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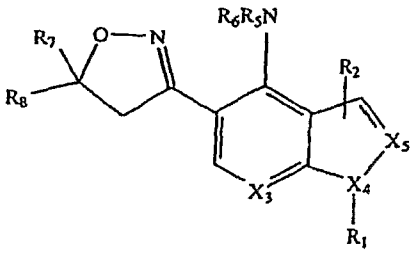
(54) Title: SUBSTITUTED PYRAZOLO [3,4-B] PYRIDINES AS PHOSPHODIESTERASE INHIBITORS



XIV

(57) Abstract: The present invention relates to phosphodiesterase (PDE) type IV selective inhibitors. Processes for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds and their use as PDE type IV selective inhibitors are provided. Prepared compounds correspond to structure XIV. Formula (XIV).

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PHOSPHODIESTERASE INHIBITORS

Field of the Invention

The present invention relates to phosphodiesterase (PDE) type IV selective inhibitors.

Compounds disclosed herein can be useful in the treatment of CNS 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, ulcerative colitis and other inflammatory diseases especially in humans.

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

Background of the Invention

It is known that cyclic adenosine-3′, 5′-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger (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. PDE4 inhibitors are designed to inhibit the activity of PDE4, the enzyme which breaks down neuronal cAMP. Studies have shown that administering PDE4 inhibitors can have a restorative effect on memory loss in animal models, including those of Alzheimer's disease (*Expert Opin. Ther. Targets*, (2005) 9(6):1283-1305; Drug *Disc. Today*, 10, (2005)). The most important role in the control of cAMP (as well as of cGMP) level is played by cyclic nucleotide phosphodiesterases (PDE) which represent a biochemically and functionally highly variable super family of enzymes. Eleven distinct families of cyclic nucleotide phosphodiesterases with more than 25 gene products are currently recognized. Although PDE I, PDE II, PDE III, PDE IV, and PDE VII all use cAMP as a substrate, only PDE IV and PDE VII are highly selective for hydrolysis of cAMP. Inhibitors of PDE, particularly the PDE IV inhibitors, such as rolipram or Ro-1724 are therefore known as cAMP-enhancers. Immune cells contain type IV and type III

PDE, the PDE IV type being prevalent in human mononuclear cells. Thus the inhibition of phosphodiesterase type IV has been a target for modulation and, accordingly, for therapeutic intervention in a range of disease processes.

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

WO 2003/047520 discloses substituted aminomethyl compounds and derivatives thereof, which have been described to be useful as inhibitors of factor Xa. WO 2000/59902 discloses aryl sulfonyls, which have been described to be useful as inhibitors of factor Xa. WO 97/48697 discloses substituted azabicyclic compounds and their reported use as inhibitors of the production of TNF and cyclic AMP phosphodiesterase. WO 98/57951 and US 6,339,099 describe nitrogen containing heteroaromatics and derivatives, which have been said to be inhibitors of factor Xa. WO 01/19798 discloses compounds, which have been described to have activity against mammalian factor Xa.

Summary of the Invention

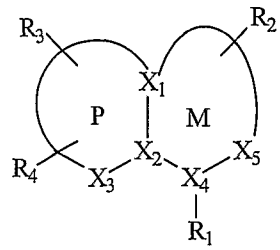
Herein are provided phosphodiesterase (PDE) type IV selective inhibitors, which can be used for the treatment of CNS diseases, AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases and the processes for the synthesis of these compounds.

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical compositions containing the compounds are provided, which may also contain pharmaceutically acceptable carriers or diluents, and which can be used for the treatment of CNS 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, 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 are provided compounds having the structure of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides, wherein ring P including X_1 , X_2 and X_3 can be a six-membered ring containing 1-3 double bonds wherein X_1 and X_2 can be carbon and X_3 can be nitrogen;

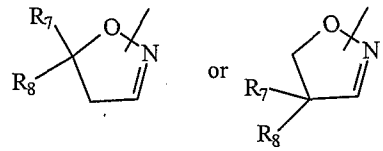
ring M including X_1, X_2, X_4 and X_5 can be a five-membered ring containing 1-2 double bonds wherein X_1 and X_2 can be carbon and X_4 and X_5 can be nitrogen;

R_1 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, aralkenyl, (cycloalkyl) alkyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl;

R_2 can be hydrogen, alkyl, halogen, cyano, nitro, -SR, NRR, $-(CH_2)_n$ OR {wherein R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or heterocyclyl and n can be an integer from 0-2}, alkenyl, alkynyl, cycloalkyl, (cycloalkyl) alkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl;

R_3 can be $-NR_5R_6$ {wherein R_5 and R_6 independently can be hydrogen, alkyl, alkenyl, alkynyl, acyl, cycloalkyl, aryl, aralkenyl, aralkyl, (cycloalkyl) alkyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl}; and

R_4 can be a radical of Formula I a or I b



Formula Ia Formula Ib

wherein R_7 and R_8 independently can be alkyl, -CN, - $(CH_2)_n$ C(=O) NR_fR_q {wherein n can be an integer from 0-2 and R_f and R_q independently can be hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, (heteroaryl)alkyl},– $(CH_2)_n$ C (=O) OR_f {wherein n and R_f are the same as defined earlier}, -$(CH_2)_n$ OR_f {wherein n and R_f are the same as defined earlier}.

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. Alkyl groups can be optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, a phenylene, sulphinyl, sulphonyl group or -NR_α-, wherein R_α can be hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, -C(=O)OR_λ, SO_mR_ψ or -C(=O)$NR_\lambda R_\pi$. 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, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, cycloalkoxy, -CH=N-O(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl)-C_{1-6}alkyl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_λ, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -NHC(=O)$NR_\lambda R_\pi$, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)$NR_\lambda R_\pi$ {wherein R_λ and R_π are independently selected from hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or

carboxy}, nitro or -SO_mR_ψ (wherein m is an integer from 0-2 and R_ψ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$OC(=O)NR_\lambda R_\pi$,-$NHC(=O)NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -SO_mR_ψ; or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_α- (wherein R_α, R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -O-$C(=O)NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the 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. Alkenyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and -NR_α- (wherein R_α is the same as defined earlier). 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, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, -$NHC(=O)R_\lambda$, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -O-$C(=O)NR_\lambda R_\pi$, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, keto, carboxyalkyl, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, hydroxyamino, alkoxyamino, nitro or SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, -CF_3, cyano, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -O-$C(=O)NR_\lambda R_\pi$ and -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are as defined earlier). Groups, such as ethenyl or vinyl ($CH=CH_2$), 1-propylene or allyl (-$CH_2CH=CH_2$), iso-propylene (-$C(CH_3)=CH_2$), bicyclo[2.2.1]heptene, and the like, exemplify this term.

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. Alkynyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and $-NR_{\alpha}-$ (wherein R_{α} is the same as defined earlier). In the event that alkynyl groups are 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, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-NHC(=O)R_{\lambda}$, $-NR_{\lambda}R_{\pi}$, $-NHC(=O)NR_{\lambda}R_{\pi}$, $-C(=O)NR_{\lambda}R_{\pi}$, $-O-C(=O)NR_{\lambda}R_{\pi}$ or $-SO_mR_{\psi}$ (wherein R_{λ}, R_{π}, m and R_{ψ} are the same as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, $-NR_{\lambda}R_{\pi}$, $-C(=O)NR_{\lambda}R_{\pi}$, $-NHC(=O)NR_{\lambda}R_{\pi}$, $-C(=O)NR_{\lambda}R_{\pi}$, cyano or $-SO_mR_{\psi}$ (wherein R_{λ}, R_{π}, m and R_{ψ} are the 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, $-NR_{\lambda}R_{\pi}$, $-NHC(=O)NR_{\lambda}R_{\pi}$, $-NHC(=O)R_{\lambda}$, $-C(=O)NR_{\lambda}R_{\pi}$, $-O-C(=O)NR_{\lambda}R_{\pi}$, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or SO_mR_{ψ} (wherein R_{λ}, R_{π}, m and R_{ψ} are the same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be

substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, CF_3, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-OC(=O)NR_\lambda R_\pi$, cyano or $-SO_mR_\psi$ (wherein R_λ, R_π, m and R_ψ are the 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 "(cycloalkyl) alkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are as defined earlier.

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

The term "aryl," unless otherwise specified, refers to aromatic system having 6 to 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or napthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3, cyano, nitro, $COOR_\psi$, $NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, $-CONHR_\pi$, $-OCOR_\pi$, $-COR_\pi$, $-NHSO_2R_\pi$ or $-SO_2NHR_\pi$ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Aryl groups optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

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, ethylphenyl, propylphenyl, naphthylmethyl and the like.

The term "aralkenyl," unless otherwise specified, refers to alkenyl-aryl linked through alkenyl (wherein alkenyl is as defined above) portion and the alkenyl portion contains 1 to 6 carbon atoms and aryl is as defined below.

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

The term "cycloalkoxy" denotes the group O-cycloalkyl, wherein cycloalkyl is as defined above.

The term "carboxy," as defined herein, refers to –C (=O) OR_f, wherein R_f is the same as defined above.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms or a bicyclic or tricyclic aromatic group having from 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S 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, $-NR_\lambda R_\pi$, CH=NOH, $-(CH_2)_wC(=O)R_\eta$ {wherein w is an integer from 0-4 and R_η is hydrogen, hydroxy, OR_λ, $NR_\lambda R_\pi$, $-NHOR_\omega$ or -NHOH}, $-C(=O)NR_\lambda R_\pi$ $-NHC(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, $-O-C(=O)NR_\lambda R_\pi$, $-O-C(=O)R_\lambda$, or $-O-C(=O)OR_\lambda$ (wherein m, R_ψ, R_λ and R_π are as defined earlier and R_ω 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, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinazonyl, carbazolyl phenothiazinyl, phenoxazinyl, 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, optionally substituted aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, $-O-C(=O)R_\lambda$, $-O-C(=O)OR_\lambda$, $-C(=O)NR_\lambda R_\pi$, SO_mR_ψ, $-O-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NR_\lambda R_\pi$, mercapto, haloalkyl, thioalkyl, $-COOR_\psi$, $-COONHR_\lambda$, $-COR_\lambda$, $-NHSO_2R_\lambda$ or SO_2NHR_λ (wherein m, R_ψ, R_λ and R_π are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more

double bonds. Such ring systems can be mono-, bi- or tricyclic. Carbonyl or sulfonyl group can replace carbon atom(s) of heterocyclyl. 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, benzoxazinyl, benzthiazinyl, imidazolyl, benzimidazolyl, tetrazolyl, carbaxolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl, tetrahydropyranyl, piperazinyl, 3H-imidazo[4,5-b]pyridine, isoquinolinyl, 1H-pyrrolo[2,3-b]pyridine or piperazinyl and the like.

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

"(Heterocyclyl) alkyl" refers to alkyl-heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

"Acyl" refers to $-C(=O)R_z$ wherein R_z is same as defined earlier.

"Thiocarbonyl" refers to –C(=S)H. "Substituted thiocarbonyl" refers to -C (=S) R‴, wherein R‴ is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl , heterocyclylalkyl, amine or substituted amine. Unless otherwise constrained by the definition, all substituents optionally may be substituted further by 1-3 substituents selected from alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, hydroxy, alkoxy, halogen, CF_3, cyano, $-C(=O)NR_fR_q$, $-O(C=O)NR_fR_q$ (wherein R_f and R_q are the same as defined earlier), $-(SO)_nR_d$ (wherein n and R_d are the same as defined earlier).

"Amine," unless otherwise specified, refers to $-NH_2$. "Substituted amino" unless otherwise specified, refers to a group $-N(R_k)_2$ wherein each R_k is independently selected from the group hydrogen provided that both R_k groups are not hydrogen (defined as "amino"), alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, $S(O)_mR_\psi$ (wherein m and R_ψ are the same as defined above), $-C(=R_v)NR_\lambda R_y$ (wherein R_v is O or S & R_λ and R_y are the same as defined earlier) or $NHC(=R_v)NR_yR_\lambda$ (wherein R_v, R_y and R_λ are the same as defined earlier).

Unless otherwise constrained by the definition, all amino substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, -$COOR_\psi$ (wherein R_ψ is the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, -$C(=R_v)NR_\lambda R_y$ (wherein R_v is the same as defined earlier), -$O(C=O)NR_\lambda R_y$, –$OC(=R_v)NR_\lambda R_y$ (wherein R_λ, R_y and R_v are the same as defined earlier), -$S(O)_mR_\psi$ (wherein R_ψ and m are the same as defined above).

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

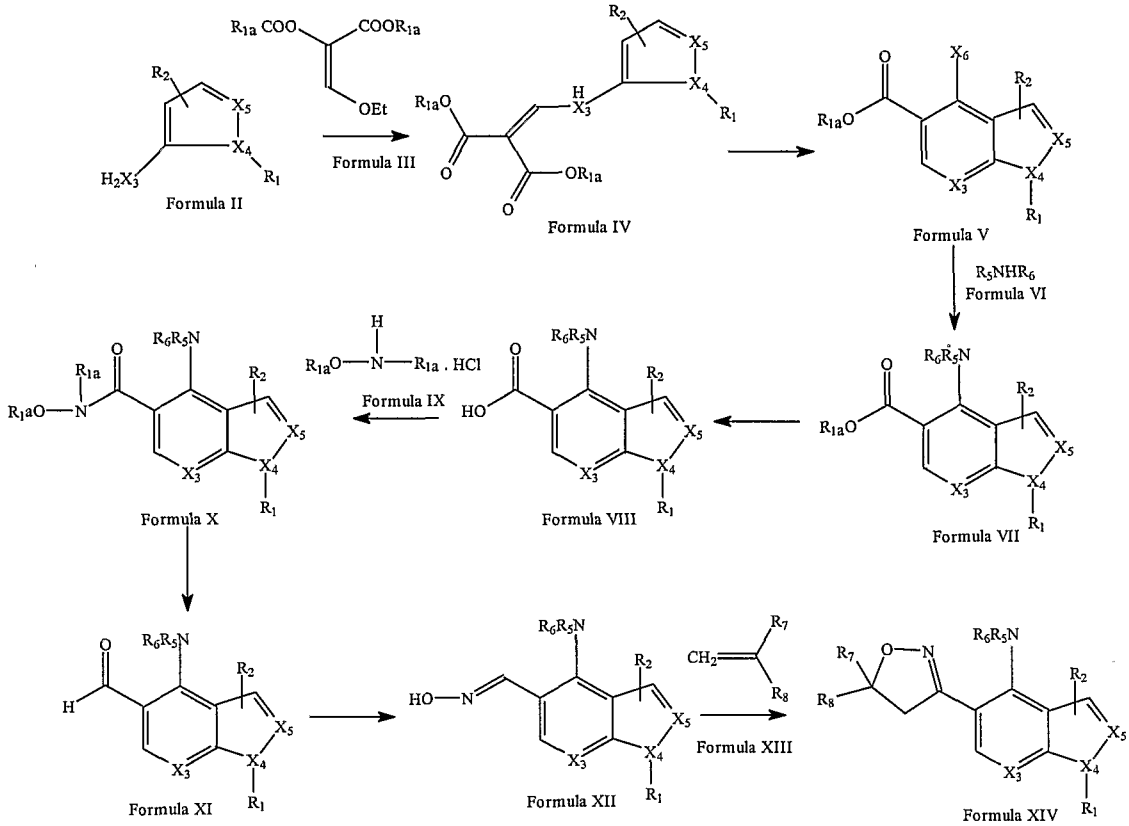
The compounds of the present invention can be used for treating CNS diseases, AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases.

In accordance with yet another aspect, there are provided processes for the preparation of the compounds as described herein.

Detailed Description of the Invention

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds of present invention may be prepared by the following, for example, reaction sequences as depicted in Scheme I.

Scheme I



The compounds of Formula XIV can be prepared, for example, by following Scheme I. Thus, compounds of Formula II can be reacted with compounds of Formula III to give compounds of Formula IV (wherein R_{1a} is alkyl), which on reaction with phosphorous oxy halidecan give compounds of Formula V (wherein X_6 is a halogen), which on reaction with compounds of Formula VI can give compounds of Formula VII (wherein R_5 and R_6 are the same as defined earlier), which on ester hydrolysis can give compounds of Formula VIII, which on reaction with compounds of Formula IX can give compounds of Formula X, which on reduction can give compounds of Formula XI, which on reaction with hydroxylamine hydrochloride can give compounds of Formula XII, which can be finally reacted with compounds of Formula XIII to give compounds of Formula XIV (wherein R_1, R_2, R_7, R_8, X_3, X_4 and X_5 are the same as defined earlier).

The compounds of Formula IV can be prepared by the reaction of compounds of Formula II with compounds of Formula III with heating.

The compounds of Formula V can be prepared by the reaction of compounds of Formula IV with phosphorous oxy halide with heating.

The reaction of compounds of Formula V with compounds of Formula VI to give compounds of Formula VII can be carried out in one or more: nitriles, for example, acetonitrile; ketones, for example, acetone; alcohols, for example, ethanol; ethers, for example, tetrahydrofuran; amides, for example, dimethylformamide; sulfoxides, for example, dimethylsulfoxide; or hydrocarbons, for example, toluene.

The ester hydrolysis of compounds of Formula VII to give compounds of Formula VIII can be carried out in one or more alcohols, for example, methanol, ethanol or an alcohol and water mixture. The ester hydrolysis of compounds of Formula VII to give compounds of Formula VIII can be carried out in the presence of one or more inorganic bases, for example, potassium hydroxide, sodium hydroxide or lithium hydroxide.

The reaction of compounds of Formula VIII with compounds of Formula IX to give compounds of Formula X can be carried out in the presence of one or more activating reagents, for example, 1-hydroxybenzotriazole, acetone oxime or 2-hydroxypyridine, and one or more coupling reagents, for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride or 1,3-dicyclohexyl carbodiimide in one or more: ethers, for example, tetrahydrofuran; amides, for example, dimethylformamide; or sulfoxides, for example, dimethylsulfoxide. The reaction of compounds of Formula VIII with compounds of Formula IX can be carried out in the presence of one or more tertiary amine bases, for example, N-methylmorpholine, N-ethyldiisopropylamine or 4-dialkylaminopyridines.

The reduction of compounds of Formula X to give compounds of Formula XI can be carried out in one or more: ethers, for example, tetrahydrofuran; amides, for example, dimethylformamide; sulfoxides, for example, dimethylsulfoxide; or hydrocarbons, for example, toluene. The reduction of compounds of Formula X to give compounds of Formula XI can be carried out in the presence of one or more reducing agents, for example, sodium bis(2-methoxyethoxy)aluminum hydride or lithium aluminium hydride.

The reaction of compounds of Formula XI with hydroxylamine hydrochloride to give compounds of Formula XII can be carried out in the presence of sodium acetate in one or more alcohols, for example, methanol or ethanol.

The reaction of compounds of Formula XII with compounds of Formula XIII to give compounds of Formula XIV can be carried out in the presence of one or more halogenating agents, for example, sodium hypochlorite, N-chlorosuccinimide or N-bromosuccinimide in one or more: nitriles, for example, acetonitrile; ketones, for example, acetone; alcohols, for example, ethanol; ethers, for example, tetrahydrofuran; amides, for example, dimethylformamide; sulfoxides, for example, dimethylsulfoxide; or hydrocarbons, for example, toluene.

In the above schemes, where the specific solvents, bases, reducing agents, oxidizing agents, activating reagents, coupling reagents, halogenating agents etc., are mentioned, it is to be understood that other solvents, bases, reducing agents, oxidizing agents, activating reagents, coupling reagents, halogenating agents etc., known to those skilled in the art may be used. Similarly, reaction parameters such as the reaction temperature and duration may be adjusted according to the desired needs.

An illustrative list of compounds of the invention includes these listed below:

- Methyl 3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 1),
- {3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 2),
- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carbonitrile (Compound No. 3),
- Methyl 3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2- oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 4),
- 5-(Carboxymethyl)-3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 5),
- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 6),
- 2-[3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(hydroxymethyl)-4,5- dihydroisoxazol-5-yl] ethanol (Compound No. 7),

- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxamide (Compound No. 8),

- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylic acid (Compound No. 9),

- Methyl 3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 10),

- 3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-*N*, 5-dimethyl-4, 5- dihydroisoxazole-5-carboxamide (Compound No.11),

- 3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxamide (Compound No. 12),

- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 13),

- Methyl 3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 14),

- {3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 15),

- Methyl 3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 16),

- Methyl 3-[4-(cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 17),

- 2-[3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl] ethanol (Compound No. 18),

- Methyl 3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 19),

- {3-[4-(Cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 20),

- *N*-cyclopropyl-3- [4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 21),

- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 22),

- Methyl 3-[4-(cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 23),
- {3-[4-(Cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 24), and

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers , prodrugs, metabolites, polymorphs or N-oxides, thereof.

The term "pharmaceutically acceptable" means approved by regulatory agency of the federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

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

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

The term "pharmaceutically acceptable solvates" refers to solvates with water (i.e. hydrates, hemihydrate or sesquihydrate) or pharmaceutically acceptable solvents, for example solvates with common organic solvents as ethanol and the like. Such solvates are also encompassed within the scope of the disclosure.

The present invention also includes within its scope prodrugs of these agents. In general, such prodrugs will be functional derivatives of these compounds, which are readily convertible *in vivo* into the required compound. Conventional procedures for the selection and preparation of prodrugs are known.

The disclosed compounds may get metabolized *in vivo* and these metabolites are also encompassed within the scope of this invention.

The term "polymorphs" includes all crystalline form as well as amorphous form for compounds described herein and are included in the present invention.

All stereoisomers of the compounds of the invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including all the substituents. Consequently, compounds of present invention can exist in enantiomeric or diastereomeric forms or in mixture thereof. The processes for the preparation can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods, for example, chromatographic or fractional crystallization.

The term "tautomer" includes one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Certain compounds of the general formula (I) may furthermore be present in tautomeric forms.

The term "regioisomers" refers to compounds, which have the same molecular formula but differ in the connectivity of the atoms.

The term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of Formula (I) as herein described, including pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides, thereof, where the context so permits. In general and preferably, the compounds of the invention and the formulas designating the compounds of the invention are understood to only include the stable compounds thereof and exclude unstable compounds, even if an unstable compound might be considered to be literally embraced by the compound formula. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts and solvates, where the context so permits.

The term "stable compound" means a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic or diagnostic agent. For example, a compound, which would have a "dangling valency" or is a "carbanion" is not a compound contemplated by the invention.

The term "racemate" includes a mixture of equal amounts of left- and right-handed stereoisomers of chiral molecules.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring.

The present disclosure includes all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the disclosed compound or a pharmaceutically acceptable salt together with a pharmaceutically acceptable carrier or diluent. Compounds disclosed herein may be administered to human or animal for treatment by any route, which effectively transports the active compound to the appropriate or desired site of action such as oral, nasal, pulmonary, transdermal or parenteral (rectal, subcutaneous, intravenous, intraurethral, intramuscular, intranasal). The pharmaceutical composition of the present invention comprises a pharmaceutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. The term "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filler, diluents, encapsulating material or formulation of any type.

Where desired, the compounds of Formula I and/ or their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides may be advantageously used in combination with one or more other therapeutic agents. Examples of other therapeutic agents, which may be used in combination with compounds of Formula I of this invention and/ or their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides include corticosteroids, ß2- agonists, leukotriene antagonists, 5-lipoxygenase inhibitors, chemokine inhibitors and muscarinic receptor antagonists.

The one or more ß2- agonists may be chosen from those in the art or subsequently discovered. The ß2-agonists may include one or more compounds described in U.S.

Patent Nos. 3,705,233; 3,644,353; 3,642,896; 3,700,681; 4,579,985; 3,994,974; 3,937,838; 4,419,364; 5,126,375; 5,243,076; 4,992,474; and 4,011,258.

Suitable ß2-agonists include, for example, one or more of albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, and their pharmaceutically acceptable salts or solvates thereof.

Corticosteroids as described herein may be chosen from those in the art or subsequently discovered. Suitable corticosteroids may be include one or more compounds described in U.S. Patent Nos. 3,312,590; 3,983,233; 3,929,768; 3,721,687; 3,436,389; 3,506,694; 3,639,434; 3,992,534; 3,928,326; 3,980,778; 3,780,177; 3,652,554; 3,947,478; 4,076,708; 4,124,707; 4,158,055; 4,298,604; 4,335,121; 4,081,541; 4,226,862; 4,290,962; 4,587,236; 4,472,392; 4,472,393; 4,242,334; 4,014,909; 4,098,803; 4,619,921; 5,482,934; 5,837,699; 5,889,015; 5,278,156; 5,015,746; 5,976,573; 6,337,324; 6,057,307; 6,723,713; 6,127,353; and 6,180,781.

Suitable corticosteroids may include, for example, one or more of alclometasone, amcinonide, amelometasone, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone, dexbudesonide, diflorasone, difluprednate, fluticasone, flunisolide, halometasone, halopredone, hydrocortisone, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol, triamcinolone, tolterodine, oxybutynin, ulobetasol, rofleponide, GW 215864, KSR 592, ST-126, dexamethasone and pharmaceutically acceptable salts, solvates thereof. Preferred corticosteroids include, for example, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, and dexamethasone, while budesonide, fluticasone, mometasone, ciclesonide. Examples of possible salts or derivatives include: sodium salts, sulfobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates, or furoates. In some cases, the corticosteroids may also occur in the form of their hydrates.

Suitable muscarinic receptor antagonists include substances that directly or indirectly block activation of muscarinic cholinergic receptors. Examples include, but are not limited to, quaternary amines (*e.g.*, methantheline, ipratropium, propantheline), tertiary

amines (*e.g.*, dicyclomine, scopolamine) and tricyclic amines (*e.g.*, telenzepine). Other suitable muscarinic receptor antagonists include benztropine (commercially available as COGENTIN® from Merck), hexahydro-sila-difenidol hydrochloride (HHSID hydrochloride disclosed in Lambrecht et al., *Trends in Pharmacol. Sci.*, 10(Suppl):60 (1989); (+/-)-3-quinuclidinyl xanthene-9-carboxylate hemioxalate (QNX-hemioxalate; Birdsall et al., *Trends in Pharmacol. Sci.*, 4:459 (1983); telenzepine dihydrochloride (Coruzzi et al., *Arch. Int. Pharmacodyn. Ther.*, 302:232 (1989); and Kawashima et al., *Gen. Pharmacol.*, 21:17 (1990)), and atropine.

The leukotriene antagonist can be selected from compounds, for example, those described in U.S. Patent Nos. 5,565,473, US 5,583,152, US 4,859,692 or US 4,780,469.

Examples of leukotriene antagonist include, but are not limited to, montelukast, zafirlukast, pranlukast and pharmaceutically acceptable salts thereof.

5-Lipoxygenase inhibitors can be selected from for example, compounds in U.S. Patent Nos. 4,826,868, or 4,873,259, or European Patent Nos. EP 419049, EP 542356 or EP 542355. Examples may include, but are not limited to, atreleuton, zyflo (zileuton), ABT-761, fenleuton or tepoxalin.

Examples of the chemokine inhibitors include, but are not limited to, endogenous ligands of chemokine receptors or derivatives thereof, and non-peptidic low molecular compounds or antibodies for chemokine receptors.

Examples of the endogenous ligands of chemokine receptors include, but are not limited to, MIP-1α, MIP-1β, Rantes, SDF-1α, SDF-1β, MCP-1, MCP-2, MCP4, Eotaxin, MDC. Examples of the derivatives of endogenous ligands include, but are not limited to, AOP-RANTES, Met-SDF-1α, Met-SDF-1β.

Examples of the antibodies for chemokine receptors include, but are not limited to, Pro-140.

Examples of the non-peptidic low molecular compounds include, but are not limited to, antagonists and agonists for CCR1, CCR2, CCR3, CCR4, CCR5, CXCR1, CXCR2, CXCR3 and CXCR4 receptors.

Examples set forth below demonstrate the synthetic procedures for the preparation of the representative compounds. The examples are provided to illustrate particular aspect

of the disclosure and do not constrain the scope of the present invention as defined by the claims.

Experimental details

Example 1: Preparation of Diethyl {[(1-ethyl -1H-pyrazol-5-yl) amino] methylene} malonate

A mixture of 5-amino-1-ethylpyrazole (1 gm, 0.0089 mole) and diethylethoxymethylenemalonate (1.9 ml, 0.0089 mole) was stirred at 120^{0}C for about 1 hour. The reaction mixture was poured into water and extraction was done with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give yellow oil. Yield: 2.5 g. m/z: (M^++1) 282.0.

The following compound was prepared similarly

- Diethyl {[(1,3-dimethyl-1H-pyrazol-5-yl) amino] methylene} malonate

Example 2: Preparation of ethyl- 4-chloro-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate

A mixture of diethyl {[(1-ethyl -1H-pyrazol-5-yl) amino] methylene} malonate (2.5g, 0.009 mole) and phosphorous oxy chloride (17.7 ml, 0.185 mole) was heated at 110-120^{0}C under stirring for about 3 hours under argon atmosphere. The reaction mixture was poured into ice water. It was extracted with dichloromethane and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give pure white solid compound. Yield: 1.8g. m/z: (M^++1) 253.9.

The following compound was prepared similarly.

- Ethyl -4-chloro-1, 3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate

Example 3: Preparation of ethyl -4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate

To a mixture of ethyl 4-chloro-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate (950 mg, 0.0037 mole) in acetonitrile, cyclopropyl amine (0.525 ml, 0.0074 mole) was added. After stirring for about 2 hours at 110^0 C, acetonitrile was removed under reduced pressure. Water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and

concentrated *in vacuo* to give light yellow solid compound. Yield: 1g. m/z: (M^++1) 275.0.

The following compounds were prepared similarly

- Ethyl 4-(cyclopropylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate
- Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate
- Ethyl 4-(cyclopentylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate

Example 4: Preparation of 4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid

To a solution of ethyl 4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate (1 g, 0.0036 mole) in ethanol, sodium hydroxide solution (440 mg in 2 ml water) was added. The reaction mixture was stirred for about 14 hours at ambient temperature. Water was added and the reaction mixture was extracted with ethyl acetate. Aqueous layer was acidified by using hydrochloric acid (2N) to pH of about 4-5. White solid, which was obtained, was filtered and dried *in vacuo*.

Yield: 560 mg. m/z: (M^++1) 274.2.

The following compounds were prepared similarly.

- 4-(Cyclopropylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid
- 4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid
- 4-(Cyclopentylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid

Example 5: Preparation of 4-(cyclopropylamino)-1-ethyl-N-methoxy-N-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid (500 mg, 0.0020 mole) and N,O-dimethylhydroxylamine hydrochloride (298 mg, 0.0030 mole) were taken in dimethylformamide . At 0^0 C, hydroxybenzotriazole (550 mg, 0.0040 mole) and N-methylmorpholine (1.34 ml, 0.012 mole) were added and the reaction mixture was stirred for about 1 hour. 1-(3-dimethylaminopropyl) 3-ethyl carbodiimide hydrochloride (780 mg, 0.0040 mole) was added and the reaction mixture was stirred for about 14 hours. Water was added and extraction was carried out with ethyl acetate. The

organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give an oily compound. Yield: 500 mg. m/z: (M^++1) 290.2.

The following compounds were prepared similarly

- 4-(Cyclopropylamino)-N-methoxy-N-1, 3-trimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxamide

- 4-(Cyclopentylamino)-1-ethyl-N-methoxy-N-methyl-1H-pyrazolo [3,4-b] pyridine-5-carboxamide

- 4-(Cyclopentylamino)-N-methoxy-N-1, 3-trimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxamide

Example 6: Preparation of 4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde

Toluene was cooled at –19 to -20^{0}C and vitride (.50 ml, 0.0034 mole) was added. After about 10 minutes, 4-(cyclopropylamino)-1-ethyl-N-methoxy-N-methyl-1H-pyrazolo [3,4-b] pyridine-5-carboxamide (500 mg, 0.0017 mole) was added and the reaction mixture was stirred for about 4 hours. Citric acid (10%) solution was added dropwise to quench the reaction and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated *in vacuo* to give an oily compound. Yield: 300 mg. m/z: (M^++1) 231.1.

The following compounds were prepared similarly.

- 4-(Cyclopropylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde

- 4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde

- 4-(Cyclopentylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde

Example 7: Preparation of 4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde oxime

To a stirred solution of 4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde (300 mg, 0.00129 mole) in ethanol, hydroxylamine hydrochloride (359 mg, 0.0051 mole) and sodium acetate (424 mg, 0.0051 mole) were added. The reaction mixture was allowed to stir at room temperature for about 50 minutes. Ethanol was removed under reduced pressure and residue was poured in water. The organic compound

was extracted with ethyl acetate. Ethyl acetate layer was dried over anhydrous sodium sulfate, filtered and finally concentrated under reduced pressure to afford white solid compound. Yield: 270 mg. m/z: (M^++1) 246.1.

The following compounds were prepared similarly.

- 4-(Cyclopropylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde oxime

- 4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde oxime

- 4-(Cyclopentylamino)-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde oxime

Example 8: Preparation of methyl 3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 1)

Methyl methacrylate (0.3 ml, 0.0028 mole) was added to 4-cyclopropylamino-1-ethyl-1H-pyrazolo [3,4-b] pyridine-5-carbaldehyde oxime (70 mg, 0.00028 mol) in tetrahydrofuran. The reaction mixture was stirred at room temperature. Sodium hypochlorite (2 ml) was added slowly to the mixture thus obtained over a period of about 5 minutes and the reaction mixture was allowed to stir at room temperature for about 4 hours. Tetrahydrofuran was evaporated and the organic layer was extracted with ethyl acetate. It was concentrated and purified by column chromatography to yield the title compound. Yield: 50 mg (51%). m/z: (M^++1) 344.1.

The following compounds were prepared similarly

- {3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 2), Yield: (26.4%). m/z: (M^++1) 316.2.

- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carbonitrile (Compound No. 3), Yield: (26%). m/z: (M^++1) 311.2.

- Methyl 3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2- oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 4), Yield: (83%). m/z: (M^++1) 402.2.

- 5-(Carboxymethyl)-3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 5), Yield: (45%). m/z: (M^++1) 374.2.

- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 6), Yield: (86%). m/z: (M^++1) 372.2.

- 2-[3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(hydroxymethyl)-4,5- dihydroisoxazol-5-yl] ethanol (Compound No. 7), Yield: (83.4%). m/z: (M^++1) 346.3.

- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxamide (Compound No. 8), Yield: (83.6%). m/z: (M^++1) 329.1.

- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylic acid (Compound No. 9), Yield: (62.5%). m/z: (M^++1) 330.0.

- Methyl 3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 10), Yield: (61.4%). m/z: (M^++1) 372.1.

- 3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-*N*, 5-dimethyl-4, 5- dihydroisoxazole-5-carboxamide (Compound No.11), Yield: (57.2%). m/z: (M^++1) 371.1.

- 3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxamide (Compound No. 12), Yield: (44.5%). m/z: (M^++1) 357.1.

- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 13), Yield: (85.8%). m/z: (M^++1) 400.1.

- Methyl 3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 14), Yield: (60%). m/z: (M^++1) 430.0.

- {3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 15), Yield: (25.2%). m/z: (M^++1) 344.1.

- Methyl 3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 16), Yield: (30.6%). m/z: (M^++1) 402.0.

- Methyl 3-[4-(cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 17), Yield: (42%). m/z: (M^++1) 372.1.

- 2-[3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl] ethanol (Compound No. 18), Yield: (90%). m/z: (M^++1) 374.2.

- Methyl 3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate (Compound No. 19), Yield: (15.3%). m/z: (M^++1) 344.0.

- {3-[4-(Cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 20), Yield: (15.62%). m/z: (M^++1) 316.1.

- *N*-cyclopropyl-3- [4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 21), Yield: (63.82%). m/z: (M^++1) 474.1.

- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide (Compound No. 22), Yield: (86.2%). m/z: (M^++1) 372.0.

- Methyl 3-[4-(cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate (Compound No. 23), Yield: (51%). m/z: (M^++1) 430.1.

- {3-[4-(Cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol (Compound No. 24), Yield: (63.9%). m/z: (M^++1) 344.2.

Example 9: Efficacy of compounds as PDE IV inhibitors

PDE-IV Enzyme Assay

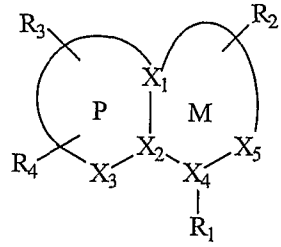
The efficacy of compounds of PDE-4 inhibitors was determined by an enzyme assay using U937 cell cytosolic fraction (*Biochem. Biophys. Res. Comm.*, 197: 1126-1131, 1993). The enzyme reaction was carried out in the presence of cAMP (1 μM) at 30°C in the presence or absence of test compound for 45 –60 min. An aliquot of this reaction mixture was taken further for the ELISA assay and the protocol of the kit was followed to determine level of cAMP in the sample. The concentration of the cAMP in the sample directly correlated with the degree of PDE-4 enzyme inhibition. Results were expressed as percent control and the IC_{50} values of test compounds were found to be in the range of lower μM to nM concentration.

The PDE-IV inhibitor IC_{50} values of the compounds specifically disclosed herein ranged from about 0.1 nM to about 10 μM, for example from about 0.1 nM to about 1.8 μM, or from about 0.1 nM to about 400 nM, or from about 0.1 nM to about 100 nM, for example from about 0.1 nM to about 50 nM, or from about 0.1 nM to about 10 nM.

5

We claim:

1. Compounds having the structure of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides, wherein ring P including X_1, X_2 and X_3 is a six-membered ring containing 1-3 double bonds wherein X_1 and X_2 are carbon and X_3 is nitrogen;

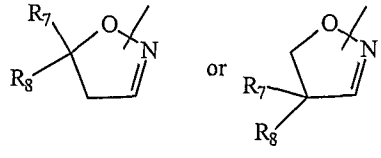
ring M (including X_1, X_2, X_4 and X_5) is a five-membered ring containing 1-2 double bonds, wherein X_1 and X_2 are carbon and X_4 and X_5 are nitrogen;

R_1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, aralkenyl, (cycloalkyl) alkyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl;

R_2 is hydrogen, alkyl, halogen, cyano, nitro, -SR, NRR, $-(CH_2)_n$ OR {wherein R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or heterocyclyl and n is an integer from 0-2}, alkenyl, alkynyl, cycloalkyl, (cycloalkyl) alkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl;

R_3 is $-NR_5R_6$ {wherein R_5 and R_6 independently are hydrogen, alkyl, alkenyl, alkynyl, acyl, cycloalkyl, aryl, aralkenyl, aralkyl, (cycloalkyl) alkyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl}; and

R_4 is a radical of Formula I a or I b



Formula Ia Formula Ib

wherein R_7 and R_8 independently are alkyl, -CN, - $(CH_2)_n$ C(=O) NR_fR_q {wherein n is an integer from 0-2 and R_f and R_q independently are hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, or(heteroaryl)alkyl},–$(CH_2)_n$ C (=O)OR_f {wherein n and R_f are the same as defined earlier}, or -$(CH_2)_n$ OR_f {wherein n and R_f are the same as defined earlier}.

2. A compound selected from:

- Methyl 3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate,
- {3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol,
- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carbonitrile,
- Methyl 3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2- oxoethyl)-4,5-dihydroisoxazole-5-carboxylate,
- 5-(Carboxymethyl)-3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxylic acid ,
- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide,
- 2-[3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(hydroxymethyl)-4,5- dihydroisoxazol-5-yl] ethanol,
- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxamide,
- 3-[4-(Cyclopropylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylic acid,
- Methyl 3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate,
- 3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-*N*, 5-dimethyl-4, 5- dihydroisoxazole-5-carboxamide,
- 3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxamide,
- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide,
- Methyl 3-[4-(cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate,
- {3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol,

- Methyl 3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate,
- Methyl 3-[4-(cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate,
- 2-[3-[4-(Cyclopentylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl] ethanol,
- Methyl 3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazole-5-carboxylate,
- {3-[4-(Cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol,
- *N*-cyclopropyl-3- [4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-[2-(cyclopropylamino)-2-oxoethyl]-4,5-dihydroisoxazole-5-carboxamide,
- 5-(2-Amino-2-oxoethyl)-3-[4-(cyclopropylamino)-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-4,5-dihydroisoxazole-5-carboxamide,
- Methyl 3-[4-(cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-(2-methoxy-2-oxoethyl)-4,5-dihydroisoxazole-5-carboxylate, or
- {3-[4-(Cyclopentylamino)-1-ethyl-1*H*-pyrazolo [3,4-*b*] pyridin-5-yl]-5-methyl-4, 5-dihydroisoxazol-5-yl} methanol,

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides.

3. Pharmaceutical compositions comprising a therapeutically effective amount of a compound of claim 1, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

4. Pharmaceutical compositions comprising a therapeutically effective amount of a compound of claim 1 and at least one other active ingredient selected from corticosteroids, ß2- agonists, leukotriene antagonists, 5-lipoxygenase inhibitors, chemokine inhibitors and muscarinic receptor antagonists.

5. A method for treating, preventing, inhibiting or suppressing an inflammatory condition or disease or CNS diseases, in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1.

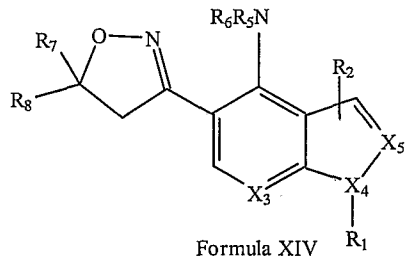
6. A method for treating, preventing, inhibiting or suppressing an inflammatory condition or disease or CNS diseases, in a patient, comprising administering to the

patient a therapeutically effective amount of a pharmaceutical composition of claim 3.

7. A method for the treatment, prevention, inhibition or suppression of CNS 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, ulcerative colitis and other inflammatory diseases in a patient comprising administering to the patient a therapeutically effective amount of a compound of claim 1.

8. A method for the treatment, prevention, inhibition or suppression of CNS 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, ulcerative colitis and other inflammatory diseases in a patient comprising administering to the patient a therapeutically effective amount of pharmaceutical composition of claim 3.

9. A method for the preparation of compounds of Formula XIV,



Formula XIV

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, tautomers, racemates, regioisomers, prodrugs, metabolites, polymorphs or N-oxides, wherein R_1, R_2, R_5, R_6, R_7, R_8, are

X_3, X_4 and X_5 are nitrogen;

R_1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, aralkenyl, (cycloalkyl) alkyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl;

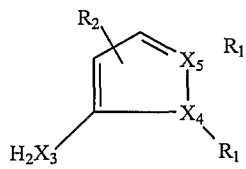
R_2 is hydrogen, alkyl, halogen, cyano, nitro, -SR, NRR, -$(CH_2)_n$ OR {wherein R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or heterocyclyl and n is an integer from 0-2}, alkenyl, alkynyl, cycloalkyl, (cycloalkyl) alkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl;

R_5 and R_6 independently are hydrogen, alkyl, alkenyl, alkynyl, acyl, cycloalkyl, aryl, aralkenyl, aralkyl, (cycloalkyl) alkyl, heterocyclyl, heteroaryl, (heterocyclyl) alkyl or (heteroaryl) alkyl; and

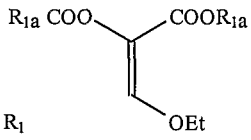
R_7 and R_8 independently are alkyl, -CN, - $(CH_2)_n$ C(=O) NR_fR_q {wherein n is an integer from 0-2 and R_f and R_q independently are hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, or(heteroaryl)alkyl},–$(CH_2)_n$ C (=O)OR_f {wherein n and R_f are the same as defined earlier}, or -$(CH_2)_n$ OR_f {wherein n and R_f are the same as defined earlier},

the method comprising

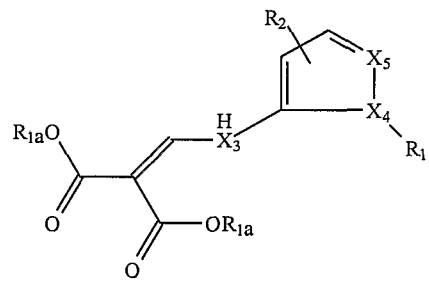
(a) reacting a compound of Formula II with a compound of Formula III to give a compound of Formula IV (wherein R_{1a} is alkyl);



Formula II

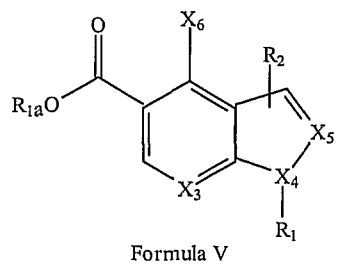


Formula III



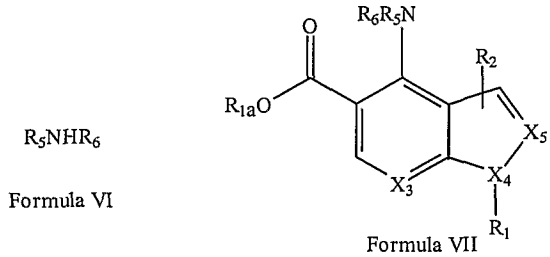
Formula IV

(b) reacting the compound of Formula IV with phosphorous oxy halide to give a compound of Formula V (wherein X_6 is a halogen);



Formula V

(c) reacting the compound of Formula V with a compound of Formula VI to give a compound of Formula VII (wherein R_5 and R_6 are the same as defined earlier);

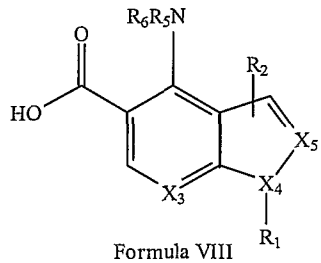


R_5NHR_6

Formula VI

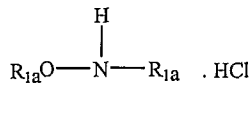
Formula VII

(d) performing ester hydrolysis on the compound of Formula VII to give a compound of Formula VIII;

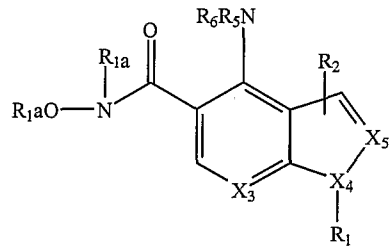


Formula VIII

(e) reacting the compound of Formula VIII with a compound of Formula IX to give a compound of Formula X;

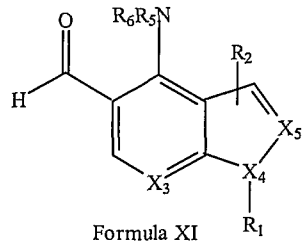


Formula IX



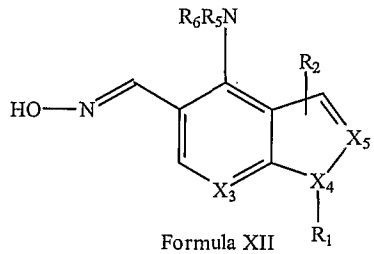
Formula X

(f) reduction of the compound of Formula X to give a compound of Formula XI;



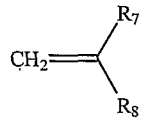
Formula XI

(g) reacting the compound of Formula XI with hydroxylamine hydrochloride to give a compound of Formula XII; and



Formula XII

(h) reacting the compound of Formula XII with a compound of Formula XIII



Formula XIII

to give a compound of Formula XIV.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/002494

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P25/00 A61P11/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/056823 A (GLAXO GROUP LTD [GB]; ALLEN DAVID GEORGE [GB]; COE DIANE MARY [GB]; CO) 8 July 2004 (2004-07-08) claims page 175; example 40a page 177; example 42 page 184; example 56	1-9
A	WO 2005/021515 A2 (RANBAXY LAB LTD [IN]; PALLE VENKATA P [IN]; BALACHANDRAN SARALA [IN];) 10 March 2005 (2005-03-10) claims	1-9

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2007	26/01/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	KOLLMANNSBERGER, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/002494

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

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

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

Although claims 5-8 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

Information on patent family members

International application No
PCT/IB2006/002494

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004056823 A	08-07-2004	AU 2003293999 A1	14-07-2004
		BR 0317645 A	06-12-2005
		CA 2511340 A1	08-07-2004
		EP 1581532 A1	05-10-2005
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WO 2005021515 A2	10-03-2005	AU 2004268847 A1	10-03-2005
		BR PI0413330 A	10-10-2006
		CA 2537185 A1	10-03-2005
		EP 1663999 A2	07-06-2006