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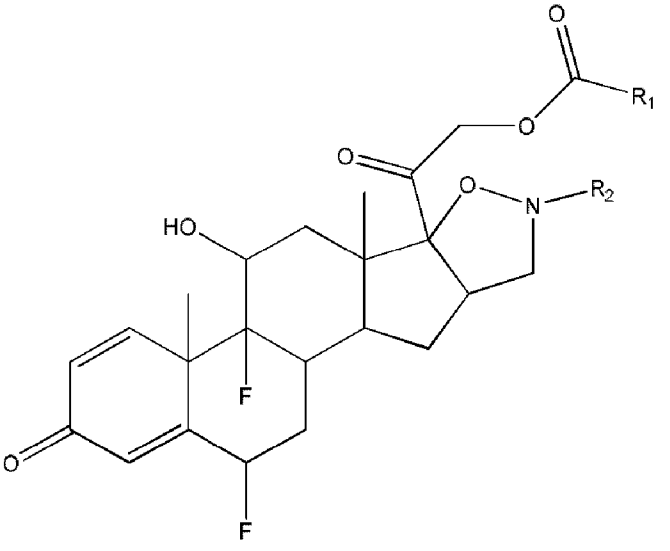
(54) Titre : DERIVES GLUCOCORTICOSTEROIDES D'ISOXAZOLIDINE N-ARYL SUBSTITUES
(54) Title: N-ARYL SUBSTITUTED ISOXAZOLIDINE GLUCOCORTICOSTEROID DERIVATIVES



(I)

(57) Abrégé/Abstract:
The present invention relates to novel anti-inflammatory and antiallergic compounds of the glucocorticosteroid series, methods of preparing such compounds, pharmaceutical compositions comprising them, combinations and therapeutic uses thereof. More particularly, the invention relates to glucocorticosteroids that are derivatives of isoxazolidine.

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(54) Title: ISOXAZOLIDINE DERIVATIVES

(57) Abstract: The present invention relates to novel anti-inflammatory and antiallergic compounds of the glucocorticosteroid series, methods of preparing such compounds, pharmaceutical compositions comprising them, combinations and therapeutic uses thereof. More particularly, the invention relates to glucocorticosteroids that are derivatives of isoxazolidine.

N-ARYL SUBSTITUTED ISOXAZOLIDINE GLUCOCORTICOSTEROID DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel anti-inflammatory and antiallergic compounds of the glucocorticosteroid series, methods of preparing such compounds, pharmaceutical compositions comprising them, combinations and therapeutic uses thereof. More particularly, the invention relates to glucocorticosteroids that are isoxazolidine derivatives.

BACKGROUND OF THE INVENTION

Corticosteroids are potent anti-inflammatory agents, able to decrease the number, activity and movement of inflammatory cells.

They are commonly used to treat a wide range of chronic and acute inflammatory conditions including asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rheumatoid arthritis, inflammatory bowel disease and autoimmune diseases.

Corticosteroids mediate their effects through the glucocorticoid receptor (GR). The binding of corticosteroids to GR induces its nuclear translocation which, in turn, affects a number of downstream pathways via DNA-binding-dependent (e.g. transactivation) and -independent (e.g. transespression) mechanisms.

Corticosteroids for treating chronic inflammatory conditions in the lung such as asthma and COPD are currently administered through inhalation. One of the advantages of employing inhaled corticosteroids (ICS) is the possibility of delivering the drug directly at site of action, limiting systemic side-effects, thus resulting in a more rapid clinical response and a higher therapeutic ratio.

Although ICS treatment can afford important benefits, expecially in asthma it is important to minimise ICS systemic exposure which leads to the occurrence and severity of unwanted side effects that may be associated with chronic administration. Moreover, the limited duration of action of ICS currently available in the clinical practice contributes to suboptimal management of the disease. While the inhaler technology is the key point to

target the lung, the modulation of the substituents on the corticosteroids molecular scaffold is important for the optimization of pharmacokinetic and pharmacodynamic properties in order to decrease oral bioavailability, confine pharmacological activity only in the lung (prodrugs and soft drugs) and increase systemic clearance. Morever, long lasting ICS activity in the lung is highly desirable as once daily administration of ICS would allow the reduction of the frequency of administration and, thus, substantially improve patient compliance and, as a result, disease management and control. In sum, there is a pressing medical need for developing ICS with improved pharmacokinetic and pharmacodynamic characteristics.

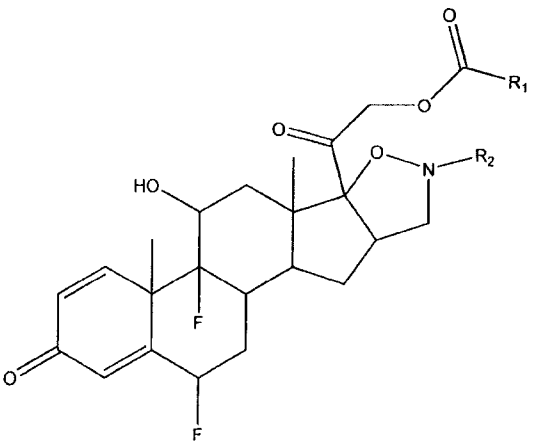
Glucocorticoids isoxazolidine derivatives are for instance described in WO 2006/005611, GB 1578446 and in "Synthesis and topical anti-inflammatory activity of some steroidal [16α,17α-d] isoxazolidines" (J. Med. Chem., 25, 1492-1495, 1982).

Some glucocorticoid isoxazolidine derivatives are also described in the co-pending patent applications WO 2011/029547, WO 2012/123482 and WO 2012/123493.

Surprisingly, it has been found that the compounds of the present invention show improved pharmacokinetic or pharmacodynamic characteristics, such as systemic exposure, selectivity and duration of action.

SUMMARY

Certain exemplary embodiments provide a compound of general formula **(I)**



(I)

wherein

R_1 is selected from the group consisting of linear or branched (C_1-C_{16})alkyl, linear or branched (C_2-C_{18})alkenyl, -OR_6, aryl, aryl(C_1-C_{16})alkyl, -SR_6, -$N(R_4)(R_5)$, (C_3-C_8)cycloalkyl, (C_3-C_8)heterocycloalkyl and heteroaryl, wherein optionally one or more hydrogen atoms are replaced by (C_1-C_6)alkyl, and wherein R_4 and R_5 are independently selected from H or linear or branched (C_1-C_6)alkyl and R_6 is linear or branched (C_1-C_{16})alkyl;

R_2 is aryl optionally substituted by one or more halogen atoms; and

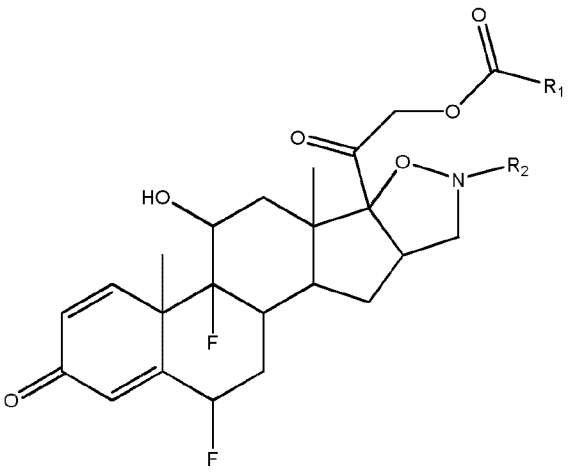
pharmaceutically acceptable salts thereof.

The present invention relates to anti-inflammatory and antiallergic compounds of the glucocorticosteroid series, to processes for their preparation, to compositions comprising them, to therapeutic uses and combinations with other pharmaceutical active ingredients for the treatment of respiratory disorders, among which beta2-agonists, antimuscarinic agents, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, human neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), antitussive agents, mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, antibiotics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma,

M3-antagonists/beta2-agonists (MABA) and M3-antagonists/PDE4-inhibitors (MAPI).

DETAILED DESCRIPTION OF THE INVENTION

In particular, the invention is directed to compounds of general formula **(I)**



(I)

wherein

$\mathbf{R_1}$ is selected from the group consisting of linear or branched $(C_1\text{-}C_{16})$alkyl, linear or branched $(C_2\text{-}C_{18})$alkenyl, $-OR_6$, aryl, aryl$(C_1\text{-}C_{16})$alkyl, $-SR_6$, $-N(R_4)(R_5)$, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$heterocycloalkyl and heteroaryl, wherein optionally one or more hydrogen atoms are replaced by $(C_1\text{-}C_6)$alkyl, and wherein $\mathbf{R_4}$ and $\mathbf{R_5}$ are independently selected from H or linear or branched $(C_1\text{-}C_6)$alkyl and $\mathbf{R_6}$ is linear or branched $(C_1\text{-}C_{16})$alkyl;

$\mathbf{R_2}$ is aryl optionally substituted by one or more halogen atoms; and

pharmaceutically acceptable salts thereof.

In the present description, unless otherwise provided, the term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "$(C_1\text{-}C_{16})$alkyl" refers to linear or branched chain alkyl groups wherein the number of carbon atoms is from 1 to 16. Examples of said groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, ethyl-butyl, propyl-butyl, methyl-butyl, ethyl-methyl-propyl, hexadecyl, undecyl, dodecyl, tridecyl, quaterdecyl, quindecyl, hexadecyl and the like.

The expression "(C_2-C_{18})alkenyl" refers to linear or branched carbon chains with one or more double bonds, wherein the number of carbon atoms is from 2 to 18. Examples of said groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, quaterdecenyl, quindecenyl, hexadecenyl, heptadecenyl and the like.

The expression "(C_3-C_8)cycloalkyl" refers to mono or bi-cycloaliphatic hydrocarbon groups with from 3 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl and the like.

The expression "(C_3-C_8)heterocycloalkyl" refers to (C_3-C_8)cycloalkyl groups, in which at least one ring carbon atom is replaced by a heteroatom or heteroaromatic group (e.g. N, NH, S or O). Examples include piperazinyl, thiazolidinyl, pyrrolidinyl, piperidinyl, morpholinyl and the like.

The expression "aryl" refers to mono or bi- or tri-cyclic ring systems which have 6 to 20 ring atoms, preferably from 6 to 15 and wherein at least one ring is aromatic.

Examples of suitable aryl monocyclic systems include benzene radical and the like.

Examples of suitable aryl bicyclic systems include naphthalene, biphenylene radicals and the like.

Examples of suitable aryl tricyclic systems include fluorene radical and the like.

The expression "aryl(C_1-C_6)alkyl" refers to (C_1-C_6)alkyl groups further substituted by aryl.

As used herein, the term "heteroaryl" refers to mono, bi- or tricyclic ring system which have 5 to 20 ring atoms, preferably from 5 to 15, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom or heteroaromatic group (e.g. N, NH, S or O).

Examples of suitable heteroaryl monocyclic systems include thiophene, pyrrole, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridine, imidazolidine, piperidine, piperazine and furan radicals such as tetrahydrofuran and the like.

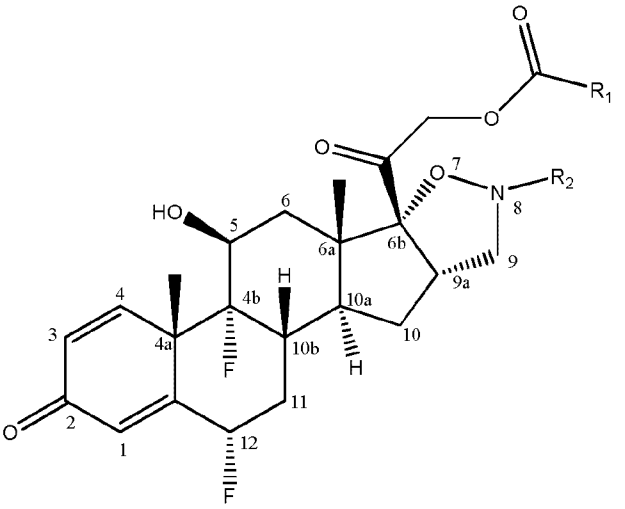
Examples of suitable heteroaryl bicyclic systems include purine, pteridine,

benzotriazole, quinoline, isoquinoline, indole, isoindole, benzofuran, benzodioxane, benzothiophene radicals and the like.

It will be apparent to those skilled in the art that compounds of general formula (I) contain asymmetric centers at least at the positions 4a, 4b, 5, 6a, 6b, 9a, 10a, 10b and therefore may exist as many optical stereoisomers and mixtures thereof.

Therefore the invention is also directed to all of these forms and mixtures thereof.

Preferred compounds are those of general formula (I) wherein the stereochemistry of stereogenic carbon atoms is as reported in formula (I') below, absolute configuration is assigned on the basis of Cahn-Ingold-Prelog nomenclature based on groups' priorities



(I')

and wherein the meanings of R_1 and R_2 are as defined above.

In one preferred embodiment, for compounds of formula (I'), absolute configuration at asymmetric center 4a is (S), at 4b is (R), at 5 is (S), at 6a is (S), at 6b is (R), at 9a is (S), at 10a is (S), at 10b is (S) and at 12 is (S).

Compounds of general formula (I) may form acid addition salts, particularly with pharmaceutically acceptable acids.

Pharmaceutically acceptable acid addition salts of the compounds of formula (I), thus encompassing also those of formula (I'), include salts with inorganic acids, for example hydrohalogen acids such as hydrofluoric, hydrochloric, hydrobromic or

hydroiodic; nitric, sulfuric, phosphoric; and organic acids, for example aliphatic monocarboxylic acids such as formic, acetic, trifluoroacetic and propionic; aliphatic hydroxyl acids such as lactic, citric, tartaric or malic; dicarboxylic acids such as maleic, fumaric, oxalic or succinic; aromatic carboxylic acids such as benzoic; aromatic hydroxy acids and sulfonic acids.

These salts may be prepared from compounds of formula (I) or (I') by known salt-forming procedures.

It is to be understood that all preferred groups or embodiments described below for compounds of formula (I) may be combined among each other and apply as well *mutatis mutandis*.

A preferred group of compounds of general formula (I) or (I') is that wherein $\mathbf{R_1}$ is selected from the group consisting of linear or branched (C_1-C_{16})alkyl, linear or branched (C_2-C_{18})alkenyl, -OR_6, aryl, aryl(C_1-C_{16})alkyl, -SR_6, -$N(R_4)(R_5)$, (C_3-C_8)cycloalkyl, (C_3-C_8)heterocycloalkyl and heteroaryl, wherein optionally one or more hydrogen atoms are replaced by (C_1-C_6)alkyl and wherein $\mathbf{R_4}$ and $\mathbf{R_5}$ are independently selected from H or linear or branched (C_1-C_6)alkyl and $\mathbf{R_6}$ is linear or branched (C_1-C_{16})alkyl; and $\mathbf{R_2}$ is aryl optionally substituted by one or more halogen atoms.

Even more preferred within this group are the compounds of general formula (I) or (I') wherein $\mathbf{R_1}$ is selected from the group consisting of methyl, isopropyl, ethyl, quindecyl, butyl, hexyl, heptadecenyl, methoxy, methylsulfanyl, isobutyl, isopentyl, tert.butyl, methylamino, dimethylamino, phenyl, cyclopropyl, cyclopentyl, methylpropanoxy, benzyl, pyridyl, piperazinyl, piperidinyl, pyrrolidinyl, thiazolidinyl and furyl; and $\mathbf{R_2}$ is p-chlorophenyl.

Hereinafter, compounds of formula (I) and (I') and their pharmaceutically acceptable salts and solvates are referred to as "compounds of the invention".

Examples of preferred compounds of the invention are:

Compound	Chemical Name
1	Isobutyric acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
3	Propionic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
4	Hexadecanoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
5	Octadec-9-enoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydro xy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
6	Pentanoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
7	Acetic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
8	Benzoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
9	Methyl carbonate (Methyl formate) 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester)
10	S-methyl carbonothioate (or S-methyl methanethioate) 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
11	3-Methylbutanoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
12	Pivalic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester

(continue)

13	2-Phenylacetic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
14	Furan-2-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
15	Cyclopentane-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
16	Cyclopropane-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
17	Isonicotinic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
18	Isobutyl methyl carbonate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
19	Hexyl carbonate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester)
20	Dimethyl 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl carbamate
21	Methyl 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl carbamate
22	Piperazine-1-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
23	Thiazolidine-4-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester

(continue)

24	Proline, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4^a,6^a-dimethyl-2-oxo-2,4a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12—tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
25	Piperidine-4-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester

According to analogous procedures and methods herein described, the following preferred compounds of the invention may be obtained:

Compound	Chemical Name
26	Butanoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
27	Butanoic acid, 2-methyl-, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
28	Cyclobutanecarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4^a,6^a-dimethyl-2-oxo-2,4^a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
29	Cyclohexanecarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4^a,6^a-dimethyl-2-oxo-2,4^a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
30	2-Thiophenecarboxylic acid, tetrahydro-, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4^a,6^a-dimethyl-2-oxo-2,4^a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
31	2H-thiopyran-4-carboxylic acid, tetrahydro-, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4^a,6^a-dimethyl-2-oxo-2,4^a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester

(continue)

5

32	Cyclopentanecarboxylic acid, 2,5-dimethyl-, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4^{a},6^{a}-dimethyl-2-oxo-2,4^{a},4b,5,6,6^{a},8,9,9^{a},10,10^{a},10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
33	Cyclohexanecarboxylic acid, 2,6-dimethyl-, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
34	3-Pyridinecarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
35	1H-pyrrole-3-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
36	3-Thiophenecarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
37	3-Furancarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
38	1H-indole-7-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
39	1H-Indene-7-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
40	8-Quinolinecarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
41	Quinoline-3-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester

(continue)

42	Benzo[b]thiophene-3-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
43	1H-Indole-3-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
44	Benzofuran-3-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
45	Benzofuran-2-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
46	2-Thiophenecarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
47	2-Furancarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
48	1H-Pyrrole-2-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
49	Tetrahydro-2H-pyran-4-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
50	4-Methylpiperazine-1-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester
51	Morpholine-4-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester

(continue)

52	2-Pyridinecarboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester

The invention also provides pharmaceutical compositions comprising a compound of the invention, either as such or as pharmaceutically acceptable salt, and one or more pharmaceutically acceptable carriers and/or excipients.

The compounds of the invention may be administered as the sole active agent or in combination with other pharmaceutical active ingredients including those currently used in the treatment of respiratory disorders, e.g. beta2-agonists, antimuscarinic agents, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, human neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), antitussive agents, mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, antibiotics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma, M3-antagonists/beta2-agonists (MABA) and M3-antagonists/PDE4-inhibitors (MAPI).

The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a β2-agonist selected from the group consisting of carmoterol, GSK-642444, indacaterol, milveterol, arformoterol, arformoterol tartrate, formoterol, formoterol fumarate, salmeterol, salmeterol xinafoate, salbutamol, albuterol, levalbuterol, terbutaline, indacaterol (QAB-149), AZD-3199, BI-1744-CL, LAS-100977, GSK159797, GSK59790, GSK159802, GSK642444, GSK678007, GSK96108, bambuterol, isoproterenol, procaterol, clenbuterol, reproterol, fenoterol, bitolterol, brodxatelor and ASF-1020 and salts thereof.

The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with an antimuscarinic agent selected from the group consisting of aclidinium, tiotropium, tiotropium bromide (Spiriva®), ipratropium, ipratropium bromide, trospium, glycopyrrolate, NVA237, LAS34273,

GSK656398, GSK233705, GSK57319, LAS35201, QAT370 and oxitropium salts.

The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a PDE4 inhibitor selected from the group consisting of AN-2728, AN-2898, CBS-3595, apremilast, ELB-353, KF-66490, K-34, LAS-37779, IBFB-211913, AWD-12-281, cipamfylline, cilomilast, roflumilast, BAY19-8004 and SCH-351591, AN-6415, indus-82010, TPI-PD3, ELB-353, CC-11050, GSK-256066, oglemilast, OX-914, tetomilast, MEM-1414 and RPL-554.

The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a P38 MAP kinase inhibitor selected from the group consisting of semapimod, talmapimod, pirfenidone, PH-797804, GSK-725, GSK856553, GSK681323, minokine and losmapimod and salts thereof.

In a preferred embodiment, the invention provides combinations of a compound of the invention with an IKK2 inhibitor.

The invention also provides combinations of a compound of the invention with a HNE inhibitor selected from the group consisting of AAT, ADC-7828, aeriva, TAPI, AE-3763, KRP-109, AX-9657, POL-6014, AER-002, AGTC-0106, respriva, AZD-9668, zemaira, AAT IV, PGX-100, elafin, SPHD-400, prolastin C and prolastin inhaled.

The invention also provides combinations of a compound of the invention with a leukotriene modulator selected from the group consisting of montelukast, zafirlukast and pranlukast.

The invention also provides combinations of a compound of the invention with a NSAID selected from the group consisting of ibuprofen and ketoprofen.

The invention also provides combinations of a compound of the invention with an antitussive agent, selected from the group consisting of codeine and dextramorphan.

The invention also provides combinations of a compound of the invention with a mucolytic, selected from the group consisting of N acetyl cysteine and fudostein.

The invention also provides combinations of a compound of the invention with an expectorant/mucokinetic modulator, selected from the group consisting of ambroxol,

hypertonic solutions (e.g. saline or mannitol) and surfactant.

The invention also provides combinations of a compound of the invention with a peptide mucolytic, selected from the group consisting of recombinant human deoxyribonuclease I (dornase-alfa and rhDNase) and helicidin.

The invention also provides combinations of a compound of the invention, with an antibiotic, selected from the group consisting of azithromycin, tobramycin and aztreonam.

The invention also provides combinations of a compound of the invention with a mucus regulator selected from the group consisting of INS-37217, diquafosol, sibenadet, CS-003, talnetant, DNK-333, MSI-1956 and gefitinib.

The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with an inhibitor of JAK, selected from the group consisting of CP-690550 and GLPG0634.

The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a SYK inhibitor selected from the group consisting of R406, R343 and PRT062607.

The invention also provides a compound of the invention for use as a medicament.

The invention also relates to the use of a compound of the invention to decrease the number, activity and movement of the inflammatory cells in vitro and/or in vivo.

The invention is also directed to compounds of the invention for use in the prevention or treatment of any disease wherein the decrease in the number, activity and movement of inflammatory cells is involved.

In a further aspect, the invention provides the use of compounds of the invention for the prevention and/or treatment of any disease wherein the decrease in the number, activity and movement of inflammatory cells is involved.

In particular, the compounds of the invention, either alone or combined with one or more active ingredients, may be administered for the prevention and/or treatment of a disease of the respiratory tract characterized by airway obstruction such as asthma and COPD.

In a further aspect the invention provides the use of compounds of the invention for the preparation of a medicament for the prevention and/or treatment of any disease wherein the decrease in the number, activity and movement of inflammatory cells is involved.

Moreover the invention provides a method for prevention and/or treatment of any disease wherein the decrease in the number, activity and movement of inflammatory cells is involved, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the invention.

The invention also provides pharmaceutical preparations of compounds of the invention suitable for administration by inhalation, by injection, orally or intra-nasally.

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

The invention is also directed to a device which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler or a nebulizer, in particular a soft mist nebulizer comprising a compound of the invention.

The invention is also directed to a kit comprising the pharmaceutical compositions of compounds of the invention alone or in combination with or in admixture with one or more pharmaceutically acceptable carriers and/or excipients and a device which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler or a nebulizer.

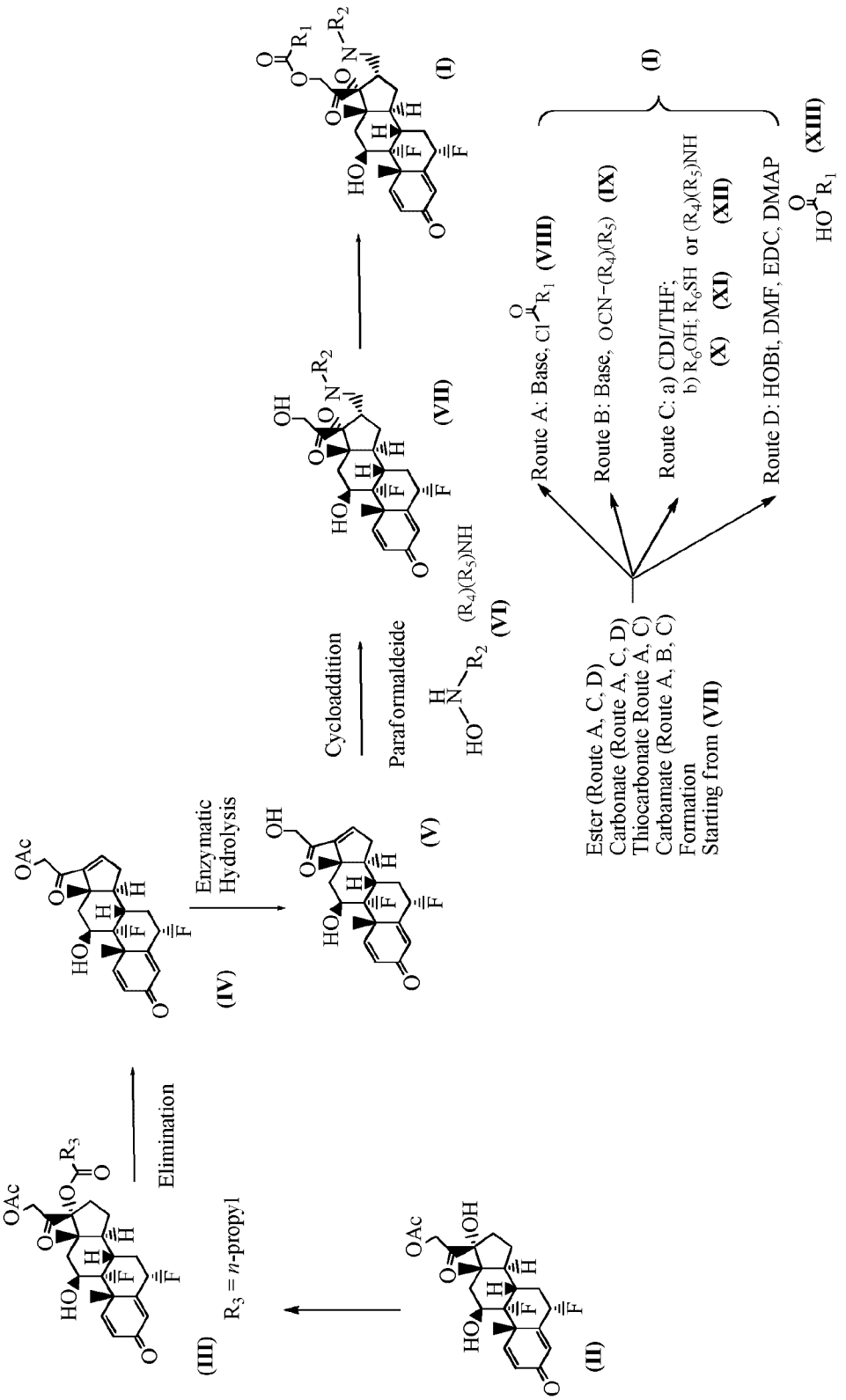
The compounds of the invention may be prepared according to a variety of synthetic steps which are carried out according to conventional methods and techniques or which are hereinbelow described.

In one aspect, the invention provides processes for the preparation of compounds of the invention and intermediates thereof.

From all of the above, it is clear to the person skilled in the art that by selecting the starting material with a proper stereochemical configuration, any of the possible stereoisomers of formula (I) can be obtained.

Some of the processes used for the preparation of the compounds of formula (I'), as described in the Scheme below, may also be applied to compounds of formula (I).

Scheme


(II)
(III)
R3 = n-propyl
Elimination
(IV)
Enzymatic Hydrolysis
(V)
Cycloaddition
Paraformaldeide
(VI)
(VII)
(I)
Route A: Basc, (VIII)
Route B: Base, (IX)
Route C: a) CDI/THF; b) (X) (XI) (XII)
Route D: HOBt, DMF, EDC, DMAP
(XIII)
Ester (Route A, C, D)
Carbonate (Route A, C, D)
Thiocarbonate Route A, C)
Carbamate (Route A, B, C)
Formation
Starting from (VII)

Procedure for the preparation of the compounds of the invention

The compounds of the invention may be prepared according to different routes described in the above scheme, depending on the nature of the substituents R_1 and R_2.

In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction scheme or by modification thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are well known to the person skilled in the art.

Compounds of formula (III) may be readily prepared from known compounds by known methods, starting from compounds of general formula (II) (*J.Med. Chem.* 1982, 25, 1492-1495). They are also commercially available.

The compounds of formula (IV) may be conveniently prepared according to standard procedures reported in the literature. For instance they may be prepared by treatment of compounds of general formula (III) with a base such as potassium acetate. This reaction is usually performed in a suitable polar solvent such as DMF and typically proceeds at a temperature range from 80 to 110°C, over a period of 0.5 to 4 hours.

The compounds of formula (V) may be prepared by hydrolyzing the compounds of formula (IV). This reaction is preferably carried out by subjecting compounds (IV) to the action of an enzyme, such as immobilized Lipase from *Candida antarctica* (Sigma Aldrich) (Tetrahedron, 50, 13165-13172, 1994).

The compounds of general formula (VII) may be prepared starting from the reaction of a compound of formula (V) with a compound of formula (VI) in the presence of paraformaldehyde, using known procedures for the isoxazolidine formation, by cycloaddition of nitrones (J. Med. Chem., 25, 1492-1495, 1982). The reaction is conveniently carried out in a protogenic solvent, such as ethanol, at temperatures ranging from 80 to 100°C. Hydroxyl amine of formula (VI) are either commercially available or may be easily prepared using known procedures, for example by reducing an oxime with a reducing agent, such as borane pyridine complex (J. Med. Chem., 40, 1955-1968, 1997)

or by reaction of O-tetrahydropyranyl hydroxylamine with a suitable alkylating agent such as alkyl halides (Chem.Pharm.Bull., 46, 966-972, 1998).

Conversion of the hydroxyl group of compounds of general formula (VII) into an ester, carbonate, carbamate or thiocarbonate, may be easily performed by reacting compounds of general formula (VII) with compounds of general formula (VIII), (IX), (X), (XI), (XII) or (XIII) following the described synthetic route (Route A-D).

The skilled person may introduce, where appropriate, suitable variations to the conditions specifically described in the experimental in order to adapt the synthetic routes to the provision of further compounds of the invention. Such variations may include, but are not limited to, use of appropriate starting materials to generate different compounds, changes in the solvent and temperature of reactions, replacements of a reactive with analogous chemical role, introduction or removal of protection/deprotection stages of functional groups sensitive to reaction conditions and reagents, as well as introduction or removal of specific synthetic steps oriented to further fictionalization of the chemical scaffold.

Reaction of the intermediates of general formula (VII) with acyl chlorides (VIII), following **route A**, to obtain compounds of general formula (I) is conveniently performed in DCM (dichloromethane) as solvent in the presence of a base such as triethylamine or DIPEA (N,N-Diisopropyl-ethylamine) or pyridine at RT over a period of 4 to 50 hours.

Alternatively, **Route B**, conversion of the hydroxyl group of compounds of general formula (VII) into a carbamate may be easily performed by reacting compounds of general formula (VII) with compounds of general formula (IX), following known procedures. The reaction is conveniently performed in DCM as solvent in the presence of a base such as DMAP, at RT over a period of 4 to 50 hours.

Following **Route C**, reaction of the intermediates of general formula (VII) with CDI (1,1'-Carbonyldiimidazole) followed by addition of desired alcohol (X) or thiol (XI) or amine (XII) to obtain compounds of general formula (I) is conveniently performed in

THF (Tetrahydrofuran) at RT over a period of 4 to 50 hours.

Alternatively, **Route D**, conversion of the hydroxyl group of compounds of general formula (VII) into compounds of general formula (I) can be achieved by reacting compounds of general formula (XIII) with HOBt (Hydroxybenzotriazole) followed by adding of compounds of general formula (VII), EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) and DMAP (4-Dimethylaminopyridine). The reaction is conveniently performed in DMF as solvent at RT over a period of 4 to 50 hours.

From all of the above, it should be clear that any of the described groups may be present as such or in any properly protected form.

In particular, functional groups present in the intermediate and compounds and which could generate unwanted side reaction and by-products, need to be properly protected before the alkylation, acylation, coupling or sulfonylation takes place. Likewise, subsequent deprotection of those same protected groups may follow upon completion of the said reactions.

In the present invention, unless otherwise indicated, the term "protecting group" designates the protective group were adapted to preserve the function of the group it is bound to. Typically, protective groups are used to preserve amino, hydroxyl, or carboxyl functions. Appropriate protecting groups may thus include, for example, benzyl, benzyloxycarbonyl, t-butoxycarbonyl, alkyl or benzyl esters or the like, which are well known to those skilled in the art [see, for a general reference, 20 T.W. Green; Protective Groups in Organic Synthesis (Wiley, N.Y. 1981)].

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

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

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

However the compounds of the invention may be administered for the prevention and/or treatment of any disease wherein the decrease in the number, activity and movement of inflammatory cells is involved.

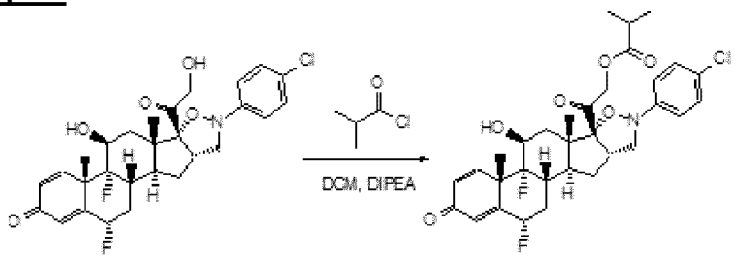
Examples of such diseases include: diseases involving inflammation such as asthma and other allergic disorders, COPD, acute rhinitis; reverse acute transplant rejection and acute exacerbations of selected autoimmune disorders, graft-versus-host disease in bone-marrow transplantation; autoimmune disorders such as rheumatoid and other arthritis; skin conditions such as systemic lupus erythematosus, systemic dermatomyositis, psoriasis; inflammatory bowel disease, inflammatory ophthalmic diseases, autoimmune hematologic disorders, and acute exacerbations of multiple sclerosis; kidney, liver, heart, and other organ transplantation; Behçet's acute ocular syndrome, endogenous uveitis, atopic dermatitis, inflammatory bowel disease, and nephrotic syndrome; Hodgkin's disease and non-Hodgkin's lymphoma, multiple myeloma and chronic lymphocytic leukemia (CLL); autoimmune hemolytic anemia and thrombocytopenia associated with CLL; leukemia and malignant lymphoma.

Preferably the compounds of the invention may be administered for the prevention and/or treatment of respiratory diseases such as from mild to acute severe conditions of asthma and COPD.

The invention will now be further described by way of the following examples.

In the reported experimental procedures, the following abbreviations may be used: TEA = triethylamine; DCM=dichloromethane; RT=room temperature; AcOEt=ethyl acetate; DMF=N,N- dimethylformamide; DMSO= dimethylsulfoxide; HATU=O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; DMAP= 4-Dimethylaminopyridine; DIPEA= ethyldiisopropylamine.

Example 1



Intermediate 2 Compound 1

Preparation of

Isobutyric acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester (compound 1)

To a stirred solution of intermediate 2 (600 mg, 1.124 mmol) and DIPEA (0.391 ml, 2.247 mmol) in dry dichloromethane (30 ml), under nitrogen atmosphere at 5°C, isobutyryl chloride (0.235 ml, 2.247 mmol) was added and the reaction mixture was stirred at 5°C for 10 min and at RT for 16 hr. DIPEA (0.196 ml, 1.124 mmol) and isobutyryl chloride (0.118 ml, 1.124 mmol) were further added and the mixture was stirred at RT for 72 h. Another portion of DIPEA (0.196 ml, 1.124 mmol) and isobutyryl chloride (0.118 ml, 1.124 mmol) were further added and the reaction mixture was stirred at RT for 1 hr and at 50°C for 1.5 hr.

The reaction mixture was diluted with DCM (100 ml) and the organic layer was washed with 1 N HCl, a saturated solution of $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The crude was purified by silica gel flash chromatography in gradient elution from DCM/AcOEt 98:2 to DCM/AcOEt 92:8, to afford 481 mg of pure compound (71% yield; R_f=0.37 in AcOEt/DCM 10:90).

^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.31 - 7.45 (m, 2 H), 7.26 (dd, 1 H), 6.98 - 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (d, 1 H), 5.42 - 5.78 (m, 1 H), 5.06 (d, 1 H), 4.90 (d, 1 H), 4.18 - 4.32 (m, 1 H), 4.17 (t, 1 H), 3.44 - 3.62 (m, 1 H), 2.56 - 2.71 (m, 2 H), 2.63 (spt, 1 H), 2.04 - 2.34 (m, 3 H), 1.84 - 1.96 (m, 1 H), 1.63 - 1.83 (m, 1 H),

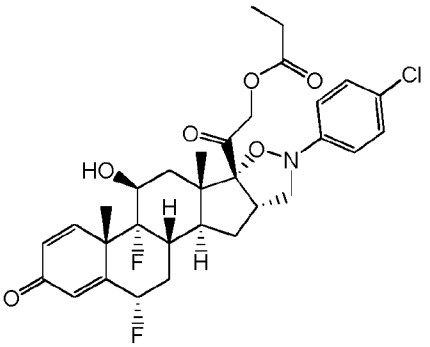
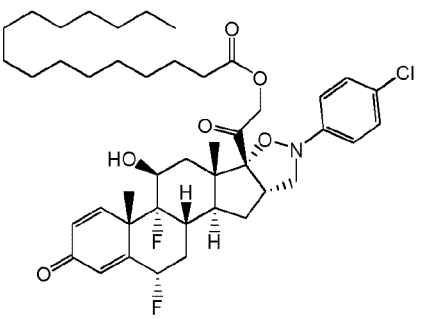
1.52 - 1.63 (m, 2 H), 1.50 (s, 3 H), 1.14 (d, 3 H), 1.13 (d, 3 H), 0.94 (s, 3 H)

LC-MS (ESI POS): 604.10 MH+

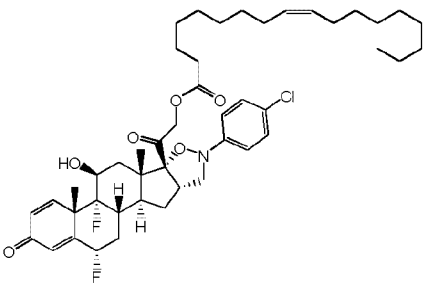
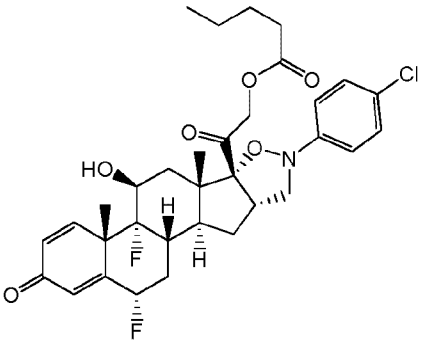
$[\alpha]_D^{25}$ = + 58.3 (c 0.2; MeOH)

The compounds listed in Table were prepared as previously described for compound 1, by acylation of intermediate 2 with suitable acyl chlorides:

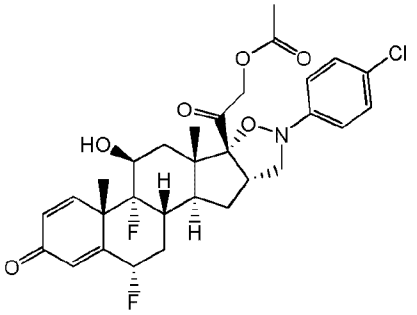
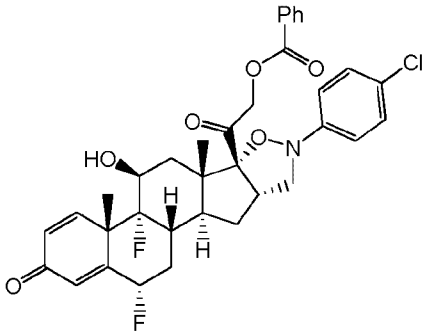
Table 1

Compound	Structure	Yield	Analytical
3		61%	LC-MS (ESI POS): 590.14 MH+ $[\alpha]_D^{25}$ = + 59.7 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.31 - 7.43 (m, 2 H), 7.26 (dd, 1 H), 6.90 - 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (dd, 0 H), 5.45 - 5.73 (m, 1 H), 5.06 (d, 1 H), 4.90 (d, 1 H), 4.19 - 4.31 (m, 1 H), 4.17 (t, 1 H), 3.45 - 3.64 (m, 1 H), 2.56 - 2.69 (m, 2 H), 2.41 (q, 2 H), 2.07 - 2.28 (m, 3 H), 1.82 - 1.93 (m, 1 H), 1.64 - 1.81 (m, 1 H), 1.51 - 1.64 (m, 3 H), 1.50 (s, 3 H), 1.07 (t, 3 H), 0.94 (s, 3 H)
4		70%	LC-MS (ESI POS): 772.6 MH+ $[\alpha]_D^{25}$ = + 65.9 (c 0.2 $CHCl_3$) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.31 - 7.41 (m, 2 H), 7.26 (d, 1 H), 6.98 - 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (d, 1 H), 5.43 - 5.79 (m, 1 H), 5.06 (d, 1 H), 4.89 (d, 1 H), 4.18 - 4.29 (m, 1 H), 4.17 (t, 1 H), 3.45 - 3.61 (m, 1 H), 2.55 - 2.73 (m, 2 H), 2.37 (t, 2 H), 2.03 - 2.31 (m, 3 H), 1.88 (d, 1 H), 1.62 - 1.81 (m, 1 H), 1.51 - 1.62 (m, 4 H), 1.50 (s, 3 H), 1.24 (s, 24 H), 0.93 (s, 3 H), 0.86 (t, 3 H)

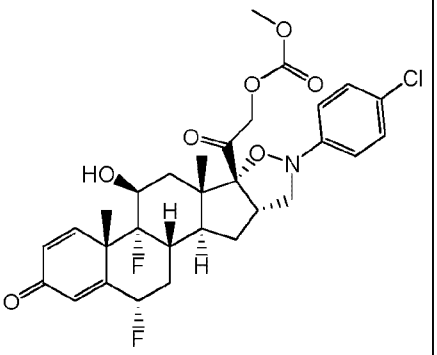
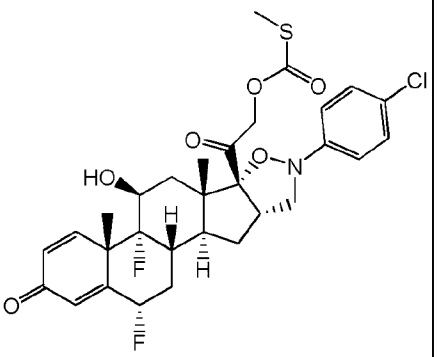
(continue)

5			LC-MS (ESI POS): 798.31 MH+ $[\alpha]_D^{25}$ = + 47 (c 0.0765; MeOH) 1H NMR (300 MHz, DMSO-d6) ppm 7.30 - 7.39 (m, 2 H), 7.26 (dd, 1 H), 6.97 - 7.09 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (d, 1 H), 5.47 - 5.81 (m, 1 H), 5.21 - 5.40 (m, 2 H), 5.06 (d, 1 H), 4.88 (d, 1 H), 4.07 - 4.31 (m, 2 H), 3.52 (q, 1 H), 2.60 (dd, 2 H), 2.37 (t, 2 H), 2.06 - 2.26 (m, 3 H), 1.92 - 2.05 (m, 4 H), 1.87 (d, 1 H), 1.62 - 1.80 (m, 1 H), 1.50 (s, 3 H), 1.45 - 1.61 (m, 4 H), 1.26 (m, 20 H), 0.93 (s, 3 H), 0.85 (t, 3 H)
6		56%	LC-MS (ESI POS): 618.23 MH+ $[\alpha]_D^{25}$ = + 68.6 (c 0.2 $CHCl_3$) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.30 - 7.42 (m, 2 H), 7.26 (dd, 1 H), 6.93 - 7.14 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (d, 1 H), 5.42 - 5.79 (m, 1 H), 5.07 (d, 1 H), 4.89 (d, 1 H), 4.23 (m, 1 H), 4.17 (t, 1 H), 3.43 - 3.63 (m, 1 H), 2.55 - 2.66 (m, 2 H), 2.39 (t, 2 H), 2.00 - 2.25 (m, 3 H), 1.88 (d, 1 H), 1.63 - 1.81 (m, 1 H), 1.42 - 1.61 (m, 4 H), 1.50 (s, 3 H), 1.26 - 1.41 (m, 2 H), 0.93 (s, 3 H), 0.81 - 0.92 (m, 3 H)

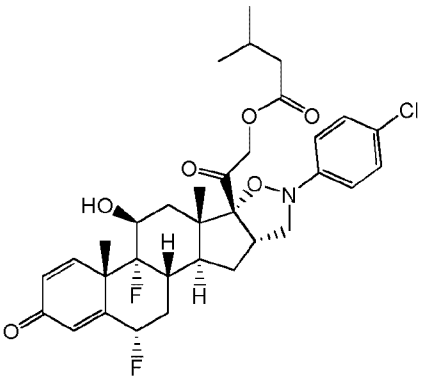
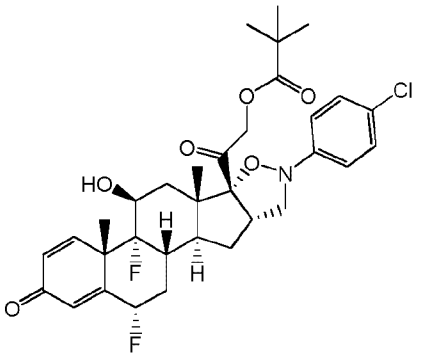
(continue)

7		47%	LC-MS (ESI POS): 576.23 MH+ $[\alpha]_D^{25}$ = + 53.8 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.30 - 7.40 (m, 2 H), 7.26 (dd, 1 H), 6.88 - 7.12 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (dd, 1 H), 5.39 - 5.77 (m, 1 H), 5.05 (d, 1 H), 4.88 (d, 1 H), 4.18 - 4.28 (m, 1 H), 4.17 (t, 1 H), 3.46 - 3.67 (m, 1 H), 2.58 - 2.71 (m, 1 H), 2.60 (dd, 1 H), 2.12 - 2.32 (m, 3 H), 2.10 (s, 3 H), 1.81 - 1.94 (m, 1 H), 1.64 - 1.81 (m, 1 H), 1.51 - 1.64 (m, 2 H), 1.50 (s, 3 H), 0.93 (s, 3 H)
8		29%	LC-MS (ESI POS): 638.15 MH+ $[\alpha]_D^{25}$ = + 66 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.93 – 8.06 (m, 2 H), 7.66 – 7.76 (m, 1 H), 7.49 – 7.63 (m, 2 H), 7.33 – 7.42 (m, 2 H), 7.28 (dd, 1 H), 7.00 – 7.15 (m, 2 H), 6.30 (dd, 1 H), 6.09 (s, 1 H), 5.67 (dd, 1 H), 5.49 – 5.85 (m, 1 H), 5.35 (d, 1 H), 5.17 (d, 1 H), 4.23 – 4.32 (m, 1 H), 4.21 (t, 1 H), 3.47 – 3.65 (m, 1 H), 2.56 – 2.69 (m, 2 H), 2.09 – 2.32 (m, 3 H), 1.91 – 2.04 (m, 1 H), 1.66 – 1.83 (m, 1 H), 1.53 – 1.65 (m, 2 H), 1.51 (s, 3 H), 1.00 (s, 3 H)

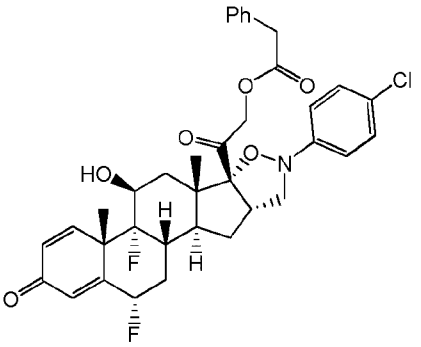
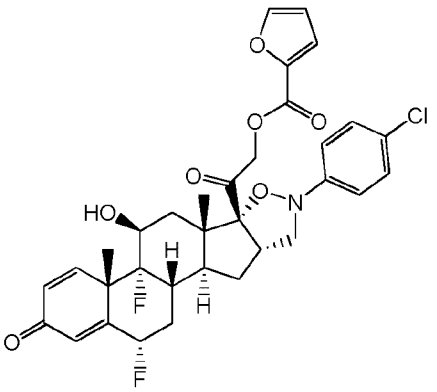
(continue)

9		54%	LC-MS (ESI POS): 592.13 MH+ $[\alpha]_D^{25}$ = + 48.6 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.30 – 7.39 (m, 2 H), 7.26 (dd, 1 H), 6.96 – 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.63 (dd, 1 H), 5.47 – 5.75 (m, 1 H), 5.07 (d, 1 H), 4.94 (d, 1 H), 4.19 – 4.29 (m, 1 H), 4.18 (t, 1 H), 3.74 (s, 3 H), 3.45 – 3.61 (m, 1 H), 2.62 – 2.72 (m, 1 H), 2.61 (dd, 1 H), 2.04 – 2.29 (m, 3 H), 1.85 (d, 1 H), 1.63 – 1.80 (m, 1 H), 1.51 – 1.63 (m, 2 H), 1.50 (s, 3 H), 0.95 (s, 3 H)
10		66%	LC-MS (ESI POS): 608.08 MH+ $[\alpha]_D^{25}$ = + 50.8 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.30 - 7.42 (m, 2 H), 7.26 (d, 1 H), 6.94 - 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.63 (dd, 1 H), 5.45 - 5.78 (m, 1 H), 5.22 (d, 1 H), 5.06 (d, 1 H), 4.19 - 4.27 (m, 1 H), 4.18 (m, 1 H), 3.44 - 3.62 (m, 1 H), 2.59 - 2.72 (m, 1 H), 2.61 (dd, 1 H), 2.34 (s, 3 H), 2.02 - 2.29 (m, 3 H), 1.80 - 1.89 (m, 1 H), 1.64 - 1.79 (m, 1 H), 1.51 - 1.62 (m, 2 H), 1.50 (s, 3 H), 0.94 (s, 3 H)

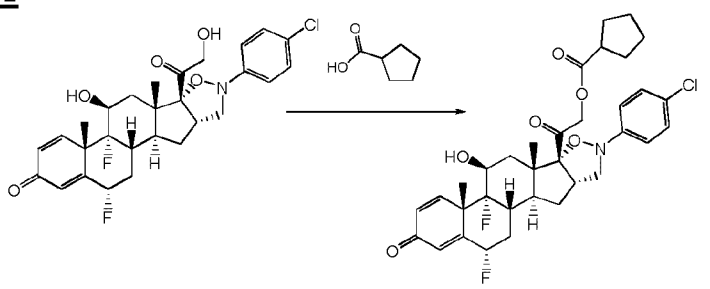
(continue)

11		54%	LC-MS (ESI POS): 618.13 MH+ $[\alpha]_D^{25}$ = + 63.4 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.29 - 7.46 (m, 2 H), 7.26 (dd, 1 H), 6.94 - 7.13 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (dd, 1 H), 5.39 - 5.81 (m, 1 H), 5.08 (d, 1 H), 4.89 (d, 1 H), 4.21 - 4.39 (m, 1 H), 4.17 (t, 1 H), 3.41 - 3.63 (m, 1 H), 2.56 - 2.70 (m, 2 H), 2.27 (d, 2 H), 2.07 - 2.25 (m, 3 H), 1.94 - 2.09 (m, 1 H), 1.80 - 1.94 (m, 1 H), 1.64 - 1.80 (m, 1 H), 1.51 - 1.62 (m, 2 H), 1.50 (s, 3 H), 0.94 (s, 3 H), 0.95 (d, 6 H)
12		33%	LC-MS (ESI POS): 618.12 MH+ $[\alpha]_D^{25}$ = + 53.6 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.30 - 7.41 (m, 2 H), 7.26 (dd, 1 H), 6.95 - 7.12 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.61 (d, 1 H), 5.48 - 5.75 (m, 1 H), 5.06 (d, 1 H), 4.91 (d, 1 H), 4.17 (t, 1 H), 4.09 - 4.35 (m, 1 H), 3.53 (q, 1 H), 2.56 - 2.68 (m, 2 H), 2.04 - 2.26 (m, 3 H), 1.89 (d, 1 H), 1.62 - 1.80 (m, 1 H), 1.50 (s, 3 H), 1.57 (d, 2 H), 1.19 (s, 9 H), 0.94 (s, 3 H)

(continue)

13		79%	LC-MS (ESI POS): 652.14 MH+ $[\alpha]_D^{25}$ = + 129.6 (c 0.3; DCM) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.13 - 7.46 (m, 8 H), 6.76 - 7.13 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.60 (d, 1 H), 5.40 - 5.77 (m, 1 H), 5.10 (d, 1 H), 4.93 (d, 1 H), 4.11 - 4.31 (m, 2 H), 3.78 (s, 2 H), 3.43 - 3.66 (m, 1 H), 2.55 - 2.66 (m, 2 H), 2.09 - 2.30 (m, 3 H), 1.86 (d, 1 H), 1.72 (d, 1 H), 1.49 (s, 3 H), 1.33 - 1.63 (m, 2 H), 0.93 (s, 3 H)
14		60%	LC-MS (ESI POS): 628.2 MH+ $[\alpha]_D^{25}$ = + 34.9 (c 0.2, MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 8.02 (dd, 1 H), 7.32 - 7.43 (m, 3 H), 7.27 (d, 1 H), 6.98 - 7.13 (m, 2 H), 6.73 (dd, 1 H), 6.30 (dd, 1 H), 6.09 (s, 1 H), 5.66 (d, 1 H), 5.46 - 5.79 (m, 1 H), 5.30 (d, 1 H), 5.11 (d, 1 H), 4.20 (t, 1 H), 4.09 - 4.36 (m, 1 H), 3.47 - 3.66 (m, 1 H), 2.63 (dd, 2 H), 2.06 - 2.27 (m, 3 H), 1.93 (d, 1 H), 1.64 - 1.83 (m, 1 H), 1.56 (dd, 2 H), 1.51 (s, 3 H), 0.97 (s, 3 H)

Example 2



Intermediate 2 Compound 15

Preparation of Cyclopentanecarboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester (compound 15)

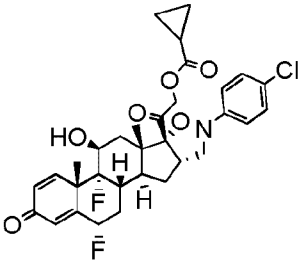
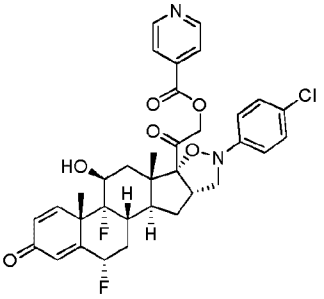
Cyclopentanecarboxylic acid (137 mg, 1.2 mmol, 1.2 eq) was dissolved in DMF (5 ml), 1-hydroxybenzotriazole hydrate (162 mg, 1.2 mmol, 1.2 eq) was added and the reaction mixture was stirred 20 minutes. Intermediate 2 (534 mg, 1 mmol), 4-(dimethylamino)pyridine (305 mg, 2.5 mmol, 2.5 eq) and EDC*HCl (230 mg, 1.2 mmol, 1.2 eq) were added in this order and the reaction mixture was stirred at RT overnight. The conversion was monitored by TLC analysis (Hex/EtOAc 7/6). The reaction was quenched with HCl 0.6N and the product extracted with EtOAc twice. The collected organic phases were washed with $NaHCO_3$ saturated solution, brine and dried over anhydrous Na_2SO_4. The crude was purified treating with NaOH 1N (10 ml), pyridine (used to transfer cyclopentanecarboxylic acid in the aqueous layer, 2 ml), and EtOAc (30 ml). The organic layer was washed twice with water and filtered on a silica pad. Compound **15** was obtained as a solid that was dried under vacuum at 50 °C for 2 hours (300 mg, yield 47.6%).

LC-MS (ESI POS): 630.10 MH+

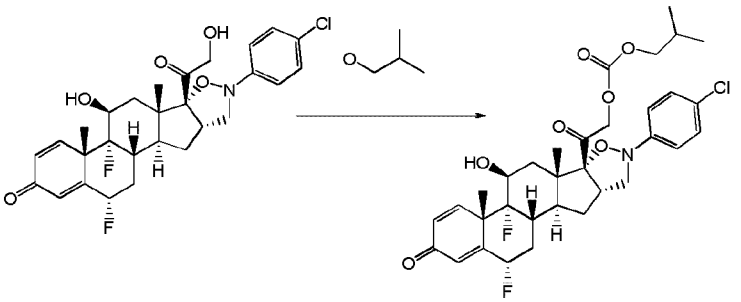
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.34 (d, *J*=8.82 Hz, 2 H), 7.19 - 7.28 (m, 1 H), 7.04 (d, *J*=8.82 Hz, 2 H), 6.18 - 6.37 (m, 1 H), 5.97 - 6.13 (m, 1 H), 5.46 - 5.75 (m, 2 H), 4.78 - 5.17 (m, 2 H), 4.06 - 4.31 (m, 2 H), 3.42 - 3.55 (m, 1 H), 2.78 - 2.93 (m, 1 H), 2.54 - 2.74 (m, 2 H), 2.09 (m, 3 H), 1.49 (m, 15 H), 0.93 (s, 3 H).

The compounds listed in Table 2 were prepared as previously described for compound 15 starting from the corresponding carboxylic acid:

Table 2

Compound	Structure	Yield	Analytical
16		71%	LC-MS (ESI POS): 602.2 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.26 - 7.37 (m, 2 H), 7.14 - 7.24 (m, 1 H), 6.90 - 7.05 (m, 2 H), 6.15 - 6.40 (m, 1 H), 5.99 - 6.06 (m, 1 H), 5.39 - 5.72 (m, 2 H), 4.74 - 5.12 (m, 2 H), 4.03 - 4.22 (m, 2 H), 3.39 - 3.57 (m, 1 H), 2.50 - 2.70 (m, 2 H), 1.94 - 2.22 (m, 3 H), 1.76 - 1.90 (m, 1 H), 1.59 - 1.73 (m, 2 H), 1.36 - 1.56 (m, 5 H), 0.71 - 1.01 (m, 7 H).
17		46%	LC-MS (ESI POS): 639.2 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 - 8.95 (m, 2 H), 7.76 - 7.88 (m, 2 H), 7.37 (d, *J*=8.82 Hz, 2 H), 7.23 - 7.31 (m, 1 H), 7.09 (d, *J*=8.82 Hz, 2 H), 6.24 - 6.35 (m, 1 H), 6.09 (s, 1 H), 5.51 - 5.76 (m, 2 H), 5.11 - 5.45 (m, 2 H), 4.09 - 4.32 (m, 2 H), 3.48 - 3.65 (m, 1 H), 2.59 - 2.75 (m, 2 H), 2.12 - 2.36 (m, 3 H), 1.89 - 2.06 (m, 1 H), 1.51 (m, 6 H), 0.98 (s, 3 H).

Example 3



Intermediate 2 Compound 18

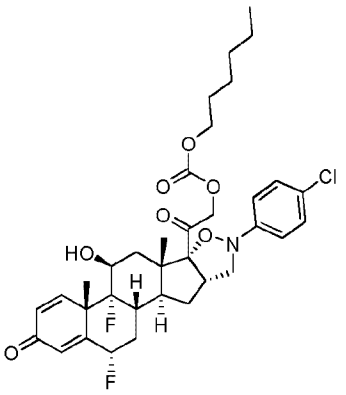
Preparation of Isobutyl methyl carbonate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester (compound 18)

Intermediate 2 (350 mg, 0.66 mmol) in THF (3 ml) was added at RT with CDI (127 mg, 0.79 mmol, 1.2 eq) at portions. The reaction mixture was stirred 1 hour: conversion was detected by TLC analysis (EtOAc 100%). The reaction mixture was added with isobutyl alcohol (1.0 ml, 10 mmol) at 0°C and stirred 1 hour at RT. Traces of the desired product were observed. The reaction mixture was then heated to 50°C for four hours: conversion increase. After 12 hours at 50°C complete conversion was detected by TLC analysis (hexane/EtOAc 3/7). The solvent was evaporated under vacuum and the crude treated with EtOAc/H_2O. The organic layers collected were dried over anhydrous Na_2SO_4, the crude was purified on a silica pad to yield **compound 18** (240 mg, yield 58%).

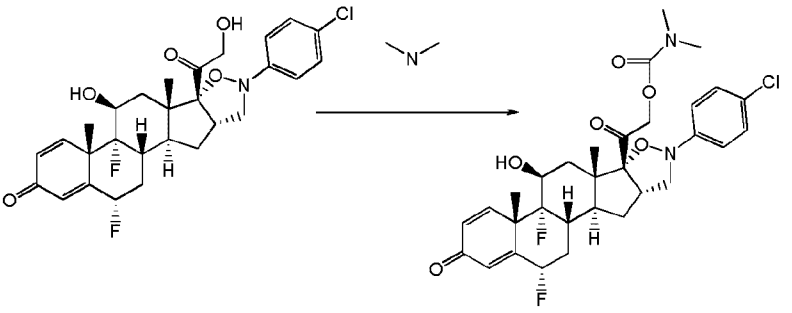
LC-MS (ESI POS): 634.2 LC-MS

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.34 (d, *J*=8.82 Hz, 2 H), 7.20 - 7.30 (m, 1 H), 7.04 (d, *J*=8.82 Hz, 2 H), 6.21 - 6.37 (m, 1 H), 6.00 - 6.12 (m, 1 H), 5.47 - 5.72 (m, 2 H), 4.83 - 5.17 (m, 2 H), 4.10 - 4.29 (m, 2 H), 3.91 (dd, *J*=6.62, 0.88 Hz, 2 H), 3.43 - 3.60 (m, 1 H), 2.55 - 2.74 (m, 2 H), 2.04 - 2.29 (m, 3 H), 1.81 - 1.99 (m, 2 H), 1.64 - 1.76 (m, 1 H), 1.49 (m, 5 H), 0.81 - 0.96 (m, 9 H).

Compound 19 was prepared as previously described for compound 18 starting from hexyl alcohol:

Compound	Structure	Yield	Analytical
19		30%	LC-MS (ESI POS): 662.2 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.33 (s, 2 H), 7.18 - 7.29 (m, 1 H), 7.00 - 7.11 (m, 2 H), 6.22 - 6.37 (m, 1 H), 6.02 - 6.11 (m, 1 H), 5.49 - 5.77 (m, 2 H), 4.79 - 5.17 (m, 2 H), 4.14 - 4.27 (m, 2 H), 4.04 - 4.13 (m, 2 H), 3.44 - 3.62 (m, 1 H), 2.53 - 2.68 (m, 2 H), 2.03 - 2.29 (m, 3 H), 1.77 - 1.90 (m, 1 H), 1.49 (m, 8 H), 1.22 - 1.36 (m, 6 H), 0.76 - 0.99 (m, 6 H).

Example 4



Intermediate 2 Compound 20

Preparation of Dimethylcarbamate2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester (compound 20)

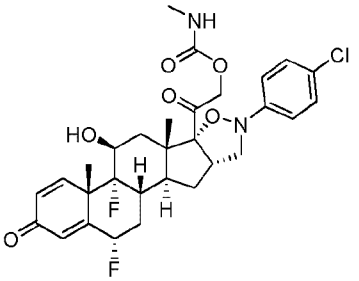
Intermediate 2 (310 mg, 0.58 mmol) in CH_2Cl_2 (3 ml) was added at RT with CDI (111 mg, 0.70 mmol, 1.2 eq) at portions. The reaction mixture was stirred 1 hour:

complete conversion was detected by TLC analysis (EtOAc 100%). CH_2Cl_2 was evaporated under vacuum and the crude was dissolved in THF (2 ml) and then was added with 2 M dimethylamine solution in THF at 0°C (1.15 ml, 2.32 mmol) and stirred 1 hour at RT. Complete conversion was detected by TLC analysis (hexane/EtOAc 2/8). The solvent was evaporated under vacuum and the crude treated with CH_2Cl_2/H_2O. The organic layers collected were dried over anhydrous Na_2SO_4, the crude was purified on a silica pad, then the obtained beige solid was triturated in a hexane/ethyl acetate mixture (8/2, 8 ml) for one night. The solid filtered was dried under vacuum at 50°C till constant weight, yielding compound **20** (200 mg, yield 57 %)

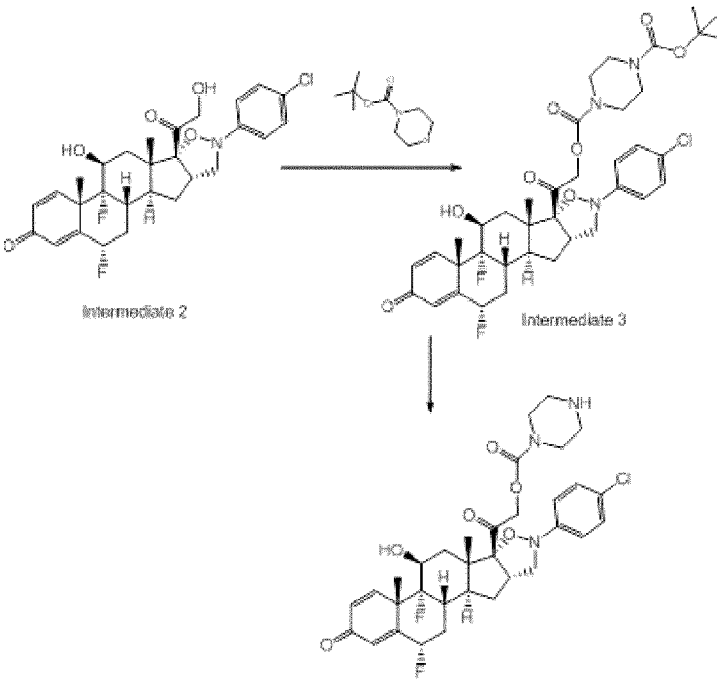
LC-MS (ESI POS): 605.2 LC-MS

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.31 - 7.44 (m, 2 H), 7.21 - 7.30 (m, 1 H), 6.99 - 7.07 (m, 2 H), 6.20 - 6.43 (m, 1 H), 6.01 - 6.12 (m, 1 H), 5.47 - 5.76 (m, 2 H), 4.69 - 5.10 (m, 2 H), 4.08 - 4.25 (m, 2 H), 3.43 - 3.59 (m, 1 H), 2.80 - 3.00 (m, 6 H), 2.55 - 2.72 (m, 2 H), 2.03 - 2.28 (m, 3 H), 1.83 - 1.96 (m, 1 H), 1.65 - 1.81 (m, 1 H), 1.49 (m, 5 H), 0.93 (s, 3 H).

Compound 21 was prepared as previously described for compound 20 starting from methylamine:

Compound	Structure	Yield	Analytical
21		56.3%	LC-MS (ESI POS): 591.1 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.34 (d, J=8.82 Hz, 2 H), 7.15 - 7.28 (m, 2 H), 7.03 (d, J=8.82 Hz, 2 H), 6.19 - 6.41 (m, 1 H), 6.02 - 6.12 (m, 1 H), 5.45 - 5.75 (m, 2 H), 4.62 - 5.07 (m, 2 H), 4.12 - 4.28 (m, 2 H), 3.40 - 3.56 (m, 1 H), 2.58 (m, 5 H), 2.05 - 2.34 (m, 3 H), 1.84 - 1.96 (m, 1 H), 1.56 - 1.77 (m, 1 H), 1.49 (s, 5 H), 0.93 (s, 3 H).

Example 5



Compound 22

Preparation of Piperazine-1-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester (compound 22)

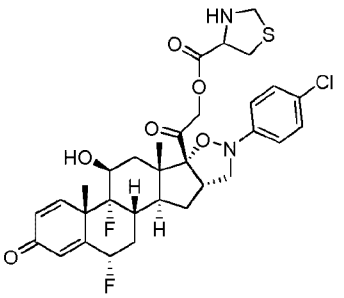
Intermediate 2 (500 mg, 0.94 mmol) in THF (3.5 ml) was added at RT with CDI (180 mg, 1.12 mmol, 1.2 eq) at portions. The reaction mixture was stirred 1 hour: complete conversion to activated intermediate was detected by TLC analysis (Hexane:EtOAc 3/7). The reaction mixture was cooled to 10°C and then was added with tert-butyl piperazine-1-carboxylate (174 mg, 0.94 mmol , 1.0 eq) and stirred at RT overnight. Conversion was detected by TLC analysis (hexane/EtOAc 3/7). The solvent was evaporated under vacuum and the crude treated with EtOAc/H_2O. The organic layers collected were dried over anhydrous Na_2SO_4 and the crude compound intermediate 3 was used in the next step without further purification (260 mg, yield 37%).

A solution of intermediate 3 (260 mg, 0.35 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C and added dropwise with trimethyl-silyl trifluoromethanesulfonate (63 µl, 1.0 eq,). The reaction mixture was stirred 1 hour at 0°C and then quenched with demineralised water. The organic layer was washed with $NaHCO_3$ saturated solution and then with demineralised water, dried over anhydrous Na_2SO_4 yielding raw compound, that was purified by column chromatography over silica gel (eluting with EtOAc/TEA 99:1) and dried under vacuum at 50°C till constant weight to give compound **22** (190 mg, 84% yield)

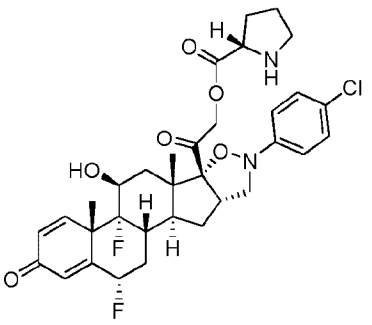
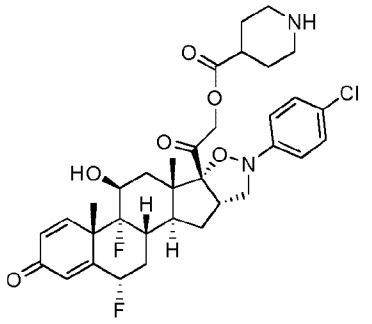
LC-MS (ESI POS): 646.4 MH+

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.33 (d, *J*=8.82 Hz, 3 H), 7.03 (d, *J*=8.82 Hz, 2 H), 6.19 - 6.39 (m, 1 H), 6.07 (s, 1 H), 5.46 - 5.76 (m, 2 H), 4.76 - 5.14 (m, 2 H), 4.05 - 4.28 (m, 2 H), 3.41 - 3.60 (m, 1 H), 3.18 -3.30 (m, 5 H), 2.66 (m, 6 H), 1.95 - 2.28 (m, 3 H), 1.81 - 1.95 (m, 1 H), 1.57 - 1.79 (m, 1 H), 1.48 (m, 5 H), 0.93 (s, 3 H).

The compounds listed in the following Table were prepared as previously described for compound 22 starting from the corresponding intermediate:

Compound	Structure	Yield	Analytical
23		26%	LC-MS (ESI POS): 649.4 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.17 - 7.40 (m, 3 H), 6.88 - 7.11 (m, 2 H), 6.21 - 6.34 (m, 1 H), 5.99 - 6.13 (m, 1 H), 5.44 - 5.74 (m, 2 H), 4.99 - 5.23 (m, 3 H), 4.04 - 4.34 (m, 2 H), 3.39 - 3.64 (m, 1 H), 3.06 - 3.25 (m, 3 H), 2.81 - 2.92 (m, 1 H), 2.70 - 2.79 (m, 1 H), 2.54 - 2.66 (m, 2 H), 2.03 - 2.29 (m, 3 H), 1.80 - 1.92 (m, 1 H), 1.64 - 1.78 (m, 1 H), 1.49 (m, 5 H), 0.93 (s, 3 H)

(continue)

24		27%	LC-MS (ESI POS): 631.2 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.34 (m, 3 H), 7.04 (d, J=8.82 Hz, 2 H), 6.22 - 6.41 (m, 1 H), 6.08 (s, 1 H), 5.41 - 5.78 (m, 2 H), 4.74 - 5.18 (m, 2 H), 4.08 - 4.26 (m, 2 H), 3.69 - 3.84 (m, 1 H), 3.42 - 3.59 (m, 1 H), 2.71 - 2.96 (m, 2 H), 2.54 - 2.69 (m, 2 H), 1.96 - 2.25 (m, 5 H), 1.80 - 1.93 (m, 2 H), 1.60 - 1.75 (m, 3 H), 1.49 (m, 5 H), 0.93 (s, 3 H)
25		31%	LC-MS (ESI POS): 645.3 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.34 (d, J=8.82 Hz, 3 H), 7.04 (d, J=8.82 Hz, 2 H), 6.21 - 6.42 (m, 1 H), 6.08 (s, 1 H), 5.42 - 5.86 (m, 2 H), 4.80 - 5.12 (m, 2 H), 4.01 - 4.30 (m, 2 H), 3.41 - 3.58 (m, 1 H), 2.81 - 2.97 (m, 2 H), 2.52 - 2.74 (m, 2 H), 2.31 - 2.47 (m, 2 H), 1.90 - 2.27 (m, 6 H), 1.63 - 1.78 (m, 3 H), 1.49 (m, 7 H), 0.93 (s, 3 H)

Legend

* NMR

s = singlet

d = doublet

t = triplet

q = quartet

dd = doublet of doublets

m = multiplet

br = broad

ESI-POS=electrospray positive ionization

LC-MS = liquid chromatography-mass spectrometry

PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION

In vivo studies

Example 6

Lipopolysaccharide (LPS)-induced lung neutrophilia

The potency and duration of action of the compounds described in the present invention were evaluated in vivo in an acute model of lung inflammation following a method described in Am. J. Respir. Crit. Care Med. Vol 162. pp1455-1461, 2000, with minor modifications.

The tests were performed on Sprague-Dawley male rats (200 g).

Intratracheal instillation of LPS resulted in a statistically significant increase in neutrophil concentration in BALF, a hallmark of acute ongoing pulmonary inflammation.

For the dose of glucocorticoid producing a 75% inhibition (ED75 dose) assessment test, compounds (0.01-1 μmoles/Kg of body weight) were administered intratracheally as suspension (0.2%Tween 80 in NaCl 0.9%) 1 hour before LPS challenge.

A dose-response curve of the inhibitory effect of the test compounds on LPS-induced lung neutrophilia was performed and the ED50 dose of glucocorticoid was taken as a measure of potency in this bioassay. The ED50 dose values for some representative compounds of the present invention were comprised between 0.05 and 0.16 μmoles/Kg of body weight.

In a second series of experiments, aimed at the evaluation of the duration of action, the compounds were administered as suspension intratracheally, at the ED75 dose, administered 24h before LPS challenge. The most interesting compounds were active (percent of inhibition higher than 50%) when administered 24 hours before LPS challenge.

In vitro studies

Example 7

Glucocorticoid Receptor (GR) translocation assay protocol

A quantitative measurement of GR nuclear translocation of the compounds of the present invention was performed according to ASSAY Drug Devel.Technol., 4(3), 263-272, 2006, through a novel cell-based GR-translocation assay in Enzyme Fragment Complementation (EFC) format developed by DiscoveRx (Fremont, CA).

In the absence of the glucocorticoid, the glucocorticoid receptor (GR) resides in the cytosol complexed with a variety of proteins including heat shock proteins.

When a glucocorticoid diffuses through the cell membrane into the cytoplasm and binds to the glucocorticoid receptor (GR), it results in release of the heat shock proteins and the translocation into the nucleus where it modulates gene transcription.

The DiscoveRx assay uses EFC of b-galactosidase (b-gal) as an indicator of GR-translocation in engineered CHO-K1 biosensor cells. The enzyme acceptor (EA) fragment of b-gal resides in the nucleus, as designed through the use of a proprietary set of sequence additions and modifications. The small peptide enzyme donor (ED) fragment of b-gal was fused directly to the C-terminus of GR, and was localized in the cytoplasm in the absence of receptor signaling. Upon binding to a GR ligand, the complex translocates to the nucleus, where intact enzyme activity was restored by complementation and b-gal activity was detected.

CHO-K1 cells stably expressing NLS-enzyme acceptor fragment (EA) of b-gal and GR-enzyme donor (ED) fragment of b-gal were maintained in F12 medium (Invitrogen, Carlsbad, CA) at 37°C under a humidified atmosphere containing 5% CO_2 and 95% air. The medium contained 10% FBS, 2 mM L-glutamine, 50 U/ml penicillin 50 µg/ml streptomycin, and 250 µg/ml hygromycin and 500 µg/ml G418 (Invitrogen).

GR-translocation was measured using the PathHunter Detection Kit containing cell membrane permeabilizing reagent and beta-gal substrate (DiscoveRx, Fremont, CA). All compounds were screened using varying concentrations ranging from 10^{-11} to 10^{-6} M. The

assay was performed in 48-wells (105 cells/well). Incubation with screened compounds was performed at 37°C for two hours. Detection was made by adding the detection buffer from the kit supplied by DiscoveRx and incubating at RT for one hour. Luminescence was detected by using a CENTRO LB 960 microplate reader (Berthold Technologies).

Statistical analysis and determinations of EC50s were performed by using Prism-version 3.0 Graphpad Software (San Diego, CA).

Some representative compounds of the invention assayed with the GR translocation displayed a EC50 comprised between 3.2 nM and 207 nM.

Example 8

Inhibition of LPS-induced nitric oxide production in RAW 264.7 macrophages

An in vitro model based on macrophagic murine cell line RAW 264.7 was used for testing the anti-inflammatory effects of the corticosteroids of the present invention.

During the inflammatory process, large amounts of nitric oxide (NO) were generated by the inducible isoforms of NO synthase (iNOS). Bacterial lipopolysaccharide (LPS) was commonly used in experimental settings to stimulate inflammatory responses in macrophages.

Cells were grown in a culture medium (RPMI supplemented with heat-inactivated 10% fetal calf serum, 2 mM glutamine, 100 U/ml penicillin and 0.1 mg/ml streptomycin) without phenol red. Cell stimulation was elicited by incubating cells for 24 hours with LPS to final concentrations ranging from 100 ng/ml. Treatments with the compounds of the invention were carried out by adding such compounds vehicled in DMSO (0.1% final concentration) to the final desired concentrations 15 minutes before LPS exposure. As an index of nitric oxide production, the concentration of nitrite was measured in the conditioned media by using the Griess colorimetric reaction (J. Neuroimmunol.,150, 29-36, 2004).

Statistical analysis and determinations of IC50s were performed by using Prism-version 3.0 Graphpad Software (San Diego, CA). The IC50 values tested on some representative compounds of the invention were comprised between 12.2 and 151 nM.

Example 9

Interleukin-8 (IL-8) release assay protocol

In order to evaluate the anti-inflammatory effects of novel inhaled corticosteroids, we assessed a selection of these compounds in inhibiting TNFα-induced IL-8 release from human airway smooth muscle cells (ASMCs).

hASMCs exposed to a variety of inflammatory mediators (Tumor Necrosis Factor (TNF)-α or IL-1β) can undergo phenotypic changes and secrete chemokines and cytokines, which may participate in or even perpetuate mucosal inflammatory changes via activation and recruitment of inflammatory cells (Damera et al., 2009; Howarth et al., 2004; Chung, 2000; Koyama et al., 2000).

Current evidence suggests that chemokines and cytokines secretion induced by inflammatory mediators is inhibited by glucocorticoids in hASMCs and lung fibroblasts (John et al., 1998; Spoelstra et al., 2002; Tobler et al., 1992). Steroids may inhibit the cytokine-induced secretion of chemokines by a direct inhibitory interaction between activated glucocorticoid receptors and activated transcription factors, such as nuclear factor-kappa B and activator protein-1 which modulated inflammatory gene expression. In addition, glucocorticoids can regulate chemokine expression by reducing mRNA stability through the rapid induction of potent endogenous inhibitor of p38 MAP Kinase, MKP-1, which is one of the genes trans-activated by steroids (King et al., 2009).

Primary human airway smooth muscle cells (ASMCs) was purchased from LONZA (Basel, CH) and cultured in DMEM medium supplemented with 10% Fetal Bovine Serum, 2 mM glutamine, 100 U penicillin and 100 µg/ml streptomycin (Invitrogen), in an atmosphere of 95% air and 5% CO_2 at 37°C.

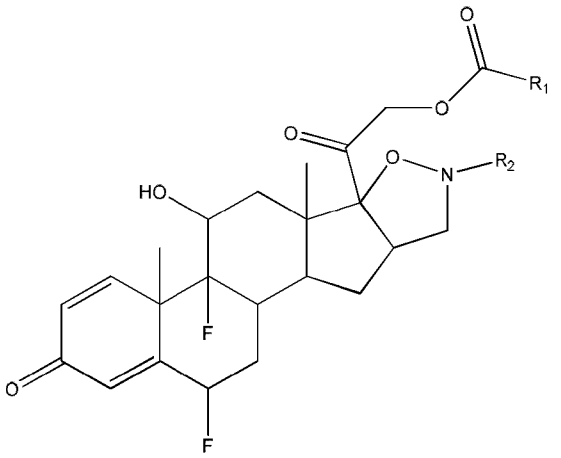
ASMCs was seeded in 0.5ml DMEM containing 10% FBS in 48-well tissue culture plates at the density of 104 cells/well and grown for 24 hours at 37°C with 5% CO_2. Then cells were serum starved for 18 hours before treatment with different concentration of LAGRA (10-12M-10-6M, final DMSO concentration 0.1%) for 60 min before stimulation with TNFα (0.1 ng/ml as final concentration for ASMCs). After 18hours

incubation in DMEM serum free, the IL8 release in the supernatant was assayed using ELISA kit (Invitrogen). Compound potencies were expresses as concentration able to inhibit the half maximal (50%) IL8 release [IC50] in the dose-response curve obtained after stimulation with TNFα.

All values stated are mean ± standard error of mean (SEM). Compound potencies (expresses as half maximal (50%) inhibitory concentration [IC50]) were derived from a four-parameter non-linear iterative curve-fitting analysis using Prism software (Graph Pad Software, San Diego, CA). Statistical analysis, Sigmoid curves design and analysis were performed by using Prism software (Graph Pad Software, San Diego, CA).

CLAIMS

1. A compound of general formula **(I)**



(I)

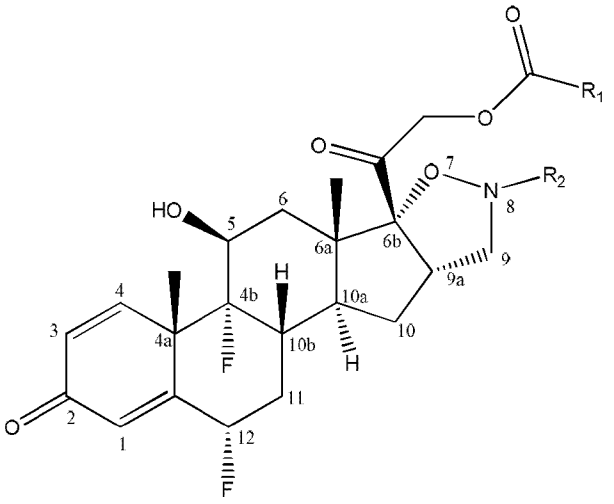
wherein

R_1 is selected from the group consisting of linear or branched (C_1-C_{16})alkyl, linear or branched (C_2-C_{18})alkenyl, -OR_6, aryl, aryl(C_1-C_{16})alkyl, -SR_6, -N(R_4)(R_5), (C_3-C_8)cycloalkyl, (C_3-C_8)heterocycloalkyl and heteroaryl, wherein optionally one or more hydrogen atoms are replaced by (C_1-C_6)alkyl, and wherein **R_4** and **R_5** are independently selected from H or linear or branched (C_1-C_6)alkyl and **R_6** is linear or branched (C_1-C_{16})alkyl;

R_2 is aryl optionally substituted by one or more halogen atoms; and

pharmaceutically acceptable salts thereof.

2. The compound according to claim 1 wherein stereogenic carbons have a stereochemistry as depicted in general formula (I')



(I')

3. The compound according to any one of claims 1 to 2, wherein $\mathbf{R_1}$ is selected from the group consisting of methyl, isopropyl, ethyl, quindecyl, butyl, hexyl, heptadecenyl, methoxy, methylsulfanyl, isobutyl, isopentyl, tert-butyl, methylamino, dimethylamino, phenyl, cyclopropyl, cyclopentyl, methylpropanoxy, benzyl, pyridyl, piperazinyl, piperidinyl, pyrrolidinyl, thiazolidinyl and furyl; and $\mathbf{R_2}$ is p-chlorophenyl; and pharmaceutically acceptable salts thereof.

4. The compound according to any one of claims 1 to 3 which is:

Isobutyric acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Propionic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Hexadecanoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Octadec-9-enoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Pentanoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Acetic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Benzoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Methyl carbonate or Methyl formate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester);

S-methyl carbonothioate or S-methyl methanethioate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

3-Methylbutanoic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Pivalic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

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2-Phenylacetic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Furan-2-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Cyclopentane-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Cyclopropane-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Isonicotinic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Isobutyl methyl carbonate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Hexyl carbonate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester);

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Dimethyl 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl carbamate;

Methyl 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl carbamate;

Piperazine-1-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Thiazolidine-4-carboxylic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Proline, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4^a,6^a-dimethyl-2-oxo-2,4a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12—tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

Piperidine-4-carboxylic acid, 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester;

or pharmaceutically acceptable salts thereof.

5. A pharmaceutical composition comprising the compound as defined in any one of claims 1 to 4, together with one or more pharmaceutically acceptable carriers and/or excipients.

6. A combination of the compound as defined in any one of claims 1 to 4 with one or more further active ingredients selected from the group consisting of: beta2-agonists, antimuscarinic agents, mitogen-activated protein kinase inhibitors, nuclear factor kappa-B

kinase subunit beta (IKK2) inhibitors, human neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), antitussive agents, mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, antibiotics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma, M3-antagonists/beta2-agonists (MABA) and M3-antagonists/PDE4-inhibitors (MAPI).

7. The compound as defined in any one of claims 1 to 4, for use as a medicament.

8. The compound as defined in any one of claims 1 to 4, for use in the prevention and/or treatment of a disease that involves a decrease in the number, activity and movement of inflammatory cells.

9. The compound as defined in any one of claims 1 to 4, or the pharmaceutical composition of claim 5, for use in the prevention and/or treatment of a respiratory disease.

10. The compound as defined in any one of claims 1 to 4, for use in the prevention and/or treatment of asthma or COPD.

11. Use of the compound as defined in any one of claims 1 to 4, as a medicament.

12. Use of the compound as defined in any one of claims 1 to 4, in the prevention and/or treatment of a disease that involves a decrease in the number, activity and movement of inflammatory cells.

13. Use of the compound as defined in any one of claims 1 to 4, or the pharmaceutical composition of claim 5, in the prevention and/or treatment of a respiratory disease.

14. Use of the compound as defined in any one of claims 1 to 4, in the prevention and/or treatment of asthma or COPD.

15. Use of a device comprising the pharmaceutical composition according to claim 5, wherein the device is a single- or multi-dose dry powder inhaler, a metered dose inhaler or a soft mist nebulizer.

16. Use of the compound as defined in any one of claims 1 to 4, in the manufacture of a medicament.

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17. Use of the compound as defined in any one of claims 1 to 4, for the manufacture of a medicament for the prevention and/or treatment of a disease that involves a decrease in the number, activity and movement of inflammatory cells.

18. Use of the compound as defined in any one of claims 1 to 4, for the manufacture of a medicament for the prevention and/or treatment a respiratory disease.

19. Use of the compound as defined in any one of claims 1 to 4, for the manufacture of a medicament for the prevention and/or treatment of asthma or COPD.

20. Use of the pharmaceutical composition according to claim 5, in the manufacture of a medicament for use in a single- or multi-dose dry powder inhaler, a metered dose inhaler or a soft mist nebulizer.

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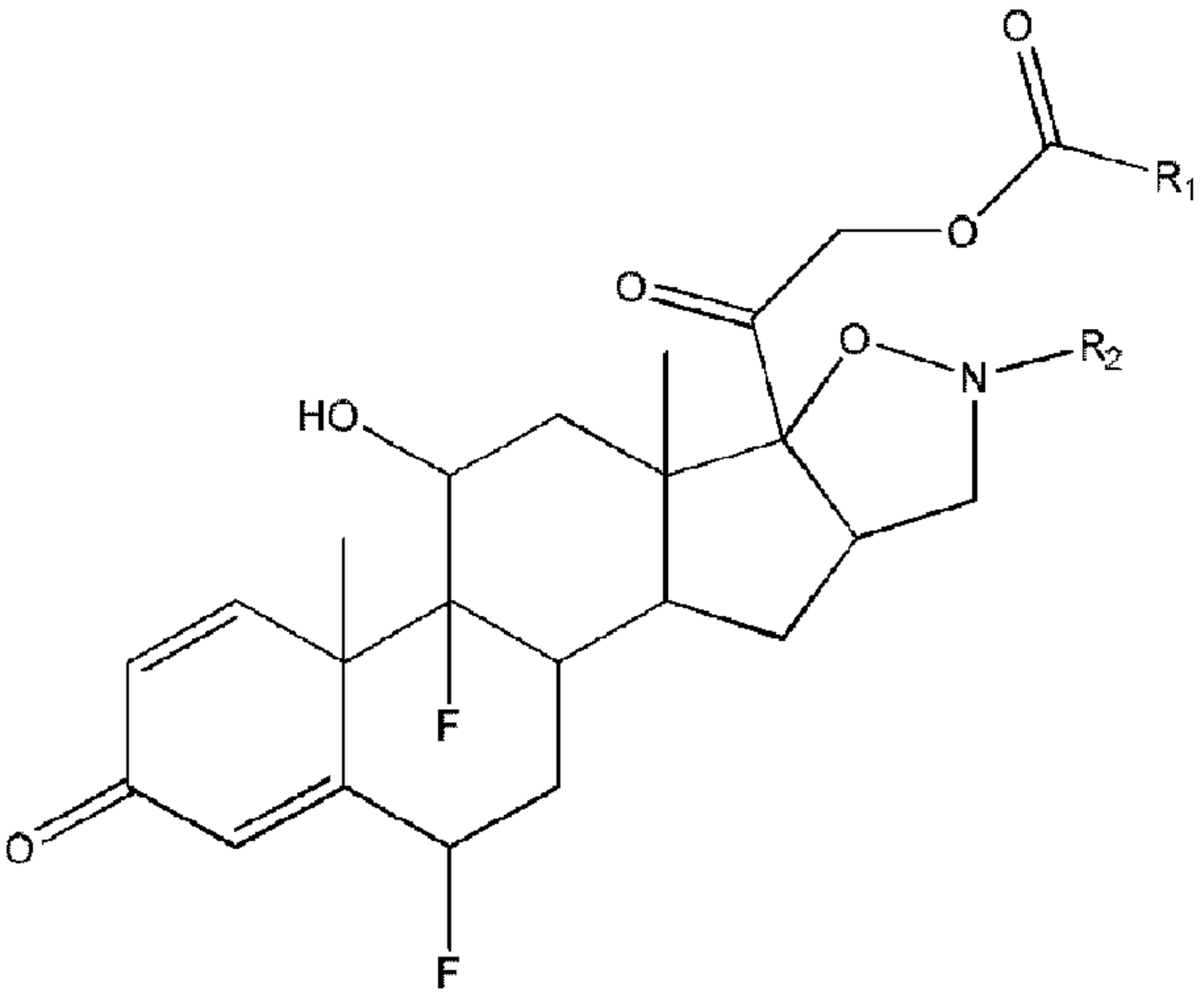

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