DERIVATIVES OF 1-PHENYL-2-PYRIDINYL ALKYL ALCOHOLS AS PHOSPHODIESTERASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to inhibitors of the phosphodiesterase 4 (PDE4) enzyme. More particularly, the invention relates to compounds that are derivatives of 1-phenyl-2-pyridinyl alkyl alcohols, methods of preparing such compounds, compositions containing them and therapeutic use thereof.

BACKGROUND OF THE INVENTION

Airway obstruction characterizes a number of severe respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD). Events leading to airway obstruction include oedema of airway walls, increased mucous production and inflammation.

Drugs for treating respiratory diseases such as asthma and COPD are currently administered through inhalation. One of the advantages of the inhalatory route over the systemic one is the possibility of delivering the drug directly at site of action, avoiding any systemic side-effects, thus resulting in a more rapid clinical response and a higher therapeutic ratio.

Inhaled corticosteroids are the current maintenance therapy of choice for asthma and together with bronchodilator $beta_2$-agonists for acute symptom relief, they form the mainstay of current therapy for the disease. The current management of COPD is largely symptomatic by means of bronchodilating therapy with inhaled anticholinergics and inhaled $beta_2$-adrenoceptor agonists. However, corticosteroids do not reduce the inflammatory response in COPD as they do in asthma.

Another class of therapeutic agents which has been widely investigated in view of its anti-inflammatory effects for the treatment of inflammatory respiratory diseases such as asthma and COPD is represented

by the inhibitors of the enzymes phosphodiesterases (PDEs), in particular of the phosphodiesterase type 4 (hereinafter referred to as PDE4).

Various compounds acting as PDE4 inhibitors have been disclosed in the prior art. However, the usefulness of several PDE4 inhibitors of the first - generation such as rolipram and piclamilast has been limited due to their undesirable side effects. Said effects include nausea and emesis due to their action on PDE4 in the central nervous system and gastric acid secretion due to the action on PDE4 in parietal cells in the gut.

The cause of said side effects has been widely investigated.

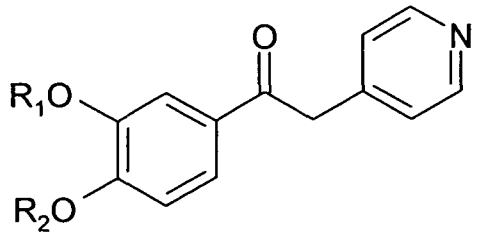
It has been found that PDE4 exists in two distinct forms representing different conformations, that were designated as high affinity rolipram binding site or HPDE4, especially present in the central nervous system and in parietal cells, and low affinity rolipram binding site or LPDE4 (Jacobitz, S et al Mol. Pharmacol, 1996, 50, 891-899), which is found in the immune and inflammatory cells. While both forms appear to exhibit catalytic activity, they differ with respect to their sensitivity to inhibitors. In particular compounds with higher affinity for LPDE4 appear less prone to induce side-effects such as nausea, emesis and increased gastric secretion.

The effort of targeting LPDE4 has resulted in a slight improvement in the selectivity for the second-generation PDE4 inhibitors such as cilomilast and roflumilast. However, even these compounds are not provided with a good selectivity towards LPDE4.

Other classes of compounds acting as PDE4 inhibitors have been disclosed in the prior art.

For example, EP 1634606 discloses, among others, ketone derivatives like benzofuran or 1,3-benzodioxole derivatives.

WO 9402465 discloses, among others, ketone derivatives of general formula



wherein R_1 is lower alkyl and R_2 may be alkyl, alkenyl, cycloalkyl, cycloalkyl, cycloalkenyl, cyclothioalkyl or cyclothioalkenyl.

WO 9535281 in the name of Celltech Therapeutics concerns tri-substituted phenyl derivatives.

Both applications are silent about the problems of the side effects associated with inhibition of HPDE4 and do not report data regarding affinity toward HPDE4 and LPDE4.

Therefore, although several PDE4 inhibitors have been disclosed so far, there is still a need for more efficacious and better tolerated compounds.

In particular, it would be highly advantageous to provide more selective compounds, e.g. endowed with a higher affinity toward the LPDE4 with respect to the affinity to HPDE4, in order to attenuate or avoid the side effects associated with its inhibition.

The present invention addresses these issues by providing PDE4 inhibitors having an improved selectivity toward LPDE4.

As a matter of fact, it has now been found that providing a PDE4 inhibitor with an additional moiety interacting with the active site of the PDE4, there is an improvement in the selectivity of the inhibitors towards LPDE4.

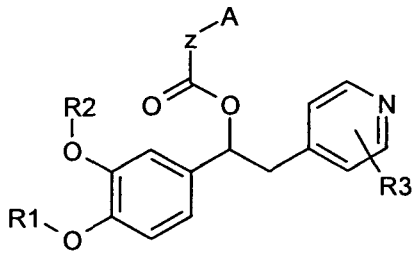
The PDE4 inhibitors of the present invention efficaciously act upon inhalation administration and could be characterized by a good persistency in the lung and a short systemic duration.

SUMMARY OF THE INVENTION

The invention is directed to compounds acting as inhibitors of the phosphodiesterase 4 (PDE4) enzyme, methods of preparing said

compounds, compositions containing them and therapeutic use thereof.

In particular the invention is directed to derivatives of 1-phenyl-2-pyridinyl alkyl alcohols of general formula (I)



(I)

wherein:

Z is selected from the group consisting of

$(CH_2)_m$ wherein m = 0, 1 or 2;

$(CH_2)_nO$ wherein n=1, 2 or 3;

$O(CH_2)_p$ wherein p=0, 1, 2 or 3;

CH_2SO_2;

$CHNR_6$;

CH_2NR_6;

NR_6 wherein R_6 is H or a linear or branched $(C_1\text{-}C_4)$ alkyl;

$OCOR_4R_5$; and

CR_4R_5 wherein

R_4 is independently selected from H or a linear or branched $(C_1\text{-}C_4)$ alkyl, preferably methyl, optionally substituted by a $(C_1\text{-}C_4)$ cycloalkyl and

R_5 is independently selected from the group consisting of

- linear or branched $(C_1\text{-}C_4)$ alkyl, preferably methyl;
- phenyl;
- benzyl;
- NH_2; and
- HNCOOR', wherein R' is linear or branched $(C_1\text{-}C_4)$ alkyl,

preferably t-butyl.

R_1 and R_2 are different or the same and are independently selected from the group consisting of

- H;
- linear or branched (C_1-C_6) alkyl, optionally substituted by one or more substituents selected from (C_3-C_7) cycloalkyl or (C_5-C_7) cycloalkenyl;
- (C_3-C_7) cycloalkyl;
- (C_5-C_7) cycloalkenyl;
- linear or branched (C_2-C_6) alkenyl; and
- linear or branched (C_2-C_6) alkynyl.

R_3 is one or more substituents independently selected from the group consisting of H, CN, NO_2, CF_3 and halogen atoms.

A is a ring system, that is a mono- or bicyclic ring which may be saturated, partially unsaturated or unsaturated, such as aryl, (C_3-C_8) cycloalkyl or heteroaryl, said ring system A having 5 to 10 ring atoms in which at least one ring atom is a heteroatom (e.g. N, S or O), in which the optional substituent R_x on the A ring system may be one or more, may be the same or different, and is independently selected from the group consisting of:

- linear or branched (C_1-C_6) alkyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
- linear or branched (C_2-C_6) alkenyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
- linear or branched (C_2-C_6) alkynyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
- (C_5-C_7) cycloalkenyl;
- phenyl;
- (C_3-C_7) heterocycloalkyl;

- OR_7 wherein R_7 is selected from the group consisting of
  - H;
  - (C_1-C_{10}) alkyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
  - (C_3-C_7) cycloalkyl;
  - (C_1-C_4) alkyl-(C_3-C_7) heterocycloalkyl;
  - CO (C_1-C_6) alkyl;
  - COO (C_1-C_6) alkyl;
  - phenyl;
  - benzyl;
  - (C_1-C_{10}) alkyl-NR_8R_9 wherein R_8 and R_9 are independently selected from the group consisting of H, linear or branched (C_1-C_6) alkyl and they form with the nitrogen atom to which they are linked a saturated, partially saturated or unsaturated ring, preferably NR_8R_9 is linked to (C_1-C_{10}) alkyl forming for example saturated, partially saturated or unsaturated piperidine, oxazine, imidazole rings, wherein these rings are optionally substituted by (C_1-C_4) alkyl; and
- halogen atoms;
- CN;
- NO_2;
- $NR_{10}R_{11}$ wherein R_{10} and R_{11} are different or the same and are independently selected from the group consisting of
  - H;
  - linear or branched (C_1-C_6) alkyl, optionally substituted with phenyl or (C_3-C_7) cycloalkyl;
  - COC_6H_5;
  - CO-(C_1-C_4) alkyl;

- COO-(C_1-C_4) alkyl;
- CONH-(C_1-C_6) alkyl-R_{12}, wherein R_{12} is selected from the group consisting of
  - H;
  - (C_1-C_4) alkyl;
  - OR_4R_5; and
- CONH (C_1-C_4) alkyl-N(C_1-C_4) alkyl;

or they form with the nitrogen atom to which they are linked a saturated or partially saturated ring, preferably a piperidyl ring;

- (C_1-C_4) alkyl-$NR_{10}R_{11}$;
- COR_{12} wherein R_{12} is phenyl or linear or branched (C_1-C_6) alkyl;
- oxo;
- $HNSO_2R_{13}$ wherein R_{13} is (C_1-C_4) alkyl or a phenyl optionally substituted with halogen atoms or with a (C_1-C_4) alkyl group;
- SO_2R_{14} wherein R_{14} is (C_1-C_4) alkyl, OH or $NR_{10}R_{11}$ wherein R_{10} and R_{11} are as defined above;
- SOR_{15} wherein R_{15} is phenyl or (C_1-C_4) alkyl;
- SR_{16} wherein R_{16} is H, phenyl or (C_1-C_4) alkyl;
- $COOR_{17}$ wherein R_{17} is H, (C_1-C_4) alkyl, phenyl or benzyl; and
- $(CH_2)_qOR_{18}$, wherein q=1, 2, 3 or 4 and R_{18} is H or (C_1-C_4) cycloalkyl.

and pharmaceutically acceptable salts and N-oxides on the pyridine ring thereof.

The invention also encompasses the pharmaceutically acceptable salts and/or solvates thereof.

The invention further involves the corresponding N-oxides on the pyridine ring.

The invention further comprises a process for the preparation of

compounds of general formula (I).

The present invention also provides pharmaceutical compositions of compounds of general formula (I) alone or in combination with in admixture with one or more pharmaceutically acceptable carriers.

In a further aspect the present invention provides the use of the compounds of general formula (I) as a medicament.

In a further aspect the present invention provides the use of the compounds of general formula (I) for the manufacture of a medicament.

In particular the present invention provides the use of the compounds of general formula (I) for the prevention and/or treatment of any disease characterized by phosphodiesterase 4 (PDE4) overactivity and/or wherein an inhibition of PDE4 activity is desirable.

In particular the compounds of general formula (I) alone or combined with other active ingredients may be administered for the prevention and/or treatment of a disease the respiratory tract characterized by airway obstruction such as asthma and COPD.

In a further aspect the present invention provides the use of compounds of general formula (I) for the preparation of a medicament for the prevention and/or treatment of an inflammatory disease, disorder or condition characterized by or associated with an undesirable inflammatory immune response or induced by or associated with an excessive secretion of TNF-α and PDE4.

Moreover the present invention provides a method for prevention and/or treatment of any disease wherein PDE4 inhibition is required, said method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula (I).

DEFINITIONS

The term "halogen atoms" as used herein includes fluorine, chlorine,

bromine, and iodine, preferably chlorine.

As used herein, the expression "linear or branched (C_1-C_x) alkyl" where x is an integer greater than 1, refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

Optionally in said groups one or more hydrogen atoms can be replaced by halogen atoms, preferably chlorine or fluorine.

The derived expressions "(C_2-C_6) alkenyl" and "(C_2-C_6) alkynyl", are to be construed in an analogous manner.

As used herein, the expression "(C_3-C_x) cycloalkyl", where x is an integer greater than 3, refers to cyclic non-aromatic hydrocarbon groups containing from 3 to x ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Optionally in said groups one or more hydrogen atoms can be replaced by halogen atoms, preferably chlorine or fluorine.

As used herein, the expression "(C_3-C_7) heterocycloalkyl", refers to cyclic non-aromatic hydrocarbon groups containing one or more heteroatoms (e.g. N, S or O), optionally substituted by one or more (C_1-C_4) alkyl.

The derived expressions "(C_1-C_x) cycloalkoxyl" is to be construed in an analogous manner.

The derived expression "(C_5-C_x) cycloalkenyl", where x is an integer greater than 5, is to be construed in an analogous manner.

As used herein, the expression "ring system" refers to mono- or bicyclic ring systems which may be saturated, partially unsaturated or unsaturated, such as aryl, (C_3-C_8) cycloalkyl or heteroaryl, having 5 to 10 ring atoms in which at least one ring atom is a hereoatom (e.g. N, S or O).

Examples of suitable monocyclic systems include phenyl, pyridyl,

piperazinyl, piperidinyl, morpholinyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, dioxane, imidazole and imidazolidine.

Examples of suitable bicyclic systems include naphthyl, quinolinyl, isoquinolinyl, indenyl, fluorene, benzimidazole, benzimidazolidine, xanthine and the partially- or fully- hydrogenated derivatives thereof.

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to a class of compounds acting as inhibitors of the phosphodiesterase 4 (PDE4) enzyme.

Said class of compounds inhibits the conversion of cyclic nucleotides, in particular cyclic adenosine monophosphate (cAMP), into their inactive 5'-mononucleotide forms.

In the airways, the physiological responses to elevated intracellular levels of cyclic nucleotides, in particular of cAMP, lead to the suppression of the activity of immune and pro-inflammatory cells such as mast cells, macrophages, T lymphocytes, eosinophils and neutrophils, resulting in a decrease of the release of inflammatory mediators which include cytokines such as IL-1, IL-3 and tumor necrosis factor -alpha (TNF-α).

It also leads to an airway smooth muscle relaxation and a decrease in oedema.

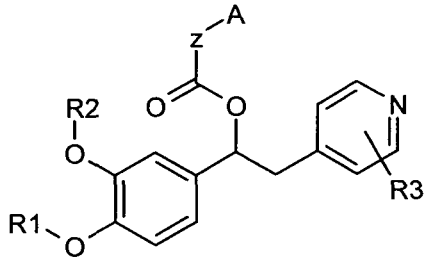
The catalytic site of PDE4 has been previously identified: it mainly comprises a hydrophobic region in which two sub-pockets are present, e.g. S_o and S_1, and a hydrophilic region containing the metal ions Zn^{2+} and Mg^{2+}, that in turn comprises the sub-pocket S_2 spreading around the metal ions and a sub-pocket S_3 which branches approximately 90° from the middle of the hydrophobic pocket.

Most of the compounds of the prior art are provided with a moiety able of interacting with the sub-pockets S_0 and S_1 of the hydrophobic region such as a substituted catechol group and with another moiety able of indirectly

interacting with the metal ions of the S_2 sub-pocket, for example a heterocycle such as pyridine or pyrrolidone.

The present invention is directed to compounds which were designed so that they could maintain the interactions with the sub-pockets S_o and S_1 by means of the substituted catechol moiety and the interaction with the metal ions region by means of the pyridine ring like other known PDE4 inhibitors but differ for the presence of a further group able of establishing an additional interaction with the sub-pocket S_3.

In particular the present invention relates to derivatives of 1-phenyl-2-pyridinyl alkyl alcohols of general formula (I)



(I)

Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid.

It will be apparent to those skilled in the art that the compounds of general formula (I) may contain asymmetric centers. Therefore the invention also includes the optical stereoisomers and mixtures thereof.

Where the compounds according to the invention have at least one asymmetric center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers. It is to be

understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

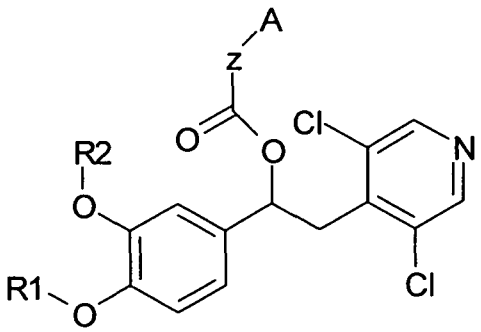
The compounds of general formula (I) were found to show an *in vitro* inhibitory activity toward the PDE4 enzyme in the nM range and they turned out to be endowed of a good activity in the lungs upon intra-tracheal administration in an animal model of COPD.

They also exhibited in some cases sustained pulmonary levels in the lungs, while no detectable plasmatic levels were found which is an index of a short systemic action.

One possible explanation for the unexpectedly high selectivity of these compounds for LPDE4 in comparison to HPDE4 is that they all feature a moiety which could fit into the S_3 sub-pocket of the catalytic site of the PDE4 enzyme through the A substituent.

As it can be appreciated from the results reported in the Example 13, a compound representative of the invention was indeed found about 1319-fold more selective toward LPDE4 versus HPDE4.

A preferred group of compounds of general formula (I) is that wherein the 2-pyridinyl ring is substituted in 3 and 5 with two atoms of chlorine, according to the general formula (II)



(II)

wherein R_1, R_2, Z and A are as defined above.

Advantageously when R_1 or R_2 is H, the other substituent on the

catechol group is different from H.

Preferably R_1 and R_2 are both different from H.

A first group of more preferred compounds of general formula (II) is that in which:

R_1 and R_2 are as defined above;

Z is $(CH_2)_n$ wherein n is 0; and

A is as defined above.

A second group of more preferred compounds is that in which:

R_1 and R_2 are as defined above;

Z is CHR_5 wherein R_5 is linear or branched $(C_1\text{-}C_4)$ alkyl, preferably methyl; and

A is as defined above.

A third group of more preferred compounds is that in which:

R_1 and R_2 are as defined above;

Z is CR_4R_5 wherein R_4 and R_5 are both linear or branched $(C_1\text{-}C_4)$ alkyl and they form a ring with the carbon atom to which they are linked having 3, 4, 5 or 6 carbon atoms, preferably having 3 carbon atoms; and

A is as defined above.

In one of the preferred embodiment A is substituted and Rx is selected from the group consisting of linear or branched $(C_1\text{-}C_6)$ alkyl, linear or branched $(C_2\text{-}C_6)$ alkenyl, linear or branched $(C_2\text{-}C_6)$ alkynyl or OR_7 wherein R_7 is as defined above.

In another preferred embodiment A is substituted and R_x is a group able of improving the aqueous solubility of the whole molecule such as $NR_{10}R_{11}$ or $HNSO_2R_{13}$ wherein R_{10}, R_{11} and R_{13} are as defined above.

In a particular embodiment of the invention, when A is a heteroaryl ring, the ring is preferably selected from the group consisting of pyrrole, pyrazole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridine, pyrimidine,

pyrazine and pyran, imidazole, imidazolidine and more preferably pyridine.

According to a preferred embodiment the present invention provides the compounds reported below:

Compound	Chemical name
1	2-(4-Isobutyl-phenyl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
2	Phenyl-acetic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
3	1-Phenyl-cyclopropanecarboxylic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
4	3,4-Dimethoxy-benzoic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)- ethyl ester
5	(S)-tert-Butoxycarbonylamino-phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
6	(R)-tert-Butoxycarbonylamino-phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
7	(S)-Amino-phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
8	(R)-Amino-phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
9	2-(4-Isobutyl-phenyl)-propionic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
11	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester

(continued)

12	2-(4-Isobutyl-phenyl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
13	2-(4-Isobutyl-phenyl)-propionic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
14	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
15	2-(4-Isobutyl-phenyl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
16	2-(4-Amino-phenyl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
17	2-(4-Methanesulfonylamino-phenyl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
25	4-(2-Piperidin-1-yl-ethoxy)-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
26	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
27	4-(2-Piperidin-1-yl-ethoxy)-benzoic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
28	Isonicotinic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
29	Nicotinic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
30	4-(2-Imidazol-1-yl-ethoxy)-benzoic acid 1-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

31	1-(2-{4-[1-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethoxycarbonyl]-phenoxy}-ethyl)-1-methyl-piperidinium
32	4-(2-Morpholin-4-yl-ethoxy)-benzoic acid cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
33	4-Difluoromethoxy-3-(2-piperidin-1-yl-ethoxy)-benzoic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
34	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
35	4-(3,4,5-Triacetoxy-6-acetoxymethyl-tetrahydro-pyran-2-yloxy)-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
36	3-Cyclopropylmethoxy-4-(2-piperidin-1-yl-ethoxy)-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
37	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
38	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
39	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
40	4-Amino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
41	2-(4-Amino-phenyl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

42	4-Amino-benzoic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
43	4-Dimethylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
44	Terephthalic acid mono-[1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl] ester
45	3-Dimethylamino-4-methoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
46	4-Imidazol-1-yl-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
47	4-Dimethylaminomethyl-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
48	1-Methyl-1H-imidazole-4-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
49	4-Methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
50	3-(Cyclopropylmethyl-methyl-amino)-4-methoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
51	4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

52	1,2-Dimethyl-1H-benzoimidazole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
53	Quinoline-3-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
54	(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
55	Hexadecanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
56 57	Pentanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
58	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
59	4-(3-Cyclopropylmethyl-ureido)-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
60	Quinoline-8-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
61	3-Cyclopropylmethoxy-4-dimethylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
62	4-[3-(2-Methoxy-ethyl)-ureido]-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
63	1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

64	2-(2-Fluoro-biphenyl-4-yl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
65	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
66	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
67	2-(6-Dimethylamino-naphthalen-2-yl)-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
68	2-(6-Dimethylamino-naphthalen-2-yl)-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
69	3-Cyclopropylmethoxy-4-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
70	4-(3,7,12-Trihydroxy-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-17-yl)-pentanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
71	4-(3,7,12-Trihydroxy-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-17-yl)-pentanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
72	Acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
73	Phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester

(continued)

74	Butyric acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
75	4-Phenyl-butyric acid 1-(3-cyclopropylmethoxydifluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
76	4-[3-(2-Dimethylamino-ethyl)-ureido]-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
77	6-Dimethylamino-naphthalene-2-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-di chloro-1-oxy-pyridin-4-yl)ethyl ester
78	Acetoxy-phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
79	1-(3-Methanesulfonylamino-4-methoxy-phenyl)-cyclopropane-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
80	1-[3-(Cyclopropylmethyl-methyl-amino)-4-methoxy-phenyl]-cyclopropanecarboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
81	Oxy-benzoic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
82	2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
83	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(2,2-difluoro-benzo[1,3]dioxol-5-yl)ethyl ester
84	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)ethyl ester

(continued)

85	3,4,5-Triethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
86	4-Fluoro-3-methoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
87	1-Methoxy-naphthalene-2-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
88	3,4,5-Trifluoro-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
89	2-(2-Fluoro-biphenyl-4-yl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
90	2-Oxo-thiazolidine-4-carboxylic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
91	4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
92	1-Cyclopropylmethyl-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
93	1-(3',4'-Dichloro-2-fluoro-biphenyl-4-yl)-cyclopropane-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
94	2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

95	6-Dimethylamino-naphthalene-2-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
96	1-Cyclopropylmethyl-1H-indole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
97	4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
98	2-Benzyloxy-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
99	(3,4-Dimethoxy-phenylsulfanyl)-acetic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
100	4-Methanesulfonylamino-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
101	4-[9-(4-Ethyl-phenoxy)-nonyloxy]-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester

Advantageously the compounds of the invention are characterized by selectivity toward LPDE4 higher than that toward HPDE4 as obtained by the determination of their IC_{50}.

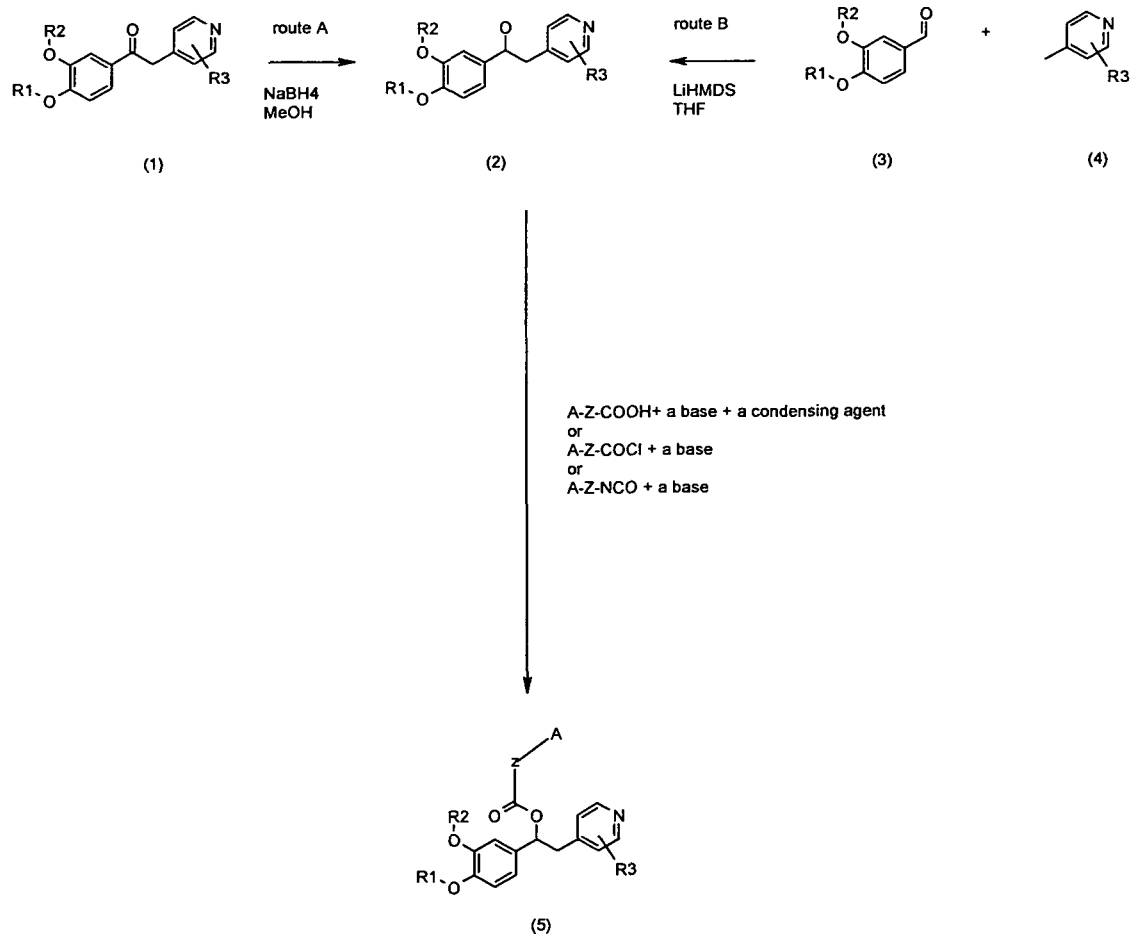
In the case of LPDE4, the IC_{50} is the molar concentration of the test compound producing 50% inhibition of cAMP disappearance, assessed as described in Cortijo J et al *Br J Pharmacol* 1993, 108: 562-568, while in the case of HPDE4, the IC_{50} is the molar concentration of the test compound producing 50% inhibition of the binding of [H^3] rolipram, assessed as described in Duplantier AJ et al *J Med Chem* 1996; 39: 120-125.

Preferably the HPDE4/LPDE4 IC_{50} ratio for the compounds of the

invention is higher than 5, preferably higher than 10, more preferably higher than 20 and even more preferably higher than 100.

The compounds of general formula (I) may be prepared conventionally according to methods disclosed in the art. Some of the processes which can be used are described below and reported in Scheme and should not be viewed as limiting the scope of the synthetic methods available for the preparation of the compounds of the invention.

Scheme



For instance, according to a particular embodiment of the present invention (scheme), the compounds of general formula (5) may be prepared according to a process which includes the following steps:

1st step - Reducing an ethanone derivative of general formula (1) to give an alcohol derivative of general formula (2) (route A).

The reaction may be carried out by using sodium boron hydride ($NaBH_4$) in a solvent such as methanol at room temperature under nitrogen atmosphere.

2nd step - Adding a suitable acid of formula AZCOOH to a solution of the alcohol derivative of general formula (2) to give a compound of general formula (5).

The reaction is carried out in the presence of a suitable strong base such as lithium diisopropylamide (LDA), NaH, dimethylaminopyridine (DMAP) and in the presence of a condensing agent such as 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC) and N-hydroxybenzotriazole (HOBT) in a solvent such as dichloromethane under nitrogen atmosphere. Other solvents may be used, such as dimethylformamide (DMF), tetrahydrofuran (THF), chloroform, dioxane and any other aprotic solvent known to those skilled in the art. In a particular embodiment, the reaction may also be carried out in absence of solvents.

In case the carboxylic acid A-Z-COOH bears reactive groups like hydroxyl, carboxyl, thio or amino groups, they may need to be protected by protecting groups such as t-butoxycarbonyl, benzyl, benzyloxycarbonyl, methyl, trimethylsilyl and similar and, at a certain step of the synthesis, deprotected to obtain again the free reactive group; the deprotected group may be then reacted with suitable reagents like alkylating, acylating, sulphonylating agents or similar.

The protection and deprotection of functional groups is described in "Protective Groups in Organic Chemistry" 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999) and "Protecting Groups", P.J. Kocienski, Georg Thieme Verlag (1994).

Compounds of general formula (5) may be also prepared by adding a suitable acyl chloride of general formula A-Z-COCl or a suitable isocyanate of

general formula A-Z-NCO to a solution of the alcohol derivative of general formula (2), with a suitable base in a stoichiometric or a catalytic amount, according to procedures well known to the skilled person.

The alcohol derivative of general formula (2) may alternatively be prepared by reacting a benzaldheyde derivative of formula (3) with a methylpyridine derivative of formula (4) (route B) using lithium-bis-(trimethylsilyl)-amide (LiHMDS) or similar strong bases and a solvent such as tetrahydrofuran (THF) or other aprotic solvents.

Intermediates of general formula (3) and (4) are commercially available or may be prepared according to methods available in the literature and well known to the person skilled in the art.

The N-oxides on the 2-pyridinyl ring of the compounds of general formula (5) may be prepared according to methods available in the literature and well known to the skilled person. For instance they may be prepared by dissolving the compound of general formula (5) in CH_2Cl_2 or $CHCl_3$, then adding an oxidizing agent such as *m*-chloro perbenzoic acid (mCPBA) to the resulting solution. Other oxidizing agents which may be used are hydrogen peroxide, perbenzoic acid and peracetic acid.

For those compounds in which A is a ring substituted with a functional group sensitive to oxidation, the corresponding N-oxides are alternatively prepared by carrying out the oxidation step before the 2nd step of the route A.

The present invention also provides pharmaceutical compositions of compounds of general formula (I) in admixture with one or more pharmaceutically acceptable carriers, for example those described in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A.

Administration of the compounds of the present invention may be accomplished according to patient needs, for example, orally, nasally,

parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by infusion), by inhalation, rectally, vaginally, topically, locally, transdermally, and by ocular administration. Various solid oral dosage forms may be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention may be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and excipients known in the art, including but not limited to suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous in administering the compounds of the present invention.

Various liquid oral dosage forms may also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable inert diluents known in the art such as water and suitable excipients known in the art such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the present invention may be injected, for example, intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

Suppositories for rectal administration of the compounds of the present invention may be prepared by mixing the compound with a suitable excipient such as cocoa butter, salicylates and polyethylene glycols.

Formulations for vaginal administration may be in the form of cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such suitable carriers as are known in the art.

For topical administration the pharmaceutical composition may be in

the form of creams, ointments, liniments, lotions, emulsions, suspensions, gels, solutions, pastes, powders, sprays, and drops suitable for administration to the skin, eye, ear or nose. Topical administration may also involve transdermal administration via means such as transdermal patches.

For the treatment of the diseases of the respiratory tract, the compounds according to the invention are preferably administered by inhalation.

Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

For administration as a dry powder, single- or multi-dose inhalers known from the prior art may be utilized. In that case the powder may be filled in gelatine, plastic or other capsules, cartridges or blister packs or in a reservoir.

A diluent or carrier, generally non-toxic and chemically inert to the compounds of the invention, e.g. lactose or any other additive suitable for improving the respirable fraction may be added to the powdered compounds of the invention.

Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the compounds of the invention either in solution or in dispersed form. The propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers and optionally other excipients.

The propellant-free inhalable formulations comprising the compounds of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known from the prior art or by soft-mist nebulizers such as Respimat®.

The compounds of the invention may be administered as the sole active agent or in combination with other pharmaceutical active ingredients including those currently used in the treatment of respiratory disorders, e.g. beta$_2$-agonists, corticosteroids and anticholinergic or antimuscarinic agents.

The dosages of the compounds of the present invention depend upon a variety of factors including the particular disease to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the efficacy, toxicology profile, and pharmacokinetic profile of the compound.

Advantageously, the compounds of general formula (I) may be administered for example, at a dosage comprised between 0.001 and 1000 mg/day, preferably between 0.1 and 500 mg/day.

When they are administered by inhalation route, the dosage of the compounds of general formula (I) is advantageously comprised between 0.01 and 20 mg/day, preferably between 0.1 and 10 mg/day.

Preferably, the compounds of general formula (I) alone or combined with other active ingredients may be administered for the prevention and/or treatment of any obstructive respiratory disease such as asthma, chronic bronchitis and chronic obstructive pulmonary disease (COPD).

However the compounds of general formula (I) may be administered for the prevention and/or treatment of any disease wherein PDE4 inhibition is required. Said disease include: allergic disease states such as atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, inflammatory arthritis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, cystic fibrosis, arterial restenosis, artherosclerosis, keratosis, rheumatoid spondylitis, osteoarthritis, pyresis, diabetes mellitus,

pneumoconiosis, toxic and allergic contact eczema, atopic eczema, seborrheic eczema, lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, systemic lupus erythematosus, follicular and wide-area pyodermias, endogenous and exogenous acne, acne rosacea, Beghet's disease, anaphylactoid purpura nephritis, inflammatory bowel disease, leukemia, multiple sclerosis, gastrointestinal diseases, autoimmune diseases and the like.

They also include neurological and psychiatric disorders such as Alzheimer's disease, multiple sclerosis, amylolaterosclerosis (ALS), multiple systems atrophy (MSA), schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, depression, stroke, and spinal cord injury.

The present invention will now be further described by way of the following non-limiting examples.

EXAMPLES

EXAMPLE 1

Preparation of 3,5-dichloro-4-methylpyridine (Intermediate (4) of scheme)

Diisopropylamine (70 mL, 500 mmol) was dissolved in dry tetrahydrofuran (THF) (500 mL), the solution was cooled to -10°C and butyl lithium (2.5 N in hexane, 210 mL, 525 mmol) was added dropwise under stirring. After 30 minutes the solution was cooled to -20°C and 3,5-dichloropyridine (66.6 g, 450 mmol) in tetrahydrofuran (200 mL) was added dropwise. The solution was stirred at -10°C for 30 minutes, cooled to -70°C and added dropwise with iodomethane (50 mL, 1.6 mol) in tetrahydrofuran (100 mL). The reaction mixture was allowed to warm to room temperature, quenched with water (100 mL) and extracted with diethyl ether (3 x 100 mL); the combined organic layers were dried over sodium sulphate (5 g) and evaporated to dryness. The crude product was crystallized twice

from aqueous ethanol than from hexane to afford 3,5-dichloro-4-methylpyridine (49.9 g, 306 mmol, 68 % yield) as a white solid.

MS/ESI+ 162-164-166 m/z [MH] +.

EXAMPLE 2

Preparation of 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)-ethanone (Intermediate (1) of scheme)

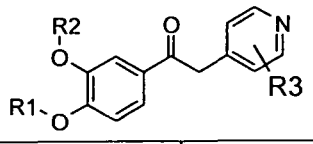
A solution of 3,5-dichloro-4-methyl-pyridine (2.06 g, 12.7 mmol) in dry tetrahydrofuran (30 ml) was cooled down to -78°C then a 1.8 M solution of lithium diisopropylamide in tetrahydrofuran (7.4 ml, 13.3 mmol) was added dropwise under stirring, keeping the temperature below -70°C. The resulting solution was stirred for 30 min., then a solution of 3,4-dimethoxy-benzoyl chloride (2.55 g, 12.7 mmol) in dry tetrahydrofuran (20 ml) was added dropwise, maintaining the temperature below -70°C. After stirring for 15 min. ice (20 g) was added, followed by further 500 ml of water. The mixture was extracted with ethyl acetate (2 x 50 ml), the combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to give an oil that was purified by flash chromatography (Eluent: ethyl acetate/petroleum ether from 10/90 to 30/70 v:v).

2.1 grams (6.4 mmol, 52% yield) of the title compound were obtained as a white solid.

MS/ESI+ 326-328-330 m/z [MH] +; ^{1}H NMR ($CDCl_3$ calibrated at 7.26 ppm) 3.91 and 3.95 (2s, 6H), 4.62 (s, 2H), 6.91-6.95 (d, 1H), 7.53-7.54 (d, 1H), 7.67-7.75 (dd, 1H), 8.49 (s, 2H).

The following intermediates were prepared using said route with suitable solvents:

Table 1



Intermediate	R_1	R_2	R_3	Analytical
1	Me	cyclopentyl	3,5 dichloro	MS/ESI+ 326-328-330 $[MH]^+$
1a	Me	cyclopropylmethyl	3,5 dichloro	MS/ESI+ 366-368-370 $[MH]^+$
1b	difluoromethyl	cyclopropylmethyl	3,5 dichloro	MS/ESI+ 402-404-406 $[MH]^+$
1c	difluoromethyl	difluoromethyl	3,5 dichloro	MS/ESI+ 398-400-402 $[MH]^+$
1d	difluoromethyl	Me	3,5 dichloro	MS/ESI+ 362-366-368 $[MH]^+$
1e	difluoromethyl	cyclopentyl	3,5 dichloro	MS/ESI+ 416-418-420 $[MH]^+$

EXAMPLE 3

Preparation of 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)-ethanol (Intermediate (2) of scheme)

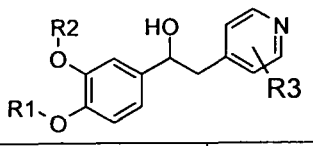
Route A

Sodium boron hydride $NaBH_4$ (45.2 mg, 2.5 eq.) is added to a suspension of 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)-ethanone (150 mg, 1 eq.) in CH_3OH (5 ml), at room temperature under nitrogen atmosphere. The mixture is stirred at room temperature overnight, then the reaction is quenched with water and extracted with EtOAc. The organic layer is dried over Na_2SO_4 and the solvent is evaporated. The crude is purified by flash chromatography on silica gel in gradient elution from petroleum ether/EtOAc 9/1 v/v to petroleum ether/EtOAc 7/3 v/v, to obtain 75 mg of the title compound (50% yield).

MS/ESI+ 328-330-332$[MH]^+$

The following intermediates were prepared using said route with suitable solvents:

Table 2



Intermediates	R_1	R_2	R_3	Analytical
2	Me	cyclopentyl	3,5-dichloro	MS/ESI+ 328-330-332 $[MH]^+$
2a	Me	cyclopropylmethyl	3,5-dichloro	MS/ESI+ 368-370-372 $[MH]^+$
2b	difluoromethyl	cyclopropylmethyl	3,5-dichloro	MS/ESI+ 404-406-408 $[MH]^+$
2c	difluoromethyl	difluoromethyl	3,5-dichloro	MS/ESI+ 400-402-404 $[MH]^+$
2d	difluoromethyl	Me	3,5-dichloro	MS/ESI+ 364-368-370 $[MH]^+$

EXAMPLE 4

Preparation of 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)-ethanol (Intermediate (2) of scheme)

Route B

3,5-Dichloro-4-methylpyridine (500 mg, 1 eq.) is dissolved in dry THF (2 mL) under nitrogen atmosphere at -60°C. $LiN(TMS)_2$ (1.0M in THF, 3.38 mL, 1.1 eq.) is added dropwise *via* syringe, keeping the temperature below -55°C. The mixture turns yellow and is stirred at -60°C for about 30 minutes. Then a solution of 3,4-dimethoxybenzaldehyde (513 mg, 1 eq.) in dry THF (2 mL) is added dropwise *via* syringe, keeping the temperature below -55°C. After the addition the mixture is slowly warmed to room temperature and stirred at room temperature for about 2h. Then it is quenched with water and extracted with EtOAc. The organic layer is dried over Na_2SO_4 and the solvent is evaporated. The crude is triturated with Et_2O, and filtered to obtain 741 mg of the title compound as a white solid (73% yield).MS/ESI+ 328-330-332 $[MH]^+$

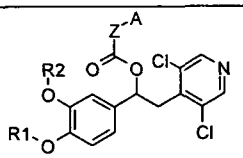
EXAMPLE 5

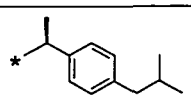
Preparation of (S)-2-(4-isobutyl-phenyl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester (compound 1)

(1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride) (EDC.HCl) (345 mg, 3 eq.) is added to a solution of 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)-ethanol (200 mg, 1 eq.), (S)-2-(4-isobutyl-phenyl)-propionic acid (148 mg, 1.2 eq.) and 4-dimethylaminopyridine (DMAP) (37 mg, 0.5 eq.) in dry CH_2Cl_2 (8 mL) at room temperature under nitrogen atmosphere. The mixture is stirred at room temperature overnight, then it is treated with a saturated solution of NH_4Cl (20 ml) and extracted with EtOAc (2x20 ml). The combined organic layer are dried over Na_2SO_4 and the solvent is evaporated. The crude is purified by flash chromatography on silica gel in gradient elution (from petroleum ether/EtOAc 9/1 v/v to petroleum ether/EtOAc 7/3 v/v) to yield 259 mg of pure compound.

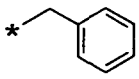
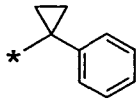
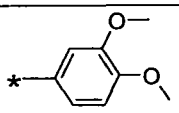
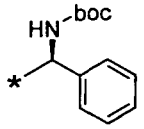
The following compounds were prepared using said route with suitable reagents:

Table 3

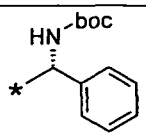
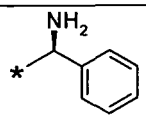
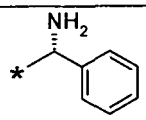


Compound	R_1	R_2	Z-A	Analytical
1	Me	Me		MS/ESI+ 516-518-520 [MH]+; ^{1}H NMR ($CDCl_3$ calibrated at 7.26 ppm, mix of diast.) δ: 8.47 and 8.31(s*, 1H); 7.05(m*, 4H); 6.96-6.63(m*, 3H); 6.10(m*, 1H); 3.89 and 3.86 (s*, 3H); 3.86 and 3.70(s*, 3H); 3.69-3.49(m*, 2H); 3.24(m*, 1H); 2.48 and 2.46(d*, 2H); 1.88(m*, 1H); 1.39(d*, 3H); 0.94 and 0.92(d*, 3H).

(continued)

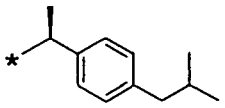
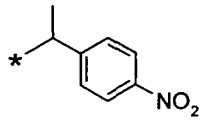
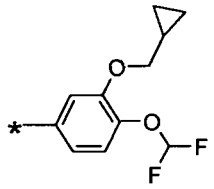
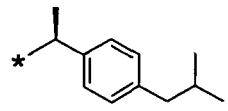
2	Me	Me		MS/ESI+ 446-448-450 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm) δ: 8.42(s*, 2H); 7.26(m*, 3H); 7.17(m*, 2H); 6.89(dd*, 1H); 6.82(d*, 1H); 6.79(d*, 1H); 6.14(dd*, 1H); 3.89(s*, 3H); 3.80(s*, 3H); 3.61(dd*, 1H); 3.58 and 3.55(ABq, 2H); 3.29(dd*, 1H).
3	Me	Me		MS/ESI+ 472-474-476 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm) δ: 8.45(s*, 2H); 7.34-7.26(m*, 5H); 6.79(m*, 2H); 6.68(m*, 1H); 6.15(dd*, 1H); 3.89(s*, 3H); 3.80(s*, 3H); 3.49(dd*, 1H); 3.15(dd*, 1H); 1.54(m*, 1H); 1.43(m*, 1H); 1.22(m*, 1H); 1.10(m*, 1H).
4	Me	Me		MS/ESI+ 492-494-496 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm) δ: 8.47(s*, 1H); 7.72(dd*, 1H); 7.54(d*, 1H); 7.04(dd*, 1H); 7.01(d*, 1H); 6.89(d*, 1H); 6.88(d*, 1H); 6.34(dd*, 1H); 3.95(s*, 3H); 3.93(s*, 3H); 3.91(s*, 3H); 3.89(s*, 3H); 3.82(dd*, 1H); 3.41(dd*, 1H).
5	CHF_2	cyclopropyl-methyl		MS/ESI+ 637-639-641 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm) δ: 8.21(s*, 2H), 7.36-7.22(m*, 3H), 7.16(m*, 3H), 7.00(m*, 2H), 6.65(dd*, 1H), 6.09(dd*, 1H), 5.31(br* s*, 2H), 3.93(d*, 2H), 3.54 (dd*, 1H), 3.17(dd*, 1H), 1.40(s*, 9H), 1.30(m*, 1H); 0.68(m*, 2H), 0.42(m*, 2H).

(continued)

6	CHF_2	cyclopropyl-methyl		MS/ESI+ 637-639-641 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm) δ: 8.21(s*, 2H), 7.36-7.22(m*, 3H), 7.16(m*, 3H), 7.00(m*, 2H), 6.65(dd*, 1H), 6.09(dd*, 1H), 5.31(br* s*, 2H), 3.93(d*, 2H), 3.54 (dd*, 1H), 3.17(dd*, 1H), 1.40(s*, 9H), 1.30(m*, 1H); 0.68(m*, 2H), 0.42(m*, 2H).
7	CHF_2	cyclopropyl-methyl		MS/ESI+ 537-539-541 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm, mix of diast.) δ: 8.49 and 8.19(s* 2H); 7.40-7.22(m*, 3H); 7.17(m*, 2H); 6.97(m*, 2H); 6.63 and 6.57(dd*, 1H); 6.53(m*, 1H); 6.08 and 6.04(dd*, 1H); 3.90(d*, 2H); 3.64-3.44(m*, 2H); 3.24 and 3.13(dd*, 1H); 1.22(m*, 1H); 0.66(m*, 2H); 0.36(m*, 2H).
8	CHF_2	cyclopropyl-methyl		MS/ESI+ 537-539-541 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm) δ: 8.25 (s*, 2 H), 7.35 - 7.22 (m*, 3 H), 7.18 (m*, 3 H), 6.99 (dd*, 1 H), 6.94 (d*, 1 H), 6.64 (dd*, 1 H), 6.10 (dd*, 1 H), 4.52 (s*, 1 H), 3.87 (m*, 2 H), 3.55 (dd*, 1 H), 3.13 (dd*, 1 H), 1.74 (br* s*, 2 H), 1.30 (m*, 1 H), 0.69 (m*, 2 H), 0.40 (m*, 2 H)

(continued)

5

9	Me	cyclopentyl		MS/ESI+ 570-572-574 [MH]+; ^{1}H NMR ($CDCl_3$ calibrated at 7.26 ppm) δ: 8.46(s*, 2H), 7.04(m*, 4H), 6.72(d*, 1H), 6.71(d*, 1H), 6.67(dd*, 1H), 6.06(dd*, 1H), 4.60(m*, 1H), 3.82(s*, 3H), 3.65(q*, 1H), 3.56(dd*, 1H), 3.26(dd*, 1H), 2.45(d*, 2H), 1.95-1.75(m*, 7H), 1.70-1.54(m*, 2H), 1.39(d*, 3H), 0.91(d*, 6H) and 8.30(s*, 2H), 7.04(m*, 4H), 6.89(dd*, 1H), 6.88(d*, 1H), 6.82(d*, 1H), 6.10(dd*, 1H), 4.75(m*, 1H), 3.85(s*, 3H), 3.63(q*, 1H), 3.56(dd*, 1H), 3.19(dd*, 1H), 2.47(d*, 2H), 1.95-1.75(m*, 7H), 1.70-1.54(m*, 2H), 1.38(d*, 3H), 0.93(d*, 6H).
10	Me	Me		MS/ESI+ 505-507-509 [MH]+
11	CHF_2	cyclopropyl-methyl		MS/ESI+ 644-646-648 [MH]+; 1H NMR ($CDCl_3$ calibrated at 7.26 ppm): 8.48(s*, 2H); 7.66(dd*, 1H); 7.58(d*, 1H); 7.21(d*, 1H); 7.19(d*, 1H); 7.08(dd*, 1H); 7.04(dd*, 1H); 6.72(dd*, 1H); 6.63(dd*, 1H); 6.30(dd*, 1H); 3.92(d*, 2H); 3.90(d*, 2H); 3.73(dd*, 1H); 3.39(dd*, 1H); 1.29(m*, 2H); 0.68(m*, 4H); 0.38(m*, 4H).
12	CHF_2	cyclopropyl-methyl		MS/ESI+ 593-595-597 [MH]+

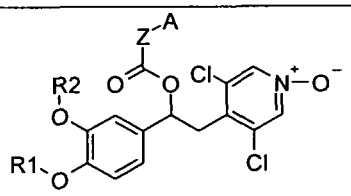
EXAMPLE 6

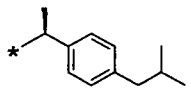
Preparation of (S)-2-(4-isobutyl-phenyl)-propionic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester (compound 13)

Compound 1 (51.5 mg, 0.1 mmoles) is dissolved in CH_2CL_2 (1 mL). *m*-Chloro perbenzoic acid (mCPBA, 15 mg, 0.12 mmoles) is added and the resulting solution is stirred at room temperature for 2 hours. The mixture is then diluted with CH_2Cl_2 (5 mL) and extracted with 1N NaOH (5 ml). The organic phase is dried over Na_2SO_4 and the solvent is evaporated. The crude is purified by preparative HPLC to yield 37 mg of the title compound.

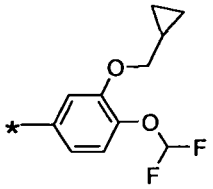
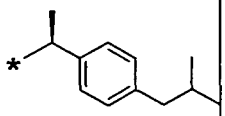
The following compounds were prepared following the same route using suitable reagents:

Table 4



Compound	R_1	R_2	Z-A	Analytical
13	Me	Me		MS/ESI+ 532-534-536 $[MH]^+$; ^1H NMR ($CDCl_3$ calibrated at 7.26 ppm, mix of diast), δ: 8.11 and 7.89 (s*, 2 H), 6.97 - 7.10 (m*, 4 H), 6.79 - 6.94 and 6.53 - 6.76 (m*, 3 H), 5.96 and 6.05 (dd*, 1 H), 3.82 and 3.82(s*, 3 H), 3.67 and 3.82(s*, 3 H), 3.60 (m*, 1 H), 3.41 and 3.46(dd*, 1 H), 3.08 and 3.17(dd*, 1 H), 2.43 and 2.49 (d*, 2 H), 1.74 - 1.93 (m*, 1 H), 1.36 and 1.39(d*, 3 H), 0.88 and 0.90 (d*, 6 H)

(continued)

14	CHF_2	cyclopropyl - methyl		MS/ESI+ 660-662-664 $[MH]^+$; 1H NMR (CDCl3 calibrated at 7.26 ppm): 8.25 (s*, 2 H), 7.65 (dd*, 1 H), 7.57 (d*, 1 H), 7.22 (d*, 1 H), 7.21 (d*, 1 H), 7.01 - 7.10 (m*, 2 H), 6.73 (t*, 1 H), 6.63 (t*, 1 H), 6.29 (dd*, 1 H), 3.92 (d*, 2 H), 3.91 (d*, 2 H), 3.73 (dd*, 1 H), 3.36 (dd*, 1 H), 1.18 - 1.43 (m*, 2 H), 0.56 - 0.77 (m*, 4 H), 0.23 - 0.50 (m*, 4 H)
15	CHF_2	cyclopropyl - methyl		MS/ESI+ 609-611-613 $[MH]^+$

The following compounds were prepared in an analogous manner to the methods already described in earlier Examples, with appropriate selection of reagents and according to the general synthesis earlier described:

Compound	Chemical name
26	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
27	4-(2-Piperidin-1-yl-ethoxy)-benzoic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
28	Isonicotinic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

29	Nicotinic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
30	4-(2-Imidazol-1-yl-ethoxy)-benzoic acid 1-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
31	1-(2-{4-[1-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethoxycarbonyl]-phenoxy}-ethyl)-1-methyl-piperidinium
32	4-(2-Morpholin-4-yl-ethoxy)-benzoic acid cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
33	4-Difluoromethoxy-3-(2-piperidin-1-yl-ethoxy)-benzoic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
34	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
35	4-(3,4,5-Triacetoxy-6-acetoxymethyl-tetrahydro-pyran-2-yloxy)-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
36	3-Cyclopropylmethoxy-4-(2-piperidin-1-yl-ethoxy)-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
37	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
38	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
39	2-(6-Methoxy-naphthalen-2-yl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
40	4-Amino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

41	2-(4-Amino-phenyl)-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
42	4-Amino-benzoic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
43	4-Dimethylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
44	Terephthalic acid mono-[1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl] ester
45	3-Dimethylamino-4-methoxy-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
46	4-Imidazol-1-yl-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
47	4-Dimethylaminomethyl-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
48	1-Methyl-1H-imidazole-4-carboxylic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro -1-oxy-pyridin-4-yl)ethyl ester
49	4-Methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
50	3-(Cyclopropylmethyl-methyl-amino)-4-methoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
51	4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

52	1,2-Dimethyl-1H-benzoimidazole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
53	Quinoline-3-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
54	(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
55	Hexadecanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
56 57	Pentanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
58	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
59	4-(3-Cyclopropylmethyl-ureido)-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
60	Quinoline-8-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
61	3-Cyclopropylmethoxy-4-dimethylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
62	4-[3-(2-Methoxy-ethyl)-ureido]-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
63	1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

64	2-(2-Fluoro-biphenyl-4-yl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
65	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
66	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
67	2-(6-Dimethylamino-naphthalen-2-yl)-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
68	2-(6-Dimethylamino-naphthalen-2-yl)-propionic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
69	3-Cyclopropylmethoxy-4-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
70	4-(3,7,12-Trihydroxy-10,13-dimethyl-hexadecahydro-cyclopenta-[a]phenanthren-17-yl)-pentanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
71	4-(3,7,12-Trihydroxy-10,13-dimethyl-hexadecahydro-cyclopenta-[a]phenanthren-17-yl)-pentanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
72	Acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
73	Phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester

(continued)

74	Butyric acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
75	4-Phenyl-butyric acid 1-(3-cyclopropylmethoxydifluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
76	4-[3-(2-Dimethylamino-ethyl)-ureido]-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
77	6-Dimethylamino-naphthalene-2-carboxylic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
78	Acetoxy-phenyl-acetic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
79	1-(3-Methanesulfonylamino-4-methoxy-phenyl)-cyclopropane-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
80	1-[3-(Cyclopropylmethyl-methyl-amino)-4-methoxy-phenyl]-cyclopropanecarboxylic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
81	Oxy-benzoic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
82	2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
83	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(2,2-difluoro-benzo[1,3]dioxol-5-yl)ethyl ester
84	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)ethyl ester

(continued)

85	3,4,5-Triethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
86	4-Fluoro-3-methoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
87	1-Methoxy-naphthalene-2-carboxylic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro -pyridin-4-yl)ethyl ester
88	3,4,5-Trifluoro-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
89	2-(2-Fluoro-biphenyl-4-yl)-propionic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
90	2-Oxo-thiazolidine-4-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
91	4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
92	1-Cyclopropylmethyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo-imidazole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
93	1-(3',4'-Dichloro-2-fluoro-biphenyl-4-yl)-cyclopropanecarboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
94	2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

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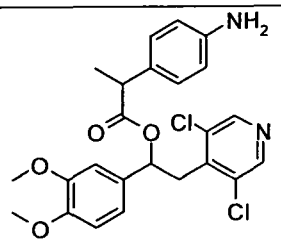
95	6-Dimethylamino-naphthalene-2-carboxylic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
96	1-Cyclopropylmethyl-1H-indole-5-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
97	4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
98	2-Benzyloxy-propionic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
99	(3,4-Dimethoxy-phenylsulfanyl)-acetic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
100	4-Methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
101	4-[9-(4-Ethyl-phenoxy)-nonyloxy]-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester

EXAMPLE 7

Preparation of 2-(4-amino-phenyl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester (compound 16)

Compound 10 (50 mg, 0.1 mmoles) is dissolved in dimethylformamide (DMF) (3 mL). Tin chloride ($SnCl_2$ x $2H_2O$, 113 mg, 0.5 mmoles) is added and the resulting mixture is stirred at room temperature for 17 hours. The mixture is then diluted with water (15 mL) and extracted with Et_2O (2 x 30 mL). The organic phase is dried over Na_2SO_4 and the solvent is evaporated. The crude is purified by preparative HPLC to yield 10 mg of the title compound.

Table 5

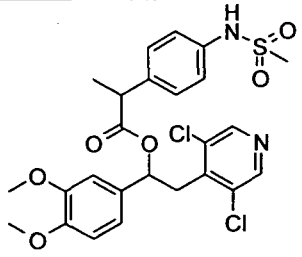
Compound	Structure	Analytical
16		MS/ESI+ 475-477-479 [MH] +; ^{1}H NMR ($CDCl_3$ calibrated at 7.26 ppm, mix of diast), δ: 8.31 and 8.47 (s*, 2H); 6.58 and 6.90 (m*, 6H); 6.76(m*, 1H); 6.05 and 6.11(dd*, 1H); 3.87 and 3.89 (s*, 3H); 3.72 and 3.87 (s*, 3H); 3.58(m*, 2H); 3.18 and 3.26(dd*, 1H); 1.33 and 1.34(d*, 3H).

EXAMPLE 8

Preparation of 2-(4-methanesulphonylamino-phenyl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester (compound 17)

Compound 16 (26 mg, 0.05 mmoles) is dissolved in dry CH_2Cl_2 (10 mL) under nitrogen atmosphere. The solution is cooled to 0°C and triethylamine (0.009 mL, 0.066 mmoles) and methanesulphonyl chloride (0.0052 mL, 0.06 mmoles) are added. The mixture is then allowed to react at room temperature for 17 hours. The reaction mixture is then diluted with water (15 mL) and extracted with AcOEt (2 x 30 mL). The organic phase is dried over Na_2SO_4 and the solvent is evaporated. The crude is purified by preparative HPLC to yield 10 mg of the title compound as a mixture of diastereoisomers.

Table 6

Compound	Structure	Analytical
17		MS/ESI+ 553-555-557 $[MH]^+$; 1H NMR ($CDCl_3$ calibrated at 7.26 ppm, mix of diast) ppm 8.28 (s*, 2 H) 7.06 - 7.12 (m*, 4 H) 6.97 (dd*, 1 H) 6.89 (d*, 1 H) 6.87 (d*, 1 H) 6.43 (br. s., 1 H) 6.12 (dd*, 1 H) 3.90 (s*, 6 H) 3.59 - 3.70 (m*, 2 H) 3.19 (dd*, 1 H) 3.08 (s*, 3 H) 1.36 (d*, 3 H) and 1H NMR (300 MHz, CHLOROFORM-d) ppm 8.47 (s*, 2 H), 7.05 - 7.21 (m*, 4 H), 6.74 - 6.79 (m*, 2 H), 6.64 - 6.70 (m*, 1 H), 6.30 - 6.38 (m*, 1 H), 6.03 - 6.18 (m*, 1 H), 3.87 (s*, 3 H), 3.77 (s*, 3 H), 3.51 - 3.64 (m*, 2 H), 3.27 (dd*, 1 H), 3.02 (s*, 3 H), 1.34 - 1.41 (d*, 3 H)

EXAMPLE 9

Preparation of 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethanol (compound 18)

Intermediate 2b (100 mg, 0.25 mmoles) is dissolved in $CHCL_3$ (3 mL).

m-Chloro perbenzoic acid (mCPBA, 80 mg, 0.46 mmoles) is added and the resulting solution is kept at 0°C overnight.

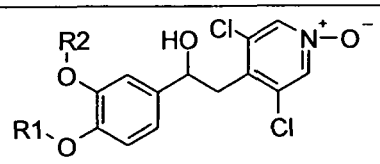
The mixture is then diluted with $CHCl_3$ (5 mL) and washed with 1N NaOH (5 ml). The organic phase is dried over Na_2SO_4 and the solvent is evaporated.

The crude product is purified by crystallization with ethanol. The white solid is filtered and washed with petroleum ether to yield 70 mg of the title

compound.

The following compounds were prepared following the same route using suitable reagents:

Table 7



Compound	R_1	R_2	Analytical
18	difluoromethyl	cyclopropylmethyl	MS/ESI$^+$ 420-422-424 [MH]$^+$
19	Me	cyclopropylmethyl	MS/ESI$^+$ 384-386-388 [MH]$^+$
20	Me	cyclopentyl	MS/ESI$^+$ 398-400-402 [MH]$^+$
21	difluoromethyl	difluoromethyl	MS/ESI$^+$ 416-418-420 [MH]$^+$
22	difluoromethyl	Me	MS/ESI$^+$ 380-382-384 [MH]$^+$
23	difluoromethyl	cyclopentyl	MS/ESI$^+$ 434-436-438 [MH]$^+$
24	Me	Me	MS/ESI$^+$ 344-346-348 [MH]$^+$

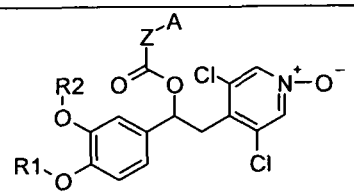
EXAMPLE 10

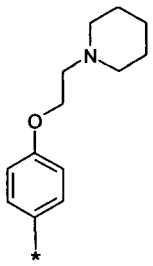
Preparation of 4-(2-piperidin-1-yl-ethoxy)-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester hydrochloride (compound 25)

(1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride) (EDC.HCl) (55 mg, eq.) is added to a solution of compound 18 (60 mg, 0.14 mmol), 4-(2-piperidin-1-yl-ethoxy)-benzoic acid (81 mg, 0.28 eq.) and 4-dimethylaminopyridine (DMAP) (37 mg, 0.5 eq.) in dry DMF (4 mL) at room temperature under nitrogen atmosphere. The mixture is stirred at room temperature overnight, then it is treated with a saturated solution of NH_4Cl (20 ml) and extracted with EtOAc (2x20 ml). The combined organic layers are dried over Na_2SO_4 and the solvent is evaporated. The crude is purified by preparative HPLC. The oily residue is dissolved in ethyl acetate (2 ml) and added with a slight excess of a 1 M solution of dry HCl in ethyl acetate. After

evaporation of the solvent the residue is crystallized from methanol/diethyl ether to give 14 mg of the hydrochloride salt.

Table 8



Compound	R_1	R_2	Z-A	Analytical
25	CHF_2	cyclopropyl- methyl		MS/ESI+ 651-653-655 [MH] + 1H NMR (CD3OD calibrated at 3.31 ppm) ppm 0.33-0.40 (m, 2H), 0.57-0.64 (m, 2H), 1.17-1.28 (m, 1H), 1.80-2.01 (m, 6H), 3.03-3.14 (m, 2H), 3.42-3.82 (m, 6H), 3.91-3.94 (d, 2H), 4.44-4.49 (t, 2H), 6.31-6.37 (m, 1H), 6.37-7.13 (t, 1H, CHF2), 7.08-7.17 (m, 5H), 7.99-8.05 (m, 2H), 8.42 (s, 2H).

Legend

* NMR

s = singlet

d = doublet

t = triplet

q = quartet

dd = doublet of doublets

m = multiplet

br = broad

ESI=electrospray

PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE 11

In vitro determination of PDE4 inhibitory activity in the cell free assay

The U937 human monocytic cell line was used as source of PDE4 enzyme. Cells were cultured, harvested and supernatant fraction prepared essentially as described in Torphy TJ et al J. Pharmacol. Exp. Ther. 1992; 263:1195-1205.

PDE4 activity was determined in cells supernatants by assaying cAMP disappearance from the incubation mixtures. 50 µl of cell supernatant were incubated at 30°C for 30 minutes in a final volume of 200 µl in the presence of 1.6 µM cAMP with or without the test compound (50 µl).

The concentration of the test compounds ranged between 10^{-12} M and 10^{-6} M. Reactions were stopped by heat inactivation (2.5 minutes at 100°C) and residual cAMP was measured using an electro-chemiluminescence (ECL) -based immunoassay.

The results, expressed as mean ± 95% confidence limits of the molar concentration of the test compound producing 50% inhibition of cAMP disappearance (IC_{50}) are reported in Table 9 of Example 12.

Percentage of inhibition of PDE4 activity was calculated, assuming cAMP disappearance in the absence of inhibitors as 100% and cAMP disappearance in heat inactivated samples as 0%.

All the IC_{50} values of the tested compounds, representative of the

invention, were less than 0.2 microM.

EXAMPLE 12

In vitro determination of PDE4 inhibitory activity in the peripheral blood mononuclear cells (PBMCs) assay

The assay, which is based on the known inhibitory activity exerted by PDE4 inhibitors on the lipopolyshaccarides (LPS)-induced tumour necrosis factor-alpha (TNF-α release in peripheral blood mononuclear cells (PBMCs), was performed according to a method previously described (Hatzelmann A et al *J. Pharmacol. Exp. Ther.* 2001; 297:267-279; Draheim R et al *J. Pharmacol. Exp. Ther.* 2004; 308:555-563.

Cryopreserved human PBMCs, (100 μl/well) were incubated in 96-well plates (10^5 cells/well), for 30 min, in the presence or absence (50 microl) of the test compounds whose concentrations ranged from 10^{-12} M to 10^{-6} M. Subsequently, LPS (3 ng/ml) was added.

After 18 h incubation at 37°C in a humidified incubator under an atmosphere of 95% air and 5% CO_2, culture medium was collected and TNF-α measured by ELISA.

The results, expressed as mean ± 95% confidence limits of the molar concentration of the test compound producing 50% inhibition of LPS-induced TNF-a release (IC_{50}) are reported in Table 9.

The effects of the tested compounds were calculated as percentage of inhibition of TNF-α release, assuming LPS-induced TNF-α production in the absence of inhibitor compound as 100% and basal TNF-α production of PBMCs in the absence of LPS as 0%.

Table 9 - In vitro PDE4 inhibition activity of representative compounds of the invention

Compound	IC50 cell free (nM)	IC50 PBMCS (nM)
1	118	69
2	-	89
3	118	52
4	3.4	34.2
6	9	95
7	7	99
8	22	-
9	22	85
11	12	51
12	12	456
13	1.5	13
14	0.2	2
15	8.6	15
16	6.3	36

EXAMPLE 13

Evaluation of the ability to inhibit the low affinity LPDE4 versus the ability to compete for the high affinity HPDE4

The affinity toward LPDE4 and HPDE4 was assessed as previously described respectively in Cortijo J et al *Br J Pharmacol* 1993, 108: 562-568 and Duplantier AJ et al *J Med Chem* 1996; 39: 120-125.

The concentration of the test compound ranged between 10^{-12} M and 10^{-5} M.

The results in terms of IC_{50} are reported in Table 10.

In the case of LPDE4, the IC_{50} is the molar concentration of the test compound producing 50% inhibition of cAMP disappearance, while in the case of HPDE4, the IC_{50} is the molar concentration of the test compound producing 50% inhibition of the binding of [H^3] rolipram.

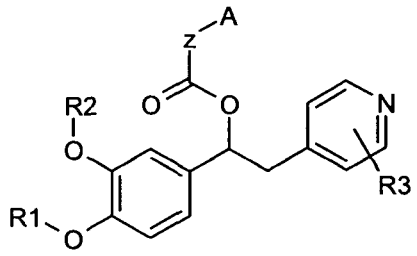
The results indicate that the compounds of the invention inhibited LPDE4 with subnanomolar affinity and are considerably more selective toward LPDE4 versus HPDE4.

Table 10 - Activity profile of representative compounds of the invention

Compound	HPDE4 IC_{50} (nM)	LPDE4 IC_{50} (nM)	HPDE4/LPDE4
14	13.9	0.0881	158
15	2.17	0.169	273
20	299	0.759	394
9	399	0.738	541
11	153	0.116	1319

CLAIMS

1. A compound of general formula (I)



(I)

wherein:

Z is selected from the group consisting of

$(CH_2)_m$ wherein m = 0, 1 or 2;

$(CH_2)_nO$ wherein n=1, 2 or 3;

$O(CH_2)_p$ wherein p=0, 1, 2 or 3;

CH_2SO_2;

$CHNR_6$;

CH_2NR_6;

NR_6 wherein R_6 is H or a linear or branched $(C_1\text{-}C_4)$ alkyl;

$OCOR_4R_5$; and

CR_4R_5 wherein

R_4 is independently selected from H or a linear or branched $(C_1\text{-}C_4)$ alkyl, preferably methyl, optionally substituted by a $(C_1\text{-}C_4)$ cycloalkyl and

R_5 is independently selected from the group consisting of

- linear or branched $(C_1\text{-}C_4)$ alkyl, preferably methyl;
- phenyl;
- benzyl;
- NH_2; and

- HNCOOR', wherein R' is linear or branched (C_1-C_4) alkyl, preferably t-butyl.

R_1 and R_2 are different or the same and are independently selected from the group consisting of

- H;
- linear or branched (C_1-C_6) alkyl, optionally substituted by one or more substituents selected from (C_3-C_7) cycloalkyl or (C_5-C_7) cycloalkenyl;
- (C_3-C_7) cycloalkyl;
- (C_5-C_7) cycloalkenyl;
- linear or branched (C_2-C_6) alkenyl; and
- linear or branched (C_2-C_6) alkynyl.

R_3 is one or more substituents independently selected from the group consisting of H, CN, NO_2, CF_3 and halogen atoms.

A is a ring system, that is a mono- or bicyclic ring which may be saturated, partially unsaturated or unsaturated, such as aryl, (C_3-C_8) cycloalkyl or heteroaryl, said ring system A having 5 to 10 ring atoms in which at least one ring atom is a heteroatom (e.g. N, S or O), in which the optional substituent R_x on the A ring system may be one or more, may be the same or different, and is independently selected from the group consisting of:

- linear or branched (C_1-C_6) alkyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
- linear or branched (C_2-C_6) alkenyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
- linear or branched (C_2-C_6) alkynyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
- (C_5-C_7) cycloalkenyl;
- phenyl;
- (C_3-C_7) heterocycloalkyl;

- OR_7 wherein R_7 is selected from the group consisting of
  - H;
  - (C_1-C_{10}) alkyl optionally substituted by one or more (C_3-C_7) cycloalkyl;
  - (C_3-C_7) cycloalkyl;
  - (C_1-C_4) alkyl-(C_3-C_7) heterocycloalkyl;
  - CO (C_1-C_6) alkyl;
  - COO (C_1-C_6) alkyl;
  - phenyl;
  - benzyl;
  - (C_1-C_{10}) alkyl-NR_8R_9 wherein R_8 and R_9 are independently selected from the group consisting of H, linear or branched (C_1-C_6) alkyl and they form with the nitrogen atom to which they are linked a saturated, partially saturated or unsaturated ring, preferably NR_8R_9 is linked to (C_1-C_{10}) alkyl forming for example saturated, partially saturated or unsaturated piperidine, oxazine, imidazole rings, wherein these rings are optionally substituted by (C_1-C_4) alkyl; and
- halogen atoms;
- CN;
- NO_2;
- $NR_{10}R_{11}$ wherein R_{10} and R_{11} are different or the same and are independently selected from the group consisting of
  - H;
  - linear or branched (C_1-C_6) alkyl, optionally substituted with phenyl or (C_3-C_7) cycloalkyl;
  - COC_6H_5;
  - CO-(C_1-C_4) alkyl;

- COO-(C_1-C_4) alkyl;
- CONH-(C_1-C_6) alkyl-R_{12}, wherein R_{12} is selected from the group consisting of
  - H;
  - (C_1-C_4) alkyl;
  - OR_4R_5; and
- CONH (C_1-C_4) alkyl-N(C_1-C_4) alkyl;

or they form with the nitrogen atom to which they are linked a saturated or partially saturated ring, preferably a piperidyl ring;

- (C_1-C_4) alkyl-$NR_{10}R_{11}$;
- COR_{12} wherein R_{12} is phenyl or linear or branched (C_1-C_6) alkyl;
- oxo;
- $HNSO_2R_{13}$ wherein R_{13} is (C_1-C_4) alkyl or a phenyl optionally substituted with halogen atoms or with a (C_1-C_4) alkyl group;
- SO_2R_{14} wherein R_{14} is (C_1-C_4) alkyl, OH or $NR_{10}R_{11}$ wherein R_{10} and R_{11} are as defined above;
- SOR_{15} wherein R_{15} is phenyl or (C_1-C_4) alkyl;
- SR_{16} wherein R_{16} is H, phenyl or (C_1-C_4) alkyl;
- $COOR_{17}$ wherein R_{17} is H, (C_1-C_4) alkyl, phenyl or benzyl; and
- $(CH_2)_qOR_{18}$, wherein q=1, 2, 3 or 4 and R_{18} is H or (C_1-C_4) cycloalkyl.

and pharmaceutically acceptable salts and N-oxides on the pyridine ring thereof.

2. The compound of claim 1 wherein A is a phenyl optionally substituted with one or more R_x groups.

3. The compound of claim 1 wherein A is a heteroaryl ring optionally substituted with one or more R_x groups.

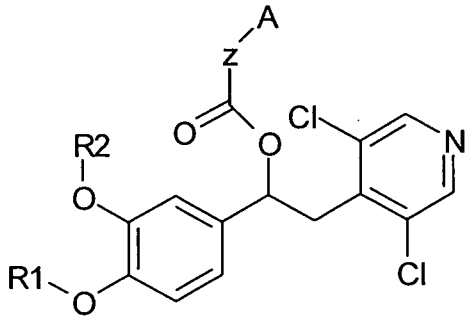
4. The compound of claim 3 wherein A is a heteroaryl ring selected from the group consisting of pyrrole, pyrazole, furan, thiophene, imidazole,

oxazole, isoxazole, thiazole, pyridine, pyrimidine, pyrazine, pyridazine, and pyran.

5. The compound of any one of claims 1 to 4 wherein R_3 is a halogen atom.

6. The compound of claim 5 wherein R_3 is chlorine.

7. The compound of claim 6 having the general formula (II)



(II)

8. The compound of claim 7 wherein Z is $(CH_2)_m$ with m equal to 0.

9. The compound of claim 8, which is 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester (compound 14).

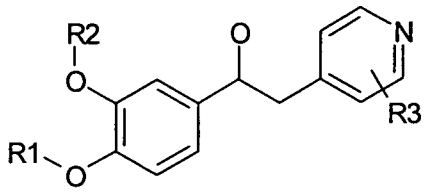
10. The compound of claim 8, which is 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester (compound 11).

11. The compound of claim 7 wherein Z is CHR_5 where R_5 is a linear or branched C_1-C_4 alkyl, preferably methyl.

12. The compound of claim 7 wherein Z is CR_4R_5 where R_4 and R_5 are both linear or branched C_1-C_4 alkyl and they form a ring with the carbon atom to which they are linked having 3, 4, 5 or 6 carbon atoms, preferably having 3 carbon atoms.

13. A process for the preparation of a compound of any of the preceding claims comprising the step of adding an acid of formula AZCOOH or an acyl

chloride of formula AZCOCl or an isocyanate of formula AZNCO wherein A and Z are as defined above, to a solution of an alcohol derivative of general formula (2)



wherein R_1, R_2 and R_3 are as defined above.

14. A pharmaceutical composition comprising a compound of any of the claims 1 to 12 as active ingredient in admixture with one or more pharmaceutically acceptable carriers and/or excipients.

15. The pharmaceutical composition of claim 20 suitable for administration by inhalation.

16. The pharmaceutical composition of claim 14 or 15 wherein said composition further comprises an additional active ingredient selected from the classes of $beta_2$-agonists, corticosteroids and anticholinergic or antimuscarinic agents.

17. The use of a compound of any of the claims 1 to 12 as a medicament.

18. The use of a compound of any of the claims 1 to 12 for the manufacture of a medicament.

19. The use of a compound of any of the claims 1 to 12 for the manufacture of a medicament for the prevention and/or treatment of any disease characterized by phosphodiesterase 4 (PDE4) overactivity and/or wherein an inhibition of PDE4 activity is desirable.

20. The use as in claim 19 wherein the disease is a disease of the respiratory tract characterized by airway obstruction.

21. The use as in claim 20 wherein the disease is selected from the group consisting of asthma or chronic bronchitis or chronic obstructive pulmonary

disease.

22. A method of treating an inflammatory disease, disorder or condition characterized by or associated with an undesirable inflammatory immune response or induced by or associated with an excessive secretion of TNF-α and PDE4 which comprises administering to a subject in need thereof a therapeutically effective amount of a compound according to any of the claims 1 to 12.