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(54) Title: INHIBITORS OF PHOSPHODIESTERASE TYPE-IV

(57) Abstract: 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 treating 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 or other inflammatory diseases especially in humans. Processes for preparing compounds described herein are provided, as well as pharmaceutical compositions comprising compounds described herein, and their use as phosphodiesterase (PDE) type IV inhibitors.

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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.

5 Compounds disclosed herein can be useful in treating 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 or other inflammatory diseases especially in humans.

10 Processes for preparing compounds described herein are provided, as well as pharmaceutical compositions comprising compounds described herein, and their use as phosphodiesterase (PDE) type IV inhibitors.

Background of the Invention

15 It is known that cyclic adenosine-3',5'-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger (E.W. Sutherland, and T.W. Roll, 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
20 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 twenty five 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
25 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.

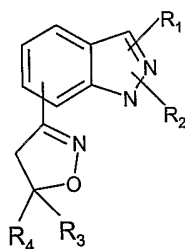
The initial observation that xanthine derivatives, theophylline and caffeine inhibit the hydrolysis of cAMP led to the discovery of the required hydrolytic activity in the cyclic nucleotide phosphodiesterase (PDE) enzymes. More recently, distinct classes of PDE have been recognized (J.A. Bervo and D.H.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

WO 03/47520 discloses substituted amino methyl factor Xa inhibitors. US 2003176421, EP 1040829 discloses 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 disclose aryl sulfonyls as factor Xa inhibitors. WO 01/19798 discloses 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.

In view of the above, there remains a need for novel PDE IV inhibitors.

Summary of the Invention

Provided are compounds having the structure of Formula Ia,



Formula Ia

R₁ and R₂ can independently be selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH; and

R₃ and R₄ can independently be selected from hydroxyalkyl or R₃ and R₄ together join to form mono or bicyclic ring containing 3-12 carbon atom, wherein the ring optionally contains 1-3 heteroatoms selected from oxygen, sulphur or -NR_a (wherein R_a can be hydrogen, aralkyl, -(C=O)OC(CH₃)₃, -(=O)OC(CH₃)₂CHBr₂ or -C(=O)OC(CH₃)₂CCl₃).

In another aspect, provided are compounds selected from:

1-Cyclopentyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 1),

1-Cyclopentyl-3-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 2),

1-Cyclopentyl-3-ethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 3),

1-Cyclopentyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 4),

1-Cyclopentyl-3-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 5),

1-Cyclopentyl-3-ethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 6),

3-(1-Cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 7),

3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 8),

- 3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 9),
3-(1-Cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 10),
5 *Tert*-butyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 11),
Tert-butyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 12),
1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 13),
10 1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-methyl-1*H*-indazole (Compound No. 14),
1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1*H*-indazole (Compound No. 15),
Hydrochloride salt of 3-(1-cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
15 (Compound No. 16),
Hydrochloride salt of 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 17),
Hydrochloride salt of 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 18),
20 2-[3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 19),
2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 20),
2-[3-(1-Cyclopentyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol
25 (Compound No. 21),
3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1,8-dioxa-2-azaspiro[4.5]dec-2-ene (Compound No. 22),
3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1,8-dioxa-2-azaspiro[4.5]dec-2-ene (Compound No. 23),
30 3-Ethyl-1-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 24),

- 3-Ethyl-1-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 25),
 3-(3-Ethyl-1-methyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 26),
 2-[3-(3-Ethyl-1-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 27),
 5 6-(1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1-methyl-1*H*-indazole (Compound No. 28),
 1,3-Dimethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 29),
 1,3-Dimethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 30),
 3-(1,3-Dimethyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 31),
 10 2-[3-(1,3-Dimethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol
 (Compound No. 32),
 6-(1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl)-1,3-dimethyl-1*H*-indazole (Compound No. 33),
 1-Cyclopentyl-3-ethyl-5-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 34),
 15 3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 35),
 2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 36), or
 1-Cyclopentyl-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1*H*-indazole (Compound
 20 No. 37).

In another aspect, provided are pharmaceutical compositions comprising a therapeutically effective amount of one or more compounds described herein and one or more pharmaceutically acceptable carriers, excipients or diluents.

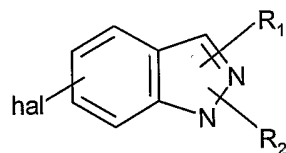
- In another aspect, provided are methods of treating AIDS, asthma, arthritis, bronchitis,
 25 chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis comprising administering to a patient in need thereof a therapeutically effective amount of one or more compounds described herein

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In yet another aspect, provided are methods of preventing, inhibiting or suppressing inflammatory conditions comprising administering to a patient in need thereof a therapeutically effective amount of one or more compounds described herein.

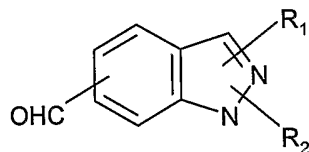
In another aspect, provided are processes for preparing a compound of Formula VII or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, enantiomer, diastereomer or N-oxide comprising the steps of:

a. formylating a compound of Formula I



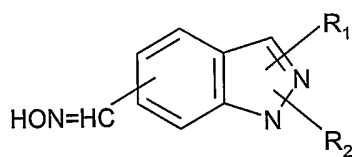
Formula I

to form a compound of Formula II



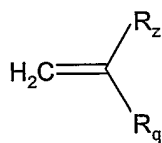
Formula II

b. reacting the compound of Formula II with hydroxylamine hydrochloride to form a compound of Formula III,



Formula III

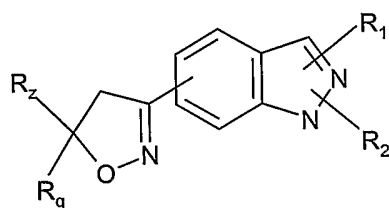
c. reacting the compound of Formula III with a compound of Formula IV



Formula IV

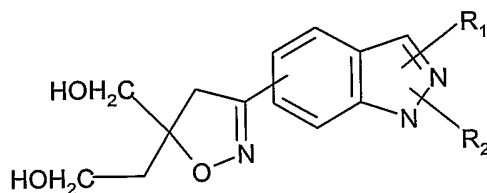
to form a compound of Formula V,

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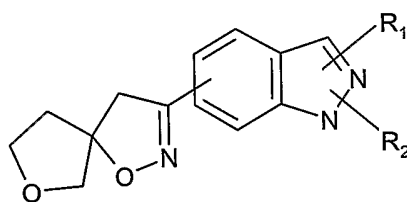
Formula V

c. reducing the compound of Formula V to form a compound of Formula VI,



Formula VI

d. cyclizing a compound of Formula VI to form a compound of Formula VII,



Formula VII

5

wherein

hal can be Br, Cl or I;

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

10 R_z can be $-\text{CH}_2\text{COOalkyl}$;

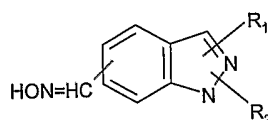
R_q can be $-\text{COOalkyl}$ or R_z and R_q together join to form a cycloalkyl ring, wherein the cycloalkyl ring optionally contains one or more heteroatoms selected from oxygen or sulphur (when R_2 is $-\text{COOR}_5$ and R_q is $-\text{CH}_2\text{COOR}_5$); and

R_5 can be alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclylalkyl or heteroarylalkyl.

In another aspect, provided are processes for preparing a compound of Formula X or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, enantiomer,

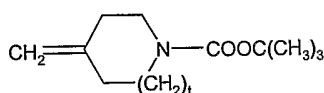
5 diastereomer or N-oxide thereof comprising the steps of:

a. reacting a compound of Formula III



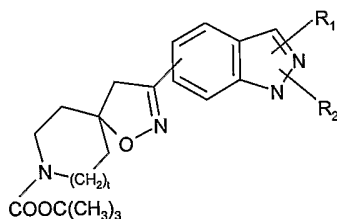
Formula III

with a compound of Formula VIII



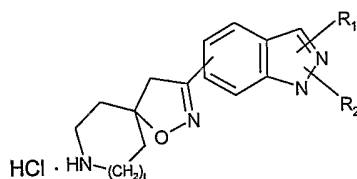
Formula VIII

10 to form a compound of Formula IX, and



Formula IX

b. deprotecting a compound of Formula IX to form a compound of Formula X,



Formula X

wherein

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

t can be 0 or 1.

Detailed Description of the Invention

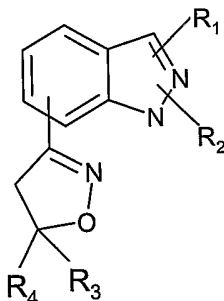
The present invention provides isoxazoline derivatives, which can be used in treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis or other inflammatory diseases, as well as processes for synthesizing such compounds.

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

Pharmaceutical compositions comprising compounds described herein and optionally one or more pharmaceutically acceptable carriers or diluents can be used in treating 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 or 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, provided are compounds having the structure of Formula Ia:



Formula Ia

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

R₁ and R₂ can independently be selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;

5 R₃ and R₄ can independently be hydroxyalkyl or R₃ and R₄ may together join to form mono or bicyclic ring containing 3-12 carbon atoms, wherein the ring may optionally contain 1-3 heteroatoms selected from oxygen, sulphur or -NR_a (wherein R_a is hydrogen, aralkyl, -(C=O)OC(CH₃)₃, -C(=O)OC(CH₃)₂CHBr₂ or -C(=O)OC(CH₃)₂CCl₃);

10 In accordance with a second aspect, provided are methods for the treatment or prophylaxis of inflammatory diseases comprising administering to a patient in need thereof an effective amount of one or more compounds described herein.

In accordance with a third aspect, provided are methods for the treatment or prophylaxis of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease
15 (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis or other inflammatory diseases comprising administering to a patient in need thereof an effective amount of one or more compounds described herein.

In accordance with a fourth aspect, provided are processes for preparing compounds
20 described herein.

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.

25 The following definitions apply to terms as used herein.

The term "*alkyl*" unless 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. Alkyl groups may further be substituted with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryloxy, heteroaryloxy, aminosulfonyl, -COOR₅ (wherein R₅ is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclalkyl or heteroarylalkyl), -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_z is the same as defined earlier; R_x and R_y are independently selected from R₅ or R_x and R_y may together join to form cycloalkyl, heteroaryl or heterocycl ring), nitro, or -S(O)_mR₆ (wherein m is an integer from 0-2 and R₆ is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclalkyl, heteroarylalkyl or NR_xR_y). Unless otherwise constrained, all substituents may be further substituted by 1-3 substituents selected from alkyl, -COOR₅, -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y, hydroxy, alkoxy, halogen, CF₃, cyano or -S(O)_mR₆. Alkyls groups may also be interrupted by 1-5 atoms or groups independently selected from oxygen, sulfur or -NR_a- (where R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, -COOR₅, -SO₂R₆, -C(=O)NR_xR_y).

The term "*alkylene*" unless otherwise specified refers to a diradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms. This term is exemplified by groups such as methylene, ethylene, propylene isomers (e.g. -CH₂CH₂CH₂ or -CH(CH₃)CH₂) and the like. Alkylene groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryloxy, heteroaryloxy, aminosulfonyl, -COOR₅ (wherein R₅ is the same as defined earlier), -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_z, R_x and R_y are the same as defined earlier), nitro, or -S(O)_mR₆ (wherein m and R₆ is the same as defined earlier). Unless otherwise constrained, all substituents may be further substituted by 1-3 substituents selected from alkyl, -COOR₅, -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y, hydroxy, alkoxy, halogen, -CF₃, cyano or -S(O)_mR₆. Alkylene groups may also be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_a (wherein R_a is selected from

hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, -COOR₅, -SO₂R₆, -C(=O)NR_xR_y).

The term "*alkenyl*" unless 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. Alkenyl groups may further be substituted with one or more substituents selected from the group alkyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy, heteroaryloxy, -COOR₅ (wherein R₅ is the same as defined earlier), -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_z, 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, or -S(O)_mR₆ (wherein R₆ and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents selected from alkyl, -COOR₅, hydroxy, alkoxy, halogen, -CF₃, cyano, -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y or -S(O)_mR₆.

The term "*alkynyl*" unless 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. Alkynyl groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, azido, cyano, halogen, hydroxy, thiol, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, aryl, aralkyl, aryloxy, aminosulfonyl, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -COOR₅ (wherein R₅ is the same as defined earlier), -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_z, R_x and R_y are the same as defined earlier), or -S(O)_mR₆ (wherein R₆ and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents selected from alkyl, -COOR₅, hydroxy, alkoxy, halogen, -CF₃, -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y, cyano or -S(O)_mR₆.

The term "*cycloalkyl*" unless otherwise specified 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, bicyclo[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. Cycloalkyl groups may further be substituted with one or more substituents selected alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, heteroaryloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryl, aralkyl, aryloxy, aminosulfonyl, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryl, aralkyl, aryloxy, aminosulfonyl, -COOR₅ (wherein R₅ is the same as defined earlier), -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_z, R_x and R_y are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or S(O)_mR₆ (wherein R₆ and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents selected from alkyl, hydroxy, alkoxy, halogen, CF₃, -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y, cyano or -S(O)_mR₆.

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

The term "*aryl*" unless otherwise specified 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 halogen (F, Cl, Br, I), hydroxy, -COOR₅ (wherein R₅ 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_z, -(SO)_mR₆ (wherein R_z, R₆, R_x, R_y and m are the same as defined earlier), aryl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl. Aryl groups may optionally be fused with cycloalkyl groups, heteroaryl groups or heterocyclyl groups.

The term "*aryloxy*" unless otherwise specified refers to the group O-aryl, wherein aryl is the same as defined above.

The term "*heteroaryl*" unless otherwise specified refers to an aromatic monocyclic or polycyclic (fused, spiro or bridged) ring system containing 1-8 heteroatom(s) independently selected from N, O or S. Heteroaryl rings can optionally be substituted with 1 to 3 substituent(s) selected from halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, aryloxy, cycloalkyloxy, acyl, thioacyl, -COOR₅ (wherein R₅ is the same as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro, -NHR_z, -NR_xR_y, -C(=O)NR_xR_y, -S(O)_mR₆, or -OC(=O)NR_xR_y (wherein m, R_z, R₆, R_x and R_y are the same as defined earlier). Unless otherwise constrained, the substituents can be attached to the ring atom, be it carbon or heteroatom. Examples of heteroaryl groups include pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, carbazolyl, isobenzofuranyl, thianthrene, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, imidazolyl, tetrazolyl, quinoliny, isoquinoliny, quinazoliny, benzoxazinonyl, benzothiazinonyl and the like.

The term "*heterocyclyl*" unless otherwise specified refers to nonaromatic monocyclic or polycyclic ring (fused, spiro or bridged) system having 1 to 8 heteroatoms selected from O, S or N. For heterocycles containing sulphur, oxidized sulphur heterocycles containing SO or SO₂ are also included. The heterocyclyl ring system can be optionally benzofused or fused with heteroaryl and/or are optionally substituted, wherein the substituents are selected from halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, thioacyl, aryl, alkoxy, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aryloxy, cyano, nitro, -COOR₅ (wherein R₅ is the same as defined earlier), -C(=O)NR_xR_y, S(O)_mR₆, -OC(=O)NR_xR_y, -NHR_z, or -NR_xR_y (wherein m, R_z, R_x and R_y are the same as defined earlier). Unless or otherwise constrained, the substituents can be attached to the ring atom via carbon atom or heteroatom. Also, unless otherwise constrained the heterocyclyl ring may optionally contain one or more olefinic bond(s). Examples of heterocyclyl groups include tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, piperidinyl, isoxazoliny, thiazoliny, thiazolidinonyl, oxazoliny or oxazolidinonyl.

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

The term "*heterocyclalkyl*" unless otherwise specified refers to heterocycl group linked through alkyl portion, wherein the alkyl and heterocycl are the same as defined earlier.

5 The term "*acyl*" unless otherwise specified refers to $-C(=O)R''$ wherein R'' is selected from the group alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocycl, heteroarylalkyl or heterocyclalkyl.

The term "*thioacyl*" unless otherwise specified refers to $-C(=S)R''$ wherein R'' is the same as defined above;

10 The term "*halogen*" unless otherwise specified refers to fluorine, chlorine, bromine or iodine;

The term "*leaving group*" unless otherwise specified 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 include, but are not limited to, hal (Cl, Br, I), triflate, tosylate, 4-
15 bromophenylsulfonate, 4-nitrophenylsulfonate, mesylate and the like.

The term "*protecting groups*" unless otherwise specified refers 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
20 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
25 subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the molecule.

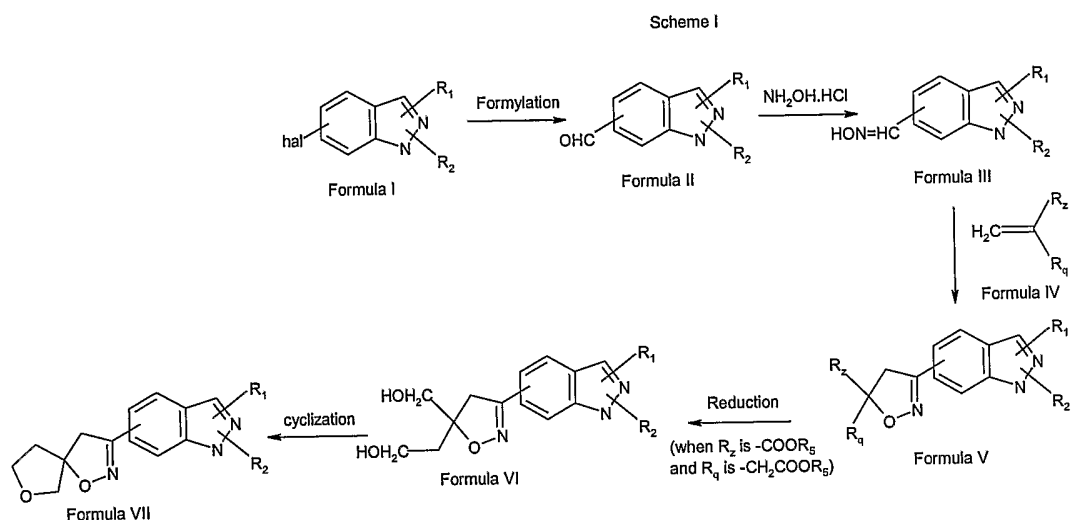
Compounds described herein contain one or more asymmetric carbon atoms and thus can exist as racemic mixtures, enantiomers or diastereomers. These compounds also exist as

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
5 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
10 carboxylic acids), and the like.

The salt forms differ from the compound described herein in certain physical properties such as solubility, but the salts are otherwise equivalent for the purpose of this invention.

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



The compounds of Formulae V, VI and VII can be prepared 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 above) can be formylated to form a compound of Formula II. The compound of Formula II can be reacted with hydroxylamine hydrochloride to form a compound of Formula III. The compound of Formula III can be reacted with a compound of Formula IV [wherein R_z is $-\text{CH}_2\text{COOalkyl}$; R_q is $-\text{COOalkyl}$ or R_z and R_q may together join to form a cycloalkyl ring wherein the ring may optionally contain heteroatom selected from oxygen or sulphur] to form a compound of Formula V. The compound of Formula V can be reduced (when R_2 is $-\text{COOR}_5$ and R_q is $-\text{CH}_2\text{COOR}_5$) to form a compound of Formula VI. The compound of Formula VI can be cyclized to form a compound of Formula VII.

Compounds of Formula I can be formylated to form compounds of Formula II in the presence of one or more formylating agents, for example, dimethylformamide, triformamide, tris (diformylamino)methane, tris(dichloromethyl)amine or N,N,N,N-tetraformyl hydrazine. The formylation reaction can also be carried out in the presence of one or more bases, for example, butyl lithium, pyridine, N-methylmorpholine or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, tetrahydrofuran, dimethylformamide, dioxane, diethylether or mixtures thereof.

Compounds of Formula II can be reacted with hydroxylamine hydrochloride to form compounds of Formula III in the presence of one or more bases, for example, sodium acetate, sodium carbonate, ammonium acetate, potassium carbonate or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, ethanol, methanol, propanol, isopropylalcohol or mixtures thereof.

Compounds of Formula III can be reacted with compounds of Formula IV to form compounds of Formula V with one or more oxidants, for example, sodium hypochlorite, N-chlorosuccinimide, tert-butoxy chloride or mixtures thereof. The reaction can also be carried out in the presence of one or more optional bases, for example, triethylamine, butyl lithium, N-methylmorpholine, diisopropylethylamine or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, tetrahydrofuran, dimethylformamide, diethylether, dioxane or mixtures thereof.

Compounds of Formula V can be reduced (when R_z is $-\text{COOR}_5$ and R_q is $-\text{CH}_2\text{COOR}_5$) to form compounds of Formula VI in the presence of one or more reducing agents, for example, sodium borohydride, sodium cyanoborohydride or mixtures thereof. The reduction reaction can also be carried out in one or more organic solvents, for example, tetrahydrofuran, dimethylformamide, diethylether, dioxane or mixtures thereof.

Compounds of Formula VI can be ring cyclized to form compounds of Formula VII in the presence of a redox couple. The oxidizing part of the redox couple can be selected from diisopropylazodicarboxylate (DIAD), diethylazodicarboxylate (DEAD), N,N,N',N'-tetramethylazodicarboxylate (TMAD), 1,1'-(azodicarbonyl) dipiperidine (ADDP), cyanomethylenetriethylphosphorane (CMBP), 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) or N,N,N',N'-tetraisopropylazodicarboxamide (TIPA). The reduction part of the redox couple can be a phosphine reagent selected from trialkylphosphine (such as tributylphosphine), triarylphosphine (such as triphenylphosphine), tricycloalkylphosphine (such as triscyclohexylphosphine) or tetraheteroarylphosphine. Phosphine reagents having a combination of aryl, alkyl or heteroaryl substituents may also be used (such as diphenylpyridylphosphine). The reaction can also be carried out in one or more

organic solvents, for example, tetrahydrofuran, dimethylformamide, dioxane, diethyl ether or mixtures thereof.

Compounds prepared following Scheme I include, for example:

- 1-Cyclopentyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 1),
- 5 1-Cyclopentyl-3-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 2),
- 1-Cyclopentyl-3-ethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 3),
- 1-Cyclopentyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 4),
- 10 1-Cyclopentyl-3-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 5),
- 1-Cyclopentyl-3-ethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 6),
- 3-(1-Cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 7),
- 15 3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 8),
- 3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 9),
- 1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 13),
- 20 1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-methyl-1*H*-indazole (Compound No. 14),
- 1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1*H*-indazole (Compound No. 15),
- 2-[3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 19),
- 25

2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 20),

2-[3-(1-Cyclopentyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 21),

5 3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1,8-dioxo-2-azaspiro[4.5]dec-2-ene (Compound No. 22),

3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1,8-dioxo-2-azaspiro[4.5]dec-2-ene (Compound No. 23),

3-Ethyl-1-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 24),

10 3-Ethyl-1-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 25),

3-(3-Ethyl-1-methyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 26),

2-[3-(3-Ethyl-1-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 27),

15 6-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1-methyl-1*H*-indazole (Compound No. 28),

1,3-Dimethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 29),

1,3-Dimethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 30),

3-(1,3-Dimethyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 31),

20 2-[3-(1,3-Dimethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 32),

6-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-1,3-dimethyl-1*H*-indazole (Compound No. 33),

1-Cyclopentyl-3-ethyl-5-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 34),

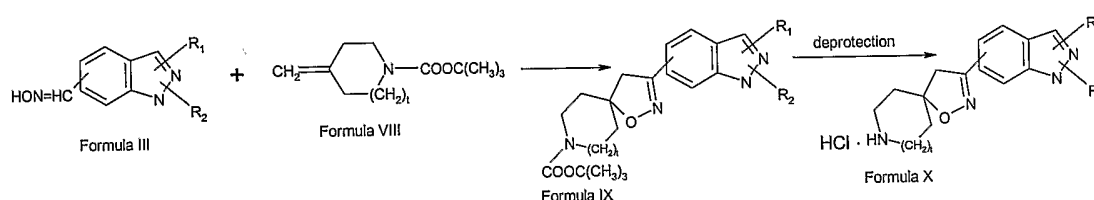
25 3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 35),

2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 36),

1-Cyclopentyl-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1*H*-indazole (Compound No. 37),

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

Scheme II



- The compounds of Formula IX and X can be prepared by following the procedure as depicted in Scheme II. Thus, a compound of Formula III (where R_1 and R_2 are the same as depicted earlier) can be reacted with a compound of Formula VIII to form a compound of
10 Formula IX (where t is 0 or 1). The compound of Formula VIII can be deprotected to form a compound of Formula X.

- Compounds of Formula III can be reacted with compounds of Formula VIII to form compounds of Formula IX in the presence of one or more oxidants, for example sodium
15 hypochlorite, *N*-chlorosuccinimide, *tert*-butoxy chloride or mixtures thereof. The reaction can also be carried out in the presence of one or more optional bases, for example, triethylamine, butyl lithium, *N*-methylmorpholine, diisopropylethylamine or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, tetrahydrofuran, dimethylformamide, diethylether, dioxane or mixtures thereof.

- 20 Compounds of Formula IX can be deprotected to form compounds of Formula X in the presence of one or more deprotection agents, for example, methanol in hydrochloric acid or ethanol in hydrochloric acid.

Compounds prepared following Scheme II include, for example:

3-(1-Cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate
(Compound No. 10),

Tert-butyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 11),

- 5 *Tert*-butyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 12),

Hydrochloride salt of 3-(1-cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
(Compound No. 16),

- 10 Hydrochloride salt of 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 17),

Hydrochloride salt of 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 18)

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

- 15 In the above schemes, where specific reagents, for example, acids, bases, solvents, condensing agents, hydrolyzing agents etc. are disclosed, it is to be understood that other reagents (acids, bases, solvents, condensing agents, hydrolyzing agents, etc, known to those skilled in an art may also be used. Similarly, reaction temperatures and durations of the reactions may be readily adjusted according to desired needs.

- 20 Compounds of Formula Ia and pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, prodrugs, metabolites, polymorphs or N-oxides thereof may be advantageously used in combination with one or more other therapeutic agents. Examples of other therapeutic agents include one or more of corticosteroids, beta agonists, leukotriene antagonists, 5-lipoxygenase inhibitors, chemokine
25 inhibitors, muscarinic receptor antagonists or mixtures thereof.

Because of their valuable pharmacological properties, compounds described herein may be administered to an animal for treatment by any route of administration and more

particularly by oral or parenteral routes. Pharmaceutical compositions described herein can be produced and administered in dosage units, each unit containing a specified amount of one or more compounds described herein and/or one or more pharmaceutically acceptable addition salt thereof. The dosage may be varied over wide limits, as the compounds are effective at low dosage levels and relatively free of toxicity. Such 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 racemic mixtures, enantiomers, diastereomers, rotamers, N-Oxides, polymorphs, solvates and pharmaceutically acceptable salts, as well as the active metabolites. Pharmaceutical compositions comprising the compounds described herein or metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with one or more pharmaceutically acceptable carriers and optionally included excipients can also be produced.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

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 U.S. Patent No. 6,262,040 or Synthesis, 1999, 4, 588-592.

Example 1: 2-[3-(1-Cyclopentyl-1H-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 21)

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 at room temperature for 1 hour. The reaction mixture was quenched with hydrochloric acid (1N) and extracted with ethyl acetate and water. The organic layer was collected, washed with brine and dried over anhydrous sodium sulphate. The reaction mixture was filtered and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield: 0.465g.

Mass (m/z): 215 ($\text{M}^+ + 1$).

^1H 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), 1.2-2.3 (m, 8H).

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

Hydroxylamine hydrochloride (311.7 mg, 4.48 mmol) and sodium acetate (367 mg, 4.48 mmol) and ethanol (10 ml) was added to a compound obtained from step a above (240 mg, 1.121 mmol). 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 ($\text{M}^+ + 1$).

^1H 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-methoxycarbonylmethyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester

Tetrahydrofuran (5 ml) was added to a mixture of compound obtained from step *b* above (300 mg, 1.310 mmol) and dimethyl-2-methylenesuccinate (414 mg, 2.620 mmol) and the reaction mixture was stirred for 10 minutes at room temperature. Sodium hypochlorite (3 ml) was added with vigorous stirring to the reaction mixture and then further stirred for 15 hours. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate 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: 410 mg.

Mass (m/z): 386.10 ($M^+ + 1$).

Step d: 2-[3-(1-Cyclopentyl-1H-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 21)

Sodium borohydride (0.296 g, 7.792 mmol) was added to a solution of the compound obtained from step *c* above (0.500 g, 1.298 mmol) in tetrahydrofuran and stirred for 15 minutes at 0-5 °C. Methanol (1.0 ml) was added to the resulting reaction mixture. The reaction mixture was stirred for 14 hours at room temperature, quenched with ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 40 % ethyl acetate in hexane as eluent to furnish the title compound. Yield: 0.390 g.

Mass (m/z): 330.10 ($M^+ + 1$).

Following compounds were prepared similarly using the appropriate corresponding starting materials,

2-[3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 19)

Mass (m/z): 344.3 ($M^+ + 1$).

2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 20)

Mass (m/z): 358.4 ($M^+ + 1$).

2-[3-(3-Ethyl-1-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 27)

Mass (m/z): 304.1 ($M^+ + 1$).

2-[3-(1,3-Dimethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 32)

Mass (m/z): 290.2 ($M^+ + 1$).

2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol (Compound No. 36)

Mass (m/z): 358.2 ($M^+ + 1$).

Example 2: Synthesis of 1-cyclopentyl-6-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 13)

A solution of succinimide (0.117g, 1.181mmol) and triphenylphosphine (0.326g, 1.244mmol) in tetrahydrofuran (10ml) was stirred at 0-5 °C for 15 minutes followed by the addition of Compound No. 21 (0.390g, 1.185mmol) obtained in Example 1. The reaction mixture was stirred at 0-5 °C for 15 minutes followed by the addition of diisopropylazodicarboxylate (0.311g, 1.540mmol). The resulting reaction mixture was stirred at room temperature for 20 hours. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 10-25 % ethyl acetate in hexane as eluent to furnish the title compound. Yield: 0.110 g.

Mass (m/z): 312.1 ($M^+ + 1$).

Following compounds were prepared similarly using the appropriate corresponding starting materials,

1-Cyclopentyl-6-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-3-methyl-1H-indazole

(Compound No. 14)

Mass (m/z): 326.2 ($M^+ + 1$).

1-Cyclopentyl-6-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1H-indazole (Compound No. 15)

Mass (m/z): 340.3 ($M^+ + 1$).

3-(1-Cyclopentyl-3-methyl-1H-indazol-6-yl)-1,8-dioxo-2-azaspiro[4.5]dec-2-ene (Compound No. 22)

Mass (m/z): 340.3 ($M^+ + 1$).

3-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1,8-dioxo-2-azaspiro[4.5]dec-2-ene (Compound No. 23)

Mass (m/z): 354.3 ($M^+ + 1$).

6-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1-methyl-1H-indazole (Compound No. 28)

6-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-1,3-dimethyl-1H-indazole (Compound No. 33)

1-Cyclopentyl-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1H-indazole (Compound No. 37)

Mass (m/z): 340.1 ($M^+ + 1$).

Example 3: Synthesis of 1-Cyclopentyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1H-indazole

(Compound No. 1)

The title compound was prepared following the procedure as described in Example 1, step c, by using methylenecyclobutane in place of dimethyl 2-methylenesuccinate.

Mass (m/z): 296.10 ($M^+ + 1$).

Following compounds were prepared similarly using the appropriate corresponding starting materials,

1-Cyclopentyl-3-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1H-indazole (Compound No. 2)

Mass (m/z): 310.20 ($M^+ + 1$).

1-Cyclopentyl-3-ethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1H-indazole (Compound No. 3)

Mass (m/z): 324.30 ($M^+ + 1$).

1-Cyclopentyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1H-indazole (Compound No. 4)

Mass (m/z): 310.10 ($M^+ + 1$).

1-Cyclopentyl-3-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1H-indazole (Compound No. 5)

Mass (m/z): 324.40 ($M^+ + 1$).

5 1-Cyclopentyl-3-ethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1H-indazole (Compound No. 6)

Mass (m/z): 338.30 ($M^+ + 1$).

3-(1-Cyclopentyl-1H-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 7)

Mass (m/z): 324.10 ($M^+ + 1$).

10 3-(1-Cyclopentyl-3-methyl-1H-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 8)

Mass (m/z): 338.30 ($M^+ + 1$).

3-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 9)

15 Mass (m/z): 352.40 ($M^+ + 1$).

3-Ethyl-1-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1H-indazole (Compound No. 24)

Mass (m/z): 270.1 ($M^+ + 1$).

3-Ethyl-1-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1H-indazole (Compound No. 25)

Mass (m/z): 284.2 ($M^+ + 1$).

20 3-(3-Ethyl-1-methyl-1H-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 26)

Mass (m/z): 298.1 ($M^+ + 1$).

1,3-Dimethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1H-indazole (Compound No. 29)

Mass (m/z): 256.2 ($M^+ + 1$).

1,3-Dimethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1H-indazole (Compound No. 30)

25 Mass (m/z): 270.2 ($M^+ + 1$).

3-(1,3-Dimethyl-1H-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 31)

Mass (m/z): 284.2 ($M^+ + 1$).

1-Cyclopentyl-3-ethyl-5-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1H-indazole (Compound No. 34)

30 Mass (m/z): 338.2 ($M^+ + 1$).

3-(1-Cyclopentyl-3-ethyl-1H-indazol-5-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 35)

Mass (m/z): 352.1 ($M^+ + 1$).

Example 4: Synthesis of *tert*-butyl 3-(1-cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 10)

The title compound was prepared following the procedure as described in Example 1 (step *c*), by using *tert*-butyl 4-methylene piperidine-1-carboxylate in place of dimethyl 2-methylenesuccinate.

Mass (*m/z*): 425.2 ($M^{+}+1$).

The following compounds were prepared similarly using the appropriate corresponding starting materials,

Tert-butyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 11)

Tert-butyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (Compound No. 12)

Example 5: Synthesis of hydrochloride salt of 3-(1-cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 16)

A solution of the Compound No. 10 (0.210g, 0.495mmol) obtained in Example 4 in methanolic hydrochloric acid (5.9 ml, 29.3 mmol) was stirred at room temperature for 14 hours. The solvent was evaporated under reduced pressure and the residue thus obtained was washed with ether and dried under high vacuum to furnish the title compound. Yield: 0.090 g.

Mass (*m/z*): 325.2 ($M^{+}+1$).

The following compounds were prepared similarly using the appropriate corresponding starting materials,

Hydrochloride salt of 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 17)

Mass (*m/z*): 339.3 ($M^{+}+1-Cl$)

Hydrochloride salt of 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 18)

Mass (*m/z*): 353.4 ($M^{+}+1$).

Example 6. 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 μ M) 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.

PDE-IV enzyme assay results were expressed as percent control and the IC₅₀ values of compounds disclosed herein were from about 0.1 nM to about 10,000 nM, from about 0.1 nM to about 2600 nM, from about 0.1 nM to about 215 nM, and even from about 0.1 nM to about 35 nM.

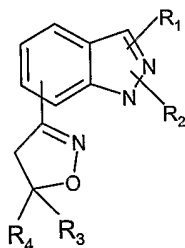
Whole Blood Assay for TNF- α release

Human whole blood was collected in vacutainer tubes containing heparin or EDTA as an anti coagulant. 0.1 ml blood per well was co-incubated with 20 μ l 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 μ g/ml, final concentration) was then added at a volume of 10 μ l per well. After 30 min, 20 μ l of fetal calf serum (final concentration of 10%) was added to each well. Samples were incubated overnight at 37°C in an atmosphere of 5% CO₂ and 95% air. Supernatant were then removed, diluted 1:20 with PBS and tested by ELISA for TNF- α release using a commercial kit (e.g. BD Biosciences).

The level of TNF- α in treated wells was compared with the vehicle treated controls and inhibitory potency of compound was expressed as IC₅₀ values calculated by using Graph pad prism and were from about 385 nM to about 8400 nM, from about 385 nM to about 2400 nM and even from about 385 nM to about 1600 nM.

We Claim:

1. A compound having the structure of Formula Ia,



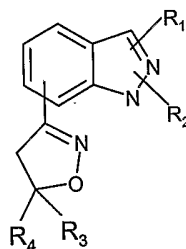
Formula Ia

- 2 R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl,
 3 aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH; and
 4 R_3 and R_4 are independently selected from hydroxyalkyl or R_3 and R_4 together join to
 5 form mono or bicyclic ring containing 3-12 carbon atom, wherein the ring
 6 optionally contains 1-3 heteroatoms selected from oxygen, sulphur or $-NR_a$
 7 (wherein R_a is hydrogen, aralkyl, $-(C=O)OC(CH_3)_3$, $-(=O)OC(CH_3)_2CHBr_2$ or -
 8 $C(=O)OC(CH_3)_2CCl_3$).
- 1 2. A compound selected from:
- 2 1-Cyclopentyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 1),
 3 1-Cyclopentyl-3-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No.
 4 2),
 5 1-Cyclopentyl-3-ethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No.
 6 3),
 7 1-Cyclopentyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 4),
 8 1-Cyclopentyl-3-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No.
 9 5),
 10 1-Cyclopentyl-3-ethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No.
 11 6),
 12 3-(1-Cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 7),
 13 3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No.
 14 8),

- 15 3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No.
16 9),
17 3-(1-Cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate
18 (Compound No. 10),
19 *Tert*-butyl 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-
20 carboxylate (Compound No. 11),
21 *Tert*-butyl 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-
22 carboxylate (Compound No. 12),
23 1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 13),
24 1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-methyl-1*H*-indazole
25 (Compound No. 14),
26 1-Cyclopentyl-6-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1*H*-indazole (Compound
27 No. 15),
28 Hydrochloride salt of 3-(1-cyclopentyl-1*H*-indazol-6-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
29 (Compound No. 16),
30 Hydrochloride salt of 3-(1-cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1-oxa-2,8-
31 diazaspiro[4.5]dec-2-ene (Compound No. 17),
32 Hydrochloride salt of 3-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1-oxa-2,8-
33 diazaspiro[4.5]dec-2-ene (Compound No. 18),
34 2-[3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-
35 yl]ethanol (Compound No. 19),
36 2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-
37 yl]ethanol (Compound No. 20),
38 2-[3-(1-Cyclopentyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol
39 (Compound No. 21),
40 3-(1-Cyclopentyl-3-methyl-1*H*-indazol-6-yl)-1,8-dioxa-2-azaspiro[4.5]dec-2-ene (Compound
41 No. 22),
42 3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1,8-dioxa-2-azaspiro[4.5]dec-2-ene (Compound
43 No. 23),
44 3-Ethyl-1-methyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 24),

45 3-Ethyl-1-methyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 25),
 46 3-(3-Ethyl-1-methyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 26),
 47 2-[3-(3-Ethyl-1-methyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-
 48 yl]ethanol (Compound No. 27),
 49 6-(1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1-methyl-1*H*-indazole (Compound No.
 50 28),
 51 1,3-Dimethyl-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-1*H*-indazole (Compound No. 29),
 52 1,3-Dimethyl-6-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No. 30),
 53 3-(1,3-Dimethyl-1*H*-indazol-6-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No. 31),
 54 2-[3-(1,3-Dimethyl-1*H*-indazol-6-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]ethanol
 55 (Compound No. 32),
 56 6-(1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl)-1,3-dimethyl-1*H*-indazole (Compound No. 33),
 57 1-Cyclopentyl-3-ethyl-5-(1-oxa-2-azaspiro[4.4]non-2-en-3-yl)-1*H*-indazole (Compound No.
 58 34),
 59 3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-1-oxa-2-azaspiro[4.5]dec-2-ene (Compound No.
 60 35),
 61 2-[3-(1-Cyclopentyl-3-ethyl-1*H*-indazol-5-yl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-
 62 yl]ethanol (Compound No. 36), or
 63 1-Cyclopentyl-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-3-ethyl-1*H*-indazole (Compound
 64 No. 37).

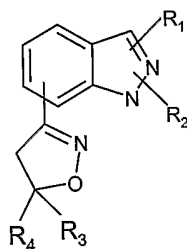
- 1 3. A pharmaceutical composition comprising a therapeutically effective amount of a
- 2 compound of Formula Ia and one or more pharmaceutically acceptable carriers, excipients or
- 3 diluents, wherein the compound of Formula Ia is:



Formula Ia

- 5 R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl,
 6 aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH; and
- 7 R_3 and R_4 are independently selected from hydroxyalkyl or R_3 and R_4 together join to
 8 form mono or bicyclic ring containing 3-12 carbon atom, wherein the ring
 9 optionally contains 1-3 heteroatoms selected from oxygen, sulphur or $-NR_a$
 10 (wherein R_a is hydrogen, aralkyl, $-(C=O)OC(CH_3)_3$, $-(=O)OC(CH_3)_2CHBr_2$ or -
 11 $C(=O)OC(CH_3)_2CCl_3$).

- 1 4. A method of treating AIDS, asthma, arthritis, bronchitis, chronic obstructer pulmonary
 2 disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult
 3 respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis,
 4 osteoarthritis, ulcerative colitis comprising administering to a patient in need thereof a
 5 therapeutically effective amount of a compound of Formula Ia:

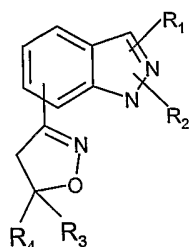


Formula Ia

- 6 R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl,
 7 aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH; and
- 8 R_3 and R_4 are independently selected from hydroxyalkyl or R_3 and R_4 together join to
 9 form mono or bicyclic ring containing 3-12 carbon atom, wherein the ring
 10 optionally contains 1-3 heteroatoms selected from oxygen, sulphur or $-NR_a$
 11 (wherein R_a is hydrogen, aralkyl, $-(C=O)OC(CH_3)_3$, $-(=O)OC(CH_3)_2CHBr_2$ or -
 12 $C(=O)OC(CH_3)_2CCl_3$).

- 1 5. A method of preventing, inhibiting or suppressing an inflammatory condition
 2 comprising administering to a patient in need thereof a therapeutically effective amount of a
 3 compound of Formula Ia:

35

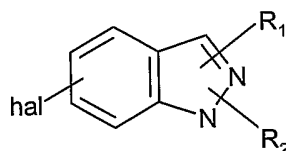


Formula Ia

R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH; and
 R_3 and R_4 are independently selected from hydroxyalkyl or R_3 and R_4 together join to form mono or bicyclic ring containing 3-12 carbon atom, wherein the ring optionally contains 1-3 heteroatoms selected from oxygen, sulphur or $-NR_a$ (wherein R_a is hydrogen, aralkyl, $-(C=O)OC(CH_3)_3$, $-(=O)OC(CH_3)_2CHBr_2$ or $-C(=O)OC(CH_3)_2CCl_3$).

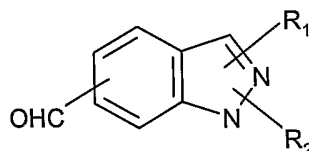
6. A process for preparing a compound of Formula VII or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, enantiomer, diastereomer or N-oxide comprising the steps of:

a. formylating a compound of Formula I



Formula I

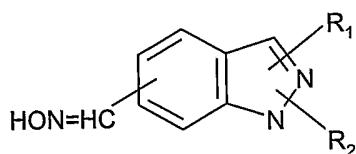
to form a compound of Formula II



Formula II

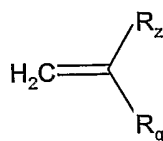
b. reacting the compound of Formula II with hydroxylamine hydrochloride to form a compound of Formula III,

36



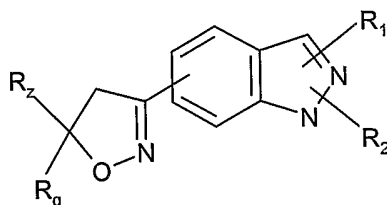
Formula III

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



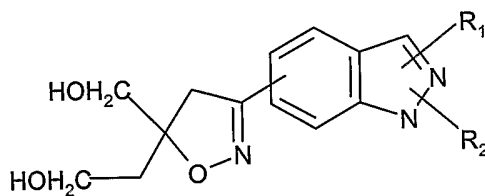
Formula IV

to form a compound of Formula V,



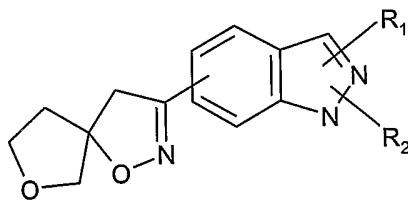
Formula V

c. reducing the compound of Formula V to form a compound of Formula VI,



Formula VI

d. cyclizing a compound of Formula VI to form a compound of Formula VII,



Formula VII

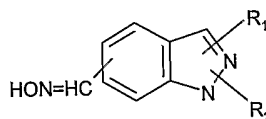
wherein

hal is Br, Cl or I;

- 21 R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl,
 22 aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or -OH;
 23 R_z is $-\text{CH}_2\text{COOalkyl}$;
 24 R_q is $-\text{COOalkyl}$ or R_z and R_q together join to form a cycloalkyl ring, wherein the
 25 cycloalkyl ring optionally contains one or more heteroatoms selected from
 26 oxygen or sulphur (when R_2 is $-\text{COOR}_5$ and R_q is $-\text{CH}_2\text{COOR}_5$); and
 27 R_5 is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclalkyl or
 28 heteroarylalkyl.

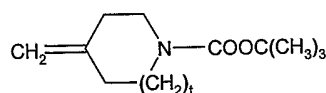
1 7. A process for preparing a compound of Formula X or a pharmaceutically acceptable
 2 salt, pharmaceutically acceptable solvate, enantiomer, diastereomer or N-oxide thereof
 3 comprising the steps of:

4 a. reacting a compound of Formula III



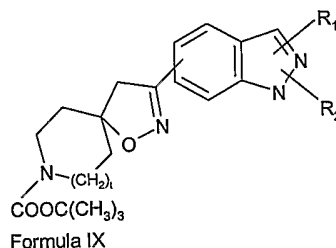
Formula III

5 with a compound of Formula VIII



Formula VIII

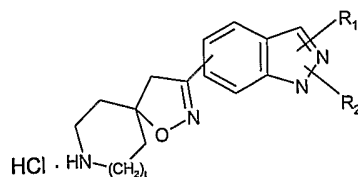
7 to form a compound of Formula IX, and



Formula IX

9 b. deprotecting a compound of Formula IX to form a compound of Formula X,
 10

38



Formula X

11

12 wherein

13 R_1 and R_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl,14 aralkyl, heteroaryl, heterocyclyl, cycloalkyl, alkoxy, halogen or $-OH$; and15 t is 0 or 1.