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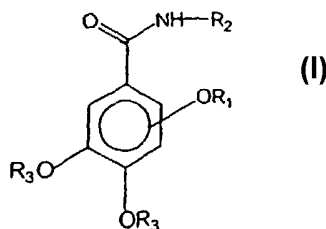
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(54) Title: N-(3,5-DICHLOROPYRIDIN-4-YL)-2,4,5-ALKOXY AND 2,3,4-ALKOXY BENZAMIDE DERIVATIVES AS PDE-IV (PHOSPHODIESTERASE TYPE-IV) INHIBITORS FOR THE TREATMENT OF INFLAMMATORY DISEASES SUCH AS ASTHMA



(57) **Abstract:** The present invention relates to benzamide derivatives, which can be used as selective inhibitors of phosphodiesterase (PDE) type IV, having the structure of Formula (I), its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers of N-oxides wherein R1 is hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl; R2 is aryl, heteroaryl, heterocyclyl of cycloalkyl; and R3 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl. Compounds disclosed herein can be useful in the treatment of inflammatory diseases, 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 and ulcerative colitis.

N- (3,5-DICHLOROPYRIDIN-4-YL) -2,4,5-ALKOXY AND 2,3,4-ALKOXY BENZAMIDE DERIVATIVES AS PDE-IV (PHOPHODIESTERASE TYPE-IV) INHIBITORS FOR THE TREATMENT OF INFLAMMATORY DISEASES SUCH AS ASTHMA

INHIBITORS OF PHOPHODIESTERASE TYPE-IV

Field of the Invention

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

5 Compounds disclosed herein can be useful in the treatment of 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.

10 Processes for the preparation of the compounds described herein are provided, as well as pharmaceutical compositions containing these 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
15 important role of acting as an intracellular secondary messenger (Sutherland, et al., *Pharmacol. Rev.*, 1960, 12, 265). Its intracellular hydrolysis to adenosine 5'-monophosphate (AMP) causes a number of inflammatory conditions which include, but are not limited to, psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic
20 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; eight distinct families with more than 15 gene products are currently recognized. Although PDE I, PDE II, PDE III, PDE IV, and PDE VII all use cAMP as a
25 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 roflumilast or rolipram 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,
30 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 (Bervo *et al.*, *TIPS*, 1990, 11, 150), and their selective
5 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).

U.S. Patent No. 5,712,298 and PCT application WO 95/01338 disclose fluoroalkoxy-substituted benzamides and their use as cyclic nucleotide phosphodiesterase
10 inhibitors. U.S. Patent Application No. 2003/0232859 and PCT application WO 02/062750 disclose cannabinoid receptor ligands which exhibit anti-inflammatory and immunodulatory activity. WO 00/42020 discloses phenylphenanthridines with PDE-IV inhibiting activity.

Summary of the Invention

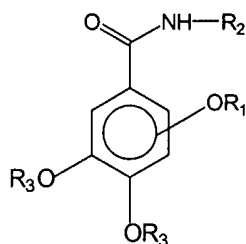
15 The present invention provides benzamide derivatives, which can be used for the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases, and the processes for the
20 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
25 pharmaceutically acceptable carriers or diluents, can be used for the treatment of 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, there is provided a compound having the structure of Formula I



Formula I

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

R_1 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl;

R_2 is aryl, heteroaryl, heterocyclyl or cycloalkyl; and

R_3 is independently alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl.

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, $-NHC(=O)R_f$, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-C(=O)heteroaryl$, $C(=O)heterocyclyl$, $-O-C(=O)NR_fR_q$ {wherein R_f and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl,

aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl}, nitro, or $-\text{SO}_2\text{R}_6$ (wherein R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, carboxy, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{OC}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3 , cyano, and $-\text{SO}_2\text{R}_6$, (wherein R_6 are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or $-\text{NR}_a$ {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-\text{C}(=\text{O})\text{OR}_f$ (wherein R_f is the same as defined earlier), SO_2R_6 (where R_6 is as defined earlier), or $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3 , cyano, and $-\text{SO}_2\text{R}_6$ (where R_6 is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans, or geminal geometry. In the event that alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted further with one or more substituents selected from alkyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, $-\text{NHC}(=\text{O})\text{R}_f$, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclalkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, nitro, or SO_2R_6 (wherein R_6 are is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, $-\text{CF}_3$, cyano, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier) and $-\text{SO}_2\text{R}_6$ (where R_6 is same as defined earlier).

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. In the event that alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -NHC(=O)R_f , $\text{-NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$, $\text{-O-C(=O)NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), or $\text{-SO}_2\text{R}_6$ (wherein R_6 is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3 , $\text{-NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), cyano, or $\text{-SO}_2\text{R}_6$ (where R_6 is same as defined earlier).

The term "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $\text{-NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$, -NHC(=O)R_f , $\text{-C(=O)NR}_f\text{R}_q$, $\text{-O-C(=O)NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or $\text{SO}_2\text{-R}_6$ (wherein R_6 is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3 , $\text{-NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$, $\text{-OC(=O)NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), cyano or $\text{-SO}_2\text{R}_6$ (where R_6 is same as

defined earlier). "Cycloalkylalkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

The term "alkoxy" denotes the group O-alkyl, wherein alkyl is the same as defined above.

5 The term "haloalkyl" refers to alkyl (wherein alkyl is the same as defined above) substituted with one or more halogen (F, Cl, Br or I).

The term "aryl," unless otherwise specified, refers to carbocyclic aromatic groups, for example, phenyl, biphenyl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, 10 cycloalkyl, alkoxy, acyl, aryloxy, CF₃, cyano, nitro, COOR_e (wherein R_e is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), NHC(=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), -SO₂R₆ (wherein R₆ is same as defined earlier), carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino. The 15 aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S.

The term "aralkyl," unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined below. Examples of aralkyl groups include benzyl, 20 ethylphenyl and the like.

The term "carboxy" as defined herein refers to -C(=O)OH.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having from 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S 25 optionally substituted with 1 to 4 substituent(s) selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, -NR_fR_q, CH=NOH, -(CH₂)_wC(=O)R_g {wherein w is an integer from 0-4 and R_g is hydrogen, hydroxy, OR_f, NR_fR_q, -NHOR_z or -NHOH}, -C(=O)NR_fR_q and -NHC(=O)NR_fR_q, -SO₂R₆, -O-C(=O)NR_fR_q, -O-C(=O)R_f, 30 O-C(=O)OR_f (wherein R₆, R_f and R_q are as defined earlier, and R_z is alkyl, cycloalkyl,

aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, and the like.

The term 'heterocyclyl,' unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, -O-C(=O)R_f, -O-C(=O)OR_f, -C(=O)NR_fR_q, SO₂R₆, -O-C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -NR_fR_q (wherein R₆, R_f and R_q are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuranyl, azabicyclohexyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl or piperazinyl.

"Heteroarylalkyl" refers to alkyl-heteroaryl group linked through alkyl portion, wherein the alkyl and heteroaryl are as defined earlier.

The term 'heterocyclyl,' unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, -O-C(=O)R_f, -O-C(=O)OR_f, -C(=O)NR_fR_q, SO₂R₆, -O-C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -NR_fR_q (wherein R₆, R_f and R_q are as defined earlier) or

guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s).

- 5 Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl or piperazinyl

“Heterocyclylalkyl” refers to alkyl-heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

- 10 “Acyl” refers to $-C(=O)R''$ wherein R'' is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

- The term “protecting groups” refers to moieties that prevent chemical reaction at a location of a molecule intended to be left unaffected during chemical modification of such molecule. Unless otherwise specified, protecting groups may be used on groups, such as
- 15 hydroxy, amino, or carboxy. Examples of protecting 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 groups employed are not critical, as long as the derivatised moieties/moiety is/are stable to conditions of
- 20 subsequent reactions and can be removed without disrupting the remainder of the molecule.

- In accordance with a further aspect, there are provided methods for treatment or prophylaxis of an animal or a human suffering from an inflammatory disease or disorder wherein the disease or disorder is mediated through phosphodiesterase Type IV enzyme.
- 25 The method includes administration of at least one compound having the structure of Formula I.

- In accordance with another aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder associated with phosphodiesterase Type IV enzyme, comprising administering to a patient in need thereof,
- 30 an effective amount of a phosphodiesterase Type IV inhibitor compound as described above.

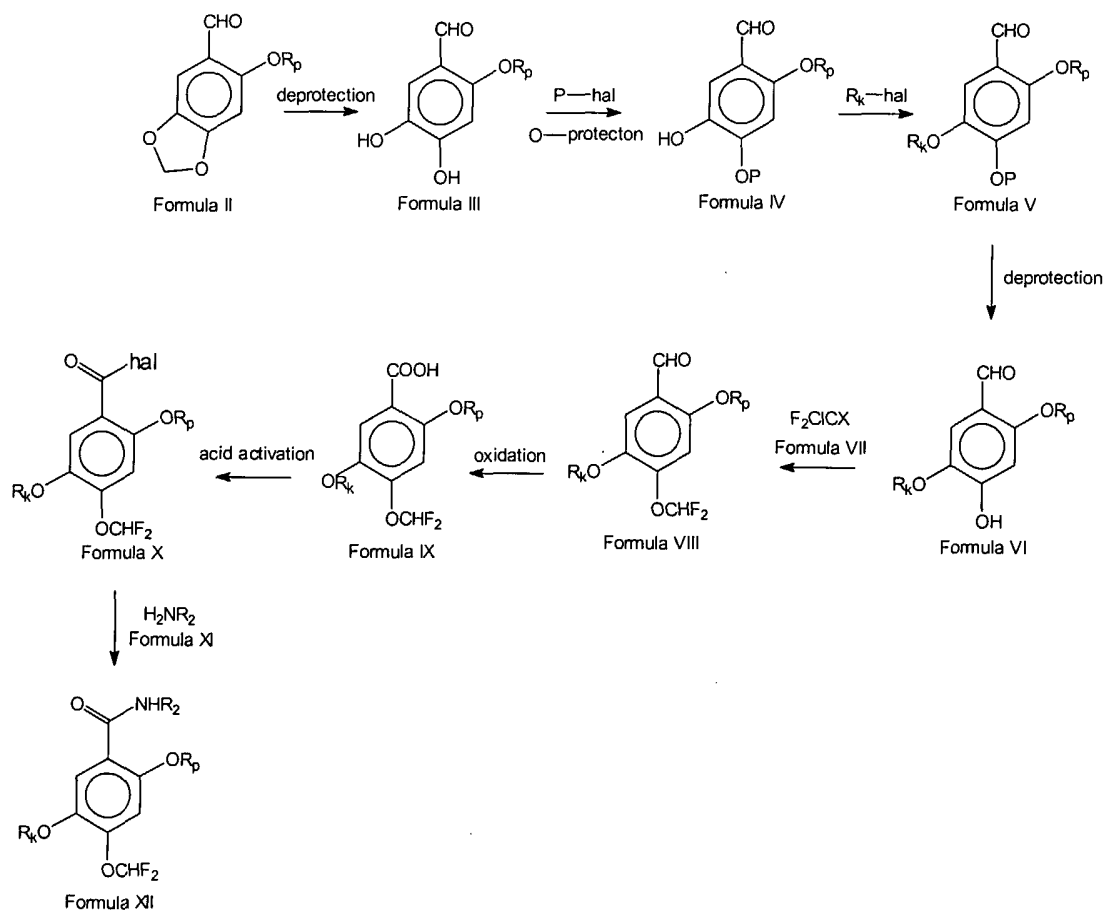
In accordance with yet another aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, shock, atopic dermatitis, crohn's disease, adult respiratory distress syndrome, eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases including administration of at least one compound having the structure of Formula I.

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

Detailed Description of the Invention

The compounds of the present invention may be prepared by techniques known in the art. In addition, the compounds of the present invention may be prepared following a reaction sequence, for example, as depicted below.

Scheme I



The compound of Formula XII can be prepared by following the procedure as depicted in Scheme I. Thus, a compound of Formula II (wherein R_p is alkyl, alkenyl or alkynyl) can be deprotected to give a compound of Formula III, which can undergo O-protection with a compound of Formula P-hal (wherein P is aralkyl (for example benzyl) or alkyl (for example methyl, isopropyl or t-butyl)) to give a compound of Formula IV, which can be reacted with a compound of Formula R_k -hal (wherein R_k is alkyl substituted with cycloalkyl, aryl, heterocyclyl or heteroaryl) to give a compound of Formula V, which can be deprotected to give a compound of Formula VI, which can be reacted with a compound of Formula VII (wherein X is -H or -COOCH₃) to give a compound of Formula VIII, which can undergo oxidation to give a compound of Formula IX, which can be converted to a compound of Formula X (wherein hal is Cl, Br or I), which can be further reacted with a compound of Formula XI (wherein R_2 is the same as defined earlier) to give a compound of Formula XII.

The deprotection of a compound of Formula II to give a compound of Formula III can be carried out with phosphorous pentachloride. Alternatively, boron and aluminum halides for example boron trichloride, aluminum tribromide or aluminum trichloride can also be used in an organic solvent, for example, pentane, benzene, toluene or dichloromethane.

The compound of Formula III can undergo O-protection with a compound of Formula P-hal to give a compound of Formula IV in dipolar aprotic solvent, for example, dimethylsulphoxide, dimethylformamide or hexamethylphosphoric triamide in the presence of a base, for example, potassium hydroxide, sodium hydroxide or lithium hydroxide.

Alternatively, monomethylation of the para-hydroxyl group can be carried out by using controlled quantity of diazomethane in an organic solvent, for example, diethyl ether, ethanol, isopropanol, methanol or dichloromethane.

The compound of Formula IV can be reacted with a compound of Formula R_k -hal to give a compound of Formula V in an organic solvent, for example, dimethylsulphoxide, dimethylformamide, diethyl ether, tetrahydrofuran or dioxane, in the presence of a base, for example, potassium hydroxide, sodium hydroxide or lithium hydroxide.

The compound of Formula V (when P is benzyl) can undergo deprotection to give a compound VI, in the presence of deprotecting agent, for example, palladium on carbon in the presence of hydrogen gas or palladium on carbon in ammonium formate solution, in an organic solvent, for example, ethyl acetate or by utilizing hydrochloric acid in acetic acid.

The compound of Formula V (when P is alkyl) can be deprotected to give a compound of Formula VI by following the procedure as described in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd Ed, John Wiley and Sons, New York, N.Y.

The compound of Formula VI can be reacted with a compound of Formula VII (when X is $-\text{COOCH}_3$) to give a compound of Formula VIII in an organic solvent, for example, dimethylformamide, dimethylsulphoxide, tetrahydrofuran, diethyl ether or dioxane in the presence of a base, for example, cesium carbonate, sodium carbonate, lithium carbonate or potassium carbonate.

The compound of Formula VI can be reacted with a compound of Formula VII (when X is $-\text{H}$) to give a compound of Formula VIII, in an organic solvent, for example, dimethylsulphoxide, dioxane, dimethylformamide, toluene, tetrahydrofuran or diethyl ether, in the presence of a base, for example, potassium hydroxide, sodium hydroxide, butyl lithium, triethyl amine or pyridine with catalyst, for example, benzyltriethyl ammonium chloride, benzyltrimethyl ammonium chloride, benzyltributyl ammonium chloride, tetrabutyl ammonium bromide.

The compound of Formula VIII can be oxidized to give a compound of Formula IX with an oxidizing agent, for example, sodium chlorite, sodium dichromate, potassium permanganate or potassium dichromate, in an organic solvent, for example, acetic acid or formic acid.

The compound of Formula IX can be converted to a compound of Formula X with an acid activating agent, for example, thionyl chloride, phosphorous pentachloride or phosphorous trichloride, in an organic solvent, for example, toluene, benzene or xylene.

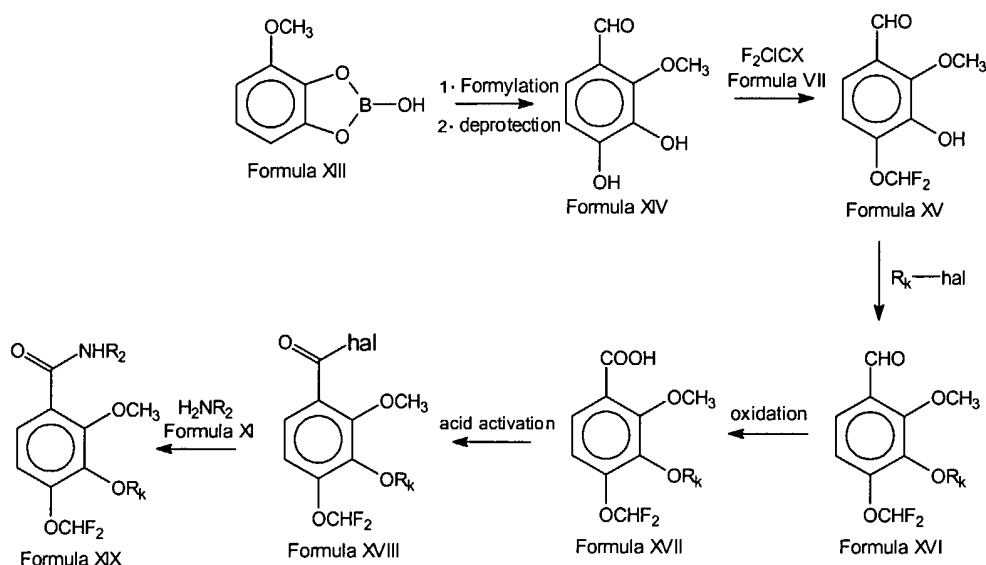
The compound of Formula X can be reacted with a compound of Formula XI to give a compound of Formula XII in an organic solvent, for example, tetrahydrofuran,

dimethylformamide, diethyl ether or dioxane, in the presence of a base, for example, sodium hydride, diisopropylethylamine or butyl lithium.

Particular illustrative compound(s) which can be prepared following Scheme I include:

- 5 5-Cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 1)

Scheme II



- The compound of Formula XIX can be prepared, for example, by following the reaction procedure as depicted in Scheme II. Thus, a compound of Formula XIII can
- 10 undergo formylation to give a compound of Formula XIV, which can be reacted with a compound of Formula VII (wherein X is -H or -COOCH₃) to give a compound of Formula XV, which can be reacted with a compound of Formula R_k-hal to give a compound of Formula XVI, which can undergo oxidation to give a compound of Formula XVII, which can be converted to a compound of Formula XVIII (wherein hal is Br, Cl or
 - 15 I), which can be reacted with a compound of Formula XI to give a compound of Formula XIX.

- The compound of Formula XIII can undergo formylation to give a compound of Formula XIV with a formylation agent, for example, dimethyl formamide, triformamide, tris(diformylamino)methane, tris(dichloromethyl)amine or N,N,N,N-tetraformylhydrazine
- 20 in the presence of a Lewis acid, for example phosphorous oxychloride, aluminum

trichloride or boron trichloride, followed by deprotection with a strong mineral acid, for example, hydrochloric acid, nitric acid or sulphuric acid.

The compound of Formula XIV can be reacted with a compound of Formula VII (wherein X is $-\text{COOCH}_3$) to give a compound of Formula XV in an organic solvent, for example dimethylsulphoxide, dimethylformamide, tetrahydrofuran, diethyl ether or dioxane, in the presence of a base, for example, cesium carbonate, sodium carbonate, lithium carbonate or potassium carbonate.

The compound of Formula XIV can be reacted with a compound of Formula VII (when X is $-\text{H}$) to give a compound of Formula XV in an organic solvent, for example, dioxane, dimethylformamide, toluene, dimethylsulphoxide, tetrahydrofuran or diethyl ether, in the presence of a base, for example, sodium hydroxide, butyl lithium, triethyl amine or pyridine with catalyst for example, benzyltriethyl ammonium chloride, benzyltrimethyl ammonium chloride, benzyltributyl ammonium chloride, tetrabutyl ammonium bromide.

The compound of Formula XV can be reacted with a compound of Formula $\text{R}_k\text{-hal}$ to give a compound of Formula XVI in an organic solvent, for example, dimethylsulphoxide, dimethylformamide, tetrahydrofuran, diethyl ether or dioxane, in the presence of a base, for example, potassium hydroxide, sodium hydroxide or lithium hydroxide.

The compound of Formula XVI can be oxidized to give a compound of Formula XVII with oxidizing agent, for example, sodium chlorite, sodium dichromate, potassium permanganate or potassium dichromate, in an organic solvent, for example, acetic acid, or formic acid.

The compound of Formula XVII can be converted to a compound of Formula XVIII with an acid activating group, for example, thionyl chloride, phosphorous pentachloride or phosphorous trichloride, in an organic solvent, for example, toluene, xylene or benzene.

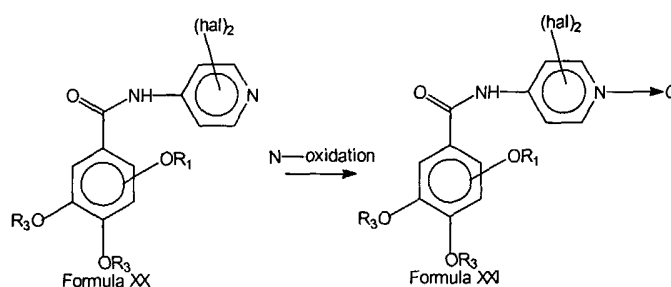
The compound of Formula XVIII can be reacted with a compound of Formula XI to give a compound of Formula XIX in an organic solvent, for example, tetrahydrofuran,

dimethylformamide, diethyl ether or dioxane, in the presence of a base, for example, sodium hydride, diisopropylethylamine or butyl lithium.

Particular illustrative compound(s) which can be prepared following Scheme II include:

- 3-Cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-2-methoxy
5 benzamide (Compound No. 3)

Scheme III



The compounds of Formula XXI can be prepared, for example, following the procedure as depicted in Scheme III. Thus, the compound of Formula XX can undergo N-oxidation to give a compound of Formula XXI.

- 10 The compound of Formula XX can be reacted with an oxidizing agent, for example, magnesium monoperoxyphthalate hexahydrate (MMPP), metachloroperbenzoic acid (m-CPBA), hydrogen peroxide (H₂O₂) or oxone (KHSO₅) in the presence of a solvent mixture, for example, dichloromethane in methanol to give a compound of Formula XXI.

Particular illustrative compounds which may be prepared following Scheme III include:

- 15 5-Cyclopropylmethoxy-N-(3,5-dichloro-1-oxido-pyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 2),
3-Cyclopropylmethoxy-N-(3,5-dichloro-1-oxido-pyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 4).

- Also, in all the above representative examples wherever ethers are specified at a
20 position ortho to the amide group, one skilled in the art could optionally deprotect them to their respective alcohols, for example deprotection of alkyl ethers (such as methyl or ethyl ethers) to their corresponding alcohols can be carried out with hydrochloric acid or hydrobromic acid in aqueous acetic acid or following the procedure as described in T.W.

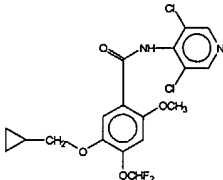
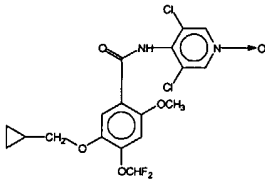
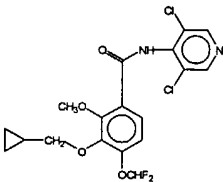
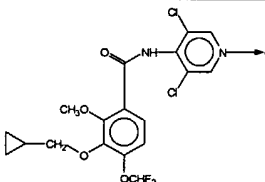
Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed, John Wiley and Sons, New York, N.Y.,

In the above scheme, where specific bases, condensing agents, protecting groups, deprotecting agents, solvents, catalysts, temperatures, etc. are mentioned, it is to be understood that other bases, protecting groups, deprotecting agents, solvents, temperatures, etc. known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

Suitable salts of the compounds represented by the Formula I can also be prepared so as to solubilize the compound in aqueous medium for biological evaluations, as well as to be compatible with various dosage formulations and also to aid in the bioavailability of the compounds. Examples of such salts include pharmacologically acceptable salts such as inorganic acid salts (for example, hydrochloride, hydrobromide, sulphate, nitrate and phosphate), organic acid salts (for example, acetate, tartarate, citrate, fumarate, maleate, tolounesulphonate and methanesulphonate). These salts may be prepared by various techniques, such as treating the compound with an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

Particular illustrative compounds which may be produced by Schemes I, II and III, are listed below in Table I

Table I

Compound No.	Structure	Compound No.	Structure
1		2	
3		4	

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
5 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.

10 The compounds described herein can be produced and formulated as their enantiomers, diastereomers, N-Oxides, polymorphs, solvates and pharmaceutically acceptable salts, as well as metabolites having the same type of activity. Pharmaceutical compositions comprising the molecules of Formula I or metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts
15 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 do not limit the scope of the present invention.

20 EXPERIMENTAL

Example 1: Synthesis of 5-cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 1)

Step a: 4,5-dihydroxy-2-methoxy benzaldehyde

To the compound 2-methoxy-4,5-methylenedioxy benzaldehyde (available
25 commercially) (4 g, 0.022 mol) was added phosphorous pentachloride (13.72 g, 0.066 mol) and stirred the reaction mixture for 3 hours at 80°C. The reaction mass was poured in water with constant stirring and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue thus obtained was triturated with a mixture of
30 isopropanol (10 ml) and hexane (20 ml). The reaction mixture was filtered and dried under reduced pressure to furnish the title compound. Yield = 0.4 g.

¹H NMR (DMSO-d₆): δ 3.79 (s, 3H), 6.54 (s, 1H), 7.06 (s, 1H), 9.2 (bs, 1H), 10.1 (s, 1H), 10.3 (bs, 1H); Mass (M⁺+1): 169.15.

Step b: 4-(Benzyloxy)-5-hydroxy-2-methoxy benzaldehyde

To a solution of the compound obtained from step *a* above (30 g, 0.17 mol) in dimethyl sulphoxide (210 ml), was added pulverized potassium hydroxide (9.6 g, 0.17 mol) and stirred at room temperature for 20 minutes. To it was added benzyl chloride (20.4 ml, 0.176 mol) and stirred the reaction mixture at 70°C for 5 hours followed by addition of next lot of benzyl chloride (2.0 ml). The resulting reaction mixture was again stirred for 1 hour at 70°C. The reaction contents were cooled to room temperature and subsequently poured into water. The product was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using dichloromethane as eluent to furnish the title compound. Yield = 18 g.

¹H NMR (CDCl₃): δ 3.85 (s, 3H), 5.20 (s, 2H), 5.38 (bs, 1H), 6.54 (s, 1H), 7.30-7.42 (m, 6H), 10.29 (s, 1H); Mass (M⁺+1): 259.1.

Step c: 4-Benzyloxy-5-(cyclopropylmethoxy)-2-methoxy benzaldehyde

To a solution of the compound obtained from step *b* above (10 g, 0.0387 mol) in dimethylsulphoxide (65 ml), was added pulverized potassium hydroxide (2.47 g, 0.044 mol) and stirred for 20 minutes followed by the addition of cyclopropylmethyl bromide (5.2 g, 0.0391 mol). The reaction mixture was stirred at 50°C for 3 hours followed by cooling it to room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with sodium hydroxide (5%), water and brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure to furnish the title compound. Yield = 11.5 g.

¹H NMR (CDCl₃): δ 0.33-0.36 (m, 2H), 0.59-0.65 (m, 2H), 1.26-1.34 (m, 1H), 3.81 (s, 3H), 3.87-3.89 (d, 2H), 5.25 (s, 2H), 6.5 (s, 1H), 7.31-7.46 (m, 6H), 10.27 (s, 1H); Mass (M⁺+1): 312.

Step d: 5-(Cyclopropylmethoxy)-4-hydroxy-2-methoxy benzaldehyde

The compound obtained from step *c* above (4.5 g, 0.0144 mol) was dissolved in ethyl acetate (90 ml) followed by the addition of palladium on carbon (10% w/w, 0.8 g).

Hydrogenation was carried out under hydrogen atmosphere at 45°C for 5 hours. The reaction mixture was filtered through celite pad and solvent was evaporated under reduced pressure. The residue thus obtained was triturated with a mixture of hexane (20 ml) and isopropylalcohol (5 ml) to furnish the title compound. Yield = 2.5 g.

- 5 ¹H NMR (CDCl₃): δ 0.31-0.36 (m, 2H), 0.62-0.68 (m, 2H), 1.23-1.28 (m, 1H), 3.87 (s, 3H), 3.89 (bs, 2H), 6.40 (s, 1H), 6.59 (s, 1H), 7.30 (s, 1H), 10.28 (s, 1H); Mass (M⁺+1): 223.0.

Step e: 5-(Cyclopropylmethoxy)-4-(difluoromethoxy)-2-methoxy benzaldehyde

- Route I: To a solution of the compound obtained from step *d* above (4.0 g, 0.018 mol) in dimethylformamide (28 ml) was added cesium carbonate (5.9 g, 0.018 mol) and stirred the mixture for 15 minutes at 27°C followed by the addition of methyl chlorodifluoroacetate (3.3 g, 0.0229 mol). The resulting reaction mixture was stirred at 80°C for 3 hours followed by cooling it to room temperature. The reaction mixture was poured into water and extracted the product with ethyl acetate. The solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography to furnish the title compound. Yield = 1.1 g.
- 10
15

- Route II: To a solution of the compound obtained from step *d* above (0.1 g, 0.00045 mol) in dimethylsulphoxide was added pulverized potassium hydroxide (0.063g, 0.0012mole) and potassium iodide (0.1g, 0.0006 mole). Chlorodifluoromethane was bubbled through it and stirred the reaction mixture for 2 hours followed by the addition of sodium hydroxide (0.5g, 0.0125 mol). The reaction mixture was again stirred for 3 hours and subsequently poured into water. The product was extracted with ethyl acetate, washed the organic layer with sodium hydroxide solution (5%) and water, dried over anhydrous sodium sulphate and evaporated the solvent under reduced pressure to furnish the title compound. Yield = 0.6 g.
- 20
25

¹H NMR (CDCl₃): δ 0.33-0.34 (m, 2H), 0.61-0.65 (m, 2H), 1.23-1.30 (m, 1H), 3.8-3.92 (m, 5H), 6.81 (t, 1H), 6.83 (s, 1H), 7.41 (s, 1H), 10.37 (s, 1H).

Step f: 5-(Cyclopropylmethoxy)-4-difluoromethoxy-2-methoxy benzoic acid

- The compound obtained from step *e* above (1.1 g, 0.004 mol) in acetic acid (5.5 ml), was added sulfamic acid (0.7 g) and cooled the reaction mixture to 10°C followed by
- 30

the addition of sodium chlorite solution dropwise (0.8 g in 1.65 ml H₂O). The reaction mixture was stirred for 20 minutes in ice bath followed by stirring it at 27°C for approx 2 hours. The reaction contents were poured into water (50 ml) and extracted with ethyl acetate (150 ml). The solvent was evaporated under reduced pressure to furnish the title compound. Yield = 1.0 g.

¹H NMR (CDCl₃): δ 0.32-0.37 (m, 2H), 0.62-0.66 (m, 2H), 1.24-1.30 (m, 1H), 3.88-3.91 (d, 2H), 4.04 (s, 3H), 6.83 (t, 1H), 6.90 (s, 1H), 7.75 (s, 1H), 10.68 (bs, 1H); Mass (M⁺+1): 289.

Step g: 5-Cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 1)

To a solution of the compound obtained from step *f* above (1.0 g, 0.0035 mol) in toluene (6.6 ml) was added thionyl chloride (8.32 g, 0.0699 mol) and toluene (6.6 ml) and stirred for 2 hours at 85°C. Excess of thionyl chloride and toluene were distilled off under reduced pressure. The acid chloride thus obtained was dissolved in tetrahydrofuran (5 ml) and this mixture was added dropwise to an already 15 minutes stirred mixture of 3,5-dichloro-4-amino pyridine (0.7 g, 0.0043 mol) and sodium hydride (60%, 0.38 g, 0.0095 mol) in tetrahydrofuran (5 ml) at 15°C. The reaction mixture was stirred for approximately 2 hours and subsequently poured the reaction mass into water (50 ml) with constant stirring. It was acidified with hydrochloric acid (3 ml) and extracted the product with ethyl acetate, washed with water, dried over anhydrous sodium sulphate and evaporated the solvent under reduced pressure. The residue thus obtained was crystallized from a mixture of isopropanol (3 ml) and dichloromethane (3 ml) followed by the addition of charcoal (30 mg) in isopropyl alcohol to furnish the title compound. The compound was again recrystallised from isopropanol (3 ml). Yield = 0.34 g.

¹H NMR (CDCl₃): δ 0.33-0.38 (m, 2H), 0.62-0.68 (m, 2H), 1.22-1.30 (m, 1H), 3.93 (d, 2H), 4.05 (s, 3H), 6.84 (t, 1H), 6.93 (s, 1H), 7.88 (s, 1H), 8.57 (s, 2H), 9.88 (s, 1H); Mass (M⁺+1): 433.1.

Example 2: Synthesis of 3-Cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 3)

Step a: 4-methoxy-benzo[1,3,2]dioxaborol-2-ol

To 3-methoxycatechol (3 g, 0.021 mol) (available commercially) was added borax (8.0 g, 0.021 mol) and water (150 ml) and stirred for 3 hours at 45-50°C. Water was evaporated under reduced pressure. Traces of water were removed azeotropically with toluene (150 ml) under reduced pressure. The residue thus obtained was diluted with dimethylformamide followed by evaporating it under reduced pressure to furnish the title compound. Yield = 8.5 g.

¹H NMR (D₂O): δ 3.88 (s, 3H), 6.49-6.74 (m, 3H).

Step b: 3,4-Dihydroxy-2-methoxy benzaldehyde

To dimethylformamide (260 ml) was added phosphorous oxychloride dropwise maintaining the temperature below 70°C and stirred at room temperature for 1 hour. To it was added the compound obtained from step *a* above (94 g) in small lots keeping the temperature below 60°C and stirred for 3 hours at 60°C. The reaction mixture was cooled to room temperature and subsequently poured into water (1000 ml) and hydrochloric acid (50 ml) solution maintaining the temperature below 55°C. The mixture was stirred at room temperature for approx. 2 hour and extracted with ethyl acetate. The mixture of isomers was purified by column chromatography using mixture of methanol (1%) and chloroform (99%) as eluent to furnish the title compound. Yield = 4.2 g.

¹H NMR (CDCl₃): δ 3.99 (s, 3H), 5.72 (s, 1H), 5.93 (s, 1H), 6.81-6.84 (d, 1H), 7.35-7.38 (d, 1H), 10.07 (s, 1H); Mass (M⁺+1): 169.

Step c: 4-(Difluoromethoxy)-3-hydroxy-2-methoxy benzaldehyde

To a solution of the compound obtained from step *b* above (0.5 g, 0.0029 mol) in dimethyl formamide (7 ml), was added cesium carbonate (0.8 g, 0.00246 mol) and stirred the reaction mixture at room temperature for 20 minutes followed by the addition of methyl chlorodifluoroacetate (0.5 g, 0.00342 mol). The mixture was again stirred at 65-70°C for 3 hours and was subsequently poured into water. The product was extracted with ethyl acetate, washed with water, borax solution (10%) and again with water, dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure. The

residue thus obtained was stirred in a mixture of hexane (20 ml) and isopropyl alcohol (2 ml). The reaction mixture was filtered and evaporated the solvent under reduced pressure to furnish the title compound. Yield = 170 mg.

¹H NMR (CDCl₃): δ 4.06 (s, 3H), 6.43-6.92 (t, 1H), 6.99-7.02 (d, 1H), 7.39-7.42 (d, 1H),
5 10.28 (s, 1H); Mass (M⁺+1): 218.9.

Step d: 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)-2-methoxy benzaldehyde

To a solution of compound obtained from step *c* above (0.55 g, 0.0025 mol) in dimethyl sulphoxide (10 ml), was added pulverized potassium hydroxide (0.132 g, 0.00233 mol) and stirred for 20 minutes followed by the addition of cyclopropylmethyl
10 bromide (0.33 g, 0.0024 mol). The reaction mixture was stirred for 2 hours at room temperature and subsequently poured into water and extracted with ethyl acetate. The organic layer was washed with sodium hydroxide (5%) and water, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue thus obtained was stirred in hexane and filtered. The solvent was evaporated under reduced pressure to
15 furnish the title compound. Yield = 0.56 g.

¹H NMR (CDCl₃): δ 0.28-0.32 (m, 2H), 0.59-0.65 (m, 2H), 1.26-1.31 (m, 1H), 3.89-3.91 (d, 2H), 4.08 (s, 3H), 6.45-6.94 (t, 1H), 6.97-6.99 (d, 1H), 7.57-7.60 (d, 1H), 10.32 (s, 1H);
Mass (M⁺+1): 273.

Step e: 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)-2-methoxy benzoic acid

To a solution of the compound obtained from step *d* above (0.2 g, 0.00073 mol) and sulfamic acid (0.154 g, 0.00015 mol) in acetic acid at 8°C, was added sodium chlorite solution (0.16 g, 0.0017 mol in 0.5 ml of H₂O) maintaining the temperature below 15°C. The resulting reaction mixture was stirred at 8°C for 1 hour and then at room temperature for 1 hour followed by the addition of water. The product was extracted with ethyl acetate.
25 The organic layer was washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish the title compound. Yield = 220 mg.

¹H NMR (CDCl₃): δ 0.27-0.32 (m, 2H), 0.6-0.66 (m, 2H), 1.25-1.31 (m, 1H), 3.88-3.9 (d, 2H), 4.16 (s, 3H), 6.42-6.92 (t, 1H), 7.04-7.07 (d, 1H), 7.89-7.92 (d, 1H); Mass (M⁺+1):
30 289.2.

Step f: 3-Cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 3)

To a solution of the compound obtained from step *e* above (220 mg, 0.000764 mol) in toluene (3.0 ml), was added thionyl chloride (0.6 ml, 0.008 mol) and stirred at 80°C for approx. 2 hours. Excess of thionyl chloride and toluene were evaporated under reduced pressure. The residue thus obtained was dissolved in tetrahydrofuran (3 ml) and the resulting mixture was added dropwise to an already 15 minutes stirred mixture of 3,5-dichloro-4-aminopyridine (154 mg, 0.00095 mol) and sodium hydride (60%, 0.083 g, 0.002 mol) in tetrahydrofuran (3 ml) at 10-12°C. The reaction mixture was stirred at 10°C for 1 hour and subsequently poured into water (50 ml). The product was extracted with ethyl acetate, washed with hydrochloric acid solution (5%), water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish the title compound. Yield = 260 mg.

¹H NMR (CDCl₃): δ 0.32-0.34 (m, 2H), 0.63-0.66 (m, 2H), 1.26-1.31 (m, 1H), 3.91-3.93 (d, 2H), 4.21 (s, 3H), 6.44-6.94 (t, 1H), 7.06-7.09 (d, 1H), 7.97-8.00 (d, 1H), 8.58 (s, 2H), 9.89 (s, 1H); Mass (M⁺+1): 433.

Example 3: Synthesis of 3-cyclopropylmethoxy-N-(3,5-dichloro-1-oxido-pyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 4)

The compound No. 3 (140 mg, 0.00032 mol) was dissolved in a mixture of dichloromethane (1 ml) and methanol (1 ml) followed by the addition of magnesium monoperoxyphthalate hexahydrate (0.32 g, 0.00064 mol). The reaction mixture was stirred at room temperature for 6 hours followed by the addition of magnesium monoperoxyphthalate hexahydrate (0.2 g). This procedure was repeated four times. The resulting mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with ammonium acetate solution and water. The solvent was evaporated under reduced pressure to furnish the title compound. Yield = 100 mg.

¹H NMR (CDCl₃): δ 0.26-0.29 (m, 2H), 0.57-0.62 (m, 2H), 1.21-1.26 (m, 1H), 3.86-3.91 (d, 2H), 4.15 (s, 3H), 6.4-6.89 (t, 1H), 7.02-7.05 (d, 1H), 7.90-7.93 (d, 1H), 8.26 (s, 2H), 9.70 (s, 1H); Mass (M⁺+1): 449.

Example 4: Synthesis of 5-Cyclopropylmethoxy-N-(3,5-dichloro-1-oxido-pyridin-4-yl)-4-difluoromethoxy-2-methoxy benzamide (Compound No. 2)

The compound No. 1 (0.2 g, 0.00046 mol) was dissolved in a mixture of dichloromethane (1 ml) and methanol (1 ml) followed by the addition of magnesium
5 monoperoxy-phthalate hexahydrate (MMPP) (0.457 g) and stirred for 24 hours at 40°C. To the resulting reaction mixture was added dichloromethane (1 ml), methanol (1 ml) and magnesium monoperoxyphthalate hexahydrate (0.248 g) and stirred for 12 hours. This process was repeated one more time. To the resulting reaction mixture was added magnesium monoperoxyphthalate hexahydrate (MMPP) (0.248 g) and stirred the reaction
10 mixture for 24 hours with a constant addition of methanol (1 ml) after every 4 hours. The reaction mixture was diluted with water and extracted the product with ethyl acetate (50 ml). The organic layer was washed with ammonium acetate solution (25%), water and brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue thus obtained was recrystallised using a mixture of isopropanol (1.5 ml) and
15 dichloromethane (2 ml) to furnish the title compound. Yield = 140 mg.

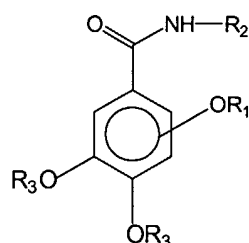
^1H NMR (CDCl_3): δ 0.34-0.38 (m, 2H), 0.62-0.69 (m, 2H), 1.22-1.31 (m, 1H), 3.91-3.93 (d, 2H), 4.05 (s, 3H), 6.85 (t, 3H), 6.94 (s, 1H), 7.86 (s, 1H), 8.26 (s, 2H), 9.67 (s, 1H); Mass ($\text{M}^+ + 1$): 449.2.

PDE-IV Enzyme Assay

20 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
25 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 test compounds 1 and 2 (three test repetitions each) were found to be approximately 1.9 (± 0.7) and 2.3 (± 0.9) nM, respectively. The values for rolipram (7 repetitions) and
30 roflumilast (two repetitions) were 463 (± 103) and 0.051 (± 0.028) nM, respectively.

WE CLAIM:

1 1. A compound having the structure of Formula I,
2



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

10 R₁ is hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl,
11 heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl;

12 R₂ is aryl, heteroaryl, heterocyclyl or cycloalkyl; and

13 R₃ is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl,
14 heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl.

1 2. A compound according to claim 1, wherein R₁ is alkyl, R₂ is heteroaryl substituted
2 with one or more of halogen and R₃ is cycloalkylalkyl or alkyl substituted with one or
3 more of halogen.

1 3. A compound according to claim 2, wherein R₁ is methyl, R₂ is dichloropyridyl, R₃
2 is difluoromethyl or cyclopropylmethyl.

1 4. A compound which is selected from

2 5-cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoro methoxy-2-methoxy
3 benzamide (Compound No. 1),

4 5-Cyclopropylmethoxy-N-(3,5-dichloro-1-oxido-pyridin-4-yl)-4-difluoromethoxy-2-
5 methoxy benzamide (Compound No. 2),

6 3-Cyclopropylmethoxy-N-(3,5-dichloropyridine-4-yl)-4-difluoromethoxy-2-methoxy
7 benzamide (Compound No. 3),

8 3-Cyclopropylmethoxy-N-(3,5-dichloro-1-oxido-pyridin-4-yl)-4-difluoromethoxy-2-
 9 methoxy benzamide (Compound No. 4), or pharmaceutically acceptable salts, or solvates
 10 thereof.

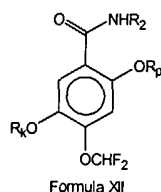
1 5. A pharmaceutical composition comprising a therapeutically effective amount of a
 2 compound of claim 1 together with pharmaceutically acceptable carriers, excipients or
 3 diluents.

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

1 7. 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 8. A method of preventing, inhibiting or suppressing inflammatory disease in an
 2 animal or human comprising administering to said animal or human a therapeutically
 3 effective amount of the pharmaceutical composition according to claim 7.

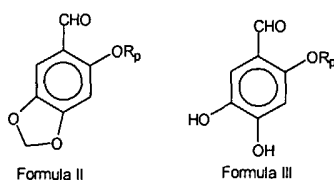
1 9. A method for preparing a compound of Formula XII and its pharmaceutically
 2 acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-
 3 oxides



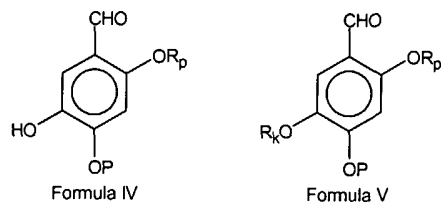
8 wherein

- 9 R_p is alkyl, alkenyl or alkynyl;
 10 P is aralkyl (for example benzyl) or alkyl (for example methyl, isopropyl or t-butyl);
 11 R_k is alkyl substituted with cycloalkyl, aryl, heterocyclyl or heteroaryl; and
 12 R_2 is aryl, heteroaryl, heterocyclyl or cycloalkyl, wherein the method comprises:

a) deprotecting a compound of Formula II to give a compound of Formula III;

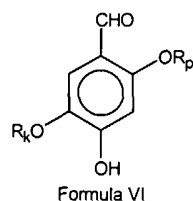


b) O-protecting the compound of Formula III with a compound of Formula P-hal (wherein P is aralkyl or alkyl) to give a compound of Formula IV;

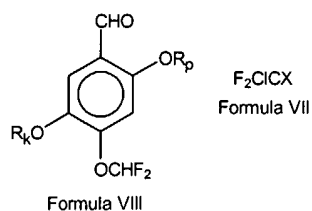


c) reacting the compound of Formula IV with a compound of Formula R_k-hal (wherein R_k is alkyl substituted with cycloalkyl, aryl, heterocyclyl or heteroaryl) to give a compound of Formula V;

d) deprotecting the compound of Formula V to give a compound of Formula VI;

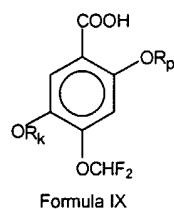


e) reacting the compound of Formula VI with a compound of Formula VII (wherein X is -H or -COOCH₃) to give a compound of Formula VIII;



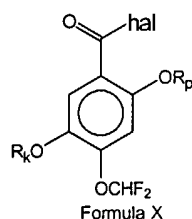
28

29 f) oxidizing the compound of Formula VIII to give a compound of Formula IX;



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31 g) converting the compound of Formula IX to a compound of Formula X
32 (wherein hal is Cl, Br or I); and



33

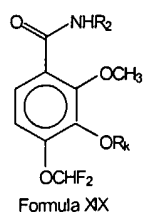
34 h) reacting the compound of Formula X with a compound of Formula XI (wherein
35 R₂ is the same as defined earlier) to give a compound of Formula XII.

1 10. A method for preparing a compound of Formula XIX and its pharmaceutically
2 acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-
3 oxides

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7 wherein
 8 P is aralkyl (for example benzyl) or alkyl (for example methyl, isopropyl or t-butyl);
 9 R_k is alkyl substituted with cycloalkyl, aryl, heterocyclyl or heteroaryl; and
 10 R_2 is aryl, heteroaryl, heterocyclyl or cycloalkyl,
 11 wherein the method comprises:

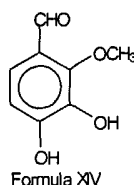
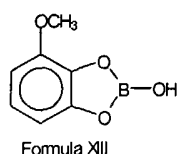
12 a) formylating a compound of Formula XIII to give a compound of Formula XIV;

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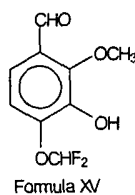
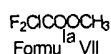


17 b) reacting the compound of Formula XIV with a compound of Formula VII
 18 (wherein X is -H or -COOCH₃) to give a compound of Formula XV;

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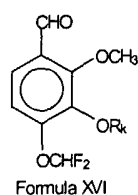
22 c) reacting the compound of Formula XV with a compound of Formula R_k -hal to
 23 give a compound of Formula XVI;

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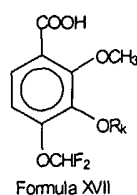
28 d) oxidizing the compound of Formula XVI to give a compound of Formula XVII;

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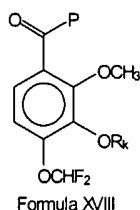
33 e) converting the compound of Formula XVII to a compound of Formula XVIII
 34 (wherein hal is Br, Cl or I); and

35

36

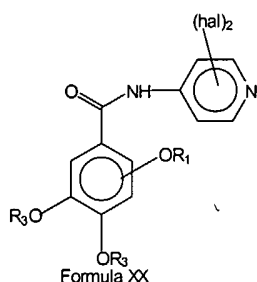
37

38



39 f) reacting the compound of Formula XVIII with a compound of Formula XI
 40 (H_2NR_2) to give a compound of Formula XIX.

1 11. A method for preparing a compound of Formula XXI and its pharmaceutically
 2 acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-
 3 oxides



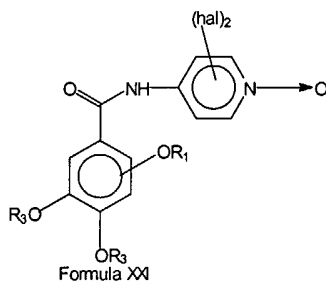
4

5 wherein

6 Hal is halogen (Cl, Br or I);

7 R_1 is hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl,
 8 heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl; and

9 R_3 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl,
 10 heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl, the method comprising N-oxidizing
 11 a compound of Formula XX to give the compound of Formula XXI.



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003017

A. CLASSIFICATION OF SUBJECT MATTER
C07D213/75 C07C235/56 A61P11/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C 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, WPI Data, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/000806 A (ELBION AG) 31 December 2003 (2003-12-31) page 1, paragraph 1 examples 2, 21	1-11
X	EP 1 052 254 A (EISAI) 15 November 2000 (2000-11-15) page 1 example 19	1-11
X	WO 96/11690 A (INSTITUT DE RECHERCHE JOUVEINAL) 25 April 1996 (1996-04-25) example 2M	1-11
	----- -/-	

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

Z document member of the same patent family

Date of the actual completion of the international search

15 February 2006

Date of mailing of the international search report

28/02/2006

Name and mailing address of the ISA/

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Authorized officer:

Cortés, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003017

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/029055 A (BAYER HEALTHCARE AG) 8 April 2004 (2004-04-08) page 1, paragraph 2 page 173 - page 174; examples 2/239, 2/241, 2/242 -----	1-11
X	WO 02/096879 A (SANOFI-SYNTHELABO) 5 December 2002 (2002-12-05) page 7, line 17 - line 26 page 16; table 1; compound 15 -----	1-11
X	WO 02/064545 A (AVENTIS) 22 August 2002 (2002-08-22) page 32, paragraph 1 examples 82, 95, 183 -----	1-11
X	WO 99/61013 A (AVANIR PHARMA) 2 December 1999 (1999-12-02) page 1 claims 1, 3 -----	1-11
X	WO 99/05104 A (PFIZER) 4 February 1999 (1999-02-04) page 1, paragraph 1 page 7, line 8 page 101; example 264 -----	1-11
X	WO 97/14681 A (FUJISAWA PHARMA) 24 April 1997 (1997-04-24) page 27, line 24 - page 28, line 3 page 263; example 234 -----	1-11
X	JP 55 022634 A (HISAMITSU PHARMACEUT CO INC) 18 February 1980 (1980-02-18) abstract compounds 1, 3, 6 -----	1-11
X	US 3 415 841 A (KUHLMANN ETS) 10 December 1968 (1968-12-10) column 1, paragraph 1 examples 2, 4 -----	1-11
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X	JP 11 222435 A (OTSUKA PHARMA) 17 August 1999 (1999-08-17) table 1; compounds 1-12 table 2; compounds 26-28, 33, 37, 40-42, 51, 52, 58, 59 table 3; compounds 66, 73 -----	1, 5
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003017

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 915 093 A (OTSUKA PHARMA) 12 May 1999 (1999-05-12) examples	1,5
X	JP 10 101672 A (OTSUKA PHARMA) 21 April 1998 (1998-04-21) compounds 1, 14-20, 46, 52-78, 94, 96,97,100-105, 107-121, 129-131, 133, 135, 136	1,5
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003017

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& DATABASE CHEMCATS 2001, ASINEX EXPRESS GOLD COLLECTION: Database accession no. 2001:543291 CHEMCATS & list of compounds published in chemcats with an entry date before 11.10.2004 abstract -----	
X	WO 01/93909 A (GLAXO) 13 December 2001 (2001-12-13) page 1, paragraph 1 claim 8 -----	1-11
X	WO 96/21435 A (EURO-CELTIQUE) 18 July 1996 (1996-07-18) page 5, line 14 - line 25 claim 1 -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/003017

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-8 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

International application No
PCT/IB2005/003017

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003017

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