C_{1-6} alkyl and carbocyclyl wherein the optional C_{1-6} alkyl and carbocyclyl substituents are optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy wherein the latter alkyl and alkoxy substituents are optionally substituted with one or more halogen.

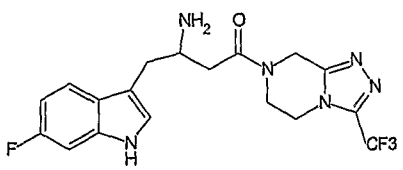
Preferably R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from hydrogen, CO_2H, $CONH_2$ and methyl. More preferably R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently hydrogen.

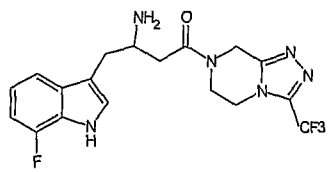
Preferably W and Y are independently selected from C and N. Preferably still W is C and Y is N.

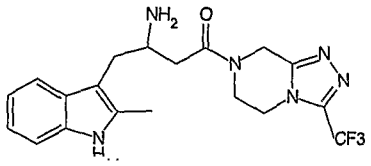
R^{23} and R^{24} are preferably independently selected from hydrogen, trifluoromethyl, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, and carbocyclyl wherein the optional C_{1-6} alkyl, C_{1-6} alkoxy, and carbocyclyl substituents are optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy wherein the latter alkyl and alkoxy substiuents are optionally substituted with one or more halogen.

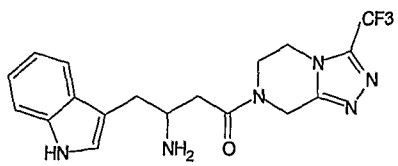
In one embodiment of the invention W is C, Y is N, R^{23} is trifluoromethyl and R^{24} is absent.

Illustrative, but non-limiting, examples of the compounds of the present invention that are useful as inhibitors of DPPIV are the following:









or a pharmaceutically acceptable salt thereof.

Several methods for preparing the compounds of the invention are illustrated in the Schemes shown in the Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.

Compounds of the invention may be in the form of salts. In particular, the salts may be pharmaceutically acceptable salts. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., US, 1985, p. 1418, the disclosure of which is hereby incorporated by reference; see also Stahl et al, Eds, *"Handbook of Pharmaceutical Salts Properties Selection and Use"*, Verlag Helvetica Chimica Acta and Wiley-VCH, 2002.

The disclosure thus includes pharmaceutically-acceptable salts of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. For example the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g. from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate,

glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The invention includes prodrugs for the active pharmaceutical species of the invention, for example in which one or more functional groups are protected or derivatised but can be converted *in vivo* to the functional group, as in the case of esters of carboxylic acids convertible *in vivo* to the free acid, or in the case of protected amines, to the free amino group. The term "prodrug," as used herein, represents in particular compounds which are rapidly transformed *in vivo* to the parent compound, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; H Bundgaard, ed, Design of Prodrugs, Elsevier, 1985; and Judkins, et al. Synthetic Communications, 26(23), 4351-4367 (1996), each of which is incorporated herein by reference.

Also to be mentioned as metabolic activations of prodrugs are nucleotide activation, phosphorylation activation and decarboxylation activation. For additional information, see "The Organic Chemistry of Drug Design and Drug Action", R B Silverman (particularly Chapter 8, pages 497 to 546), incorporated herein by reference.

The use of protecting groups is fully described in `Protective Groups in Organic Chemistry`, edited by J W F McOmie, Plenum Press (1973), and `Protective Groups in Organic Synthesis`, 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Thus, it will be appreciated by those skilled in the art that, although protected derivatives of compounds of the disclosure may not possess pharmacological activity as such, they may be administered, for example parenterally or orally, and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives are therefore examples of "prodrugs". All prodrugs of the described compounds are included within the scope of the disclosure.

Some groups mentioned herein (especially those containing heteroatoms and conjugated bonds) may exist in tautomeric forms and all these tautomers are included in the scope of the disclosure. More generally, many species may exist in equilibrium, as for example in the case of organic acids and their counterpart anions; a reference herein to a species accordingly includes reference to all equilibrium forms thereof.

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. All diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the disclosure. Where a single enantiomer or diasteromer is disclosed, the disclosure also covers the other enantiomers or diastereomers, and also racemates; in this regard, particular reference is made to the specific compounds listed herein.

Geometric isomers may also exist in the compounds of the present disclosure. The present disclosure contemplates the various geometric isomers and mixtures thereof resulting

from the arrangement of substituents around a carbon-carbon double bond and designates such isomers as of the Z or E configuration, wherein the term "Z" represents substituents on the same side of the carbon--carbon double bond and the term "E" represents substituents on opposite sides of the carbon--carbon double bond.

The disclosure therefore includes all variant forms of the defined compounds, for example any tautomer or any pharmaceutically acceptable salt, ester, acid or other variant of the defined compounds and their tautomers as well as substances which, upon administration, are capable of providing directly or indirectly a compound as defined above or providing a species which is capable of existing in equilibrium with such a compound.

Administration & Pharmaceutical Formulations

The compounds of the invention in free form or in pharmaceutically acceptable salt form possess pharmacological activity. They are therefore intended for use as a pharmaceutical. In particular they inhibit DPPIV.

Where used in therapy, the compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route, as an oral or nasal spray or via inhalation, The compounds may be administered in the form of pharmaceutical preparations comprising prodrug or active compound either as a free compound or, for example, a pharmaceutically acceptable non-toxic organic or inorganic acid or base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Typically, therefore, the pharmaceutical compounds of the invention may be administered orally or parenterally ("parenterally" as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion) to a host to obtain an protease-inhibitory effect. In the case of larger animals, such as humans, the compounds may be administered alone or as compositions in combination with pharmaceutically acceptable diluents, excipients or carriers.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

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

According to a further aspect of the invention there is thus provided a pharmaceutical composition including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Pharmaceutical compositions of this invention for parenteral injection suitably comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions,

suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol or phenol sorbic acid. It may also be desirable to include isotonic agents such as sugars or sodium chloride, for example. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents (for example aluminum monostearate and gelatin) which delay absorption.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are suitably made by forming microencapsule matrices of the drug in biodegradable polymers, for example polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid

compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is typically mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or one or more: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycol, for example.

Suitably, oral formulations contain a dissolution aid. The dissolution aid is not limited as to its identity so long as it is pharmaceutically acceptable. Examples include nonionic surface active agents, such as sucrose fatty acid esters, glycerol fatty acid esters, sorbitan fatty acid esters (e.g. sorbitan trioleate), polyethylene glycol, polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, methoxypolyoxyethylene alkyl ethers, polyoxyethylene alkylphenyl ethers, polyethylene glycol fatty acid esters, polyoxyethylene alkylamines, polyoxyethylene alkyl thioethers, polyoxyethylene polyoxypropylene copolymers, polyoxyethylene glycerol fatty acid esters, pentaerythritol fatty acid esters, propylene glycol monofatty acid esters, polyoxyethylene propylene glycol monofatty acid esters, polyoxyethylene sorbitol fatty acid esters, fatty acid alkylolamides, and alkylamine oxides; bile acid and salts thereof (e.g. chenodeoxycholic acid, cholic acid, deoxycholic acid, dehydrocholic acid and salts thereof, and glycine or taurine conjugate thereof); ionic surface active agents, such as

sodium laurylsulfate, fatty acid soaps, alkylsulfonates, alkylphosphates, ether phosphates, fatty acid salts of basic amino acids; triethanolamine soap, and alkyl quaternary ammonium salts; and amphoteric surface active agents, such as betaines and aminocarboxylic acid salts.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, and/or in delayed fashion. Examples of embedding compositions include polymeric substances and waxes.

The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

The active compounds may be in finely divided form, for example it may be micronised.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents. Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p 33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Advantageously, the compounds of the invention may be orally active, have rapid onset of activity and low toxicity.

The compounds of the invention may have the advantage that they are more efficacious, less toxic, longer acting, have a broader range of activity, more potent, produce fewer side effects, more easily absorbed than, or have other useful pharmacological properties over, compounds known in the prior art.

Compounds of the invention may be useful in the therapy of a variety of diseases and conditions. In particular, compounds of the invention may be useful in the treatment or

prevention of diseases or disorders which can be prevented, alleviated or treated by modulation of DPPIV activity (referred to herein as DPPIV mediated diseases or disorders). Such diseases include but are not limited to Type II diabetes and related disorders, arthritis, obesity and osteoporosis. Diseases, disorders and conditions related to Type II diabetes include hyperglycemia, impaired glucose tolerance, insulin resistance, obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, reduced HDL levels, excessive HDL levels, atherosclerosis and its sequelae, vascular restinosis, irritable bowel syndrome, inflammatory bowel disease including Crohn's disease and ulcerative colitis, other inflammatory conditions, pancreatitis, neurodegenerative disease, depression, retinopathy, nephropathy, neuropathy, retinopathy, hypertension, Syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component. Other conditions or diseases that may be treated and/or prevented by the compounds of the invention include growth hormone deficiency, neutropenia, intestinal injury, autoimmune diseases for example, rheumatoid arthritis, multiple sclerosis, Graves' disease and Hashimoto's thyroiditis, inflammatory disorders such as asthma, HIV infection or AIDS, hematopoiesis, neuronal disorders, cancer including tumour metastasis (for example, T cell lymphoma, T cell acute lymphoblastic leukaemia, thyroid carcinomas, basal cell carcinomas and breast carcinomas), benign prostatic hypertrophy and gingivitis. The compounds of the invention may also be useful in altering sperm motility for example improving sperm motility or reducing sperm motility the latter rendering the compounds of the invention useful as a male contraceptive.

Thus a further aspect of the invention provides a method of treating or preventing a DPPIV-mediated disease, or disorder as described herein, in a subject which method comprises administering to said subject a compound or composition according to the invention. Preferably the subject is human.

The extent of protection includes counterfeit or fraudulent products which contain or purport to contain a compound of the invention irrespective of whether they do in fact contain such a compound and irrespective of whether any such compound is contained in a therapeutically effective amount.

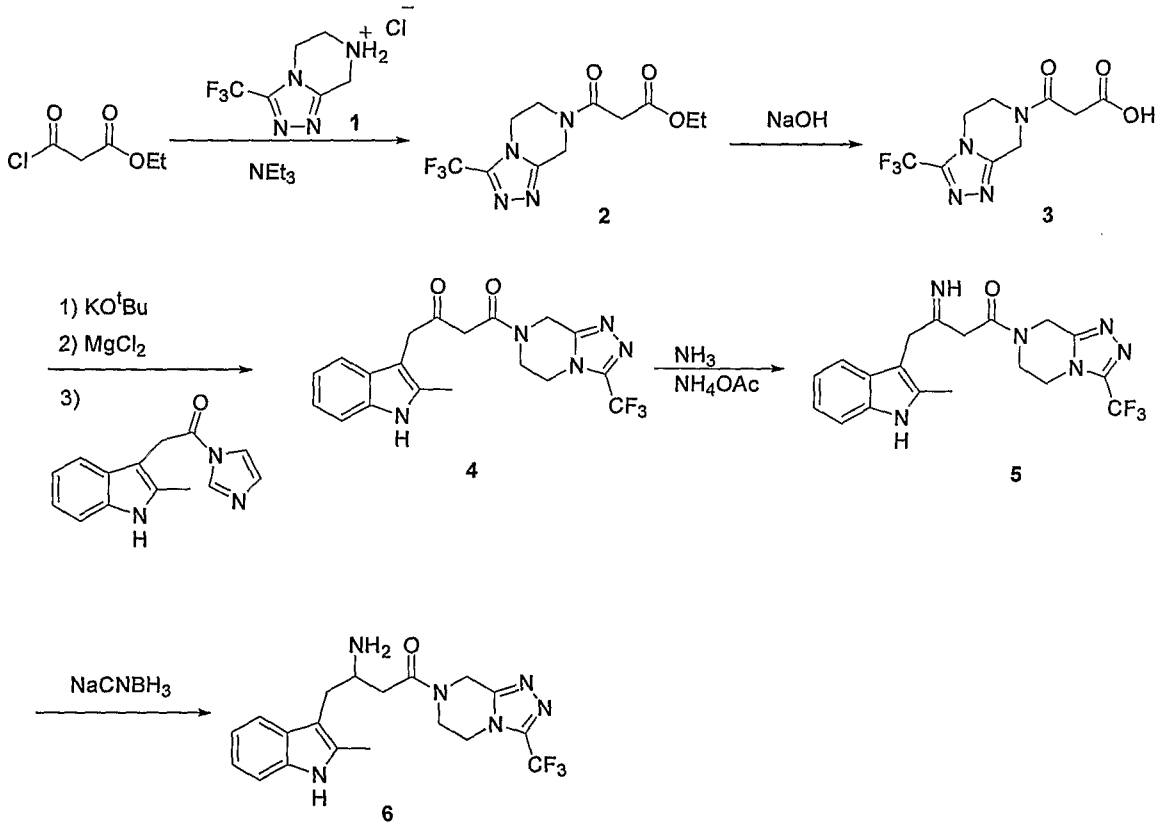
Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

EXAMPLES

Synthesis of Compounds

Preparation of 3-Amino-4-(2-methyl-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (6)



Preparation of **2**

To a solution of triazole base **1** (0.75g, 3.3mmol) in acetonitrile (15mL) at 5°C was added triethylamine (0.96mL, 6.9mmol) followed by ethylmalonyl chloride (0.45mL, 3.5mmol) over 5min. After being stirred for 10min the reaction mixture was allowed to self warm to

room temperature and stirred for a further 90min. The reaction mixture was diluted with ethyl acetate and washed with 1N $HCl_{(aq)}$. The aqueous phase was back extracted with ethyl acetate and the organic phases combined, dried over $MgSO_4$ and evaporated. The residue was purified on silica, eluting with ethyl acetate to give amide **2** (0.76g, 76%) as a yellow oil.

Preparation of **3**

To a solution of amide **2** (0.76g, 2.5mmol) in methanol (30mL) was added 10% $NaOH_{(aq)}$ (15mL). After 1h the reaction was made acidic (pH 2) with 1N $HCl_{(aq)}$ and extracted with ethyl acetate. The organic phases were combined, dried over $MgSO_4$ and evaporated to give acid **3** (0.67g, 97%) as a yellow foam.

Preparation of **4**

To a solution of acid **3** (0.2g, 0.76mmol) in tetrahydrofuran (5mL) was added KO^tBu (1.0M in tetrahydrofuran0.76mL, 0.76mmol) and then $MgCl_2$ (0.066g, 0.69mmol). The reaction mixture was then heated at 40°C for 1h. In a second flask carbonyldiimidazole (0.12g, 0.72mmol) was added to a solution of 2-methylindole-3-acetic acid (0.12g, 0.69mmol) in tetrahydrofuran (5mL) and heated at 30°C for 1h. The two reaction mixtures were combined and heated at 60°C for 3.5h. The reaction mixture was cooled, diluted with 1N $HCl_{(aq)}$ and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified on silica, eluting with a gradient from ethyl acetate to 3% methanol/ethyl acetate, to give β-ketoamide **4** (0.13g, 48%) as a colourless oil.

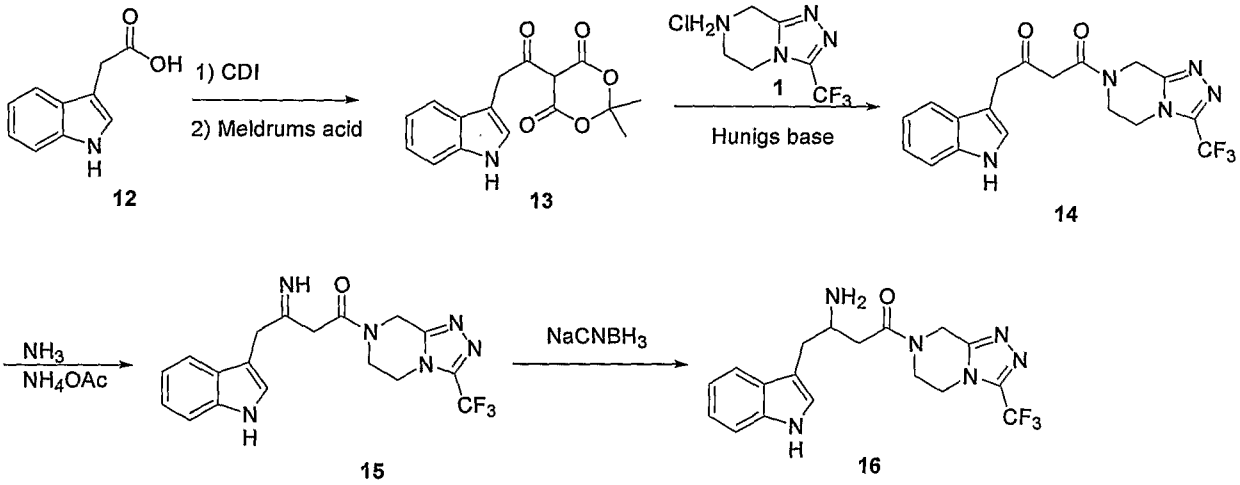
Preparation of **5**

A mixture of β-ketoamide **4** (0.22g, 0.54mmol), ammonium acetate (0.21g) and 16% NH_3/methanol (50mL) was stirred for 48h. The reaction mixture was poured into dichloromethane (450mL) and washed with brine (250mL) and water (75mL). The organic phase was dried over $MgSO_4$ and evaporated to give enamine **5** (0.22g, 100%) as a yellow foam.

Preparation of **6**

To a solution of enamine **5** (0.22g, 0.54mmol) in methanol (15mL) was added $NaCNBH_3$ (0.14g, 2.2mmol) followed by acetyl chloride (0.10mL, 1.4mmol) over 5min. The reaction mixture was stirred for 45min, poured into 1N $HCl_{(aq)}$ (15mL) and stirred for 5min. The reaction was then diluted with Sat. $NaHCO_{3(aq)}$ and extracted with dichloromethane. The organic phase was dried over $MgSO_4$, evaporated and the residue was purified on silica, eluting with 10% (16%NH_3/MeOH)/dichloromethane to give 2-methylindole **6** (0.067g, 30%) as a yellow foam. *m/z* (relative intensity) 407.10 $[M+H]^+$

3-Amino-4-(1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (16)



Preparation of **13**

To a mixture of indole-3-acetic acid (0.5g, 2.9mmol), Meldrum's acid (0.45g, 3.1mmol), Hünig's base (1.04mL, 6.0mmol) and dichloromethane (25mL) was added isobutyl chloroformate (0.37mL, 2.9mmol) over 10min. The reaction mixture was stirred for 1.5h, diluted with dichloromethane and washed with 1N $HCl_{(aq)}$. The organic phase was dried over $MgSO_4$ and evaporated to give Meldrum's adduct **13** (0.86g), which was used directly in the next reaction.

Preparation of **14**

A mixture of the Meldrum's adduct **13** (0.86g, 4.9mmol), triazole base **1** (1.18g, 5.1mmol) and Hünig's base (0.98mL) in acetonitrile (10mL) was heated at reflux temperature for 19h. The reaction mixture was cooled, diluted with ethyl acetate and washed with 1N $HCl_{(aq)}$. The organic phase was dried over $MgSO_4$ and evaporated. The

residue was purified on silica, eluting with 5% methanol/ethyl acetate to give β-ketoamide **14** (0.62g, 32%) as a yellow foam.

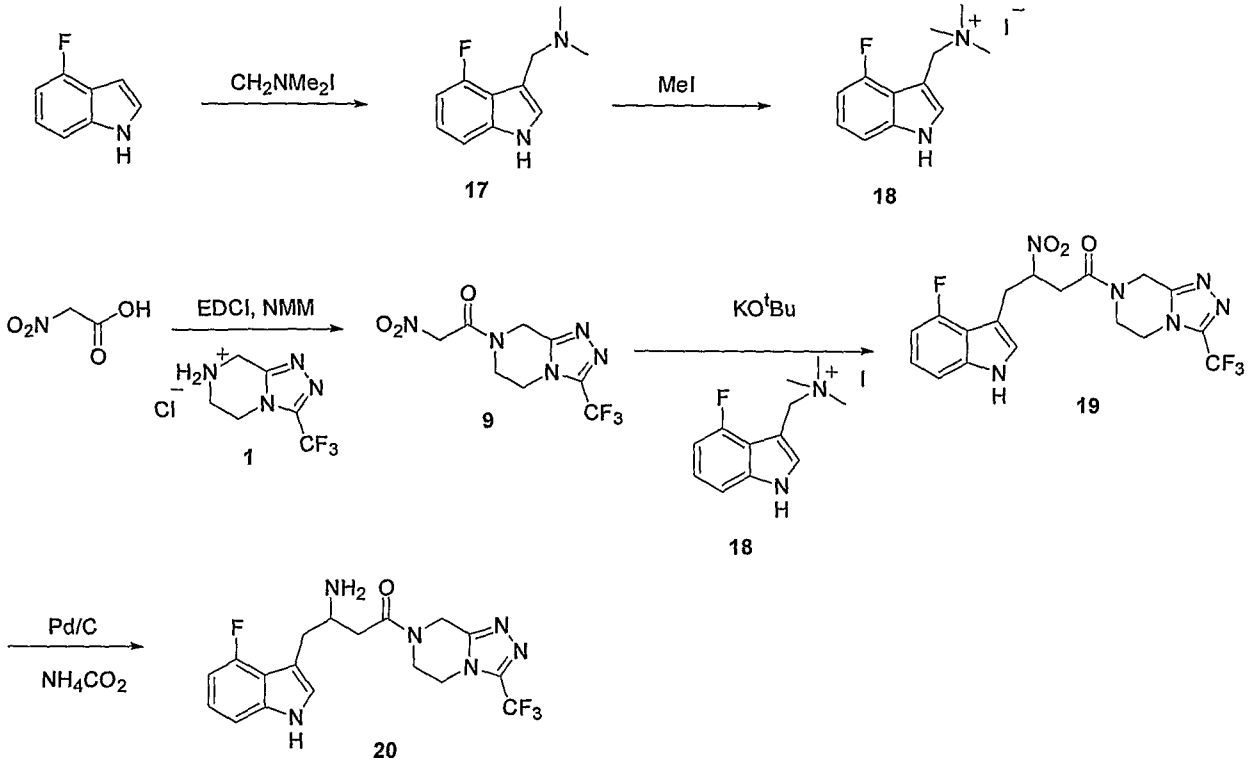
Preparation of **15**

A mixture of β-ketoamide **14** (0.62g, 1.6mmol), NH_4OAc (0.5g) and 16% NH_3/methanol (30mL) was heated at reflux temperature for 3h. The reaction mixture was evaporated and purified on silica, eluting with 3% methanol/ethyl acetate to give enamine **15** (0.30g, 48%) as a yellow foam.

Preparation of **16**

To a solution of enamine **15** (0.35g, 0.86mmol) in methanol (60mL) was added $NaCNBH_3$ (0.22g, 3.4mmol), followed by a solution of acetyl chloride (0.13mL, 1.7mmol) in methanol (5mL) over 5min. The reaction mixture was stirred for 1.5h, diluted with ethyl acetate and washed with sat. $NaHCO_{3\,(aq)}$. The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified on silica, eluting with 10% (16% NH_3/methanol)/dichloromethane to give the major product as a yellow oil (0.18g). This was dissolved in ethyl acetate and hexane was added to precipitate a white solid. This was filtered, washed with hexane and dried to give indole **16** (0.13g, 37%) as a white solid. *m/z* (relative intensity) 393.04 $[M+H]^+$

3-Amino-4-(4-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (20)



Preparation of **9**

To a solution of 3-nitropropionic acid (1.0g, 8.4mmol) and triazole base **1** (2.4g, 10.5mmol) in acetonitrile (20mL) at 0°C was added N-methylmorpholine (0.92mL, 8.4mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.42g, 12.6mmol) and the reaction mixture stirred for 1h. The reaction mixture was allowed to self warm to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with water, sat. $NaHCO_{3(aq)}$, and brine. The organic phase was dried over $MgSO_4$, evaporated and the residue triturated with diethyl ether to give amide **9** (2.1g, 85%) as a white solid.

Preparation of **17**

A suspension of 4-Fluoroindole (500 mg, 3.7 mmol) and Eschenmoser's salt (890 mg, 4.81 mmol) in dichloromethane (12 ml) was stirred at room temperature overnight. The reaction mixture was partitioned between 1M $NaOH_{(aq)}$ and ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated. The residue was stirred in hexane and filtered to give dimethylaminomethyl indole **17** (391 mg, 55%) as a cream solid.

Preparation of **18**

Methyl iodide (10 ml, excess) in ethanol (20 ml) was cooled to 0 °C before the dropwise addition of a solution of dimethylaminomethyl indole **17** (385 mg, 2.0 mmol) in ethyl acetate (20 ml). The reaction mixture was left in the fridge overnight then evaporated. The residue was triturated from 9:1 ethyl acetate:hexane to give ammonium salt **18** (245 mg, 37%) as a beige solid.

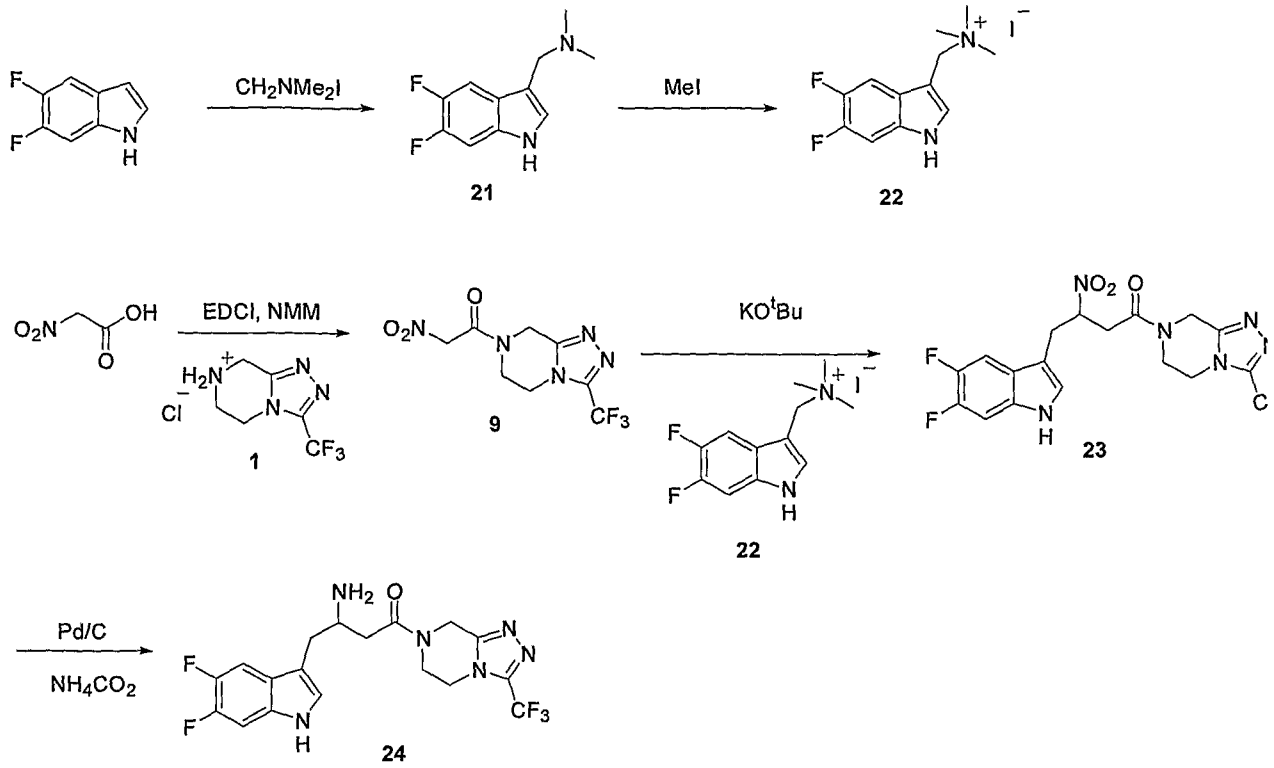
Preparation of **19**

A solution of amide **9** (215 mg, 0.73 mmol) and ammonium salt **18** (245 mg, 0.73 mmol) in dimethylformamide (10 ml) was cooled to –60 °C. KO^{t}Bu (1M in THF, 0.73ml, 0.73 mmol) was added dropwise and the mixture stirred at –60 °C for 1h. The reaction mixture was diluted with ethyl acetate, washed with 1M $HCl_{(aq)}$, brine, dried over $MgSO_4$. and evaporated. The residue was purified on silica, eluting with 9:1 ethyl acetate:hexanes to give nitroindole **19** (226 mg, 70%) as a yellow foam.

Preparation of **20**

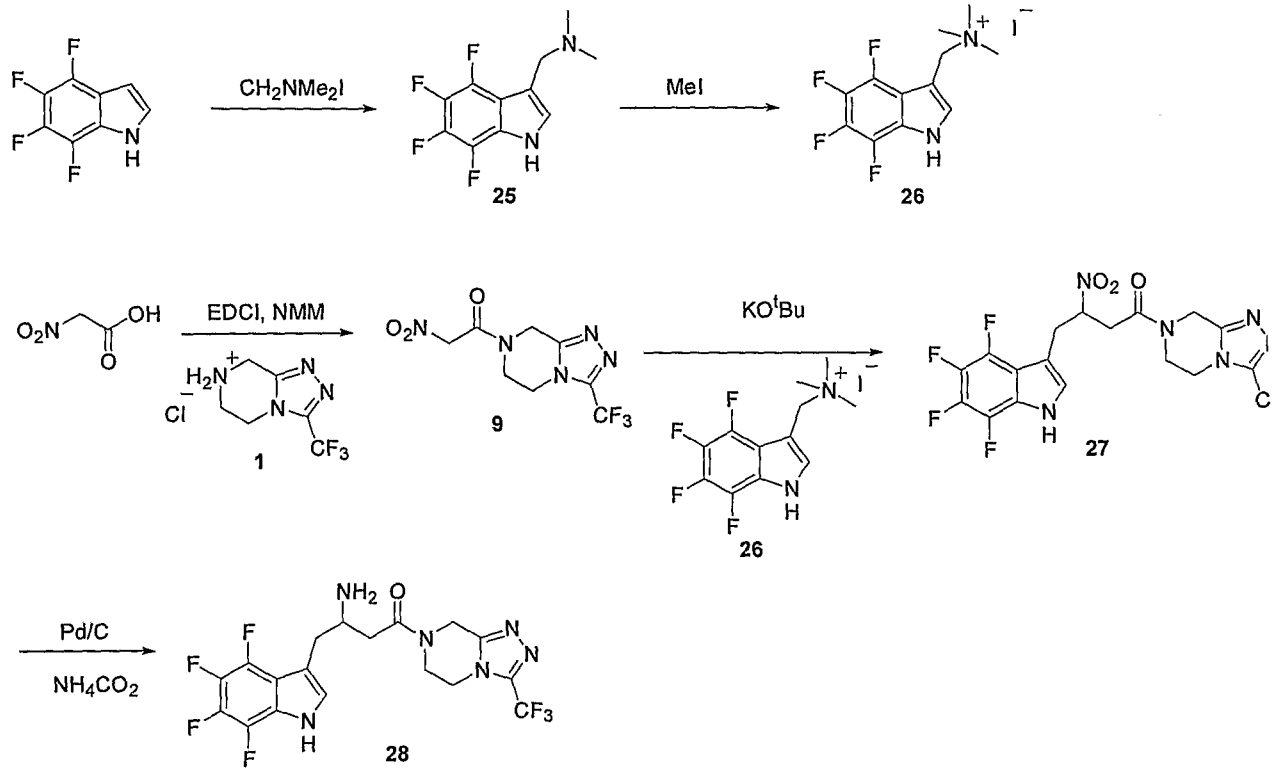
A mixture of nitroindole **19** (215 mg, 0.488 mmol), ammonium formate (215 mg) and 5% palladium on carbon (215 mg) in methanol (15 ml) was heated at reflux temperature for 4h. The reaction mixture was filtered through celite, evaporated and the residue purified on silica, eluting with 10% (16% NH_3/methanol)/dichloromethane to give 4-fluoroindole **20** (104 mg, 65:35 desired product: defluorinated material by LCMS) as a white foam. *m/z* (relative intensity) 411.12 $[M+H]^+$

3-Amino-4-(5,6-difluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (24)



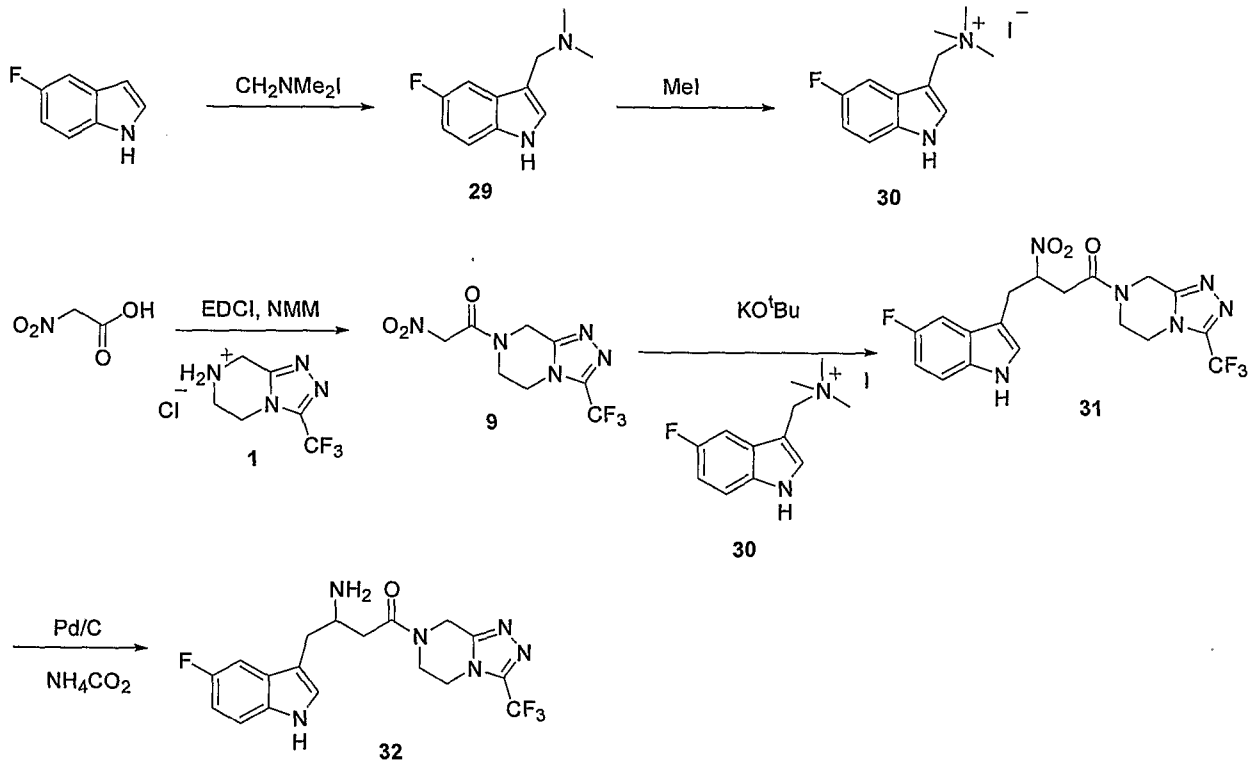
This was prepared by the above route in exactly the same way as for 4-fluoroindole **20**. 5,6-difluoroindole **24** (120mg) was obtained as a white foam. *m/z* (relative intensity) 429.11 $[M+H]^+$

3-Amino-4-(4,5,6,7-tetrafluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (28)



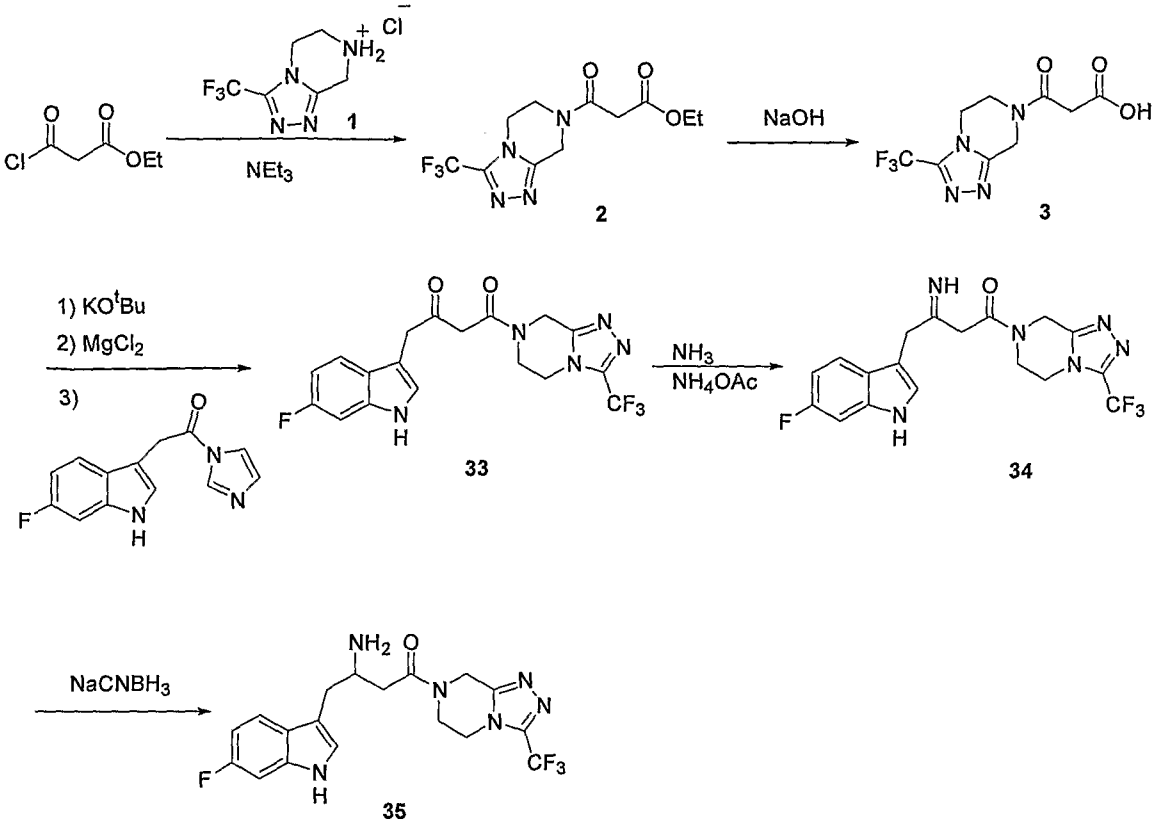
This was prepared by the above route in exactly the same way as for 4-fluoroindole **20**. 4,5,6,7-tetrafluoroindole **28** (9mg) was obtained as a colourless oil. *m/z* (relative intensity) 465.02 $[M+H]^+$

3-Amino-4-(5-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (32)



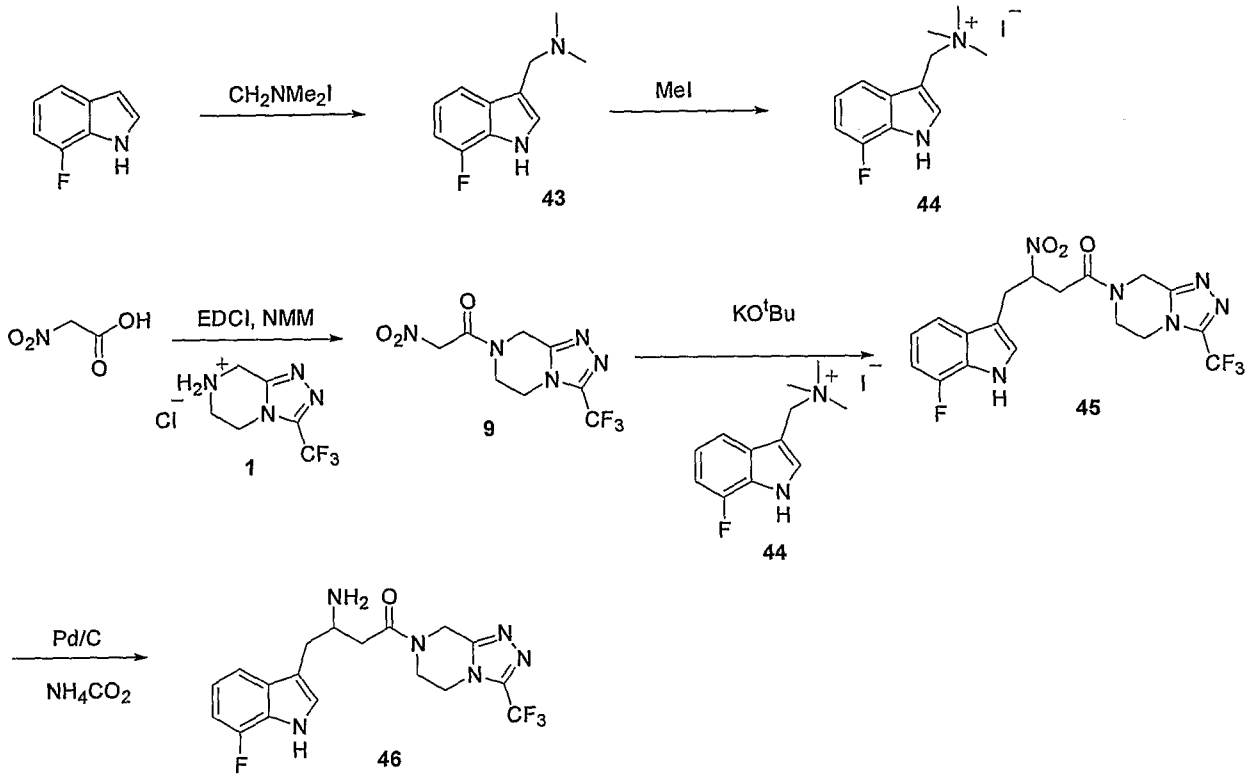
This was prepared by the above route in exactly the same way as for 4-fluoroindole **20**. 5-fluoroindole **32** (50mg) was obtained as a colourless oil. *m/z* (relative intensity) 411.04 $[M+H]^+$

3-Amino-4-(6-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (35)



This was prepared by the above route in a similar way to 2-methylindole **6**. 6-Fluoroindole **35** (76mg) was obtained as a white foam. *m/z* (relative intensity) 411.11 $[M+H]^+$

3-Amino-4-(7-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one (46)



This was prepared by the above route in a similar way to 4-fluoroindole **20**. 7-Fluoroindole **46** was obtained as a white foam. *m/z* (relative intensity) 411.13 $[M+H]^+$

Determination of DPP-IV activity

Experimental

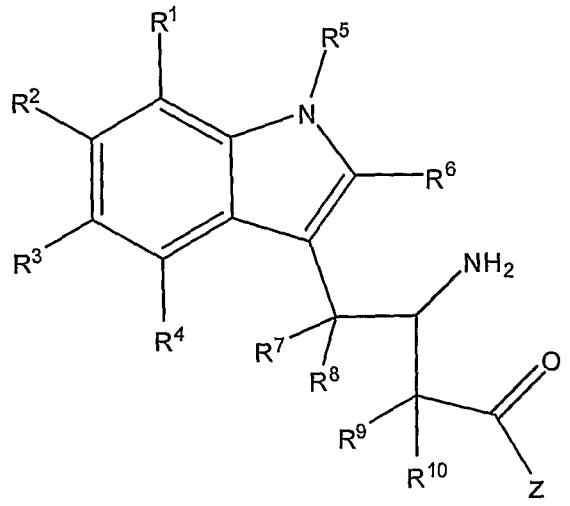
DPP-IV inhibitory activity of compounds was tested by employing an enzyme assay that measures the ability of test compounds to inhibit the activity of a human recombinant DPP-IV expressed in insect Sf9 cells (available from MDS Pharma Services). A test compound was pre-incubated with 0.02 μg/ml of the DPP-IV enzyme in Tris-HCl buffer pH 8.0 for 15 mins at 15°C. The reaction was initiated by addition of 20 μM Ala-Pro-AFC (where AFC = 7-amino-trifluoromethyl-coumarin) for another 30 minute incubation period. Determination of the amount of AFC formed was read spectrofluorimetrically with excitation at 400nm and emission at 510nm. Percentage inhibitions are shown in Table 1.

Table 1

Chemical name	inhibition at 150nM concentration
3-Amino-4-(2-methyl-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	23%
3-Amino-4-(1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	33%
3-Amino-4-(4-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	17%
3-Amino-4-(5,6-difluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	2%
3-Amino-4-(4,5,6,7-tetrafluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	2%
3-Amino-4-(5-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	1%
3-Amino-4-(6-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	56%
3-Amino-4-(7-fluoro-1*H*-indol-3-yl)-1-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-butan-1-one	45%

CLAIMS

1. A compound of Formula I:



(I)

wherein

R^1, R^2, R^3 and R^4 are each independently selected from hydrogen, R^{12}, hydrocarbyl optionally substituted with R^{12}, and -$(CH_2)_k$-heterocyclyl optionally substituted with R^{12}, wherein each R^{12} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR^{13}, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$S(O)_lR^{13}$, -$N(R^{13})R^{14}$, -$C(O)N(R^{13})R^{14}$, -$SO_2N(R^{13})R^{14}$ and R^{15};

wherein R^{13} and R^{14} are each independently selected from hydrogen or R^{15};

wherein R^{15} is selected from hydrocarbyl and -$(CH_2)_m$-heterocyclyl, and each R^{15} is optionally and independently substituted with one or more of halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6;

l is 0, 1 or 2;

m is 0, 1, 2, 3, 4, 5 or 6;

or one or more R^1 and R^2, R^2 and R^3, R^3 and R^4 taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12};

R^5 is independently selected from hydrogen and hydrocarbyl and each R^5 is optionally and independently substituted with one or more of halogen, cyano, amino, hydroxyl, and hydrocarbyl wherein each optional hydrocarbyl substituent is optionally and independently substituted with one or more of halogen, hydroxyl and hydrocarbyl optionally and independently substituted with one or more halogen;

R^6 is hydrogen or R^{15};

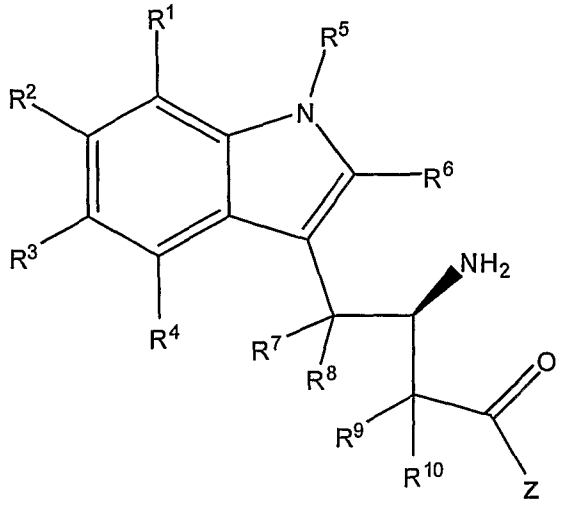
R^7 and R^8 are each independently selected from hydrogen or R^{12}; or R^7 and R^8 taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12}; or R^7 or R^8 together with R^9 or R^{10} form a carbocycle or a heterocycle optionally substituted with one or more R^{12};

R^9 and R^{10} are independently selected from hydrogen or R^{12}; or R^9 and R^{10} taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12};

Z is selected from the group consisting of hydrocarbyl optionally substituted with R^{12}, and $-(CH_2)_k$-heterocyclyl optionally substituted with R^{12}, wherein each R^{12} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^{13}$, $-OR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-S(O)_lR^{13}$, $-N(R^{13})R^{14}$, $-C(O)N(R^{13})R^{14}$, $-SO_2N(R^{13})R^{14}$ and R^{15};

or a salt thereof.

2. A compound as claimed in claim 1 wherein the compound is of Formula Ib



(Ib)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and Z are as defined in claim 1.

3. A compound as claimed in claim 1 or 2 wherein $R^1$and R^2 are each independently selected from hydrogen, halogen, cyano, OH, C_{1-6} alkyl and -O(C_{1-6} alkyl) wherein C_{1-6} alkyl and -O(C_{1-6} alkyl) are each optionally and independently substituted by one or more halogen.

4. A compound as claimed in claim 3 wherein R^1 and R^2 are each independently selected from hydrogen and F.

5. A compound as claimed in claim 4 wherein R^1 is F and R^2 is hydrogen.

6. A compound as claimed in claim 4 wherein R^1 is hydrogen and R^2 is F.

7. A compound as claimed in claim 4 wherein R^1 is F and R^2 is F.

8. A compound as claimed in any one preceding claim wherein R^3 and R^4 are each independently selected from hydrogen, halogen, cyano, OH, C_{1-6} alkyl and -O(C_{1-6} alkyl) wherein C_{1-6} alkyl and -O(C_{1-6} alkyl) are each optionally and independently substituted by one or more halogen.

9. A compound as claimed in claim 8 wherein R^3 and R^4 are each independently hydrogen.

10. A compound as claimed in any one preceding claim wherein R^5 is independently selected from hydrogen, C_{1-6} alkyl and carbocyclyl optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and OC_{1-6} alkyl or carbocyclyl; wherein each optional C_{1-6} alkyl and OC_{1-6} alkyl substituent is optionally and independently substituted with one or more halogen; and wherein each optional carbocyclyl substituent is optionally and independently substituted with one or more halogen, hydroxyl, C_{1-6} alkyl optionally substituted with one or more halogen, or OC_{1-6} alkyl optionally substituted with one or more halogen.

11. A compound as claimed in claim 10 wherein R^5 is independently selected from hydrogen, C_{1-6} alkyl, C3-6 cycloalkyl and phenyl optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and OC_{1-6} alkyl or phenyl; wherein each optional C_{1-6} alkyl and OC_{1-6} alkyl substituent is optionally and independently substituted with one or more halogen; and wherein each optional phenyl substituent is optionally and independently substituted with one or more halogen, hydroxyl, C_{1-6} alkyl optionally substituted with one or more halogen, or OC_{1-6} alkyl optionally substituted with one or more halogen.

12. A compound as claimed in claim 11 wherein R^5 is hydrogen or C_{1-6} alkyl.

13. A compound as claimed in claim 12 wherein R^5 is hydrogen.

14. A compound as claimed in any one preceding claim wherein R^7 and R^8 are each independently selected from hydrogen, hydroxyl, halogen and C_{1-6} alkyl wherein C_{1-6} alkyl is optionally and independently substituted with one or more halogen; or R^7 and R^8 taken together with the atoms to which they are attached form C_{3-6} cycloalkyl optionally and independently substituted with one or more halogen.

15. A compound as claimed in claim 14 wherein R^7 and R^8 are each independently hydrogen.

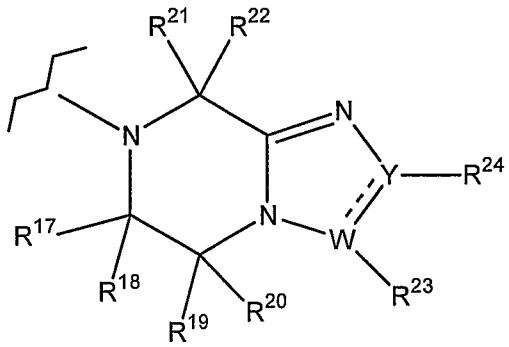
16. A compound as claimed in any one preceding claim wherein R^9 and R^{10} are each independently selected from hydrogen, hydroxyl, halogen and C_{1-6} alkyl wherein C_{1-6} alkyl is optionally and independently substituted with one or more halogen; or R^9 and R^{10} taken together with the atoms to which they are attached form C_{3-6} cycloalkyl optionally and independently substituted with one or more halogen.

17. A compound as claimed in claim 16 wherein R^9 and R^{10} are each independently hydrogen.

18. A compound as claimed in any one preceding claim wherein Z is a heterocyclic group.

19. A compound as claimed in claim 18 wherein Z is a nitrogen-containing heterocyclic group.

20. A compound as claimed in claim 19 wherein Z is a group of Formula (II)



(II)

wherein

R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from hydrogen, R^{12}, hydrocarbyl optionally and independently substituted with R^{12}, and -$(CH_2)_k$-heterocyclyl optionally substituted with R^{12};

W and Y are independently selected from N, C, O and S; and

R^{23} and R^{24}, which may be absent, are each independently selected from hydrogen, R^{12}, hydrocarbyl optionally and independently substituted with R^{12}, and -$(CH_2)_k$-heterocyclyl optionally substituted with R^{12}; or R^{23} and R^{24} taken together with the atoms to which they are attached form a carbocycle or a heterocycle, optionally substituted with one or more R^{12}.

21. A compound as claimed in claim 20 wherein R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from hydrogen, halogen, hydroxyl, cyano, CO_2H, $CONH_2$, C_{1-6} alkyl and carbocyclyl wherein the optional C_{1-6} alkyl and carbocyclyl substituents are optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy wherein the latter alkyl and alkoxy substituents are optionally substituted with one or more halogen.

22. A compound as claimed in claim 21 wherein R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from hydrogen, CO_2H, $CONH_2$ and methyl.

23. A compound as claimed in claim 22 wherein R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently hydrogen.

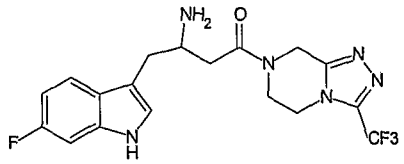
24. A compound as claimed in any of claims 20 to 23 wherein W and Y are independently selected from C and N.

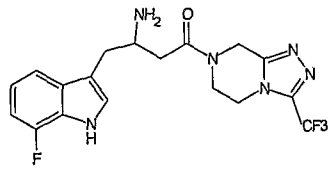
25. A compound as claimed in claim 24 wherein W is C and Y is N.

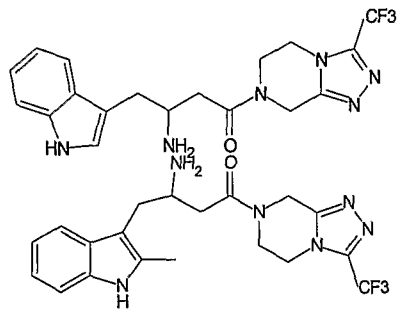
26. A compound as claimed in any of claims 20 to 25 wherein R^{23} and R^{24} are independently selected from hydrogen, trifluoromethyl, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, and carbocyclyl wherein the optional C_{1-6} alkyl, C_{1-6} alkoxy, and carbocyclyl substituents are optionally and independently substituted with one or more of halogen, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy wherein the latter alkyl and alkoxy substituents are optionally substituted with one or more halogen.

27. A compound as claimed in any one of claims 20 to 26 wherein W is C, Y is N, R^{23} is trifluoromethyl and R^{24} is absent.

28. A compound as claimed in any one preceding claim wherein the compound is selected from the following:







or a pharmaceutically acceptable salt thereof.

29. A compound as claimed in any one of the preceding claims for use as a pharmaceutical.

30. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 28 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

31. A method of treating or preventing a DPPIV-mediated disease or disorder in a subject which method comprises administering to said subject a compound as claimed in any one of claims 1 to 28 or a composition as claimed in claim 30.

32. A method as claimed in claim 31 wherein the DPPIV-mediated disease or disorder is Type II diabetes or a related disease or disorder.

33. A method as claimed in claim 32 wherein the DPPIV-mediated disease or disorder is selected from the group consisting of arthritis, obesity and osteoporosis.

34. A method as claimed in claim 32 wherein the Type II diabetes related disease or disorder is selected from the group consisting of hyperglycemia, impaired glucose tolerance, insulin resistance, obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, reduced HDL levels, excessive HDL levels, atherosclerosis and its sequelae, vascular restinosis, irritable bowel syndrome, inflammatory bowel disease including Crohn's disease and ulcerative colitis, inflammatory conditions, pancreatitis, neurodegenerative disease, depression, retinopathy, nephropathy, neuropathy, retinopathy, hypertension, Syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component.

35. Use of a compound as claimed in any one of claims 1 to 28 in the manufacture of a medicament for the treatment or prevention of a DPPIV mediated disease or disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003758

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/4985 A61P9/00

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 A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LI X G ET AL: "Chemoenzymatic preparation of the enantiomers of beta-tryptophan ethyl ester and the beta-amino nitrile analogue" TETRAHEDRON: ASYMMETRY, PERGAMON, OXFORD, GB, vol. 16, no. 9, 2 May 2005 (2005-05-02), pages 1709-1714, XP004861957 ISSN: 0957-4166 rac-5 and S-5	1-4,8-17
A	WO 2006/009886 A (MERCK & CO INC [US]; BIFTU TESFAYE [US]; FENG DANQING DENNIS [US]; GAO) 26 January 2006 (2006-01-26) the whole document	1,30,31, 35

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2008	22/01/2008

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	Diederen, Jeroen

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/003758

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

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

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

Although claims 31-34 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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/003758

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