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(54) **1-fenil-2-piridinil-alkilalkohol-származékok mint foszfodiészteráz inhibitorok**

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(54) **DERIVATIVES OF 1-PHENYL-2-PYRIDINYL ALKYL ALCOHOLS AS PHOSPHODIESTERASE INHIBITORS**

DERIVATE VON 1-PHENYL-2-PYRIDINYLALKYL-ALKOHOLEN ALS PHOSPHODIESTERASEHEMMER

DÉRIVÉS D'ALCOOLS ALKYL 1-PHÉNYL-2-PYRIDINYLES EN TANT QU'INHIBITEURS DE PHOSPHODIESTÉRASE

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(56) References cited:
EP-A- 1 634 606

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to formulations comprising inhibitors of the phosphodiesterase 4 (PDE4) enzyme. More particularly, the invention relates to formulations of 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

[0002] 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.

[0003] 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.

[0004] 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.

[0005] 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).

[0006] 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.

[0007] The cause of said side effects has been widely investigated.

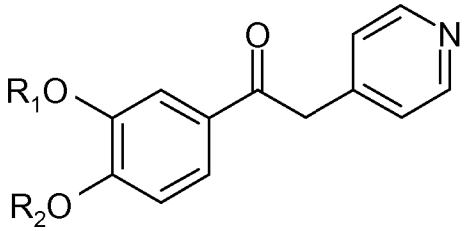
[0008] It has been found that PDE4 exists in two distinct forms representing different conformations, that were designated as high affinity rolipram binding site or HPDE4, especially present in the central nervous system and in parietal cells, and low affinity rolipram binding site or LPDE4 (Jacobitz, 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.

[0009] 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.

[0010] Other classes of compounds acting as PDE4 inhibitors have been disclosed in the prior art.

[0011] For example, EP 1634606 discloses, among others, ketone derivatives like benzofuran or 1,3-benzodioxole derivatives.

[0012] 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.

[0013] WO 9535281 in the name of Celltech Therapeutics concerns tri-substituted phenyl derivatives.

[0014] 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.

[0015] Therefore, although several PDE4 inhibitors have been disclosed so far, there is still a need for more efficacious and better tolerated compounds.

[0016] 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.

[0017] The present invention addresses these issues by providing PDE4 inhibitors having an improved selectivity toward LPDE4.

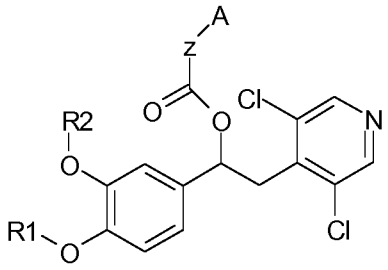
[0018] As a matter of fact, it has now been found that providing a PDE4 inhibitor with an additional moiety interacting with the active site of the PDE4, there is an improvement in the selectivity of the inhibitors towards LPDE4.

[0019] 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

[0020] The invention is directed to inhalable formulations comprising compounds acting as inhibitors of the phosphodiesterase 4 (PDE4) enzyme, methods of preparing said compounds, compositions containing them and therapeutic use thereof.

[0021] In particular the invention is directed to formulations comprising derivatives of 1-phenyl-2-pyridinyl alkyl alcohols of general formula (II)



(II)

wherein:

Z is selected from the group consisting of
$(CH_2)_m$ wherein m = 0, 1 or 2;
CR_4R_5 wherein
R_4 is independently selected from H or a linear or branched $(C_1\text{-}C_4)$ alkyl optionally substituted by one or more halogen atoms or 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, optionally substituted by one or more halogen atoms;
- phenyl;
- benzyl;
- NH_2; and
- HNCOOR', wherein R' is linear or branched $(C_1\text{-}C_4)$ alkyl optionally substituted by one or more halogen atoms, 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 $(C_1\text{-}C_6)$ alkyl, optionally substituted by one or more substituents selected from halogen atoms, $(C_3\text{-}C_7)$ cycloalkyl or $(C_5\text{-}C_7)$ cycloalkenyl;
- $(C_3\text{-}C_7)$ cycloalkyl;
- $(C_5\text{-}C_7)$ cycloalkenyl;
- linear or branched $(C_2\text{-}C_6)$ alkenyl; and
- linear or branched $(C_2\text{-}C_6)$ alkynyl.

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

[0022] A is a phenyl optionally substituted with one or more R_x groups or A is a heteroaryl ring optionally substituted with one or more Rx groups, 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, 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 halogen atoms or (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 halogen atoms or (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 wherein the (C_1-C_6) alkyl is optionally substituted by one or more halogen atoms;
  - COO (C_1-C_6) alkyl wherein the (C_1-C_6) alkyl is optionally substituted by one or more halogen atoms;
  - 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 optionally substituted by one or more halogen atoms 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 one or more halogen atoms or phenyl or (C_3-C_7) cycloalkyl;
  - COC_6H_5;
  - CO-(C_1-C_4) alkyl wherein the (C_1-C_4) alkyl is optionally substituted by one or more halogen atoms ;
  - COO-(C_1-C_4) alkyl wherein the (C_1-C_4) alkyl is optionally substituted by one or more halogen atoms;
  - CONH-(C_1-C_6) alkyl-R_{12}, wherein R_{12} is selected from the group consisting of

    - H;
    - (C_1-C_4) alkyl optionally substituted by one or more halogen atoms;
    - OR_4R_5; and

  - CONH (C_1-C_4) alkyl-N(C_1-C_4) alkyl wherein the N(C_1-C_4) alkyl is optionally substituted by one or more halogen atoms;

  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 optionally substituted by one or more halogen atoms;;
- oxo;
- $HNSO_2R_{13}$ wherein R_{13} is (C_1-C_4) alkyl optionally substituted by one or more halogen atoms;or a phenyl optionally substituted with halogen atoms or with a (C_1-C_4) alkyl group optionally substituted by one or more halogen atoms;;

- SO_2R_{14} wherein R_{14} is (C_1-C_4) alkyl optionally substituted by one or more halogen atoms; , 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 optionally substituted by one or more halogen atoms;
- SR_{16} wherein R_{16} is H, phenyl or (C_1-C_4) alkyl optionally substituted by one or more halogen atoms;
- $COOR_{17}$ wherein R_{17} is H, (C_1-C_4) alkyl optionally substituted by one or more halogen atoms;, 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.

[0023] The present invention provides pharmaceutical compositions of compounds of general formula (II) alone or in combination with in admixture with one or more pharmaceutically acceptable carriers.

[0024] In particular the compounds of general formula (II) 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.

DEFINITIONS

[0025] The term "halogen atoms" as used herein includes fluorine, chlorine, bromine, and iodine, preferably chlorine.

[0026] 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.

[0027] Optionally in said groups one or more hydrogen atoms can be replaced by halogen atoms, preferably chlorine or fluorine.

[0028] The derived expressions "(C_2-C_6) alkenyl" and "(C_2-C_6) alkynyl", are to be construed in an analogous manner.

[0029] 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.

[0030] Optionally in said groups one or more hydrogen atoms can be replaced by halogen atoms, preferably chlorine or fluorine.

[0031] 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.

[0032] The derived expressions "(C_1-C_x) cycloalkoxyl" is to be construed in an analogous manner.

[0033] The derived expression "(C_5-C_x) cycloalkenyl", where x is an integer greater than 5, is to be construed in an analogous manner.

[0034] 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).

[0035] Examples of suitable monocyclic systems include phenyl, pyridyl, piperazinyl, piperidinyl, morpholinyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, dioxane, imidazole and imidazolidine.

[0036] 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

[0037] The invention is directed to formulations of a class of compounds acting as inhibitors of the phosphodiesterase 4 (PDE4) enzyme.

[0038] Said class of compounds inhibits the conversion of cyclic nucleotides, in particular cyclic adenosine monophosphate (cAMP), into their inactive 5'-mononucleotide forms.

[0039] 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).

[0040] It also leads to an airway smooth muscle relaxation and a decrease in oedema.

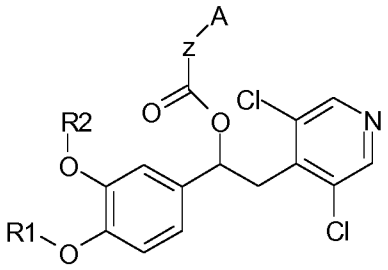
[0041] The catalytic site of PDE4 has been previously identified: it mainly comprises a hydrophobic region in which two sub-pockets are present, e.g. So and S_1, and a hydrophilic region containing the metal ions Zn^{2+} and Mg^{2+}, that in turn comprises the sub-pocket S_2 spreading around the metal ions and a sub-pocket S_3 which branches approximately 90° from the middle of the hydrophobic pocket.

[0042] Most of the compounds of the prior art are provided with a moiety able of interacting with the sub-pockets So 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.

[0043] The present invention is directed to formulations of compounds which were designed so that they could maintain the interactions with the sub-pockets So 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.

[0044] In particular the present invention relates to formulations of derivatives of 1-phenyl-2-pyridinyl alkyl alcohols of general formula (II)



(II)

[0045] 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.

[0046] It will be apparent to those skilled in the art that the compounds of general formula (II) may contain asymmetric centers. 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.

[0047] The compounds of general formula (II) 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] Advantageously when R_1 or R_2 is H, the other substituent on the catechol group is different from H.

[0052] Preferably R_1 and R_2 are both different from H.

[0053] 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 $(CH_2)_m$ wherein m is 0; and
A is as defined above.

[0054] 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.

[0055] 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
A is as defined above.

[0056] In one of the preferred embodiment A is substituted and Rx is selected from the group consisting of linear or branched (C_1-C_6) alkyl, linear or branched (C_2-C_6) alkenyl, linear or branched (C_2-C_6) alkynyl or OR_7 wherein R_7 is as defined above.

[0057] 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.

[0058] 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, and more preferably pyridine.

[0059] According to a preferred embodiment the present invention provides formulations of 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
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-oxypyridin-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-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxypyridin-4-yl)ethyl ester
26	3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopentyloxy-4-methoxy-phenyl)-2-(3,5-dichloro-1-oxypyridin-4-yl)ethyl ester
27	4-(2-Piperidin-1-yl-ethoxy)-benzoic acid 2-(3,5-dichloro-1-oxypyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester
28	Isonicotinic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxyphenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester

(continued)

Compound	Chemical name
29	Nicotinic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-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-oxypyridin-4-yl)ethyl ester
31	1-(2-{4-[1-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-d ich loro-1-oxy-pyridi1n-4-yl)-eth oxycarbonyl]-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-methoxyphenyl)-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-dichloropyridin-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
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-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
47	4-Dimethylaminomethyl-benzoic acid 1-(3-cyclopropyl-methoxy-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-oxypyridin-4-yl)ethyl ester
49	4-Methanesulfonylamino-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxypyridin-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

(continued)

Compound	Chemical name
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
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-difluoromethoxyphenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
56 57	Pentanoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-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
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-hexadecahydrocyclopenta[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-difluoromethoxyphenyl)-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)

Compound	Chemical name
74	Butyric acid 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
75	4-Phenyl-butyric acid 1-(3-cyclopropylmethoxydifluoromethoxyphenyl)-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-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester
79	1-(3-Methanesulfonylamino-4-methoxy-phenyl)-cyclopropanecarboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-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
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
95	6-Dimethylamino-naphthalene-2-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester

(continued)

Compound	Chemical name
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

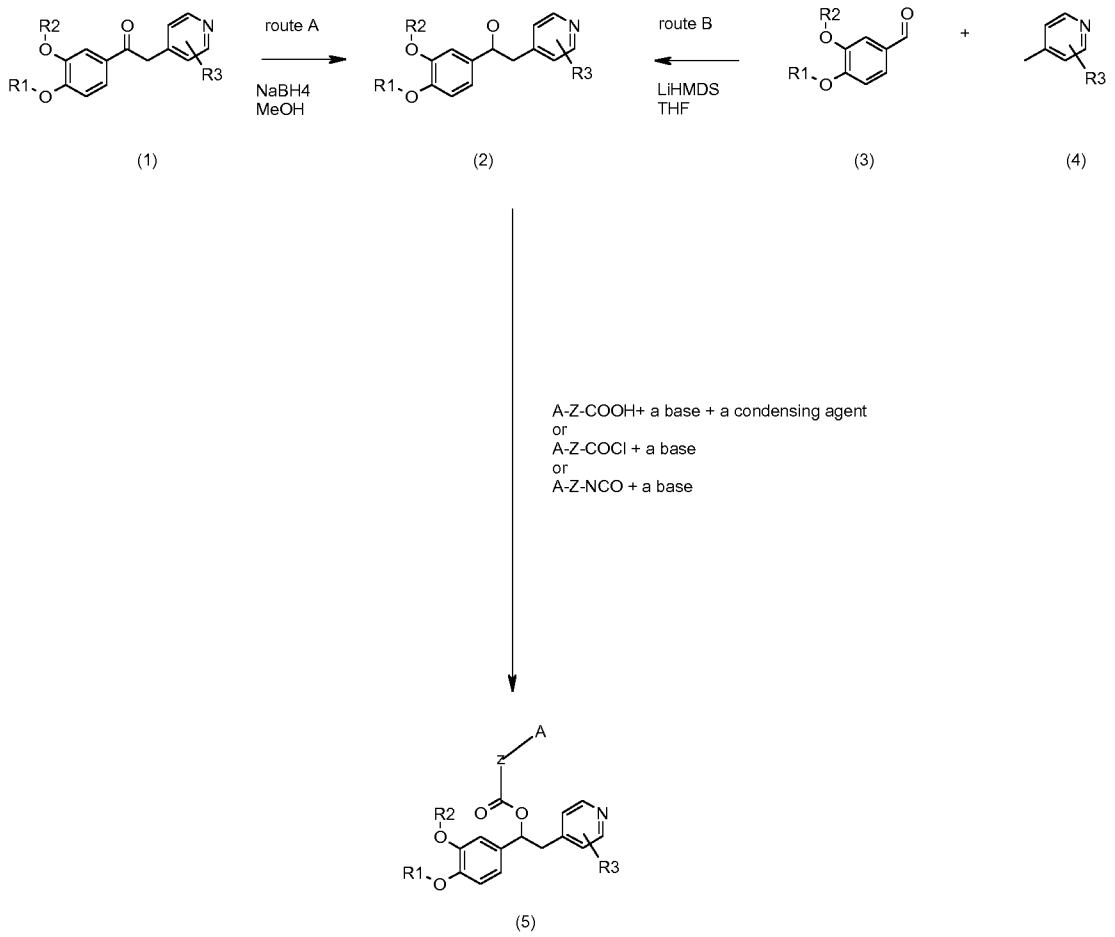
[0060] Advantageously the compounds of general formula (II) are characterized by selectivity toward LPDE4 higher than that toward HPDE4 as obtained by the determination of their IC_{50}.

[0061] 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.

[0062] Preferably the HPDE4/LPDE4 IC_{50} ratio for the compounds of general formula (II) is higher than 5, preferably higher than 10, more preferably higher than 20 and even more preferably higher than 100.

[0063] The compounds of general formula (II) 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



[0064] In formulae (1), (2), (4) and (5) of the Scheme R3 is 3,5-dichloro.

[0065] For instance, 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).

[0066] 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.

[0067] 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).

[0068] 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-dimethylamino-propyl]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.

[0069] 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.

[0070] 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).

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] The present invention provides pharmaceutical compositions of compounds of general formula (II) 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.

[0077] For the treatment of the diseases of the respiratory tract, the compounds of general formula (II) are administered by inhalation.

[0078] Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

[0079] 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.

[0080] 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.

[0081] Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the compounds of general formula (II) 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.

[0082] The propellant-free inhalable formulations comprising the compounds of general formula (II) 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®.

[0083] The compounds of general formula (II) 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.

[0084] The dosages of the compounds of general formula (II) 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.

[0085] Advantageously, the compounds of general formula (II) may be administered for example, at a dosage comprised between 0.001 and 1000 mg/day, preferably between 0.1 and 500 mg/day.

[0086] When they are administered by inhalation route, the dosage of the compounds of general formula (II) is advantageously comprised between 0.01 and 20 mg/day, preferably between 0.1 and 10 mg/day.

[0087] Preferably, the compounds of general formula (II) 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).

[0088] However the compounds of general formula (II) 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.

[0089] 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.

[0090] 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)

[0091] 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.
[0092] MS/ESI$^+$ 162-164-166 m/z $[MH]^+$.

EXAMPLE 2

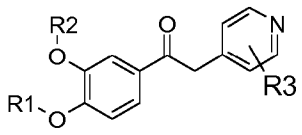
Preparation of 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)-ethanone (Intermediate (1) of scheme)

[0093] 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.

[0094] 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).
[0095] 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)

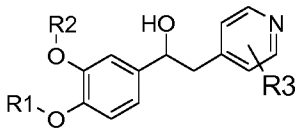
Route A

[0096] 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).

[0097] MS/ESI$^+$ 328-330-332[MH]$^+$

[0098] 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

[0099] 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

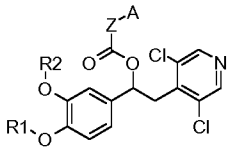
Preparation of (S)-2-(4-isobutyl-phenyl)-propionic acid 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester (compound 1)

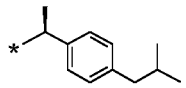
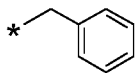
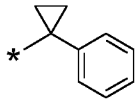
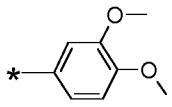
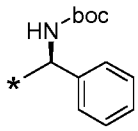
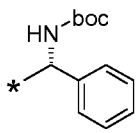
[0100] (1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride) (EDC.HCl) (345 mg, 3 eq.) is added to a solution of 2-(3,5-dichloro-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)-ethanol (200 mg, 1 eq.), (S)-2-(4-isobutylphenyl)-propionic acid (148 mg, 1.2 eq.) and 4-dimethylaminopyridine (DMAP) (37 mg, 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.

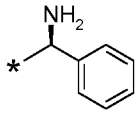
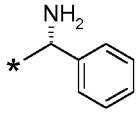
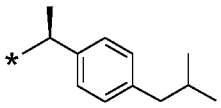
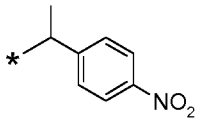
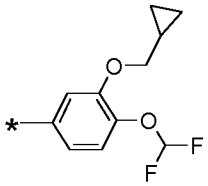
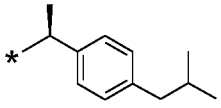
[0101] The following compounds were prepared using said route with suitable reagents:

Table 3



Compound	R_1	R_2	Z-A	Analytical
1	Me	Me		MS/ESI+ 516-518-520 $[MH]^+$; ^1H 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).
2	Me	Me		MS/ESI+ 446-448-450 $[MH]^+$; ^1H NMR (CDCl3 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	cyclopropylmethyl		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).
6	CHF_2	cyclopropylmethyl		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)

Compound	R_1	R_2	Z-A	Analytical
7	CHF_2	cyclopropylmethyl		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	cyclopropylmethyl		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)
9	Me	cyclopentyl		MS/ESI+ 570-572-574 $[MH]^+$; ^1H 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	cyclopropylmethyl		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	cyclopropylmethyl		MS/ESI+ 593-595-597 $[MH]^+$

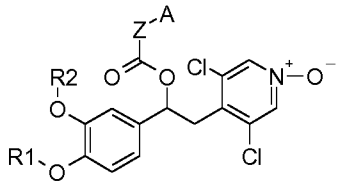
EXAMPLE 6

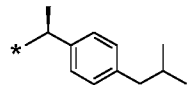
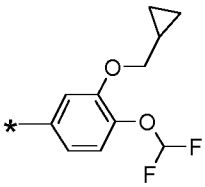
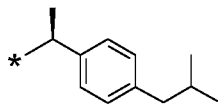
Preparation of (S)-2-(4-isobutyl-phenyl)-propionic acid 2-(3,5-dichloro-1-oxy-pyridin-4-yl)-1-(3,4-dimethoxy-phenyl)ethyl ester (compound 13)

[0102] 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.

[0103] 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)
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 $[MH]^+$

[0104] 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-difluoromethoxyphenyl)-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

(continued)

Compound	Chemical name
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
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)

Compound	Chemical name
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
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
74	Butyric acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester

(continued)

Compound	Chemical name
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
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
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

(continued)

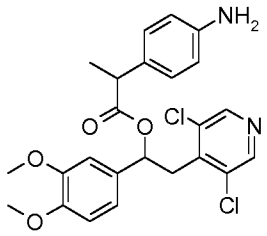
Compound	Chemical name
97	4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester
98	2-Benzyloxy-propionic acid 1-(3-cyclopropylmethoxy-4-difluoro-methoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl 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)

[0105] 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

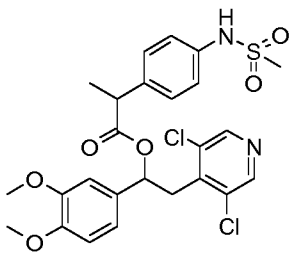
Compound	Structure	Analytical
16		MS/ESI$^+$ 475-477-479 [MH] $^+$; ^{1}H NMR ($CDCl_3$ calibrated at 7.26 ppm, mix of diast), δ: 8.31 and 8.47 (s*, 2H); 6.58 and 6.90 (m*, 6H); 6.76(m*, 1H); 6.05 and 6.11(dd*, 1H); 3.87 and 3.89 (s*, 3H); 3.72 and 3.87 (s*, 3H); 3.58(m*, 2H); 3.18 and 3.26(dd*, 1H);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

[0106] 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 ($COCl_3$ 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 (dd*, 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*,3H)

EXAMPLE 9

Preparation of 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethanol (compound 18; not part of the invention)

[0107] Intermediate 2b (100 mg, 0.25 mmoles) is dissolved in $CHCL_3$ (3 mL).

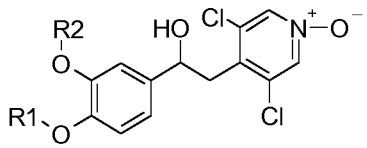
[0108] *m*-Chloro perbenzoic acid (mCPBA, 80 mg, 0.46 mmoles) is added and the resulting solution is kept at 0°C overnight.

[0109] 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.

[0110] 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.

[0111] The following compounds, not part of the invention, 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]+

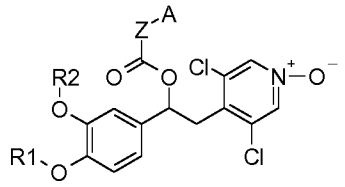
EXAMPLE 10

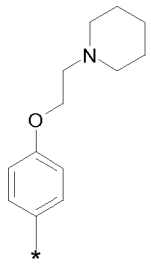
Preparation of 4-(2-piperidin-1-yl-ethoxy)-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester hydrochloride (compound 25)

[0112] (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

[0113] 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.

[0114] 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).

[0115] 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.

[0116] 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.

[0117] 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%.

[0118] 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

[0119] 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.

[0120] 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.

[0121] 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.

[0122] The results, expressed as mean $\pm$ 95% confidence limits of the molar concentration of the test compound producing 50% inhibition of LPS-induced TNF-α release (IC_{50}) are reported in Table 9.

[0123] 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

[0124] 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.

[0125] The concentration of the test compound ranged between 10^{-12} M and 10^{-5} M.

[0126] The results in terms of IC_{50} are reported in Table 10.

[0127] 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.

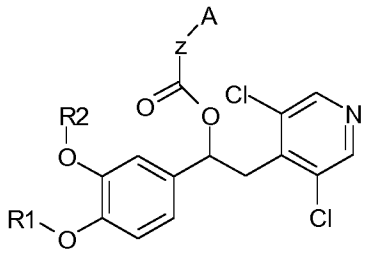
[0128] The results indicate that the compounds of the invention inhibited LPDE4 with subnanomolar affinity and are considerably more selective toward LPDE4 versus HPDE4.

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. An inhalable powder formulation comprising a compound of general formula (II)



(II)

wherein:

Z is selected from the group consisting of

$(CH_2)_m$ wherein m = 0, 1 or 2;
and
CR_4R_5 wherein

R_4 is independently selected from H or a linear or branched (C_1-C_4) alkyl optionally substituted by one or more halogen atoms or by a (C_1-C_4) cycloalkyl and
R_5 is independently selected from the group consisting of
- linear or branched (C_1-C_4) alkyl optionally substituted by one or more halogen atoms;
- phenyl;
- benzyl;
- NH_2; and
- HNCOOR', wherein R' is linear or branched (C_1-C_4) alkyl optionally substituted by one or more halogen atoms.

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 halogen atoms, (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.

A is a phenyl optionally substituted with one or more Rx groups, or A is a heteroaryl ring optionally substituted

with one or more Rx groups, 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, 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 halogen atoms or (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 halogen atoms or (C_3-C_7) cycloalkyl;
  - (C_3-C_7) cycloalkyl;
  - (C_1-C_4) alkylene-(C_3-C_7) heterocycloalkyl;
  - CO-(C_1-C_6) alkyl, wherein the (C_1-C_6) alkyl is optionally substituted by one or more halogen atoms;
  - COO-(C_1-C_6) alkyl, wherein the (C_1-C_6) alkyl is optionally substituted by one or more halogen atoms;
  - 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 optionally substituted by one or more halogen atoms and they form with the nitrogen atom to which they are linked a saturated, partially saturated or unsaturated ring; 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 one or more halogen atom, phenyl or (C_3-C_7) cycloalkyl;
  - COC_6H_5;
  - CO-(C_1-C_4) alkyl, wherein the (C_1-C_4) alkyl is optionally substituted by one or more halogen atoms;
  - COO-(C_1-C_4) alkyl, wherein the (C_1-C_4) alkyl is optionally substituted by one or more halogen atoms;
  - CONH-(C_1-C_6) alkyl-R_{12}, wherein R_{12} is selected from the group consisting of
  - H;
  - (C_1-C_4) alkyl optionally substituted by one or more halogen atoms;
  - OR_4R_5; and

  - CONH (C_1-C_4) alkyl-N(C_1-C_4) alkyl, wherein the N(C_1-C_4) alkyl is optionally substituted by one or more halogen atoms;
  or they form with the nitrogen atom to which they are linked a saturated or partially saturated 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 optionally substituted by one or more halogen atoms;
- oxo;
- $HNSO_2R_{13}$ wherein R_{13} is (C_1-C_4) alkyl optionally substituted by one or more halogen atoms or a phenyl optionally substituted with halogen atoms or with a (C_1-C_4) alkyl group optionally substituted by one or more halogen atoms;
- SO_2R_{14} wherein R_{14} is (C_1-C_4) alkyl optionally substituted by one or more halogen atoms, 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 optionally substituted by one or more halogen atoms;
- SR_{16} wherein R_{16} is H, phenyl or (C_1-C_4) alkyl optionally substituted by one or more halogen atoms;
- $COOR_{17}$ wherein R_{17} is H, (C_1-C_4) alkyl optionally substituted by one or more halogen atoms, phenyl or benzyl;

and
- $(CH_2)_qOR_{18}$, wherein q=1, 2, 3 or 4 and R_{18} is H or $(C_1\text{-}C_4)$ cycloalkyl.

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

2. A formulation according to claim 1 comprising a diluent or carrier.

3. A formulation according to claim 2 wherein the diluent is lactose.

4. A dry powder, single- or multi-dose inhaler comprising the inhalable powder formulation of claim 1.

5. A dry powder inhaler according to claim 4, wherein the powder is filled in gelatin, plastic or other capsules, cartridges or blister packs or in a reservoir.

6. A propellant-containing metering aerosol formulation comprising a compound of general formula (II) as defined in claim 1.

7. A formulation according to claim 6 wherein said propellant is an hydrofluoroalkane.

8. A formulation according to claims 6 or 7 wherein the compound is in solution or in dispersed form.

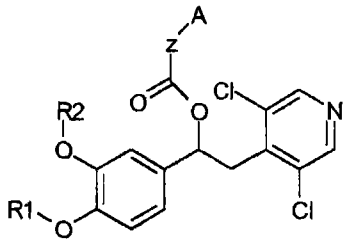
9. A formulation according to claims 6 to 8 which contains co-solvents, stabilizers and optionally other excipients.

10. A propellant-free inhalable formulation comprising a compound of general formula (II) as defined in claim 1.

11. A formulation according to claim 10 wherein the compounds of the invention are in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium.

Patentansprüche

1. Inhalierbare Pulverformulierung, umfassend eine Verbindung der allgemeinen Formel (II)



(II)

worin:

Z ausgewählt ist aus der Gruppe, bestehend aus

$(CH_2)_m$, worin m = 0, 1 oder 2;
und
CR_4R_5, worin
R_4 unabhängig ausgewählt ist aus H oder einem linearen oder verzweigten $(C_1\text{-}C_4)$-Alkyl, das gegebenenfalls mit einem oder mehreren Halogenatom(en) oder mit einem $(C_1\text{-}C_4)$-Cycloalkyl substituiert ist, und R_5 unabhängig ausgewählt ist aus der Gruppe, bestehend aus
- linearem oder verzweigtem $(C_1\text{-}C_4)$-Alkyl, das gegebenenfalls mit einem oder mehreren Halogenatom(en) substituiert ist;
- Phenyl;
- Benzyl;

- NH_2 und
- HNCOOR', worin R' lineares oder verzweigtes (C_1-C_4)-Alkyl ist, das gegebenenfalls mit einem oder mehreren Halogenatom(en) substituiert ist;

R_1 und R_2 unterschiedlich oder dieselben sind und unabhängig ausgewählt sind aus der Gruppe, bestehend aus

- H;
- linearem oder verzweigtem (C_1-C_6)-Alkyl, das gegebenenfalls mit einem oder mehreren Substituenten, ausgewählt aus Halogenatomen, (C_3-C_7)-Cycloalkyl oder (C_5-C_7)-Cycloalkenyl, substituiert ist;
- (C_3-C_7)-Cycloalkyl;
- (C_5-C_7)-Cycloalkenyl;
- linearem oder verzweigtem (C_2-C_6)-Alkenyl und
- linearem oder verzweigtem (C_2-C_6)-Alkinyl;

A ein Phenyl, gegebenenfalls substituiert mit einer oder mehreren Rx-Gruppe(n), ist oder A ein Heteroarylring, gegebenenfalls substituiert mit einer oder mehreren Rx-Gruppe(n), ist, wobei A ein Heteroarylring ist, der ausgewählt ist aus der Gruppe, bestehend aus Pyrrol, Pyrazol, Furan, Thiophen, Imidazol, Oxazol, Isoxazol, Thiazol, Pyridin, Pyrimidin, Pyrazin, Pyridazin und Pyran, wobei der optionale Substituent Rx an dem A-Ringsystem einer oder mehrere sein kann, gleich oder unterschiedlich sein kann und unabhängig ausgewählt ist aus der Gruppe, bestehend aus:

- linearem oder verzweigtem (C_1-C_6)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en) oder (C_3-C_7)-Cycloalkyl;
- linearem oder verzweigtem (C_2-C_6)-Alkenyl, gegebenenfalls substituiert mit einem oder mehreren (C_3-C_7)-Cycloalkyl;
- linearem oder verzweigtem (C_2-C_6)-Alkinyl, gegebenenfalls substituiert mit einem oder mehreren (C_3-C_7)-Cycloalkyl;
- (C_5-C_7)-Cycloalkenyl;
- Phenyl;
- (C_3-C_7)-Heterocycloalkyl;
- OR_7, worin R_7 ausgewählt ist aus der Gruppe, bestehend aus

  - H;
  - (C_1-C_{10})-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en) oder (C_3-C_7)-Cycloalkyl;
  - (C_3-C_7)-Cycloalkyl;
  - (C_1-C_4)-Alkylen-(C_3-C_7)-heterocycloalkyl;
  - CO-(C_1-C_6)-Alkyl, worin das (C_1-C_6)-Alkyl gegebenenfalls substituiert ist mit einem oder mehreren Halogenatom(en);
  - COO-(C_1-C_6)-Alkyl, worin das (C_1-C_6)-Alkyl gegebenenfalls mit einem oder mehreren Halogenatom(en) substituiert ist;
  - Phenyl;
  - Benzyl;
  - (C_1-C_{10})-Alkyl-NR_8R_9, worin R_8 und R_9 unabhängig ausgewählt sind aus der Gruppe, bestehend aus H, linearem oder verzweigtem (C_1-C_6)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en), und sie mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten, teilweise gesättigten oder ungesättigten Ring bilden, und

- Halogenatomen;
- CN;
- NO_2;
- $NR_{10}R_{11}$, worin R_{10} und R_{11} unterschiedlich sind oder dieselben sind und unabhängig ausgewählt sind aus der Gruppe, bestehend aus

  - H;
  - linearem oder verzweigtem (C_1-C_6)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en), Phenyl oder (C_3-C_7)-Cycloalkyl;
  - COC_6H_5;

- CO-(C_1-C_4)-Alkyl, worin das (C_1-C_4)-Alkyl gegebenenfalls substituiert ist mit einem oder mehreren Halogenatom(en);
- COO-(C_1-C_4)-Alkyl, worin das (C_1-C_4)-Alkyl gegebenenfalls mit einem oder mehreren Halogenatom(en) substituiert ist;
- CONH-(C_1-C_6)-Alkyl-R_{12}, worin R_{12} ausgewählt ist aus der Gruppe, bestehend aus

  - H;
  - (C_1-C_4)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en);
  - OR_4R_5 und

- CONH-(C_1-C_4)-Alkyl-N(C_1-C_4)-alkyl, worin das N(C_1-C_4)-Alkyl gegebenenfalls mit einem oder mehreren Halogenatom(en) substituiert ist;

oder sie bilden mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise gesättigten Ring;
- (C_1-C_4)-Alkyl-$NR_{10}R_{11}$;
- COR_{12}, worin R_{12} Phenyl oder lineares oder verzweigtes (C_1-C_6)-Alkyl ist, das gegebenenfalls mit einem oder mehreren Halogenatom(en) substituiert ist;
- Oxo;
- $HNSO_2R_{13}$, worin R_{13} (C_1-C_4)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en), oder ein Phenyl, gegebenenfalls substituiert mit Halogenatomen oder mit einer (C_1-C_4)-Alkylgruppe, die gegebenenfalls mit einem oder mehreren Halogenatom(en) substituiert ist, ist;
- SO_2R_{14}, worin R_{14} (C_1-C_4)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en), OH oder $NR_{10}R_{11}$, worin R_{10} und R_{11} wie oben definiert sind, ist;
- SOR_{15}, worin R_{15} Phenyl oder (C_1-C_4)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en), ist;
- SR_{16}, worin R_{16} H, Phenyl oder (C_1-C_4)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en), ist;
- $COOR_{17}$, worin R_{17} H, (C_1-C_4)-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Halogenatom(en), Phenyl oder Benzyl ist und
- $(CH_2)_qOR_{18}$, worin q = 1, 2, 3 oder 4 und R_{18} H oder (C_1-C_4)-Cycloalkyl ist,

und pharmazeutisch annehmbare Salze und N-Oxide an dem Pyridinring davon.

2. Formulierung nach Anspruch 1, umfassend ein Verdünnungsmittel oder einen Trägerstoff.

3. Formulierung nach Anspruch 2, wobei das Verdünnungsmittel Lactose ist.

4. Trockenpulver-, Einzel- oder Multi-Dosis-Inhalator, umfassend die inhalierbare Pulverformulierung nach Anspruch 1.

5. Trockenpulverinhalator nach Anspruch 4, wobei das Pulver gefüllt ist in Gelatine-, Kunststoff- oder andere Kapseln, Patronen oder Blisterpackungen oder in ein Reservoir.

6. Treibmittel enthaltende Dosieraerosolformulierung, umfassend eine Verbindung der allgemeinen Formel (II) wie in Anspruch 1 definiert.

7. Formulierung nach Anspruch 6, wobei das Treibmittel ein Hydrofluoroalkan ist.

8. Formulierung nach Anspruch 6 oder 7, wobei die Verbindung in Lösung oder in dispergierter Form vorliegt.

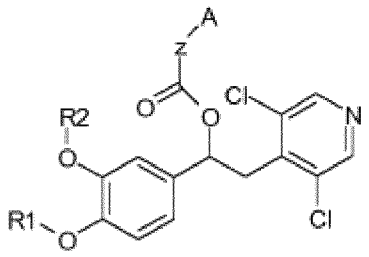
9. Formulierung nach Ansprüchen 6 bis 8, welche Co-Lösungsmittel, Stabilisatoren und gegebenenfalls andere Exzipientien enthält.

10. Treibmittelfreie inhalierbare Formulierung, umfassend eine Verbindung der allgemeinen Formel (II) wie in Anspruch 1 definiert.

11. Formulierung nach Anspruch 10, wobei die Verbindungen der Erfindung in Form von Lösungen oder Suspensionen in einem wässrigen, alkoholischen oder hydroalkoholischen Medium vorliegen.

Revendications

1. Formulation pulvérulente inhalable comprenant un composé répondant à la formule générale (II)



(II)

dans laquelle :

Z est choisi parmi le groupe constitué par :

un groupe $(CH_2)_m$ dans lequel m = 0, 1 ou 2 ;
et
un groupe CR_4R_5 dans lequel
R_4 est choisi de manière indépendante parmi un atome d'hydrogène ou un groupe alkyle en C_1-C_4 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs atomes d'halogène ou par un groupe cycloalkyle en C_1-C_4 ; et R_5 est choisi de manière indépendante parmi le groupe constitué par :

- un groupe alkyle en C_1-C_4 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs atomes d'halogène ;
- un groupe phényle ;
- un groupe benzyle ;
- un groupe NH_2 ; et
- un groupe HNCOOR' dans lequel R' représente un groupe alkyle en C_1-C_4 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs atomes d'halogène ;

R_1 et R_2 sont différents ou identiques et sont choisis de manière indépendante parmi le groupe constitué par :

- un atome d'hydrogène ;
- un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs substituants choisis parmi des atomes d'halogène, des groupes cycloalkyle en C_3-C_7 ou des groupes cycloalcényle en C_5-C_7 ;
- un groupe cycloalkyle en C_3-C_7 ;
- un groupe cycloalcényle en C_5-C_7 ;
- un groupe alcényle en C_2-C_6 à chaîne droite ou ramifiée ; et
- un groupe alcynyle en C_2-C_6 à chaîne droite ou ramifiée.

A représente un groupe phényle substitué de manière facultative avec un ou plusieurs groupes R_x, ou bien A représente un noyau hétéroaryle substitué de manière facultative avec un ou plusieurs groupes R_x, A représentant un noyau hétéroaryle choisi parmi le groupe constitué par un noyau pyrrole, un noyau pyrazole, un noyau furanne, un noyau thiophène, un noyau imidazole, un noyau oxazole, un noyau isoxazole, un noyau thiazole, un noyau pyridine, un noyau pyrimidine, un noyau pyrazine, un noyau pyridazine et un noyau pyrane, dans lequel le nombre de substituants facultatifs R_x sur le système cyclique A peut être égal à un ou plusieurs, lesdits substituants facultatifs pouvant être identiques ou différents et étant choisis de manière indépendante parmi le groupe constitué par :

- un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs atomes d'halogène ou par un ou plusieurs groupes cycloalkyle en C_3-C_7 ;
- un groupe alcényle en C_2-C_6 à chaîne droite ou ramifiée, substitué de manière facultative par un ou

plusieurs groupes cycloalkyle en C_3-C_7 ;
- un groupe alcynyle en C_2-C_6 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs groupes cycloalkyle en C_3-C_7 ;
- un groupe cycloalcényle en C_5-C_7 ;
- un groupe phényle ;
- un groupe hétérocycloalkyle en C_3-C_7 ;
- un groupe OR_7 dans lequel R_7 est choisi parmi le groupe constitué par:

  - un atome d'hydrogène ;
  - un groupe alkyle en C_1-C_{10} substitué de manière facultative par un ou plusieurs atomes d'halogène ou par un ou plusieurs groupes cycloalkyle en C_3-C_7 ;
  - un groupe cycloalkyle en C_3-C_7 ;
  - un groupe alkylène en C_1-C_4-hétérocycloalkyle en C_3-C_7 ;
  - un groupe CO(alkyle en C_1-C_6), le groupe alkyle en C_1-C_6 étant substitué de manière facultative par un ou plusieurs atomes d'halogène ;
  - un groupe COO(alkyle en C_1-C_6), le groupe alkyle en C_1-C_6 étant substitué de manière facultative par un ou plusieurs atomes d'halogène ;
  - un groupe phényle ;
  - un groupe benzyle ;
  - un groupe alkyl(en C_1-C_{10})-NR_8R_9 dans lequel R_8 et R_9 sont choisis de manière indépendante parmi le groupe constitué par un atome d'hydrogène, un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs atomes d'halogène, et forment avec l'atome d'azote auquel ils sont liés un noyau saturé, partiellement saturé ou insaturé ; et

- des atomes d'halogène ;
- un groupe CN ;
- un groupe NO_2 ;
- un groupe $NR_{10}R_{11}$ dans lequel R_{10} et R_{11} sont différents ou identiques et sont choisis de manière indépendante parmi le groupe constitué par :

  - un atome d'hydrogène ;
  - un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs atomes d'halogène, un ou plusieurs groupes phényle ou un ou plusieurs groupes cycloalkyle en C_3-C_7 ;
  - un groupe COC_6H_5 ;
  - un groupe CO(alkyle en C_1-C_4), le groupe alkyle en C_1-C_4 étant substitué de manière facultative par un ou plusieurs atomes d'halogène ;
  - un groupe COO(alkyle en C_1-C_4), le groupe alkyle en C_1-C_4 étant substitué de manière facultative par un ou plusieurs atomes d'halogène ;
  - un groupe CONH(alkyle en C_1-C_6)-R_{12} dans lequel R_{12} est choisi parmi le groupe constitué par :

    - un atome d'hydrogène ;
    - un groupe alkyle en C_1-C_4 substitué de manière facultative par un ou plusieurs atomes d'halogène ;
    - un groupe OR_4R_5 ; et

  - un groupe CONH(alkyl en C_1-C_4)-N(alkyle en C_1-C_4), dans lequel le groupe N(alkyle en C_1-C_4) est substitué de manière facultative par un ou plusieurs atomes d'halogène ;

ou forment avec l'atome d'azote auquel ils sont liés un noyau saturé ou partiellement saturé ;
- un groupe alkyl(en C_1-C_4)-$NR_{10}R_{11}$;
- un groupe COR_{12} dans lequel R_{12} représente un groupe phényle ou un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée, substitué de manière facultative par un ou plusieurs atomes d'halogène ;
- un groupe oxo ;
- un groupe $HNSO_2R_{13}$ dans lequel R_{13} représente un groupe alkyle en C_1-C_4 substitué de manière facultative par un ou plusieurs atomes d'halogène ou un groupe phényle substitué de manière facultative avec des atomes d'halogène ou avec un groupe alkyle en C_1-C_4 substitué de manière facultative par un ou plusieurs atomes d'halogène ;
- un groupe SO_2R_{14} dans lequel R_{14} représente un groupe alkyle en C_1-C_4 substitué de manière facultative

par un ou plusieurs atomes d'halogène, un groupe OH ou un groupe $NR_{10}R_{11}$ dans lequel R_{10} et R_{11} sont tels que définis ci-dessus ;
- un groupe SOR_{15} dans lequel R_{15} représente un groupe phényle ou un groupe alkyle en C_1-C_4 substitué de manière facultative par un ou plusieurs atomes d'halogène ;
- un groupe SR_{16} dans lequel R_{16} représente un atome d'hydrogène, un groupe phényle ou un groupe alkyle en C_1-C_4 substitué de manière facultative par un ou plusieurs atomes d'halogène ;
- un groupe $COOR_{17}$ dans lequel R_{17} représente un atome d'hydrogène, un groupe alkyle en C_1-C_4 substitué de manière facultative par un ou plusieurs atomes d'halogène, un ou plusieurs groupes phényle ou un ou plusieurs groupes benzyle ; et
- un groupe $(CH_2)_qOOR_{18}$ dans lequel q est égal à 1, 2, 3 ou 4, et R_{18} représente un atome d'hydrogène ou un groupe cycloalkyle en C_1-C_4 ;

ainsi que ses sels et ses N-oxydes sur son noyau pyridine pharmaceutiquement acceptables.

2. Formulation selon la revendication 1, comprenant un diluant ou un support.

3. Formulation selon la revendication 2, dans laquelle le diluant est du lactose.

4. Inhalateur de poudre sèche à dose unitaire ou à doses multiples comprenant la formulation pulvérulente inhalable selon la revendication 1.

5. Inhalateur de poudre sèche selon la revendication 4, dans lequel la poudre remplit des capsules de gélatine, en matière plastique ou analogue, des cartouches ou des emballages coque ou un réservoir.

6. Formulation d'aérosol-doseur contenant un propulseur comprenant un composé répondant à la formule générale (II) tel que défini à la revendication 1.

7. Formulation selon la revendication 6, dans laquelle ledit propulseur est un hydrofluoroalcane.

8. Formulation selon la revendication 6 ou 7, dans laquelle le composé se présente sous la forme d'une solution ou sous une forme dispersée.

9. Formulation selon les revendications 6 à 8, qui contient des cosolvants, des stabilisateurs et de manière facultative d'autres excipients.

10. Formulation inhalable exempte de propulseur comprenant un composé répondant à la formule générale (II) tel que défini à la revendication 1.

11. Formulation selon la revendication 10, dans laquelle les composés de l'invention se présentent sous la forme de solutions ou de suspensions dans un milieu aqueux, alcoolique ou hydroalcoolique.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

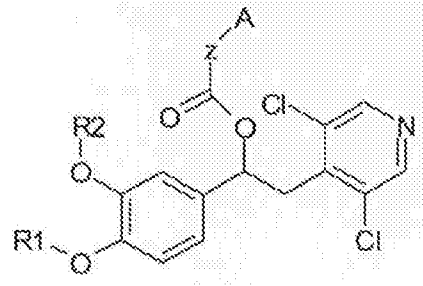
- EP 1634606 A **[0011]**
- WO 9402465 A **[0012]**
- WO 9535281 A **[0013]**

Non-patent literature cited in the description

- **JACOBITZ, S et al.** *Mol. Pharmacol,* 1996, vol. 50, 891-899 **[0008]**
- **CORTIJO J et al.** *Br J Pharmacol,* 1993, vol. 108, 562-568 **[0061] [0124]**
- **DUPLANTIER AJ et al.** *J Med Chem,* 1996, vol. 39, 120-125 **[0061] [0124]**
- **T.W. GREENE ; P.G.M. WUTS.** Protective Groups in Organic Chemistry. Wiley-Interscience, 1999 **[0070]**
- **P.J. KOCIENSKI.** Protecting Groups. Georg Thieme Verlag, 1994 **[0070]**
- Remington's Pharmaceutical Sciences Handbook. Mack Pub, **[0076]**
- **TORPHY TJ et al.** *J. Pharmacol. Exp. Ther.,* 1992, vol. 263, 1195-1205 **[0113]**
- **HATZELMANN A et al.** *J. Pharmacol. Exp. Ther.,* 2001, vol. 297, 267-279 **[0119]**
- **DRAHEIM R et al.** *J. Pharmacol. Exp. Ther.,* 2004, vol. 308, 555-563 **[0119]**

SZABADALMI IGÉNYPONTOK

1. Inhalálható por készítmény, amely tartalmaz (II) általános képletű vegyületet



(II)

ahol:

Z jelentése az alábbi csoportból megválasztott:

$(CH_2)_m$ ahol m = 0, 1 vagy 2;

és

CR_4R_5 ahol

R_4 jelentése egymástól függetlenül H vagy egyenes vagy elágazó (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom vagy (C_1-C_4) cikloalkil szubsztituenssel, közül megválasztott, és

R_5 jelentése egymástól függetlenül az alábbi csoportból megválasztott:

- egyenes vagy elágazó (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
- fenil;
- benzil;
- NH_2; és
- HNCOOR', ahol R' jelentése egyenes vagy elágazó (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;

R_1 és R_2 jelentése azonos vagy eltérő és egymástól függetlenül az alábbi csoportból megválasztott:

- H;
- egyenes vagy elágazó (C_1-C_6) alkil, amely adott esetben szubsztituált egy vagy több szubsztituenssel, amely halogénatom, (C_3-C_7) cikloalkil vagy (C_5-C_7) cikloalkenil közül megválasztott;
- (C_3-C_7) cikloalkil;
- (C_5-C_7) cikloalkenil;
- egyenes vagy elágazó (C_2-C_6) alkenil; és
- egyenes vagy elágazó (C_2-C_6) alkinil.

A jelentése fenil, amely adott esetben szubsztituált egy vagy több Rx szubsztituenssel, vagy A jelentése heteroaril gyűrű, amely adott esetben szubsztituált egy vagy több Rx szubsztitunessel, ahol A jelentése heteroaril gyűrű, amely pirrol, pirazol, furán, tiofén, imidazol, oxazol, izoxazol, tiazol, piridin, pirimidin, pirazin, piridazin és pirán közül megválasztott, ahol az adott esetben előforduló R_x szubsztituens az A gyűrűrendszeren lehet egy vagy több, lehet azonos vagy eltérő, és egymástól függetlenül az alábbi csoportból megválasztott:

- egyenes vagy elágazó (C_1-C_6) alkil, amely adott esetben szubsztituált egy vagy több halogénatom vagy (C_3-C_7) cikloalkil szubsztituenssel;
- egyenes vagy elágazó (C_2-C_6) alkenil, amely adott esetben szubsztituált egy vagy több (C_3-C_7) cikloalkil szubsztituenssel;
- egyenes vagy elágazó (C_2-C_6) alkinil, amely adott esetben szubsztituált egy vagy több (C_3-C_7) cikloalkil szubsztituenssel;
- (C_3-C_7) cikloalkenil;
- fenil;
- (C_3-C_7) heterocikloalkil;
- OR_7 ahol R_7 jelentése az alábbi csoportból megválasztott:
    - H;
    - (C_1-C_{10}) alkil, amely adott esetben szubsztituált egy vagy több halogénatom vagy (C_3-C_7) cikloalkil szubsztituenssel;
    - (C_3-C_7) cikloalkil;
    - (C_1-C_4) alkilén-(C_3-C_7) heterocikloalkil;
    - CO-(C_1-C_6) alkil, ahol a (C_1-C_6) alkil adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
    - COO-(C_1-C_6) alkil, ahol a (C_1-C_6) alkil adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
    - fenil;
    - benzil;
    - (C_1-C_{10}) alkil-NR_8R_9, ahol R_8 és R_9 jelentése egymástól függetlenül az alábbi csoportból megválasztott: H, egyenes vagy elágazó (C_1-C_6) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel, vagy a kapcsolódó nitrogénatommal együtt telített, részben telített vagy telítetlen gyűrű; és
- halogénatom;
- CN;
- NO_2;
- $NR_{10}R_{11}$ ahol R_{10} és R_{11} jelentése azonos vagy eltérő és egymástól függetlenül az alábbi csoportból megválasztott:

- H;
- egyenes vagy elágazó (C_1-C_6) alkil, amely adott esetben szubsztituált egy vagy több halogénatom, fenil vagy (C_3-C_7) cikloalkil szubsztituenssel;
- COC_6H_5;
- CO-(C_1-C_4) alkil, ahol a (C_1-C_4) alkil adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
- COO-(C_1-C_4) alkil, ahol a (C_1-C_4) alkil adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
- CONH-(C_1-C_6) alkil-R_{12}, ahol R_{12} jelentése az alábbi csoportból megválasztott:
- H;
- (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
- OR_4R_5; és
- CONH(C_1-C_4) alkil-N(C_1-C_4) alkil, ahol az N(C_1-C_4) alkil adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;

vagy a kapcsolódó nitrogénatommal együtt telített vagy részben telített gyűrű;

- (C_1-C_4) alkil-$NR_{10}R_{11}$;
- COR_{12} ahol R_{12} jelentése fenil vagy egyenes vagy elágazó (C_1-C_6) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
- oxo;
- $HNSO_2R_{13}$ ahol R_{13} jelentése (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel, vagy fenil, amely adott esetben szubsztituált halogénatom vagy (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel; szubsztituenssel,
- SO_2R_{14} ahol R_{14} jelentése (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel, OH vagy $NR_{10}R_{11}$, ahol R_{10} és R_{11} jelentése a fenti;
- SOR_{15} ahol R_{15} jelentése fenil vagy (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
- SR_{16} ahol R_{16} jelentése H, fenil vagy (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel;
- $COOR_{17}$ ahol R_{17} jelentése H, (C_1-C_4) alkil, amely adott esetben szubsztituált egy vagy több halogénatom szubsztituenssel, fenil vagy benzil; és
- $(CH_2)_qOR_{18}$, ahol q=1, 2, 3 vagy 4 és R_{18} jelentése H vagy (C_1-C_4) cikloalkil.

és ennek gyógyszerészetileg alkalmazható sóját és a piridin gyűrűn képzett N-oxidját.

2. Az 1. igénypont szerinti készítmény, amely higítószert vagy hordozó anyagot tartalmaz.

3. A 2. igénypont szerinti készítmény, ahol a higítószer laktóz.

4. Száraz por, egyszeres vagy többszörös dózisú inhaláló, amely tartalmazza az 1. igénypont szerinti inhalálható por készítményt.

5. A 4. igénypont szerinti száraz por inhaláló, ahol a por zselatin, műanyag vagy más kapszulákba, patronokba vagy hólyagos csomagokba vagy tartályba van töltve.

6. Hajtóanyagot tartalmazó adagolós aeroszol készítmény, amely tartalmazza az 1. igénypont szerinti (II) általános képletű vegyületet.

7. A 6. igénypont szerinti készítmény, ahol az említett hajtóanyag hidrofluoralkán.

8. A 6. vagy 7. igénypont szerinti készítmény, ahol a vegyület oldott vagy diszpergált formában van.

9. A 6-8. igénypontok szerinti készítmény, amely tartalmaz társoldószereket, stabilizátorokat és adott esetben más segédanyagokat.

10. Hajtóanyagtól mentes inhalálható készítmény, amely tartalmazza az 1. igénypont szerinti (II) általános képletű vegyületet.

11. A 10. igénypont szerinti készítmény, ahol a találmány szerinti vegyület oldatok vagy szuszpenziók formájában van, vizes, alkoholos vagy hidroalkoholos közegben.