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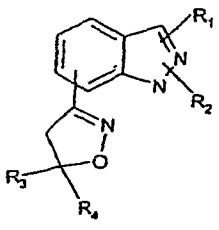
(54) Title: SUBSTITUTED INDAZOLES AS INHIBITORS OF PHOSPHODIESTERASE TYPE-IV



(Ia)

(57) Abstract: The present invention relates to isoxazoline derivatives of structure Ia, which can be used as selective inhibitors of phosphodiesterase (PDE) type IV. Compounds disclosed herein can be useful in the treatment of CNS disorders, AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS) , eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases especially in humans. Processes for the preparation of disclosed compounds are provided, as well as pharmaceutical compositions containing the disclosed compounds, and their use as phosphodiesterase (PDE) type IV inhibitors. Formula (Ia)

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SUBSTITUTED INDAZOLES AS INHIBITORS OF PHOSPHODIESTERASE TYPE-IV

Field of The Invention

The present invention relates to isoxazoline derivatives, which can be used as selective inhibitors of phosphodiesterase (PDE) type IV.

Compounds disclosed herein can be useful in the treatment of CNS disorders, AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases especially in humans.

Processes for the preparation of disclosed compounds are provided, as well as pharmaceutical compositions containing the disclosed compounds, and their use as phosphodiesterase (PDE) type IV inhibitors.

Background of the Invention

It is known that cyclic adenosine-3',5'-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger (Sutherland, *Pharmacol. Rev,* (1960), 12, 265). Its intracellular hydrolysis to adenosine 5'-monophosphate (AMP) causes number of inflammatory conditions which are not limited to psoriasis, allergic rhinitis, shock, atopic dermatitis, crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis. The most important role in the control of cAMP (as well as of cGMP) levels is played by cyclic nucleotide phosphodiesterases (PDE) which represent a biochemically and functionally, highly variable superfamily of the enzyme; eleven distinct families with more than 25 gene products are currently recognized. Although PDE I, PDE II, PDE III, PDE IV, and PDE VII all use cAMP as a substrate, only the PDE IV and PDE VII types are highly selective for hydrolysis of cAMP. Inhibitors of PDE, particularly the PDE IV inhibitors, such as rolipram or Ro-1724 are therefore known as cAMP-enhancers. Immune cells contain type IV and type III PDE, the PDE IV type being prevalent in human mononuclear cells. Thus the inhibition of

phosphodiesterase type IV has been a target for modulation and, accordingly, for therapeutic intervention in a range of disease processes.

The initial observation that xanthine derivatives, theophylline and caffeine inhibit the hydrolysis of cAMP led to the discovery of the required hydrolytic activity in the cyclic nucleotide phosphodiesterase (PDE) enzymes. More recently, distinct classes of PDEs have been recognized (Bervo, *TIPS*, (1990), 11, 150), and their selective inhibition has led to improved drug therapy (Nicholus, et al. *TIPS*, 1991, 12, 19). Thus it was recognized that inhibition of PDE IV could lead to inhibition of inflammatory mediator release (Verghese et. al., *J. Mol. Cell. Cardiol.*, 1989, 12 (Suppl.II), S 61).

WO 03/47520 discloses substituted amino methyl factor Xa inhibitors. U.S. Patent Publication No. 2003176421, and EP 1040829 disclose prokinetic agents for treating gastric hypomotility and related disorders. WO 02/50070 discloses piperidine derivatives as subtype-selective N-methyl-D-aspartate antagonists. EP 1251128 discloses cyclohexylamine derivatives as subtype-selective N-methyl-D-aspartate antagonists. WO 00/59902 discloses aryl sufonyls as factor Xa inhibitors. WO 01/19798 and WO01/19788 disclose novel compounds as factor Xa inhibitors. WO 99/23076, WO 99/23077 discloses indazole bioisostere replacement of catechol in therapeutically active compounds. WO 97/49702 and WO 98/09961 disclose indazole derivatives and their use as inhibitor of phosphodiesterase type IV and production of tumor necrosis factor (TNF). WO 97/48697 discloses substituted azabicyclo compounds and their use as inhibitors of the production of TNF and cyclic AMP phosphodiesterase. WO 99/57951, US 6,339,099 discloses guanidine mimics as factor Xa inhibitor.

Summary of the Invention

The present invention provides isoxazoline derivatives, which can be used for the treatment of, but not limited to, CNS disorders, AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma,

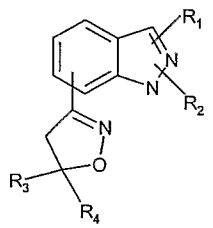
allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases, and the processes for the synthesis of these compounds.

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical compositions containing the compounds, which may also contain pharmaceutically acceptable carriers or diluents, can be used for the treatment of CNS disorders, AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome, eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases.

Other aspects will be set forth in the accompanying description which follows and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, a compound is provided having the structure of Formula Ia



Formula Ia

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein

R_1 and R_2 can be independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;

R_3 can be alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, heteroaryl, heterocyclyl, aryl, heteroarylalkyl, heterocyclylalkyl, aralkyl or carboxyalkyl; and

R_4 is cyano, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl,-$CONHNH_2$, -C(=NOH) NH_2 or carboxyalkyl

In accordance with another aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from inflammatory diseases, comprising administering to a patient in need thereof, an effective amount of a phosphodiesterase type IV inhibitors as described above.

In accordance with a further aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from CNS disorders, AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases.

In accordance with still another aspect, there are provided processes for preparing the compounds as described above.

A number of the compounds described herein were tested as phosphodiesterase type IV inhibitors. Therefore, pharmaceutical compositions for the possible treatment of diabetes and diabetes-associated complications are provided. In addition, the compounds can be administered orally or parenterally.

The following definitions apply to terms as used herein

The term *"alkyl"* unless and otherwise specified refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. Groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, n-hexyl, n-decyl, tetradecyl, and the like exemplify this term.

It may further be substituted with one or more substituents selected from the groups consisting of alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryloxy, heteroaryloxy, aminosulfonyl, -$COOR_5$ (wherein R_5 is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclylalkyl or heteroarylalkyl), -NHR_x, -NH_2, -NR_xR_y, -$C(=O)NR_xR_y$, -

$OC(=O)NR_xR_y$ (R_x and R_y are independently selected from R_5 or R_x and R_y may together join to form cycloalkyl, heteroaryl or heterocyclyl ring), nitro, $-S(O)_mR_6$ (wherein m is an integer from 0-2 and R_6 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclylalkyl, heteroarylalkyl or NR_xR_y). Unless otherwise constrained, all substituents may be further substituted by 1-3 substituents chosen from alkyl, $-COOR_5$, $-NHR_x$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, hydroxy, alkoxy, halogen, CF_3, cyano and $-S(O)_mR_6$.

Alkyl group as defined above may also be interrupted by 1-5 atoms or groups independently chosen from oxygen, sulfur and $-NR_a-$ (where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, $-COOR_5$, $-SO_2R_6$, $-C(=O)NR_xR_y$).

The term *"alkenyl"* unless and otherwise specified refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with *cis* or *trans* geometry. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy, heteroaryloxy, $-COOR_5$ (wherein R_5 is the same as defined earlier), $-NHR_x$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), azido, cyano, halogen, hydroxy, thiol, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, aminosulfonyl, alkoxyamino, nitro, $-S(O)_mR_6$ (wherein R_6 and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, $-COOR_5$, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NHR_x$, $-NH_2$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ and $-S(O)_mR_6$.

The term *"alkynyl"* unless and otherwise specified refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms.

In the event that alkynyl is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, azido, cyano, halogen, hydroxy, thiol, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, aryl, aralkyl, aryloxy, aminosulfonyl, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-COOR_5$ (wherein R_5 is the same as defined earlier), $-NHR_x$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), $-S(O)_mR_6$ (wherein R_6 and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, $-COOR_5$, hydroxy, alkoxy, halogen, $-CF_3$, $-NHR_x$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-C(=O)NR_xR_y$, cyano and $-S(O)_mR_6$.

The term *"cycloalkyl"* refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a monocyclic ring or polycyclic (fused, spiro or bridged) rings, which may optionally contain one or more olefinic bonds, unless or otherwise constrained. Such cycloalkyl groups include, by way of example, monocyclic structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, or polycyclic ring structures such as, tricyclo[3.3.1.1]decane, bicyclo[2.2.2]octane, bicyclo[4.4.0]decane, bicylco[4.3.0]nonane, bicyclo[3.3.0]octane, bicyclo [2.2.1] heptane and the like, or cyclic alkyl groups to which is fused an aryl group, for example indane, and the like.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, heteroaryloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryl, aralkyl, aryloxy, aminosulfonyl, $-COOR_5$ (wherein R_5 is the same as defined earlier), $-NHR_x$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $S(O)_mR_6$ (wherein R_6 and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, hydroxy, alkoxy, halogen, CF_3, $-NHR_x$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, cyano and $-S(O)_mR_6$.

The term *"aralkyl"* refers to aryl linked through alkyl portion and the said alkyl portion contains carbon atoms from 1-6 and aryl is the same as defined below.
The examples of aralkyl groups are benzyl and the like.

The term *"aryl"* herein refers to a carbocyclic aromatic group for example, phenyl, naphthyl or anthryl ring and the like optionally substituted with 1 to 3 substituents selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, $-COOR_5$ (wherein R_5 is the same as defined earlier), alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, heterocyclyloxy, heteroaryloxy, cycloalkyloxy, acyl, thioacyl, aryloxy, cyano, nitro, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHR_x$, $-NH_2$, $-(SO)_mR_6$ (wherein R_6, R_x, R_y and m are the same as defined earlier), aryl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl. The said aryl group may optionally be fused with cycloalkyl group, heteroaryl group or heterocyclyl group.

The term *"aryloxy"* denotes the group O-aryl wherein aryl is the same as defined above.

The term *"heteroaryl"* unless and otherwise specified refers to an aromatic monocyclic or polycyclic (fused, spiro or bridged) ring system containing 1-8 heteroatom(s) independently selected from the group consisting of N, O and S. The said heteroaryl ring is optionally substituted with 1 to 3 substituent(s) selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, aryloxy, cycloalkyloxy, acyl, thioacyl, $-COOR_5$ (wherein R_5 is the same as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro, $-NHR_x$, $-NH_2$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-S(O)_mR_6$, $-OC(=O)NR_xR_y$ (wherein m, R_6, R_x and R_y are the same as defined earlier). Unless otherwise constrained, the substituents are attached to the ring atom, be it carbon or heteroatom.

Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, carbazolyl, isobenzofuranyl, thianthrene, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, imidazolyl, tetrazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinonyl, benzothiazinonyl and the like.

The term *"heterocyclyl"* unless and otherwise specified refers to nonaromatic monocyclic or polycyclic ring (fused, spiro or bridged) system having 1 to 8 heteroatoms selected from the group consisting of O, S and N. For heterocycles containing sulphur, the oxidized sulphur heterocycles containing SO or SO_2 are also included. The said heterocyclyl ring system is optionally benzofused or fused with heteroaryl and/or are optionally substituted wherein the substituents are selected from the group consisting of halogen, hydroxy, alkyl, alkenyl,

alkynyl, cycloalkyl, acyl, thioacyl, aryl, alkoxy, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aryloxy, cyano, nitro, -$COOR_5$ (wherein R_5 is the same as defined earlier), -$C(=O)NR_xR_y$, $S(O)_mR_6$, -$OC(=O)NR_xR_y$, -NHR_x, -NH_2, -NR_xR_y (wherein m, R_x and R_y are the same as defined earlier). Unless or otherwise constrained, the substituents are attached to the ring atom, be it carbon or heteroatom. Also, unless or otherwise constrained the said heterocyclyl ring may optionally contain one or more olefinic bond(s).

Examples of heterocyclyl groups are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, piperidinyl, isoxazolinyl, thiazolinyl, thiazolidinonyl, oxazolinyl or oxazolidinonyl.

The term *"Heteroarylalkyl"* refers to heteroaryl group linked through alkyl portion, wherein the alkyl and heteroaryl are the same as defined earlier.

The term *"Heterocyclylalkyl"* refers to heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are the same as defined earlier.

The term *"acyl"* refers to –C(=O)R" wherein R" is selected from the group alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

The term *"thioacyl"* refers to –C(=S)R" wherein R" is the same as defined above;

The term *"halogen"* refers to fluorine, chlorine, bromine or iodine;

The term *"leaving group"* generally refers to groups that exhibit the desirable properties of being labile under the defined synthetic conditions and also, being easily separated from synthetic products under defined conditions. Examples of such leaving groups includes but not limited to hal (Cl, Br, I), triflate, tosylate, 4-bromophenylsulfonate, 4-nitrophenylsulfonate, mesylate and the like.

The term "*Protecting groups*" is used herein to refer to known moieties which have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also the term protecting group, unless or other specified may be used with groups such as hydroxy, amino, carboxy and examples of such groups are found in T.W.

Greene and P.G.M. Wuts, "Protective groups in organic synthesis", 2nd ED, John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting group employed is not so critical so long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed at the appropriate point without distrupting the remainder of the molecule.

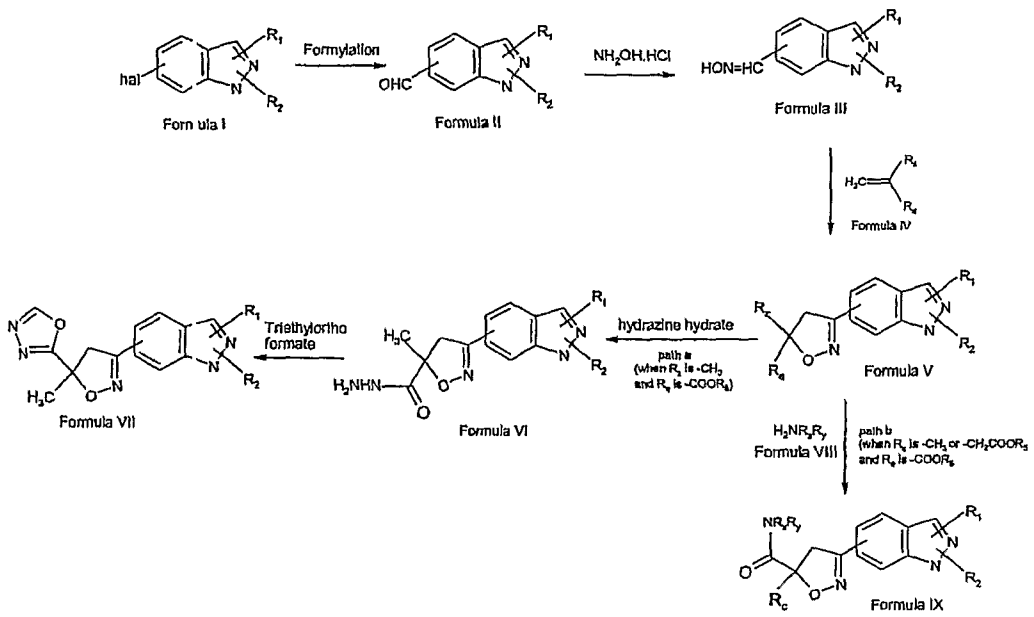
The compounds of this invention contain one or more asymmetric carbon atoms and thus occur as racemic mixtures, enantiomers and diastereomers. Some compounds may also exist as conformers/rotamers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the *R* or *S* configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are envisioned as part of the invention.

The term "*pharmaceutically acceptable salts*" refers to derivatives of compounds that can be modified by forming their corresponding acid or base salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids salts of basic residues (such as amines), or alkali or organic salts of acidic residues (such as carboxylic acids), and the like.

Detailed Description of the Invention

The compounds of the present invention may be prepared by techniques well known in the art and familiar to a practitioner skilled in art of this invention. In addition, the compounds of the present invention may be prepared, for example, by processes described herein, although such processes are not the only means by which the compounds may be synthesised. Further, the various synthetic steps described herein may be performed in an alternate sequence in order to give the desired compounds.

Scheme I



The compounds of Formulae V, VI, VII and IX can be prepared, for example, by following the procedure as described in Scheme I. Thus a compound of Formula I (wherein hal is Br, Cl or I; R_1 and R_2 are the same as described earlier) can undergo formylation reaction to give a compound of Formula II, which on reaction with hydroxylamine hydrochloride can give a compound of Formula III, which can be reacted with a compound of Formula IV [wherein R_z is alkyl or $-CH_2COOR_5$; R_q is –CN or $-COOR_5$ (wherein R_5 is the same as defined earlier)] to give a compound of Formula V,

path *a*: the compound of Formula V can be reacted with hydrazine hydrate (when R_z is $-CH_3$ and R_q is $-COOR_5$) to give a compound of Formula VI, which can be reacted with triethyl orthoformate to give a compound of Formula VII, or

Path *b*: the compound of Formula V can be reacted with a compound of Formula VIII (wherein R_x and R_y are the same as defined earlier) to give a compound of Formula IX (wherein R_c is $-CH_3$ or $-CH_2CONR_xR_y$).

The formylation of a compound of Formula I give a compound of Formula II can be carried out with a formylating agent for example, dimethylformamide, triformamide, tris (diformylamino)methane, tris(dichloromethyl)amine or N,N,N,N-tetraformyl hydrazine in the

presence of a base for example, butyl lithium in an organic solvent for example, tetrahydrofuran, dioxane or diethylether. The reaction of a compound of Formula II with hydroxylamine hydrochloride to give a compound of Formula III can be carried out in an organic solvent for example, ethanol, methanol, propanol or isopropylalcohol in the presence of a base for example, sodium acetate, sodium carbonate, ammonium acetate or potassium carbonate.

The compound of Formula V can be reacted with hydrazine hydrate (path *a*, when R_z is $-CH_3$ and R_q $-CH_2COOR_5$) to give a compound of Formula VI.

The compound of Formula VI can be reacted with triethyl orthoformate to give a compound of Formula IX.

The compound of Formula V can be reacted with a compound of Formula VIII (path b) to give a compound of Formula IX.

Particular illustrative compounds which can be prepared following Scheme I include:

3-(1-Cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 1),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 2),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 3),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 4)

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 5)

1-Cyclopentyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 6)

1-Cyclopentyl-3-methyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 7)

1-Cyclopentyl-3-ethyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 8),

3-(1-Cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 16),

Methyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 41),

Methyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 44),

Methyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 46),

Methyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 49),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*,5-dimethyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 51),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 52),

3-(1-Cyclopentyl-3-methyl-1H-indazol-6-yl)-N-cyclopropyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 53),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*-methyl-5-[2-(methylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 54),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-[2-oxo-2-(propylamino)ethyl]-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 55),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 56),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*,5-dimethyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 57),

2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]-*N*-propylacetamide (Compound No. 58),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 59),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-methyl-5-[2-(methylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 60),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-[2-oxo-2-(propylamino)ethyl]-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 61),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 62),

Methyl 3-(3-ethyl-1-methyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 63),

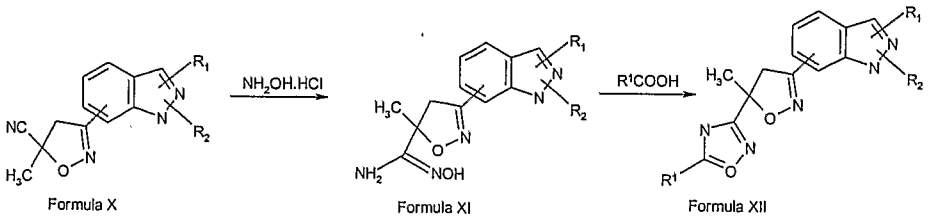
Methyl 3-(1,3-dimethyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 64),

Methyl 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 65),

Methyl 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 66), and

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 67).

Scheme II



The compounds of Formula XI and XII can be prepared by, for example, procedures as depicted in Scheme II. Thus a compound of Formula X (wherein R_1 and R_2 are the same as defined earlier) can be reacted with hydroxylamine hydrochloride to give a compound of Formula XI, which can be reacted with a compound of Formula R^1COOH (wherein R^1 is aryl, cycloalkyl or heteroaryl) to give a compound of Formula XII.

The compound of Formula X can be reacted with hydroxylamine hydrochloride to give a compound of Formula XI in an organic solvent, for example, ethanol, methanol, propanol or isopropyl alcohol, in the presence of a base, for example, potassium carbonate, sodium carbonate or lithium carbonate.

The compound of Formula XI can be reacted with a compound of Formula R^1COOH to give a compound of Formula XII in an organic solvent, for example, dimethylformamide, tetrahydrofuran, diethylether or dioxane, in the presence of a base, for example N-methylmorpholine, pyridine, diisopropylethylamine, 1,8-diazabicyclo [5,4,0]-undec-7-ene or 1,4-diazabicyclo[2,2,2]octane, with a coupling agent, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI.HCl) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Particular illustrative compounds which can be prepared following Scheme II include:

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*'-hydroxy-5-methyl-4,5-dihydroisoxazole-5-carboximidamide (Compound No. 9),

1-Cyclopentyl-6-{5-[5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1H-indazole (Compound No. 10),

6-{5-[5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-ethyl-1*H*-indazole (Compound No. 11),

1-Cyclopentyl-3-ethyl-6-[5-methyl-5-(5-pyridin-3-yl-1,2,4-oxadiazol-3-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 12),

1-Cyclopentyl-3-ethyl-6-{5-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1*H*-indazole (Compound No. 13),

1-Cyclopentyl-6-{5-[5-(3,4-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 14),

1-Cyclopentyl-6-{5-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 15),

1-Cyclopentyl-6-{5-[5-(3,5-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 35),

1-Cyclopentyl-6-{5-[5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole,

1-Cyclopentyl-6-{5-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 37),

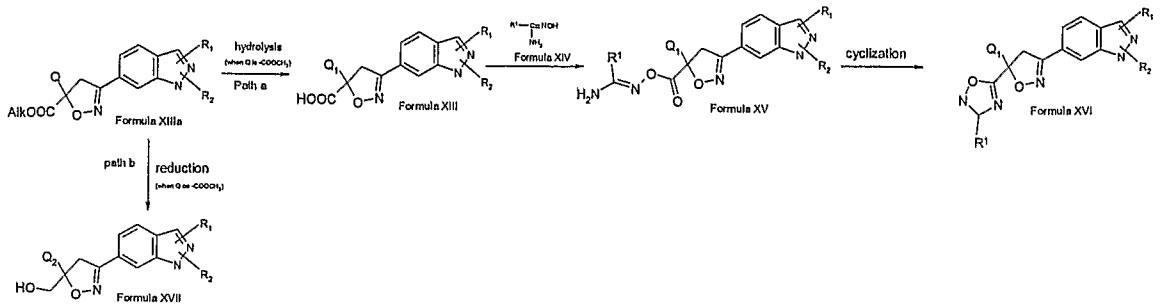
6-{5-[5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-methyl-1*H*-indazole (Compound No. 38),

1-Cyclopentyl-6-{5-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 39),

1-Cyclopentyl-3-methyl-6-[5-methyl-5-(5-pyridin-4-yl-1,2,4-oxadiazol-3-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 40), and

1-Cyclopentyl-6-{5-[5-(2,6-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 68).

Scheme III



The compounds of Formula XIII, XVI and XVII can be prepared, for example, by following procedures as depicted in Scheme III. Thus, a compound of Formula XIIIa (wherein Alk is alkyl; Q=CH_3, -$CH_2CO_2CH_3$) can undergo hydrolysis (path a) to give a compound of Formula XIII (where R_1 and R_2 are the same as depicted earlier; Q_1=CH_3, -CH_2CO_2H), which can be reacted with a compound of Formula XIV (wherein R^1 is the same as defined earlier) to give a compound of Formula XV, which can undergo cyclisation to give a compound of Formula XVI. The compound of Formula XIIIa can undergo reduction (path b) to give a compound of Formula XVII (Q_2=CH_3, -CH_2CH_2OH).

The hydrolysis of a compound of Formula XIIIa to give a compound of Formula XIII can be carried out in an organic solvent, for example, tetrahydrofuran, dimethylformamide, diethylether or dioxane, in the presence of a base, for example, lithium hydroxide, potassium hydroxide or sodium hydroxide.

The reaction of a compound of Formula XIII with a compound of Formula XIV to give a compound of Formula XV can be carried out in an organic solvent, for example, dimethylformamide, tetrahydrofuran, diethylether or dioxane, in the presence of a base for example, N-methylmorpholine, diisopropylethylamine, pyridine or triethylamine, with a condensing agent, for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI.HCl) or dicyclohexylcarbodiimide (DCC).

The compound of Formula XV can undergo ring cyclisation to give a compound of Formula XVI in an organic solvent, for example, ethanol, methanol, propanol or isopropylalcohol, in the presence of buffer, for example, sodium acetate or potassium acetate or ammonium formate.

The reduction of a compound of Formula XIIIa to give a compound of Formula XVII can be carried out in an organic solvent, for example, tetrahydrofuran, dimethylformamide, diethylether or dioxane, with reducing agent, for example, sodium borohydride or sodium triacetoxyborohydride, in the presence of protic solvent, for example, methanol, ethanol or isopropylalcohol.

Some particular illustrative the compounds which may be prepared following Scheme III include:

6-{5-[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-methyl-1*H*-indazole (Compound No. 17),

1-Cyclopentyl-6-{5-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 18),

1-Cyclopentyl-6-{5-[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 19),

1-Cyclopentyl-6-{5-[3-(2,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 20),

1-Cyclopentyl-6-{5-[3-(2,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 21),

1-Cyclopentyl-6-{5-[3-(2,5-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 22),

1-Cyclopentyl-6-{5-[3-(2,5-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 23),

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 24),

1-Cyclopentyl-6-{5-[3-(2,3-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 25),

6-{5-[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-ethyl-1*H*-indazole (Compound No. 26),

1-Cyclopentyl-6-{5-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 27),

1-Cyclopentyl-6-{5-[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 28),

1-Cyclopentyl-6-{5-[3-(2,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 29),

1-Cyclopentyl-6-{5-[3-(2,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 30),

1-Cyclopentyl-6-{5-[3-(2,5-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 31),

1-Cyclopentyl-6-{5-[3-(2,5-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 32),

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 33),

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 34),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 42),

[3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (Compound No. 43),

5-(Carboxymethyl)-3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 45),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 47),

[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (Compound No. 48),

5-(Carboxymethyl)-3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 50), and

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs.

In the above schemes, where specific bases, solvents, condensing agents, etc. are mentioned, it is to be understood that other acids, bases, solvents, condensing agents, hydrolyzing agents, etc, known to those skilled in an art may also be used. Similarly, the reaction temperature and duration of the reactions may be adjusted according to desired needs.

Where desired, the compounds of Formula Ia and/ or their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, prodrugs, metabolites, polymorphs or N-oxides may be advantageously used in combination with one or more other therapeutic agents. Examples of other therapeutic agents, which may be used in combination with compounds of Formula Ia of this invention and/ or their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, prodrugs, metabolites, polymorphs or N-oxides include corticosteroids, beta agonists, leukotriene antagonists, 5-lipoxygenase inhibitors, chemokine inhibitors and muscarinic receptor antagonists.

Because of their valuable pharmacological properties, the compounds described herein may be administered to an animal for treatment orally, or by a parenteral route. The pharmaceutical compositions described herein can be produced and administered in dosage units, each unit containing a certain amount of at least one compound described herein and/or at least one physiologically acceptable addition salt thereof. The dosage may be varied over extremely wide limits, as the compounds are effective at low dosage levels and relatively free

of toxicity. The compounds may be administered in the low micromolar concentration, which is therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

The compounds described herein can be produced and formulated as their racemic mixtures, enantiomers, diastereomers, rotamers, N-oxides, polymorphs, solvates and pharmaceutically acceptable salts, as well as the active metabolites. Pharmaceutical compositions comprising the molecules of Formula Ia or metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable carrier and optionally included excipient can also be produced.

The examples mentioned below demonstrate general synthetic procedures, as well as specific preparations of particular compounds. The examples are provided to illustrate the details of the invention and should not be constrained to limit the scope of the present invention.

Examples

Synthesis of 6-bromo-1-cyclopentyl-1H-indazole, 6-bromo-1-cyclopentyl-3-methyl-1H-indazole and 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole

The title compounds were prepared following the procedure as described in US 6,262,040 or Synthesis, 1999, 4, 588-592)

Example 1: 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 1)

Step a: 1-Cyclopentyl-1H-indazole-6-carboxaldehyde

A solution of the compound 6-bromo-1-cyclopentyl-1H-indazole (1.19 g, 4.15 mmol) in dry tetrahydrofuran (10 ml) was stirred at -78°C for 15 minutes followed by the addition of butyl lithium (0.532 g, 8.3 mmol). The reaction mixture was again stirred for 30 minutes at -78°C followed by the dropwise addition of dimethylformamide (1.212 g, 16.6 mmol). The reaction mixture was stirred for 30 minutes at the same temperature followed by stirring it at

room temperature for 1 hour. The reaction mixture was quenched with hydrochloric acid (1N) and extracted the compound with ethyl acetate and water. The organic layer was collected, washed with brine and dried over anhydrous sodium sulphate. The mixture was filtered and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield: 465 mg.

Mass (m/z): 215 (M^++1). ^{1}H NMR ($CDCl_3$):δ 10.07 (1H, s), 8.23 (1H, s), 8.03 (1H, s), 7.7 (1H, d), 7.62 (1H, d), 5.00 (1H, m), 2.3-1.2 (m, 8H).

Step b: 1-Cyclopentyl-1H-indazole-6-carboxaldehyde oxime

To a compound obtained from step *a* above (240 mg, 1.121 mmol) was added hydroxylamine hydrochloride (311.7 mg, 4.48 mmol) and sodium acetate (367 mg, 4.48 mmol) and ethanol (10 ml). The reaction mixture was stirred for 18 hours. The solvent was evaporated under reduced pressure and extracted the compound with ethyl acetate. The organic layer was collected, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate in hexane solvent mixture as eluent to furnish the title compound. Yield: 260 mg.

Mass (m/z): 230.13 (M^++1). ^{1}H NMR ($CDCl_3$):δ 8.28 (s, 1H), 7.99 (s, 1H), 7.71-7.70 (d, 1H), 7.61 (s, 1H), 7.45-7.42 (dd, 1H), 5.05-4.98 (m, 1H), 2.2-1.75 (m, 8H).

Step c: 3-(1-Cyclopentyl-1H-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile

To a mixture of compound obtained from step *b* above (50 mg, 0.218 mmol) and methylacrylonitrile (29.3 mg, 0.436 mmol) was added tetrahydrofuran (5 ml) and stirred the reaction mixture for 10 minutes at room temperature. To the resulting reaction mixture was added sodium hypochlorite (3 ml) with vigorous stirring, which was continued for 15 hours. The solvent was evaporated under reduced pressure and extracted the compound with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound. The residue thus obtained was purified by column chromatography using ethylacetate in hexane solvent mixture as eluent to furnish the title compound. Yield: 65 mg.

Mass (m/z): 295.10 (M^++1).

^{1}H NMR ($CDCl_3$):δ 8.02 (1H, s), 7.77 (2H, dd), 7.45 (1H, d), 5.05 (1H, m), 3.99 (1H, d), 3.55 (1H, d), 2.22 (3H, m), 2.05-1.57 (8H, m).

The following compounds were prepared analogously,

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 2)

Mass (m/z): 309.30 (M^++1).

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 3)

Mass (m/z): 323.30 (M^++1).

Methyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 41)

Mass (m/z): 342 (M^++1).

Methyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 44)

Mass (m/z): 400 (M^++1).

Methyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 46)

Mass (m/z): 356.1 (M^++1).

Methyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 49)

Mass (m/z): 414.1 (M^++1).

Methyl 3-(3-ethyl-1-methyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 63)

Mass (m/z): 360.1 (M^++1).

Methyl 3-(1,3-dimethyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 64)

Mass (m/z): 346.1 (M^++1).

Methyl 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 65)

Mass (m/z): 329.00 (M^++1).

Methyl 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 66).

Mass (m/z): 386.1 (M^++1).

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 67).

Mass (m/z): 323.1(M^++1).

Scheme I, Formula VI, Path a:

Example 2: Synthesis of 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 16)

To the compound no. 65 (122 mg, 0.317 mmol) was added hydrazine hydrate (117.16 mg, 2.3 mmol) and refluxed the reaction mixture for 4 hours at 80-85°C. The reaction mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate, filtered and dried under reduced pressure to furnish the title compound.

Yield: 85 mg.

The following compounds were prepared analogously,

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 4)

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 5)

Example 3: Synthesis of 1-cyclopentyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 6)

To the compound no. 16 (85 mg, 0.259 mmol) was added triethyl orthoformate (0.275 g, 1.85 mmol) and stirred the reaction mixture for 3 hours at 120-125°C. Excess of triethyl orthoformate was evaporated under reduced pressure under inert atmosphere. Residual mixture was again stirred for 12 hours stirred for at 140-145°C and subsequently extracted the compound with ethyl acetate. The organic extracts were collected, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using ethylacetate in hexane solvent mixture was eluent to furnish the title compound. Yield: 70 mg.

Mass (m/z): 338 (M^++1). ^{1}H NMR ($CDCl_3$):δ 8.46 (1H, s), 8.02 (1H, s), 7.76 (2H, d), 7.74 (1H, d), 5.03 (1H, m), 4.41 (1H, d), 3.61 (1H, d), 2.20-1.59 (8H, m), 1.37 (3H, s).

The following compound were prepared analogously,

1-Cyclopentyl-3-methyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 7)

Mass (m/z): 352.30 (M^++1).

1-Cyclopentyl-3-ethyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 8)

Mass (m/z): 366.30 (M^++1).

Example 4: Synthesis of 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*,5-dimethyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 51)

A solution of the Compound No. 41 (0.146mmol) and methylamine (1.0ml) was refluxed for 10 hours at 55-60°C. The mixture was cooled to room temperature and washed with hexane. The solid thus separated was diluted with chloroform and purified by preparative column chromatography using 10% methanol in dichloromethane to furnish the title compound. Yield: 0.024 g

^{1}H NMR ($CDCl_3$):δ 7.65 (1H, d), 7.56 (1H, s), 7.45 (1H, d), 6.93 (1H, b), 4.90 (1H, m), 3.97-3.93 (1H, dd), 3.35-3.31 (1H, dd), 2.85 (3H, d), 2.57 (3H, s), 2.16-1.71 (11H, m).

The following compound were prepared analogously,

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 52)

Mass (m/z): 369.1 (M^++1).

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 53)

Mass (m/z): 367.1 (M^++1).

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*-methyl-5-[2-(methylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 54)

^{1}H NMR ($CDCl_3$):δ 7.64 (1H, d), 7.54 (1H, s), 7.45 (1H, d), 6.97 (1H, b), 6.19 (1H, bs), 4.89 (1H, m), 3.84 (2H, s), 3.00-2.80 (5H, dd), 2.57 (3H, s), 2.17-1.73 (8H, m), 1.57 (3H, bs).

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-[2-oxo-2-(propylamino)ethyl]-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 55)

Mass (m/z): 454.2 (M^++1).

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 56)

^{1}H NMR ($CDCl_3$):δ 7.65 (1H, d), 7.53 (1H, s), 7.46 (1H, d), 6.94 (1H, bs), 6.24 (1H, bs), 4.92 (1H, m), 3.82 (2H, s), 2.89 (2H, d), 2.80-2.60 (2H, m), 2.57 (3H, s), 2.16-1.73 (8H, m), 1.59 (3H, bs), 0.81-0.73 (4H, m), 0.56-0.50 (4H, m).

3-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-N,5-dimethyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 57)

Mass (m/z): 355.1 (M^++1).

2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]-*N*-propylacetamide (Compound No. 58)

Mass (m/z): 383.1 (M^++1).

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 59)

Mass (m/z): 380.1 (M^++1).

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-methyl-5-[2-(methylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 60)

Mass (m/z): 412.1 (M^++1).

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-[2-oxo-2-(propylamino)ethyl]-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 61)

Mass (m/z): 468.2 (M^++1).

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 62)

Mass (m/z): 464.1 (M^++1).

Example 5: Synthesis of 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*'-hydroxy-5-methyl-4,5-dihydroisoxazole-5-carboximidamide (Compound No. 9)

To Compound No. 3 (1.5 g, 4.8 mmol) was added hydroxylamine hydrochloride (1.33 g, 19.2 mmol) and potassium carbonate (1.99 g, 14.4 mmol) followed by the addition of ethanol (15 ml) and refluxed the reaction mixture for 24 hours at 80-90°C. The solvent was evaporated under reduced pressure and extracted the product with ethyl acetate. The organic extracts were collected, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure and the residue thus obtained was purified by column chromatography using ethyl acetate in hexane solvent mixture as eluent to furnish the title compound. Yield: 920mg.

Mass (m/z): 356.3 (M^++1).

Example 6: Synthesis of 1-cyclopentyl-6-{5-[5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1H-indazole (Compound No. 10)

To a mixture of compound No. 9 (100 mg, 0.282 mmol) and 3,5-dimethoxybenzoic acid (56 mg, 0.309 mmol) was added dimethylformamide (5 ml) and cooled the reaction mixture to 0°C. To it was added hydroxybenzotriazole (38 mg, 0.282 mmol) and N-methylmorpholine (0.113 g, 1.128 mmol) followed by the addition 1-(3-dimethylamino propyl)-3-ethylcarbodiimide hydrochloride (0.108 g, 0.564 mmol). The resulting reaction mixture was stirred for 18 hours. It was diluted with water and extracted with ethyl acetate. The organic extracts were collected, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. To the residue thus obtained was added dimethylformamide (2 ml) and refluxed the reaction mixture for 20 hours. Dimethyl formamide was evaporated under reduced pressure and extracted the compound with ethyl acetate. The organic extracts were collected, dried over anhydrous sodium sulphate, filtered and dried under reduced pressure. The residue thus obtained was purified by preparative column chromatography to furnish the title compound. Yield: 70 mg.

Mass (m/z): 502.2 (M^++1). ^{1}H NMR ($CDCl_3$):δ 7.71 (2H, d), 7.50 (1H, d), 7.28 (4H, d), 4.95 (1H, m), 4.27 (1H, d), 3.86 (6H, s), 3.5 (1H, d), 2.97 (2H, q), 2.17 (3H, s), 2.01-1.73 (8H, m), 1.37 (3H, t).

The following compounds were prepared analogously,

6-{5-[5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-ethyl-1*H*-indazole (Compound No. 11)

Mass (m/z): 476.2 (M^++1). m.p: 154-155°C.

1-Cyclopentyl-3-ethyl-6-[5-methyl-5-(5-pyridin-3-yl-1,2,4-oxadiazol-3-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 12)

Mass (m/z): 443.10 (M^++1). m.p: 161-168°C.

1-Cyclopentyl-3-ethyl-6-{5-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1*H*-indazole (Compound No. 13)

Mass (m/z): 460.10 (M^++1). m.p: 87-88°C.

1-Cyclopentyl-6-{5-[5-(3,4-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 14)

Mass (m/z): 478.1 (M^++1).

1-Cyclopentyl-6-{5-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 15)

Mass (m/z): 502.2 (M^++1).

1-Cyclopentyl-6-{5-[5-(3,5-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 35)

Mass (m/z): 464.1 (M^++1).

1-Cyclopentyl-6-{5-[5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 36)

Mass (m/z): 488.1 (M^++1).

1-Cyclopentyl-6-{5-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 37)

Mass (m/z): 446.1 (M^++1).

6-{5-[5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-methyl-1*H*-indazole (Compound No. 38)

Mass (m/z): 462 (M^++1).

1-Cyclopentyl-6-{5-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 39)

Mass (m/z): 446.1 (M^++1).

1-Cyclopentyl-3-methyl-6-[5-methyl-5-(5-pyridin-4-yl-1,2,4-oxadiazol-3-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 40)

Mass (m/z): 429 (M^++1).

1-Cyclopentyl-6-{5-[5-(2,6-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 68)

Mass (m/z): 478.1 (M^++1).

Example 7: Synthesis of 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 47)

To a solution of compound No. 46 (0.050g, 0.140 mmol) in tetrahydrofuran, lithium hydroxide (0.015g, 0.352 mmol) was added and refluxed at 55-60°C for overnight. The reaction mixture was cooled and water (15 ml) was added. The aqueous layer was washed with ethyl acetate (5 ml). The aqueous layer was acidified and extracted with ethyl acetate. The organic extracts were collected, dried over anhydrous sodium sulphate, filtered and dried under reduced pressure. The residue thus obtained was purified by preparative column chromatography to furnish the title compound. Yield: 0.025g

Mass (m/z): 342 (M^++1).

Following compound were prepared analogously,

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 42)

Mass (m/z): 328 (M^++1).

5-(Carboxymethyl)-3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 45)

5-(Carboxymethyl)-3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 50)

Mass (m/z): 386 (M^++1).

Example 8: Synthesis of 6-{5-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-ethyl-1*H*-indazole (Compound No. 26)

Step a: Synthesis of 2-chloro-*N*'-({[3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]carbonyl}oxy)benzenecarboximidamide

A solution of the Compound No. 47 (0.100g, 0.294 mmol) and 2-chloro-N-hydroxy benzamidine (0.055g, 0.323 mmol) in dimethylformamide (5ml) was cooled at 0°C and stirred for 15 minutes followed by the addition of hydroxybenzotriazole (0.040g, 0.294 mmol) and N-methylmorpholine (0.0118g, 1.168 mmol) at the same temperature. The resulting reaction mixture was stirred for 1 hour followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.113g, 0.589 mmol). The reaction mixture was stirred for 18 hours at room temperature. The mixture was extracted with ethylacetate and water. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish the title compound. Yield: 115mg.

Step b: 6-{5-[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-ethyl-1*H*-indazole (Compound No. 26)

To a solution of the compound obtained from step *a* above (0.110g, 0.222 mmol) in ethanol (6ml), water (1.0 mL) and sodium acetate (0.036g, 0.444 mmol) were added. The reaction mixture was refluxed at 90°C for 16 hours. Solvent was evaporated under reduced pressure and the residue thus obtained was diluted with water. The solid thus separated was washed with water and dried under reduced pressure.

Yield: 0.030g. Mass (m/z): 476 (M^++1).

The compounds described below were prepared analogously,

6-{5-[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-methyl-1*H*-indazole (Compound No. 17)

Mass (m/z): 462 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 18)

Mass (m/z): 464 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 19)

Mass (m/z): 464 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 20)

Mass (m/z): 488 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1H-indazole (Compound No. 21)

Mass (m/z): 488 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,5-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 22)

Mass (m/z): 496 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,5-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 23)

Mass (m/z): 464 (M^++1).

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 24)

Mass (m/z): 464 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,3-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 25)

Mass (m/z): 488 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 27)

Mass (m/z): 478.1 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 28)

Mass (m/z): 478.1 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 29)

Mass (m/z): 502.1 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 30)

Mass (m/z): 502 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,5-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 31)

Mass (m/z): 510 (M^++1).

1-Cyclopentyl-6-{5-[3-(2,5-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 32)

Mass (m/z): 478.1 (M^++1).

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 33)

Mass (m/z): 478.1 (M^++1).

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 34)

Mass (m/z): 502.1 (M^++1).

Example 8: Synthesis of [3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (Compound No. 48)

To a solution of compound No. 46 (0.050g, 0.140 mmol) in tetrahydrofuran, sodium borohydride (0.013, 0.352 mmol) were added at 0-5°C. The reaction mixture was stirred at room temperature for 6 h. Excess of sodium borohydride was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish the title compound. Yield: 0.024g. Mass (m/z): 328.1 (M^++1).

The following compound was prepared analogously,

[3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (Compound No. 43)

Mass (m/z): 314 (M^++1).

Efficacy of Compounds as PDE IV Inhibitors

PDE-IV Enzyme Assay:

The efficacy of compounds as PDE-4 inhibitor was determined by an enzyme assay (Burnouf et al; J. Med. Chem. 2000, 43:4850-4867). The PDE-4 enzyme source used was U937 cell cytosolic fraction prepared by sonication. The enzyme reaction was carried out, with the cytosolic fraction as the enzyme source, in the presence of cAMP (1 μM) at 30°C in the presence or absence of NCE for 45 -60 min. An aliquot of this reaction mixture was taken further for the ELISA assay to determine level of cAMP in the sample. The concentration of the cAMP in the sample directly correlates with the degree of PDE-4 enzyme inhibition. Results were expressed as percent control and the IC_{50} values of compounds 1-3, 6-8, 10-15 and 17-36 were found to be in the range of between about 0.1 nm to about 10,000 nM, for example, from about 0.1nM to about 1000 nM, for example, from about o.1 nM to about 500 nM, for example, from about 0.1 nM to about 200 nM, or for example, from about 0.1nM to about 25nM.

The standard compound, (n=7) rolipram, had activity of about 460nM in the PDE-4 assay.

Cell based Assay for TNF-α release

Method of isolation of Human Peripheral Blood Mononuclear Cells:

Human whole blood was collected in vacutainer tubes containing heparin or EDTA as an anti coagulant. The blood was diluted (1:1) in sterile phosphate buffered saline and 10 ml. was carefully layered over 5 ml Ficoll Hypaque gradient (density 1.077 g/ml) in a 15 ml conical centrifuge tube. The sample was centrifuged at 3000 rpm for 25 minutes in a swing-out rotor at room temperature. After centrifugation, interface of cells were collected, diluted at least 1:5 with PBS and washed three times by centrifugation at 2500 rpm for 10 minutes at

room temperature. The cells were resuspended in serum free RPMI 1640 medium at a concentration of 2 million cells/ml. Alternatively whole blood was used.

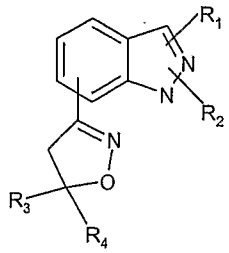
LPS stimulation of Human PBMNC's :

PBMN cells (0.1 ml; 2 million/ml) were co-incubated with 20 µl of compound (final DMSO concentration of 0.2 %) for 10 min in a flat bottom 96 well microtiter plate. Compounds were dissolved in DMSO initially and diluted in medium for a final concentration of 0.2 % DMSO. LPS (1 µg/ml, final concentration) was then added at a volume of 10 µl per well. After 30 min, 20 µl of fetal calf serum (final concentration of 10 %) was added to each well. Cultures were incubated overnight at 37 °C in an atmosphere of 5 % CO_2 and 95 % air. Supernatant were then removed and tested by ELISA for TNF-α release using a commercial kit (e.g. BD Biosciences). For whole blood, the plasma samples were diluted 1:20 for ELISA. The level of TNF-α in treated wells was compared with the vehicle treated controls and inhibitory potency of compound was expressed as IC_{50} values calculated by using Graph pad prism.

Compounds 2, 3, 23, 31 and 32 were tested by the TNF assay, giving IC_{50} from about 4.2 µM to about 10 µM, or from about 4.2 µM to about 8.0µM, or from 4.2 µM to about 4.9 µM, as compared to the standard (M=6) rolipram (1.2 µM).

We claim:

1. A compound having the structure of Formula Ia



Formula Ia

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein

$\mathbf{R_1}$ and $\mathbf{R_2}$ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;

$\mathbf{R_3}$ is alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, heteroaryl, heterocyclyl, aryl, heteroarylalkyl, heterocyclylalkyl, aralkyl or carboxyalkyl; and

$\mathbf{R_4}$ is cyano, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, -CONHNH$_2$, -C(=NOH)NH$_2$ or carboxyalkyl.

2. A compound selected from:

3-(1-Cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 1),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 2),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 3),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 4)

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 5)

1-Cyclopentyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 6)

1-Cyclopentyl-3-methyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 7)

1-Cyclopentyl-3-ethyl-6-[5-methyl-5-(1,3,4-oxadiazol-2-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 8),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*'-hydroxy-5-methyl-4,5-dihydroisoxazole-5-carboximidamide (Compound No. 9),

1-Cyclopentyl-6-{5-[5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1H-indazole (Compound No. 10),

6-{5-[5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-ethyl-1*H*-indazole (Compound No. 11),

1-Cyclopentyl-3-ethyl-6-[5-methyl-5-(5-pyridin-3-yl-1,2,4-oxadiazol-3-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 12),

1-Cyclopentyl-3-ethyl-6-{5-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1*H*-indazole (Compound No. 13),

1-Cyclopentyl-6-{5-[5-(3,4-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 14),

1-Cyclopentyl-6-{5-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 15),

3-(1-Cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carbohydrazide (Compound No. 16),

6-{5-[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-methyl-1*H*-indazole (Compound No. 17),

1-Cyclopentyl-6-{5-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 18),

1-Cyclopentyl-6-{5-[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 19),

1-Cyclopentyl-6-{5-[3-(2,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 20),

1-Cyclopentyl-6-{5-[3-(2,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 21),

1-Cyclopentyl-6-{5-[3-(2,5-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 22),

1-Cyclopentyl-6-{5-[3-(2,5-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 23),

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 24),

1-Cyclopentyl-6-{5-[3-(2,3-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 25),

6-{5-[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-ethyl-1*H*-indazole (Compound No. 26),

1-Cyclopentyl-6-{5-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 27),

1-Cyclopentyl-6-{5-[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 28),

1-Cyclopentyl-6-{5-[3-(2,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 29),

1-Cyclopentyl-6-{5-[3-(2,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 30),

1-Cyclopentyl-6-{5-[3-(2,5-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 31),

1-Cyclopentyl-6-{5-[3-(2,5-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 32),

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 33),

1-Cyclopentyl-6-{5-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 34),

1-Cyclopentyl-6-{5-[5-(3,5-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 35),

1-Cyclopentyl-6-{5-[5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole(Compound No. 36)

1-Cyclopentyl-6-{5-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 37),

6-{5-[5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-1-cyclopentyl-3-methyl-1*H*-indazole (Compound No. 38),

1-Cyclopentyl-6-{5-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3-methyl-1*H*-indazole (Compound No. 39),

1-Cyclopentyl-3-methyl-6-[5-methyl-5-(5-pyridin-4-yl-1,2,4-oxadiazol-3-yl)-4,5-dihydroisoxazol-3-yl]-1*H*-indazole (Compound No. 40),

Methyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 41),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 42),

[3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (Compound No. 43),

Methyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 44),

5-(Carboxymethyl)-3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 45),

Methyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 46),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 47),

[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (Compound No. 48),

Methyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 49),

5-(Carboxymethyl)-3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 50),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*,5-dimethyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 51),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-methyl-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 52),

3-(1-Cyclopentyl-3-methyl-1H-indazol-6-yl)-N-cyclopropyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 53),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*-methyl-5-[2-(methylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 54),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-[2-oxo-2-(propylamino)ethyl]-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 55),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 56),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*,5-dimethyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 57),

2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazol-5-yl]-*N*-propylacetamide (Compound No. 58),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 59),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-methyl-5-[2-(methylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 60),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-[2-oxo-2-(propylamino)ethyl]-*N*-propyl-4,5-dihydroisoxazole-5-carboxamide (Compound No. 61),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-*N*-cyclopropyl-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 62),

Methyl 3-(3-ethyl-1-methyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 63),

Methyl 3-(1,3-dimethyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 64),

Methyl 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 65),

Methyl 3-(1-cyclopentyl-1*H*-indazol-6-yl)-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 66),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 67).

136 1-Cyclopentyl-6-{5-[5-(2,6-difluorophenyl)-1,2,4-oxadiazol-3-yl]-5-methyl-4,5-
137 dihydroisoxazol-3-yl}-3-ethyl-1*H*-indazole (Compound No. 68).

1 3. A pharmaceutical composition comprising a therapeutically effective amount of a
2 compound of claim 1 together with a pharmaceutically acceptable carrier, excipient or diluent.

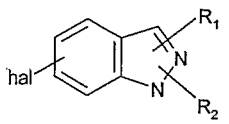
1 4. A method of treatment of CNS disorders, AIDS, asthma, arthritis, bronchitis, chronic
2 obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis,
3 Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma,
4 allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases
5 especially in or a human suffering therefrom comprising administering to said animal or
6 human a therapeutically effective amount of a compound according to claim 1.

1 5. A method of preventing, inhibiting or suppressing inflammatory condition in an
2 animal or human comprising administering to said animal or human a therapeutically
3 effective amount of a compound according to claim 1.

1 6. A method of preventing, inhibiting or suppressing inflammatory disease in an animal
2 or human comprising administering to said animal or human a therapeutically effective
3 amount of the pharmaceutical composition according to claim 3.

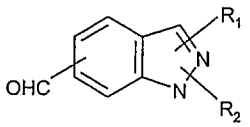
1 7. A method for preparing a compound of FormulaVII and its pharmaceutically
2 acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-
3 oxides wherein the method comprises:

4 a. formylating a compound of Formula I



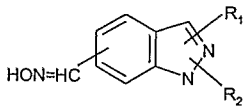
5 Formula I

6 to give a compound of Formula II;



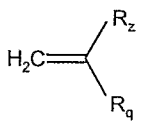
Formula II

b. reacting a compound of Formula II with $NH_2OH.HCl$ to give a compound of Formula III;



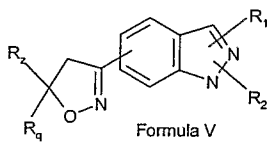
Formula III

c. reacting compound of Formula III with a compound of Formula IV



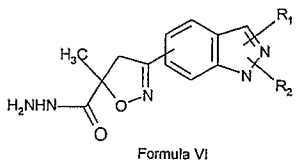
Formula IV

to give a compound of Formula V;



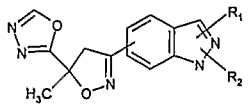
Formula V

d. reacting a compound of Formula V with hydrazine hydrate (when R_z is $-CH_3$ and R_q is $-COOR_5$) to give a compound of Formula VI; and



Formula VI

e. reacting a compound of Formula VI with triethyl orthoformate to give a compound of Formula VII,



Formula VII

wherein

R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;

R_z is alkyl or $-CH_2COOR_5$;

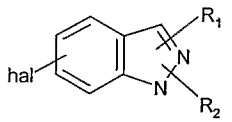
R_q is –CN or $–COOR_5$;

R_5 is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclylalkyl or heteroarylalkyl; and

R_c is $–CH_3$ or $–CH_2CONR_xR_y$.

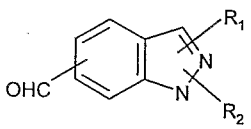
8. A method for preparing a compound of Formula IX and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein the method comprises:

a. formylating a compound of Formula I



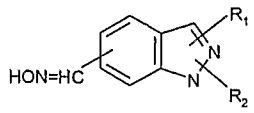
Formula I

to give a compound of Formula II;



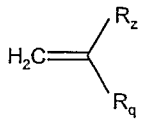
Formula II

b. reacting a compound of Formula II with $NH_2OH.HCl$ to give a compound of Formula III;



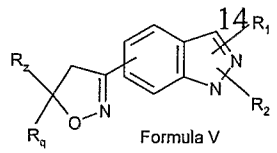
Formula III

c. reacting compound of Formula III with a compound of Formula IV



Formula IV

to give a compound of Formula V; and



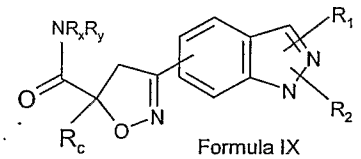
Formula V

d. reacting a compound of Formula V with a compound of Formula VIII

$H_2NR_xR_y$

Formula VIII

to give a compound of Formula IX,



Formula IX

wherein R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;

R_z is alkyl or $-CH_2COOR_5$;

R_q is –CN or $–COOR_5$;

R_5 is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclylalkyl or heteroarylalkyl;

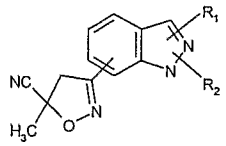
R_c is $–CH_3$ or $–CH_2CONR_xR_y$;

R_x and R_y are independently selected from R_5 or R_x and R_y may together join to form cycloalkyl, heteroaryl or heterocyclyl ring), nitro, $-S(O)_mR_6$ (wherein m is an integer from 0-2

and R_6 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclylalkyl, heteroarylalkyl or NR_xR_y).

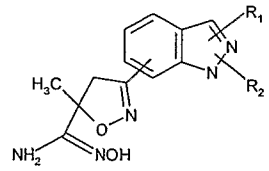
9. A method for preparing a compound of Formula XII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein the method comprises:

a. reacting a compound of Formula X



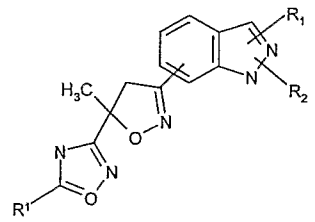
Formula X

with hydroxylamine hydrochloride to give a compound of Formula XI; and



Formula XI

b. reacting a compound of Formula XI with a compound of Formula R^1COOH to give a compound of Formula XII,



Formula XII

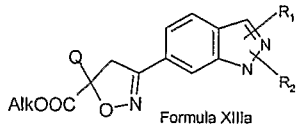
wherein

R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH; and

R^1 is aryl, cycloalkyl or heteroaryl.

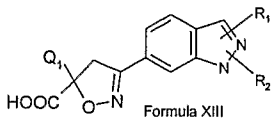
10. A method for preparing a compound of Formula XVI and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein the method comprises.

a. hydrolyzing a compound of Formula XIIIa



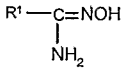
Formula XIIIa

to give a compound of Formula XIII;



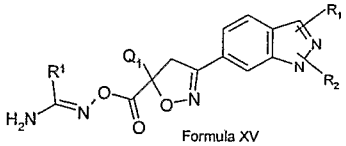
Formula XIII

b. reacting a compound of Formula XIII with a compound of Formula XIV



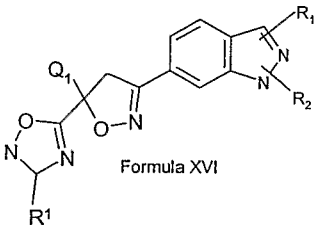
Formula XIV

to give a compound of Formula XV; and



Formula XV

c. cyclizing a compound of Formula XV to give a compound of Formula XVI,



Formula XVI

wherein

R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;

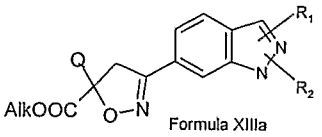
R^1 is aryl, cycloalkyl or heteroaryl;

Alk is alkyl; Q is CH_3, or $-CH_2CO_2CH_3$; and

Q_1 is $-CH_3$ or $-CH_2CO_2H$.

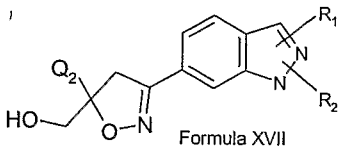
11. A method for preparing a compound of Formula XVI and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein the method comprises:

a. reduction of compound of Formula XIIIa



Formula XIIIa

to give a compound of Formula XVII



Formula XVII

wherein

R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;

Alk is alkyl; Q=CH_3, or $-CH_2CO_2CH_3$; and

Q_2 is $-CH_3$, or $-CH_2CH_2OH$.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/002369

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 A61K31/416 A61P25/00 A61P11/00

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, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2006/129158 A (RANBAXY LAB LTD [IN]; PALLE VENKATA P [IN]; BALACHANDRAN SARALA [IN];) 7 December 2006 (2006-12-07) claim 1 claim 2; compounds 19-21,27,32,36	1-11
X	WO 97/49702 A (PFIZER [US]; MARFAT ANTHONY [US]) 31 December 1997 (1997-12-31) claim 1 formulae (I) and (II), definition of R24 and R25	1-11
Y	WO 98/09661 A (STEINEL GMBH & CO KG [DE]; STEINEL HEINRICH WOLFGANG JR [DE]) 12 March 1998 (1998-03-12) claim 1 formula (Ib) definiiton of R4 and R5	1-11

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[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
17 January 2007	26/01/2007

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	KOLLMANNSBERGER, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/002369

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/051931 A2 (RANBAXY LAB LTD [IN]; PALLE VENKATA P [IN]; BALACHANDRAN SARALA [IN];) 9 June 2005 (2005-06-09) claims	1-11
Y	WO 95/14680 A (PFIZER [US]; KLEINMAN EDWARD F [US]) 1 June 1995 (1995-06-01) claim 1 definition of R4 and R5	1-11
Y	WO 99/23077 A (PFIZER PROD INC [US]; MARFAT ANTHONY [US]) 14 May 1999 (1999-05-14) claims 1,2	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/002369

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 4-6 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/IB2006/002369

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/002369

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