(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 March 2014 (20.03.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/040837 A1

(51) International Patent Classification:
C07J 71/00 (2006.01) *A61P 11/00* (2006.01)
A61K 31/58 (2006.01)

(21) International Application Number:
PCT/EP2013/067509

(22) International Filing Date:
23 August 2013 (23.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12184286.8 13 September 2012 (13.09.2012) EP

(71) Applicant: **CHIESI FARMACEUTICI S.P.A.** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).

(72) Inventor: **GHIDINI, Eleonora**; c/o Chiesi Farmaceutici S.p.A., Via Palermo, 26/A, I-43100 Parma (IT).

(74) Agent: **MINOJA, Fabrizio**; Bianchetti Bracco Minoja S.r.L., Via Plinio, 63, I-20129 Milano (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2014/040837 A1

(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.

ISOXAZOLIDINE 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.

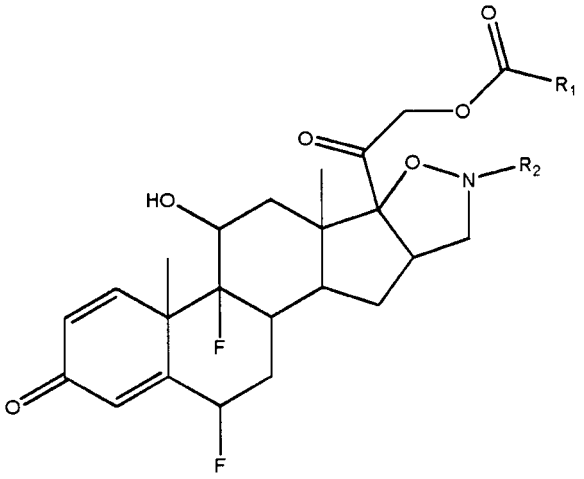
SUMMARY OF THE INVENTION

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.

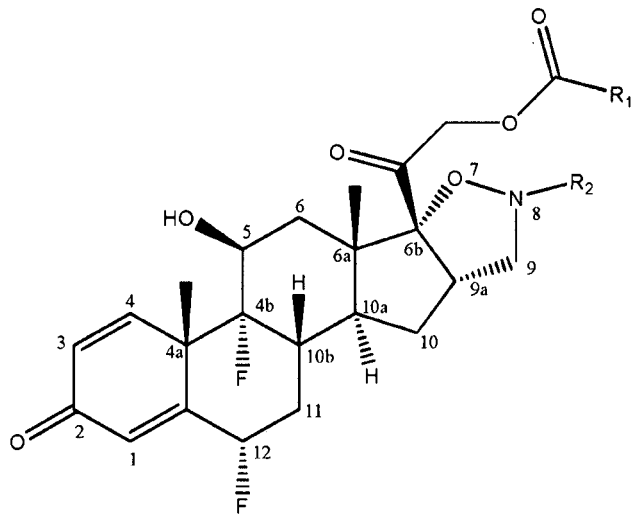
Examples of suitable heteroaryl bicyclic systems include purine, pteridine,

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.

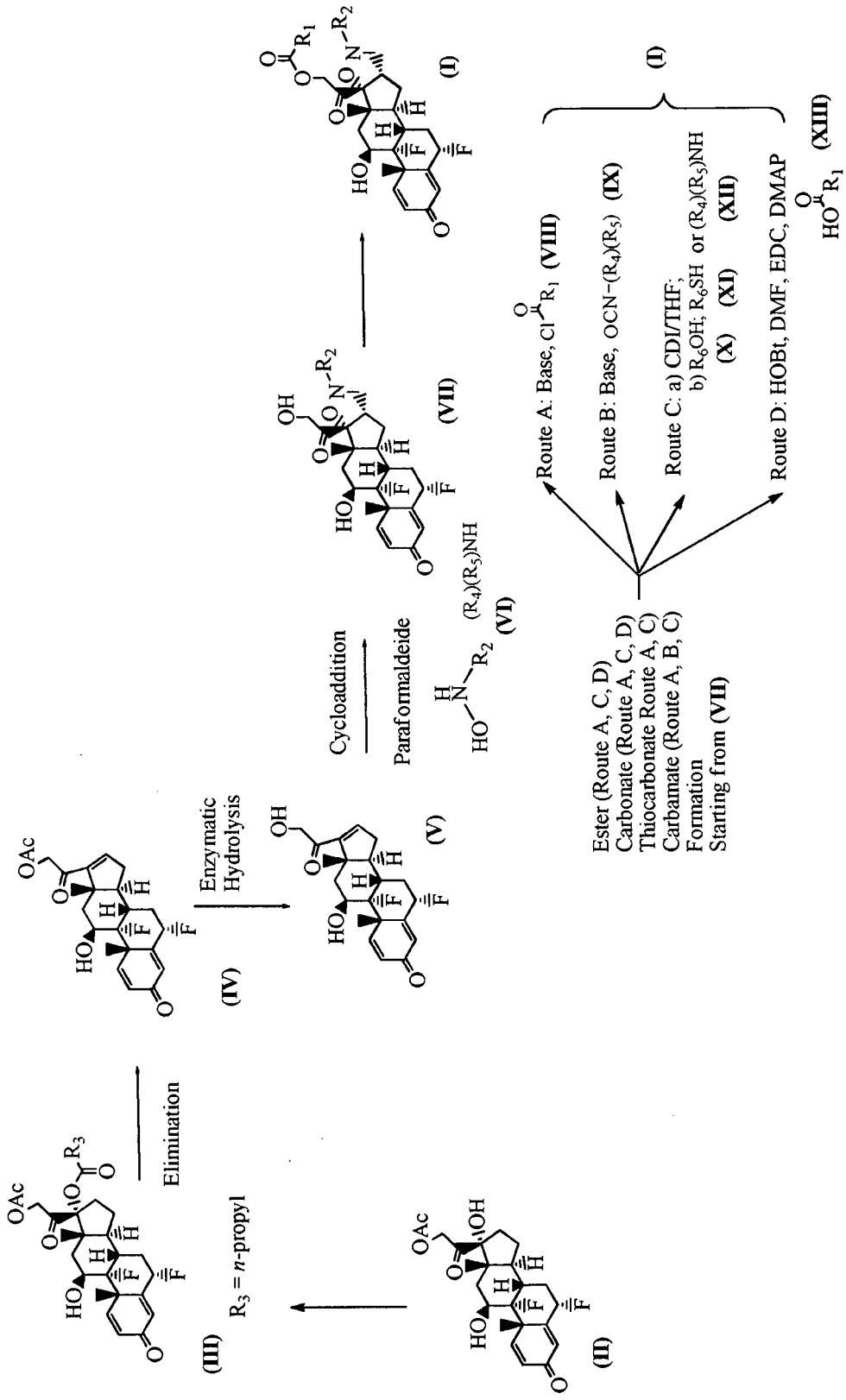
The compounds of the invention may be prepared according to a variety of synthetic steps which are carried out according to conventional methods and techniques or which are hereinbelow described.

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


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

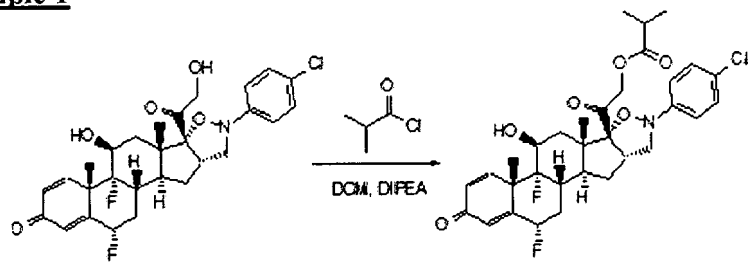
Examples of such diseases include: diseases involving inflammation such as asthma and other allergic disorders, COPD, acute rhinitis; reverse acute transplant rejection and acute exacerbations of selected autoimmune disorders, graft-versus-host disease in bone-marrow transplantation; autoimmune disorders 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),

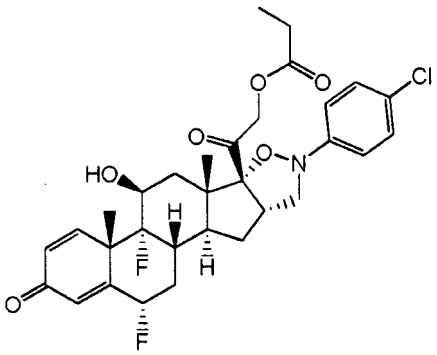
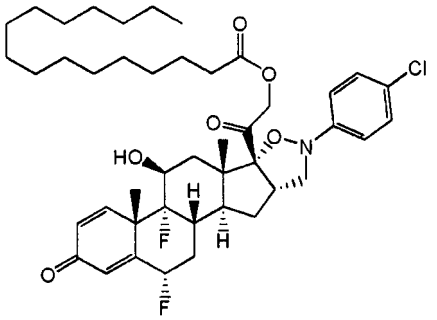
1.52 - 1.63 (m, 2 H), 1.50 (s, 3 H), 1.14 (d, 3 H), 1.13 (d, 3 H), 0.94 (s, 3 H)

LC-MS (ESI POS): 604.10 MH+

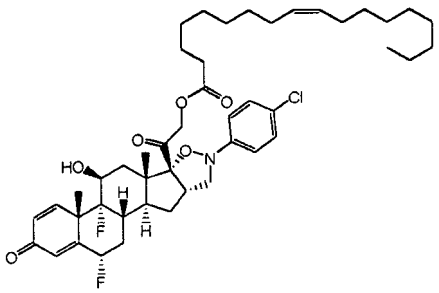
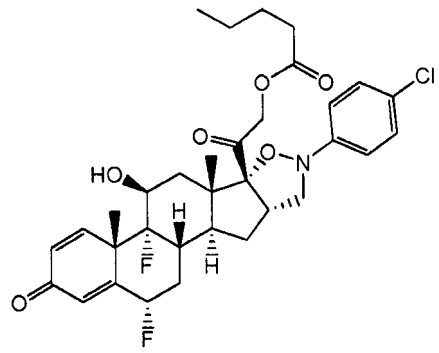
$[\alpha]_D^{25}$ = + 58.3 (c 0.2; MeOH)

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

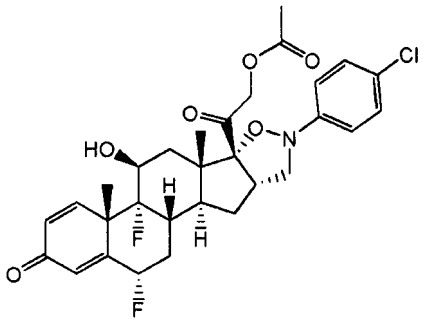
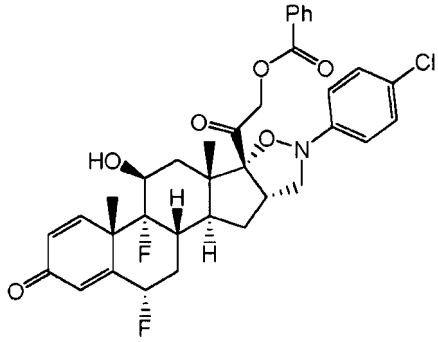
Table 1

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)

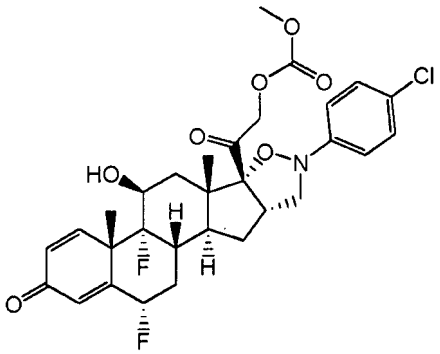
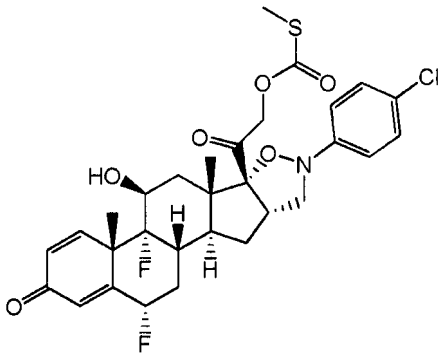
(continue)

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)

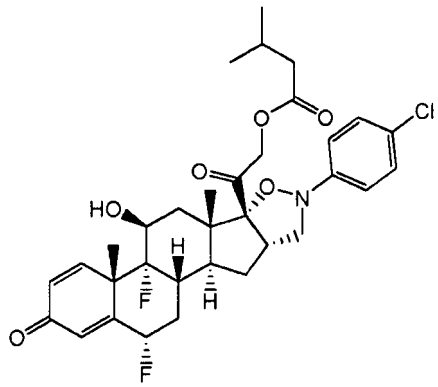
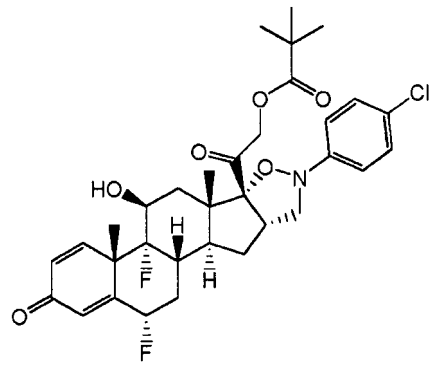
(continue)

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)

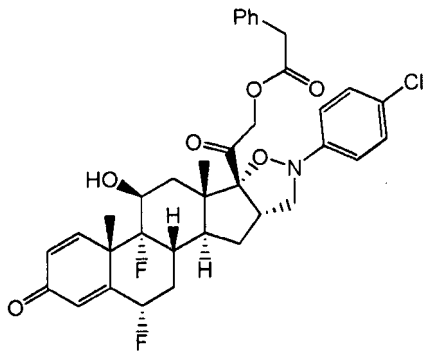
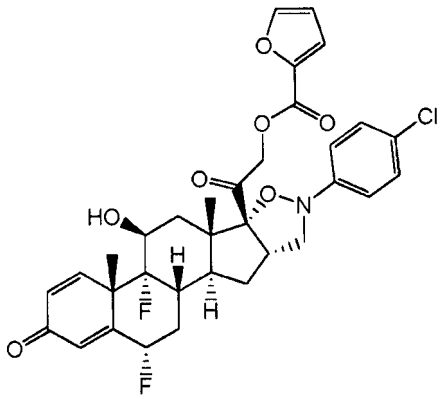
(continue)

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)

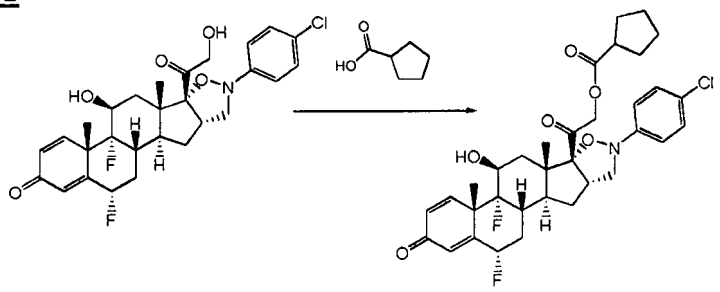
(continue)

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)

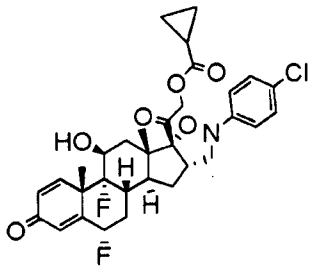
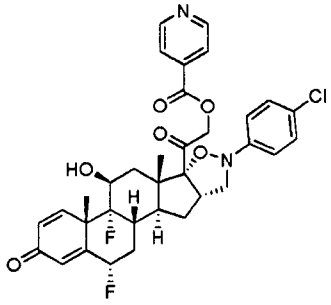
Cyclopentanecarboxylic acid (137 mg, 1.2 mmol, 1.2 eq) was dissolved in DMF (5 ml), 1-hydroxybenzotriazole hydrate (162 mg, 1.2 mmol, 1.2 eq) was added and the reaction mixture was stirred 20 minutes. Intermediate 2 (534 mg, 1 mmol), 4-(dimethylamino)pyridine (305 mg, 2.5 mmol, 2.5 eq) and EDC*HCl (230 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).

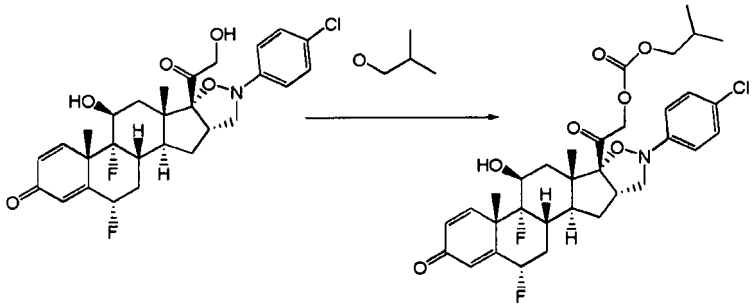
The compounds listed in Table 2 were prepared as previously described for compound 15 starting from the corresponding carboxylic acid:

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).

5

Example 3



Intermediate 2 Compound 18

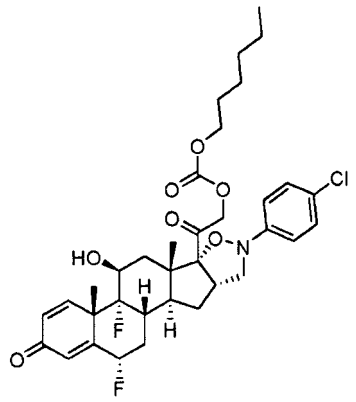
Preparation of Isobutyl methyl carbonate 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-6b-yl]-2-oxo-ethyl ester (compound 18)

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%).

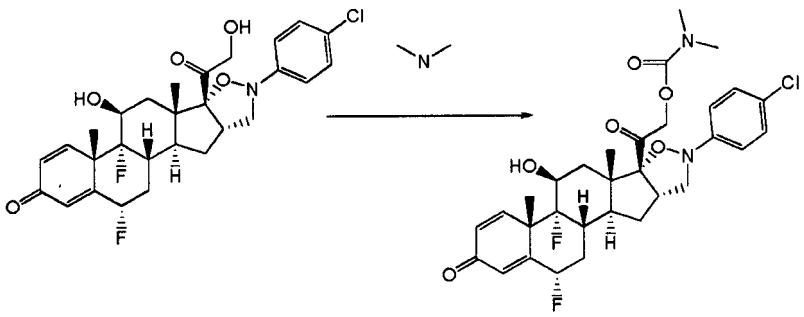
LC-MS (ESI POS): 634.2 LC-MS

^{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)

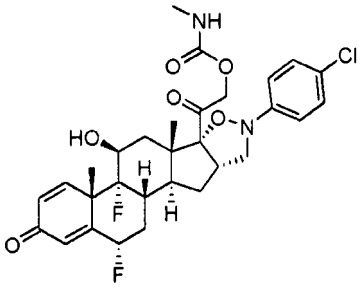
Intermediate 2 (310 mg, 0.58 mmol) in CH_2Cl_2 (3 ml) was added at RT with CDI (111 mg, 0.70 mmol, 1.2 eq) at portions. The reaction mixture was stirred 1 hour:

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 %)

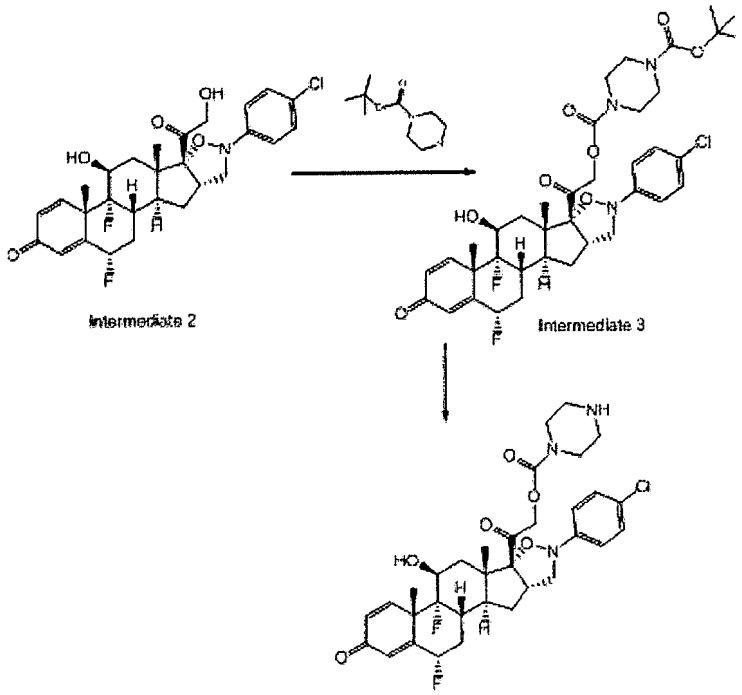
LC-MS (ESI POS): 605.2 LC-MS

^{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)

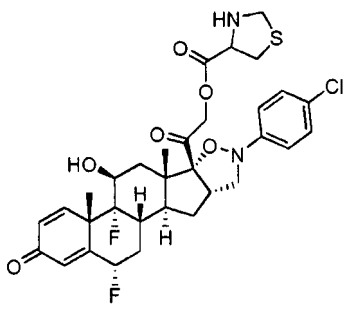
Intermediate 2 (500 mg, 0.94 mmol) in THF (3.5 ml) was added at RT with CDI (180 mg, 1.12 mmol, 1.2 eq) at portions. The reaction mixture was stirred 1 hour: complete conversion to activated intermediate was detected by TLC analysis (Hexane:EtOAc 3/7). The reaction mixture was cooled to 10°C and then 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)

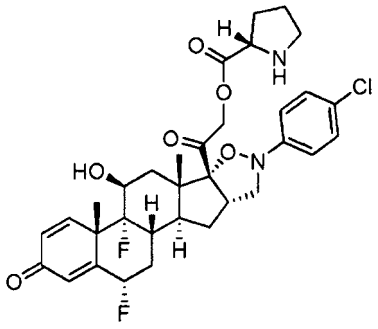
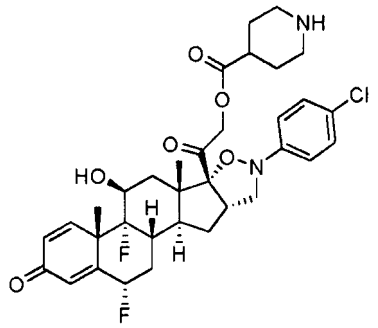
LC-MS (ESI POS): 646.4 MH+

^{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.

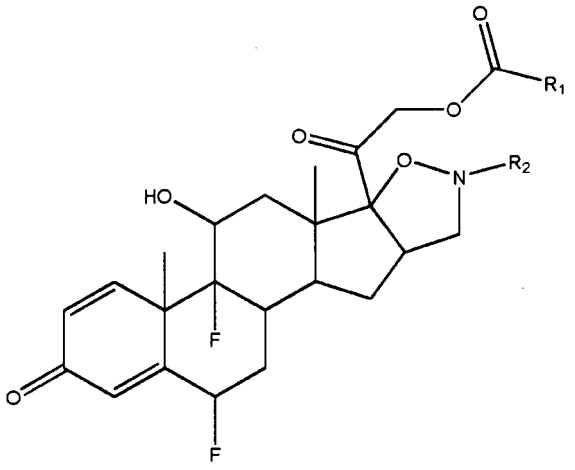
ASMCs was seeded in 0.5ml DMEM containing 10% FBS in 48-well tissue culture plates at the density of 104 cells/well and grown for 24 hours at 37°C with 5% CO_2. Then cells were serum starved for 18 hours before treatment with different concentration of LAGRA (10-12M-10-6M, final DMSO concentration 0.1%)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

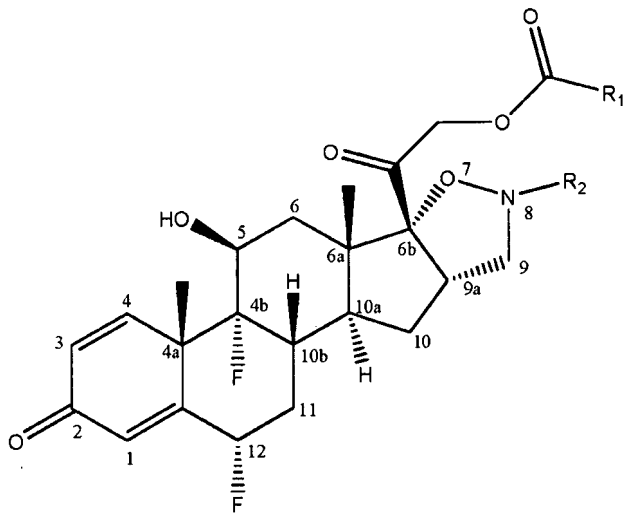
wherein

$\mathbf{R_1}$ 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.

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



(I')

3. A compound according to anyone 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. A compound according to anyone 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-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;

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 (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;

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);

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 a compound as defined in anyone of the claims 1 to 4, together with one or more pharmaceutically acceptable carriers and/or excipients.

6. A combination of a compound as defined in anyone of the claims 1 to 4 with one or more active ingredients selected from the classes of 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).

7. A compound as defined in anyone of claims 1 to 4, for use as a medicament.

8. A compound as defined in anyone of claims 1 to 4, for use in the prevention and/or treatment of any disease wherein the decrease in the number, activity and movement of inflammatory cells is involved.

9. A compound as defined in anyone of claims 1 to 5, for use in the prevention and/or treatment a respiratory disease.

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

11. A device comprising the pharmaceutical composition according to claim 5, which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler or soft mist nebulizer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/067509

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J71/00 A61K31/58 A61P11/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07J A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/029547 A2 (CHIESI FARMA SPA [IT]; ARMANI ELISABETTA [IT]; GHIDINI ELEONORA [IT];) 17 March 2011 (2011-03-17) cited in the application the whole document pages 10-13	1-11
X,P	WO 2012/123482 A2 (CHIESI FARMA SPA [IT]; GHIDINI ELEONORA [IT]; RIZZI ANDREA [IT]) 20 September 2012 (2012-09-20) cited in the application compound 187 the whole document	1,2,5-11
X,P	WO 2013/017374 A1 (CHIESI FARMA SPA [IT]; GHIDINI ELEONORA [IT]; CAPELLI ANNA MARIA [IT]) 7 February 2013 (2013-02-07) compounds 22, 25 the whole document	1-11

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2013	28/11/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tabanella, Stefania

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/067509

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011029547 A2	17-03-2011	AR 078164 A1	19-10-2011
		AU 2010294598 A1	05-04-2012
		CA 2773594 A1	17-03-2011
		CN 102482318 A	30-05-2012
		CO 6511204 A2	31-08-2012
		EA 201290091 A1	28-12-2012
		EP 2475676 A2	18-07-2012
		JP 2013504524 A	07-02-2013
		KR 20120055651 A	31-05-2012
		MA 33561 B1	01-09-2012
		PE 08942012 A1	13-08-2012
		SG 179055 A1	27-04-2012
		TW 201114776 A	01-05-2011
		US 2011065678 A1	17-03-2011
		WO 2011029547 A2	17-03-2011
WO 2012123482 A2	20-09-2012	AR 085817 A1	30-10-2013
		AU 2012228334 A1	03-10-2013
		CN 103391945 A	13-11-2013
		US 2012234316 A1	20-09-2012
		WO 2012123482 A2	20-09-2012
WO 2013017374 A1	07-02-2013	US 2013035320 A1	07-02-2013
		WO 2013017374 A1	07-02-2013

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104619714 A
(43)申请公布日 2015.05.13

(21)申请号 201380047423.2
(22)申请日 2013.08.23
(30)优先权数据
12184286.8 2012.09.13 EP
(85)PCT国际申请进入国家阶段日
2015.03.12
(86)PCT国际申请的申请数据
PCT/EP2013/067509 2013.08.23
(87)PCT国际申请的公布数据
WO2014/040837 EN 2014.03.20
(71)申请人 奇斯药制品公司
地址 意大利帕尔马
(72)发明人 E·吉蒂尼
(74)专利代理机构 中国国际贸易促进委员会专利商标事务所 11038
代理人 焦丽雅
(51)Int.Cl.
C07J 71/00(2006.01)
A61K 31/58(2006.01)
A61P 11/00(2006.01)

权利要求书4页 说明书41页

(54)发明名称

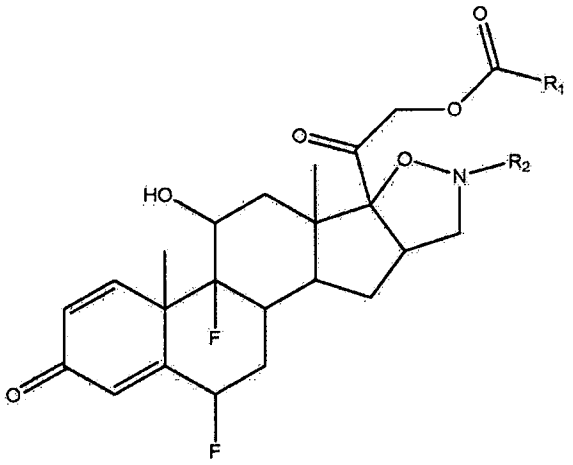
异噁唑烷衍生物

(57)摘要

本发明涉及新的糖皮质激素系列的抗炎和抗过敏化合物、这样的化合物的制备方法、包含它们的药物组合物、其组合和治疗用途。更具体地，本发明涉及为异噁唑烷衍生物的糖皮质激素。

CN 104619714 A

1. 式 (I) 的化合物及其药学上可接受的盐：



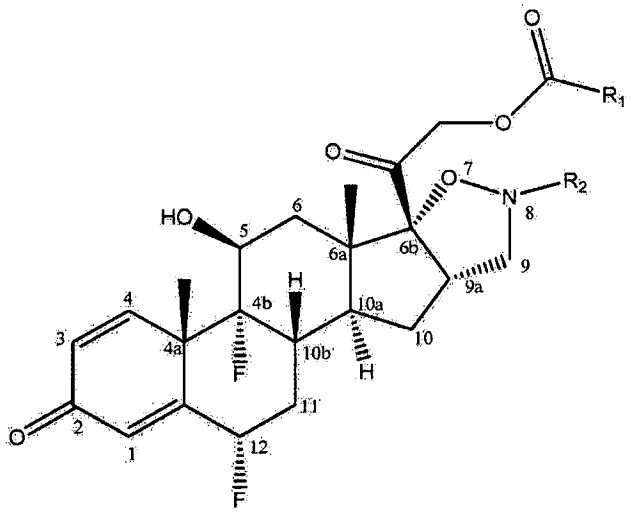
(I)

其中

R_1选自直链或支链 (C_1-C_{16}) 烷基、直链或支链 (C_2-C_{18}) 烯基、-OR_6、芳基、芳基 (C_1-C_{16}) 烷基、-SR_6、-N(R_4)(R_5)、(C_3-C_8) 环烷基、(C_3-C_8) 杂环烷基和杂芳基，其中一个或多个氢原子任选地被 (C_1-C_6) 烷基替代，且其中 R_4和 R_5独立地选自 H 或直链或支链 (C_1-C_6) 烷基，且 R_6是直链或支链 (C_1-C_{16}) 烷基；

R_2是任选地被一个或多个卤原子取代的芳基。

2. 权利要求 1 的化合物，其中立体碳具有式 (I') 中所示的立体化学：



(I')

3. 权利要求 1 — 2 任一项的化合物及其药学上可接受的盐，其中 R_1选自甲基、异丙基、乙基、十五烷基、丁基、己基、十七碳烯基、甲氧基、甲基硫烷基、异丁基、异戊基、叔丁基、甲基氨基、二甲基氨基、苯基、环丙基、环戊基、甲基丙氧基、苄基、吡啶基、哌嗪基、哌啶基、吡咯烷基、噻唑烷基和呋喃基；且 R_2是对 - 氯苯基。

4. 权利要求 1 — 3 任一项的化合物，其为：

异丁酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4- 氯 - 苯基)-4b,12- 二

氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

丙 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯 基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

十 六 烷 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

十 八 碳 -9- 烯 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

戊 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯 基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

乙 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯 基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

苯甲酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

甲基碳酸酯 (甲酸甲酯)2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯) ;

S- 甲基硫代碳酸酯 (或 S- 甲基甲硫代酸酯)2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

3- 甲 基 丁 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

新戊酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

2- 苯 乙 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并 [2, 1-a] 菲 -6b- 基]-2- 氧代 - 乙酯 ;

呋 喃 -2- 甲 酸 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4- 氯 - 苯基)-4b, 12- 二氟 -5- 羟基 -4a, 6a- 二甲基 -2- 氧代 -2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b

,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

环戊烷-甲酸2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

环丙烷-甲酸2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

异烟酸2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

异丁基甲基碳酸酯2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

己基碳酸酯2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯）；

2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙基氨基甲酸二甲酯；

2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙基氨酸甲酸甲酯；

哌嗪-1-甲酸2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

噻唑烷-4-甲酸2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

脯氨酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4^a,6^a-二甲基-2-氧代-2,4a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12—十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

哌啶-4-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯；

或其药学上可接受的盐。

5.药物组合物，包含如权利要求1—4任一项中所定义的化合物与一种或多种药学上可接受的载体和/或赋形剂。

6.如权利要求1—4任一项中所定义的化合物与一种或多种活性成分的组合，所述一种或多种活性成分选自如下种类：β2-激动剂、抗毒蕈碱药、促分裂原活化蛋白激酶

(P38MAP 激酶) 抑制剂、核因子 κ -B 激酶亚单位 β (IKK2) 抑制剂、人嗜中性细胞弹性蛋白酶 (HNE) 抑制剂、磷酸二酯酶 4(PDE4) 抑制剂、白三烯调节剂、非类固醇抗炎药 (NSAIDs)、镇咳药、粘液调节剂、粘液溶解药、祛痰药 / 粘液动力学调节剂、肽粘液溶解药、抗生素、JAK 抑制剂、SYK 抑制剂、PI3K δ 或 PI3K γ 抑制剂、M3- 拮抗剂 / β 2- 激动剂 (MABA) 和 M3- 拮抗剂 /PDE4- 抑制剂 (MAPI)。

7. 如权利要求 1 — 4 任一项中所定义的化合物,用作药剂。

8. 如权利要求 1 — 4 任一项中所定义的化合物,用于预防和 / 或治疗其中涉及炎症细胞数量、活性和运动减少的任意疾病。

9. 如权利要求 1 — 5 任一项中所定义的化合物,用于预防和 / 或治疗呼吸系统疾病。

10. 如权利要求 1 — 4 任一项中所定义的化合物,用于预防和 / 或治疗哮喘和 COPD。

11. 装置,包含权利要求 5 的药物组合物,该装置可以是单剂量或多剂量干粉吸入器、定量定压式气雾器或柔和雾喷雾器。

异噁唑烷衍生物

发明领域

[0001] 本发明涉及糖皮质激素系列新的抗炎和抗过敏化合物、这样的化合物的制备方法、包含它们的药物组合物、其组合和治疗用途。更具体地，本发明涉及为异噁唑烷衍生物的糖皮质激素。

[0002] 发明背景

[0003] 皮质类固醇是有效的抗炎药，其能够减少炎症细胞的数量、活性和运动。

[0004] 它们常用于治疗广泛的慢性和急性炎性病症，包括哮喘、慢性阻塞性肺疾病(COPD)、过敏性鼻炎、类风湿性关节炎、炎性肠病和自身免疫疾病。

[0005] 皮质类固醇通过糖皮质激素受体(GR)介导其作用。皮质类固醇结合GR诱导其核易位，由此通过DNA-结合-依赖性（例如反式激活）和-不依赖性（例如反式表达(transespression)）机制影响许多下游途径。

[0006] 用于治疗肺中慢性炎性病症例如哮喘和COPD的皮质类固醇目前通过吸入施用。使用吸入的皮质类固醇(ICS)的优点之一在于将药物直接递送至作用部位、限制全身副作用、由此导致更快速的临床响应和更高的治疗比率的可能性。

[0007] 尽管ICS治疗可以提供重要的有益性，尤其是在哮喘中，但是重要的是将ICS全身暴露减少至最低限度，ICS全身暴露可以导致不需要的副作用的发生和严重性，它们与长期施用相关。此外，目前临床实践中可得到的ICS的有限作用期限促成了对疾病的最适度以下的处置。尽管吸入器技术是靶向肺的关键点，但是调整皮质类固醇分子平台上的取代基对于优化药代动力学和药效学特性而言是重要的，以便降低口服生物利用度、将药理学活性限于肺中（前药和柔和药）并且增加全身清除率。此外，在肺中的长效ICS活性是高度期望的，因为每日1次施用ICS能够降低施用频率，且由此基本上改善了患者的依从性，且结果是处置和控制疾病。总之，对于研发具有改善的药代动力学和药效学特征的ICS存在迫切的医学需求。

[0008] 糖皮质激素异噁唑烷衍生物例如描述在WO 2006/005611、GB1578446和“Synthesis and topical anti-inflammatory activity of some steroidal[16α,17α-d]isoxazolidines”(J.Med.Chem.,25,1492-1495,1982).

[0009] 一些糖皮质激素异噁唑烷衍生物还描述在共同悬而未决的专利申请WO 2011/029547、WO 2012/123482和WO 2012/123493中。

[0010] 令人意外地，已经发现本发明的化合物显示改善的药代动力学和药效学特征，例如全身暴露、选择性和作用期限。

[0011] 发明概述

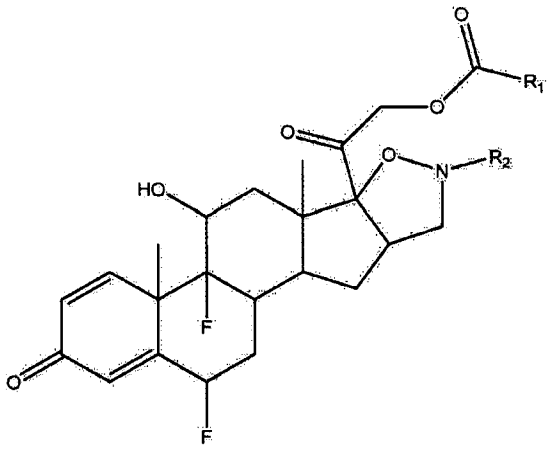
[0012] 本发明涉及糖皮质激素系列的抗炎和抗过敏化合物、其制备方法、包含它们的组合物、治疗用途和与其它用于治疗呼吸系统疾病的药物活性成分的组合，在所述其它用于治疗呼吸系统疾病的药物活性成分中有β2-激动剂、抗毒蕈碱药、丝裂原激活蛋白激酶类(P38MAP激酶）抑制剂、核因子κ-B激酶亚单位β(IKK2)抑制剂、人嗜中性细胞弹性蛋白酶(HNE)抑制剂、磷酸二酯酶4(PDE4)抑制剂、白三烯调节剂、非类固醇抗炎药(NSAIDs)、镇

咳药、粘液调节剂、粘液溶解药、祛痰药 / 粘液动力学调节剂 (mucokinetic modulators)、肽粘液溶解药、抗生素、JAK 抑制剂、SYK 抑制剂、PI3K δ 或 PI3K γ 抑制剂、M3- 拮抗剂 / β 2- 激动剂 (MABA) 和 M3- 拮抗剂 /PDE4- 抑制剂 (MAPI)。

[0013] 发明详述

[0014] 特别地，本发明涉及式 (I) 的化合物及其药学上可接受的盐：

[0015]



(I)

[0016] 其中

[0017] R_1选自直链或支链 (C_1-C_{16}) 烷基、直链或支链 (C_2-C_{18}) 烯基、-OR_6、芳基、芳基 (C_1-C_{16}) 烷基、-SR_6、-N(R_4)(R_5)、(C_3-C_8) 环烷基、(C_3-C_8) 杂环烷基和杂芳基，其中一个或多个氢原子任选地被 (C_1-C_6) 烷基替代，且其中 R_4和 R_5独立地选自 H 或直链或支链 (C_1-C_6) 烷基，且 R_6是直链或支链 (C_1-C_{16}) 烷基；

[0018] R_2是任选地被一个或多个卤原子取代的芳基。

[0019] 在本说明书中，除非另有提供，否则术语“卤素”包括氟、氯、溴和碘原子。

[0020] 术语“(C_1-C_{16}) 烷基”是指直链或支链烷基，其中碳原子数为 1 — 16。所述基团的实例是甲基、乙基、正 - 丙基、异丙基、正 - 丁基、异丁基、仲 - 丁基、叔 - 丁基、戊基、己基、庚基、辛基、乙基 - 丁基、丙基 - 丁基、甲基 - 丁基、乙基 - 甲基 - 丙基、十六烷基、十一基、十二烷基、十三烷基、十四烷基 (quaterdecyl)、十五烷基 (quindecyl)、十六烷基等。

[0021] 表述“(C_2-C_{18}) 烯基”是指具有一个或多个双键的直链或支链碳链，其中碳原子数为 2 — 18，所述基团的实例包括乙烯基、丙烯基、丁烯基、戊烯基、己烯基、庚烯基、辛烯基、壬烯基、癸烯基、十一碳烯基、十二碳烯基、十三碳烯基、十四碳烯基、十五碳烯基、十六碳烯基、十七碳烯基等。

[0022] 表述“(C_3-C_8) 环烷基”是指具有 3 — 8 个碳原子的单 - 或双 - 脂环族烃基。实例包括环丙基、环丁基、环戊基、环己基、环庚基、双环 [2.2.1] 庚 -2- 基等。

[0023] 表述“(C_3-C_8) 杂环烷基”是指 (C_3-C_8) 环烷基，其中至少一个环碳原子被杂原子或杂芳族基团 (例如 N、NH、S 或 O) 替代。实例包括哌嗪基、噻唑烷基、吡咯烷基、哌啶基、吗啉基等。

[0024] 表述“芳基”是指具有 6 — 20 个环原子、优选 6 — 15 个环原子的单环或双环或三环环系，且其中至少一个环是芳族的。

[0025] 适合的芳基单环系统的实例包括苯基等。

[0026] 适合的芳基双环系统的实例包括萘、亚联苯基等。

[0027] 适合的芳基三环系统的实例包括芴基等。

[0028] 表述“芳基 (C_1-C_6) 烷基”是指进一步被芳基取代的 (C_1-C_6) 烷基。

[0029] 本文所用的术语“杂芳基”是指具有 5 — 20 个环原子、优选 5 — 15 个环原子的单环、双环或三环环系，其中至少一个环是芳族的且其中至少一个环原子是杂原子或杂芳族基团（例如 N、NH、S 或 O）。

[0030] 适合的杂芳基单环系统的实例包括噻吩、吡咯、吡唑、咪唑、异噁唑、噁唑、异噻唑、噻唑、吡啶、咪唑烷、哌啶、哌嗪和呋喃基团，例如四氢呋喃等。

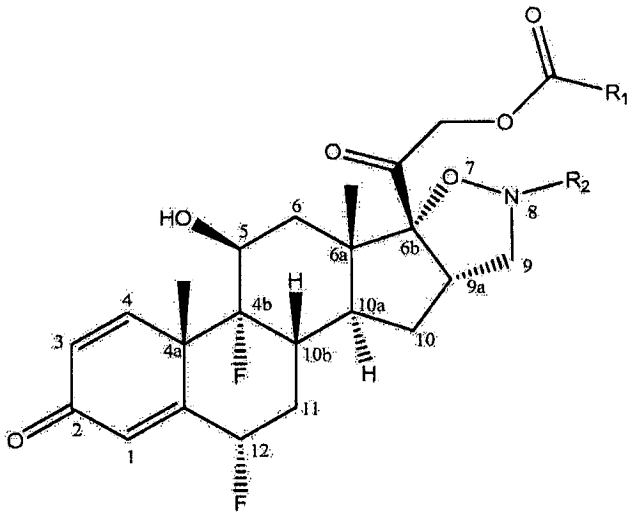
[0031] 适合的杂芳基双环系统的实例包括嘌呤、蝶啶、苯并三唑、喹啉、异喹啉、吲哚、异吲哚、苯并呋喃、苯并二噁烷、苯并噻吩基团等。

[0032] 本领域技术人员显而易见，式 (I) 的化合物至少在 4a、4b、5、6a、6b、9a、10a、10b 位置上包含不对称中心且由此可以作为许多光学立体异构体及其混合物存在。

[0033] 因此，本发明还涉及所有这些形式及其混合物。

[0034] 优选的化合物是式 (I) 这样的化合物，其中立体碳原子的立体化学报道在如下的式 (I') 中，绝对构型以基于组优先级的 Cahn-Ingold-Prelog 命名法为基础指定。

[0035]



(I')

[0036] 且其中 R_1 和 R_2 如上述所定义。

[0037] 在一个优选的实施方案中，对于式 (I') 的化合物，不对称中心 4a 上的绝对构型是 (S)，在 4b 上的是 (R)，在 5 上的是 (S)，在 6a 上的是 (S)，在 6b 上的是 (R)，在 9a 上的是 (S)，在 10a 上的是 (S)，在 10b 上的是 (S)，且在 12 上的是 (S)。

[0038] 式 (I) 的化合物可以特别地与药学上可接受的酸形成酸加成的盐。

[0039] 式 (I) 的化合物的药学上可接受的酸形成酸加成的盐、由此也包括式 (I') 的那些包括与无机酸和有机酸形成的盐，所述无机酸例如氢卤酸，例如氢氟酸、盐酸、氢溴酸或氢碘酸；硝酸、硫酸、磷酸；和有机酸，例如脂族一元羧酸，例如甲酸、乙酸、三氟乙酸和丙酸；脂族羟基酸，例如乳酸、柠檬酸、酒石酸或苹果酸；二羧酸，例如马来酸、富马酸、草酸或琥珀

酸；芳族羧酸，例如苯甲酸；芳族羟基酸和磺酸。

[0040] 可以通过已知的成盐方法由式（I）或（I'）的化合物制备这些盐。

[0041] 应理解，下述对式（I）化合物描述的所有优选的基团或实施方案可以彼此合并并且也可以根据实际情况做必要的修正应用。

[0042] 式（I）或（I'）的优选组的化合物为这样的化合物，其中 R_1 选自直链或支链（C_1-C_{16}）烷基、直链或支链（C_2-C_{18}）烯基、-OR_6、芳基、芳基（C_1-C_{16}）烷基、-SR_6、-$N(R_4)(R_5)$、（C_3-C_8）环烷基、（C_3-C_8）杂环烷基和杂芳基，其中一个或多个氢原子任选地被（C_1-C_6）烷基替代，且其中 R_4 和 R_5 独立地选自 H 或直链或支链（C_1-C_6）烷基，且 R_6 是直链或支链（C_1-C_{16}）烷基；且 R_2 是任选地被一个或多个卤原子取代的芳基。

[0043] 在该组中甚至更优选的是式（I）或（I'）的化合物，其中 R_1 选自甲基、异丙基、乙基、十五烷基、丁基、己基、十七碳烯基、甲氧基、甲基硫烷基、异丁基、异戊基、叔丁基、甲基氨基、二甲基氨基、苯基、环丙基、环戊基、甲基丙氧基、苄基、吡啶基、哌嗪基、哌啶基、吡咯烷基、噻唑烷基和呋喃基；且 R_2 是对－氯苯基。

[0044] 下文式（I）和（I'）的化合物及其药学上可接受的盐和溶剂合物称作“本发明的化合物”。

[0045] 本发明优选化合物的实例是：

[0046]

化合物	化学名
1	异丁酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
3	丙酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
4	十六烷酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
5	十八碳-9-烯酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
6	戊酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代

[0047]

	-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
7	乙酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
8	苯甲酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
9	甲基碳酸酯(甲酸甲酯) 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯)
10	S-甲基硫代碳酸酯(carbonothioate)(或 S-甲基甲硫代酸酯) 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
11	3-甲基丁酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
12	新戊酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯

[0048] （接续）

[0049]

13	2-苯乙酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
14	呋喃-2-甲酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
15	环戊烷-甲酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
16	环丙烷-甲酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
17	异烟酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
18	异丁基甲基碳酸酯 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
19	己基碳酸酯 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯)

[0050]

20	2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4- 氯 - 苯基)-4b,12- 二 氟 -5- 羟 基 -4a,6a- 二 甲 基 -2- 氧 代 -2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并[2,1-a]菲 -6b- 基]-2- 氧代 - 乙基氨基甲酸二甲酯
21	2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4- 氯 - 苯基)-4b,12- 二 氟 -5- 羟 基 -4a,6a- 二 甲 基 -2- 氧 代 -2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并[2,1-a]菲 -6b- 基]-2- 氧代 - 乙基氨基甲酸甲酯
22	哌嗪 -1- 甲酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4- 氯 - 苯基)-4b,12- 二 氟 -5- 羟 基 -4a,6a- 二 甲 基 -2- 氧 代 -2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并[2,1-a]菲 -6b- 基]-2- 氧代 - 乙酯
23	噻 唑 烷 -4- 甲 酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4- 氯 - 苯基)-4b,12- 二 氟 -5- 羟 基 -4a,6a- 二 甲 基 -2- 氧 代 -2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并[2,1-a]菲 -6b- 基]-2- 氧代 - 乙酯
24	脯氨酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4- 氯 - 苯基)-4b,12- 二 氟 -5- 羟 基 -4^a,6^a- 二 甲 基 -2- 氧 代 -2,4a,4b,5,6,6^a,8,9,9^a,10,10^a,10b,11,12— 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并[2,1-a]菲 -6b- 基]-2- 氧代 - 乙酯
25	哌啶 -4- 甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4- 氯 - 苯基)-4b,12- 二 氟 -5- 羟 基 -4a,6a- 二 甲 基 -2- 氧 代 -2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12- 十四氢 -7- 氧杂 -8- 氮杂 - 并戊二环烯并[2,1-a]菲 -6b- 基]-2- 氧代 - 乙酯

[0051] 根据本文所述的类似操作和方法，可以得到如下本发明的优选化合物：

[0052]

化合物	化学名
26	丁酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
27	丁酸,2-甲基-,2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
28	环丁烷甲酸,2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
29	环己烷甲酸,2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
30	2-噻吩甲酸,四氢-,2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
31	2H-噻喃-4-甲酸,四氢-,2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯

[0053] （接续）

[0054]

32	环戊烷甲酸，2,5-二甲基-，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
33	环己烷甲酸，2,6-二甲基-，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
34	3-吡啶甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
35	1H-吡咯-3-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
36	3-噻吩甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
37	3-呋喃甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-

[0055]

	并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
38	1H-吲哚-7-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
39	1H-茚-7-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
40	8-喹啉甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
41	喹啉-3-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
42	苯并[b]噻吩-3-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
43	1H-吲哚-3-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯

[0056]

44	苯并呋喃-3-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
45	苯并呋喃-2-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
46	2-噻吩甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
47	2-呋喃甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
48	1H-吡咯-2-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
49	四氢-2H-吡喃-4-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
50	4-甲基哌嗪-1-甲酸，

[0057]

	2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯
51	吗啉-4-甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯

[0058] （接续）

[0059]

52	2-吡啶甲酸，2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氟-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯

[0060] 本发明还提供了药物组合物，其包含本发明这样或作为药学上可接受的盐的化合物和一种或多种药学上可接受的载体和/或赋形剂。

[0061] 可以将本发明的化合物作为单独的活性剂或与其它药物活性成分的组合施用，所述其它药物活性成分包括常用于治疗呼吸系统疾病的那些，例如β2-激动剂、抗毒蕈碱药、丝裂原激活蛋白激酶类（P38MAP激酶）抑制剂、核因子κ-B激酶亚单位β（IKK2）抑制剂、人嗜中性细胞弹性蛋白酶（HNE）抑制剂、磷酸二酯酶4（PDE4）抑制剂、白三烯调节剂、非类固醇抗炎药（NSAIDs）、镇咳药、粘液调节剂、粘液溶解药、祛痰药/粘液动力学调节剂、肽粘液溶解药、抗生素、JAK抑制剂、SYK抑制剂、PI3Kδ或PI3Kγ抑制剂、M3-拮抗剂/β2-激动剂（MABA）和M3-拮抗剂/PDE4-抑制剂（MAPI）。

[0062] 本发明还提供了本发明这样或作为药学上可接受的盐的化合物与选自卡莫特罗、GSK-642444、茚达特罗、米维特罗、阿福特罗、酒石酸阿福特罗、福莫特罗、富马酸福莫特罗、沙美特罗、沙美特罗昔萘酸酯、舒喘灵、沙丁胺醇、左旋沙丁胺醇、特布他林、茚达特罗（QAB-149）、AZD-3199、BI-1744-CL、LAS-100977、GSK159797、GSK59790、GSK159802、GSK642444、GSK678007、GSK96108、班布特罗、异丙肾上腺素、丙卡特罗、克仑特罗、瑞普特罗、非诺特罗、比托特罗、brodxatelor和ASF-1020及其盐的β2-激动剂的组合。

[0063] 本发明还提供了本发明这样或作为药学上可接受的盐的化合物与选自aclidinium、噻托溴铵、噻托溴铵(Spiriva®)、异丙托铵、异丙托溴铵、曲司氯铵(trospium)、格隆溴铵、NVA237, LAS34273, GSK656398, GSK233705, GSK57319, LAS35201, QAT370和氧托品盐的抗毒蕈碱药的组合。

[0064] 本发明还提供了本发明这样或作为药学上可接受的盐的化合物与选自 AN-2728、AN-2898、CBS-3595、阿普斯特 (apremilast)、ELB-353、KF-66490、K-34、LAS-37779、IBFB-211913、AWD-12-281、西潘茶碱、西洛司特、罗氟司特、BAY19-8004 和 SCH-351591、AN-6415、indus-82010、TPI-PD3、ELB-353、CC-11050、GSK-256066、奥米司特、OX-914、替托司特、MEM-1414 和 RPL-554 的 PDE4 抑制剂的组合。

[0065] 本发明还提供了本发明这样或作为药学上可接受的盐的化合物与选自塞马莫德、他美莫德、吡非尼酮、PH-797804、GSK-725、GSK856553、GSK681323、minokine 和洛吡莫德及其盐的 P38MAP 激酶抑制剂的组合。

[0066] 在一个优选的实施方案中，本发明提供了本发明的化合物与 IKK2 抑制剂的组合。

[0067] 本发明还提供了本发明的化合物与选自 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、弹力素、SPHD-400、α 1- 蛋白酶抑制剂 C 和吸入的 α 1- 蛋白酶抑制剂的 HNE 抑制剂的组合。

[0068] 本发明还提供了本发明的化合物与选自孟鲁司特、扎鲁司特和普仑司特的白三烯调节剂的组合。

[0069] 本发明还提供了本发明的化合物与选自布洛芬和酮洛芬的 NSAID 的组合。

[0070] 本发明还提供了本发明的化合物与选自可待因和优选吗啡烷 (dextramorphan) 的镇咳药的组合。

[0071] 本发明还提供了本发明的化合物与选自 N 乙酰半胱氨酸和 fudostein 的粘液溶解药的组合。

[0072] 本发明还提供了本发明的化合物与选自氨溴索、高渗溶液（例如盐水或甘露糖醇）和表面活性剂的祛痰药 / 粘液动力学调节剂的组合。

[0073] 本发明还提供了本发明的化合物与选自重组人脱氧核糖核酸酶 I(α 链道酶和 rhDNase) 和螺杀菌素的肽粘液溶解药的组合。

[0074] 本发明还提供了本发明的化合物与选自阿奇霉素、妥布霉素和氨曲南的抗生素的组合。

[0075] 本发明还提供了本发明的化合物与选自 INS-37217、地夸磷索、西贝那德、CS-003、他奈坦、DNK-333、MSI-1956 和吉非替尼的黏液调节剂的组合。

[0076] 本发明还提供了本发明这样或作为药学上可接受的盐的化合物与选自 CP-690550 和 GLPG0634 的 JAK 抑制剂的组合。

[0077] 本发明还提供了本发明这样或作为药学上可接受的盐的化合物与选自 R406、R343 和 PRT062607 的 SYK 抑制剂的组合。

[0078] 本发明还提供了用作药剂的本发明的化合物。

[0079] 本发明还涉及本发明的化合物在减少体外和 / 或体内炎症细胞数量、活性和运动中的用途。

[0080] 本发明还涉及本发明的化合物，其用于预防和 / 或治疗其中涉及炎症细胞数量、活性和运动减少的任意疾病。

[0081] 在另一个方面中，本发明提供了本发明的化合物在预防和 / 或治疗其中涉及炎症细胞数量、活性和运动减少的任意疾病中的用途。

[0082] 特别地，可以施用单独或与一种或多种活性成分组合的本发明的化合物以便预防和/或治疗特征在于气道阻塞的呼吸道疾病，例如哮喘和 COPD。

[0083] 在另一个方面中，本发明提供了本发明的化合物在制备用于预防和/或治疗其中涉及炎症细胞数量、活性和运动减少的任意疾病的药剂中的用途。

[0084] 本发明还提供了用于预防和/或治疗其中涉及炎症细胞数量、活性和运动减少的任意疾病的方法，该方法包括对有这种治疗需求的患者施用治疗有效量的本发明的化合物。

[0085] 本发明还提供了适合于通过吸入、注射、口服或鼻内施用的本发明化合物的药物制剂。

[0086] 可吸入制剂包括可吸入粉末、包含抛射剂的计量气雾剂或不含抛射剂的可吸入制剂。

[0087] 本发明还涉及装置，其可以为包含本发明化合物的单剂量或多剂量干粉吸入器、定量定压式气雾器或喷雾器，特别是柔和雾喷雾器 (softmist nebulizer)。

[0088] 本发明还涉及药盒，其包含单独的本发明化合物或它们与一种或多种药学上可接受的载体和/或赋形剂的组合或混合物的药物组合物，本发明还涉及装置，其可以为包含本发明化合物的单剂量或多剂量干粉吸入器、定量定压式气雾器或喷雾器。

[0089] 可以根据各种合成步骤制备本发明的化合物，所述各种合成步骤根据常规方法或如下所述进行。

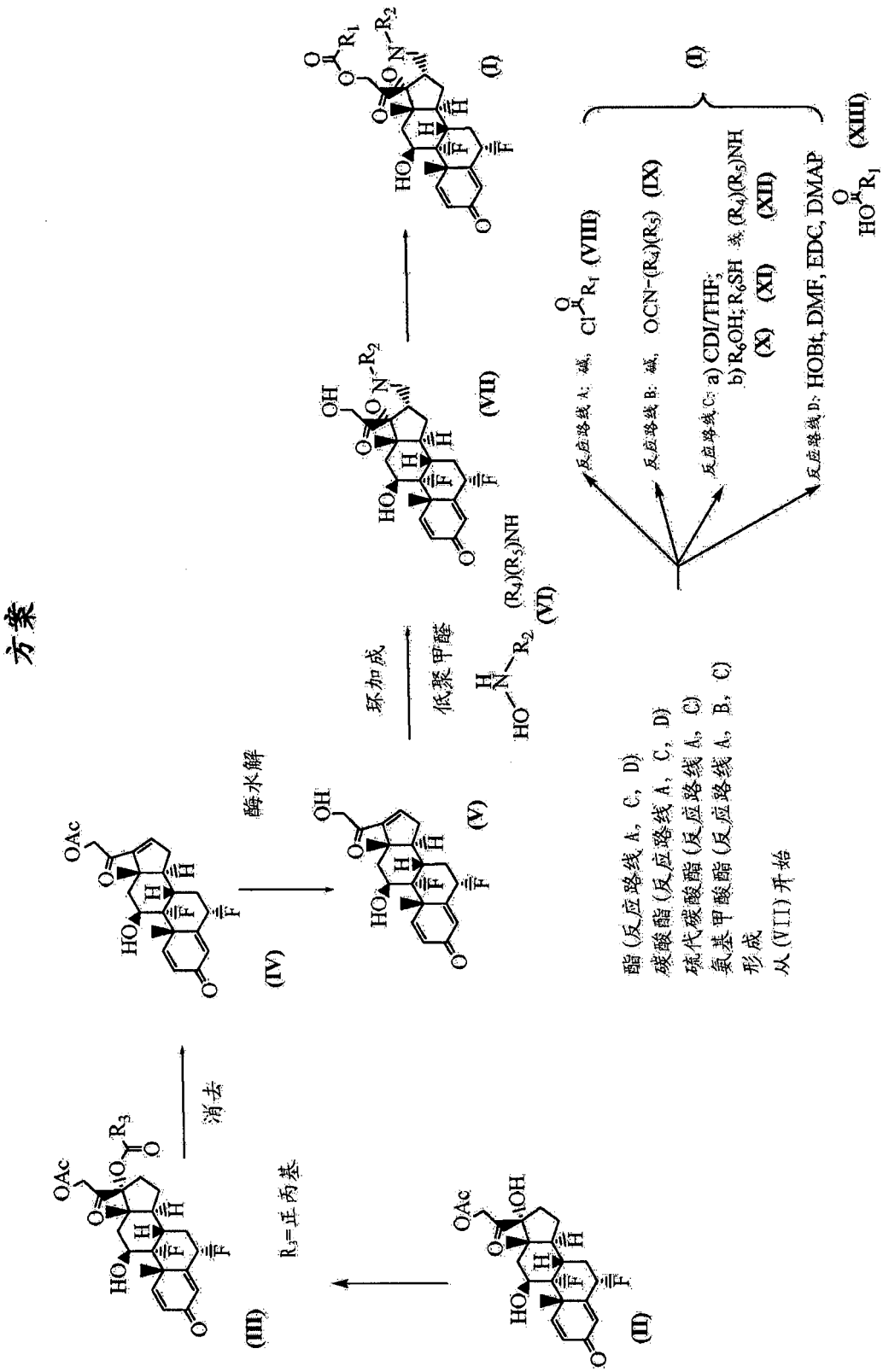
[0090] 在一个方面中，本发明提供了本发明化合物及其中间体的制备方法。

[0091] 综上所述，本领域技术人员显而易见，通过选择具有适合的立体化学结构的原料，可以得到式 (I) 的任意可能的立体异构体。

[0092] 用于制备如下方案中所述的式 (I') 的化合物的一些方法也可以适用于式 (I) 的化合物。

[0093]

方案



[0094] 本发明化合物的制备方法

[0095] 可以根据上述方案中所述的不同反应路线、根据取代基 R_1 和 R_2 性质的不同制备本发明的化合物。

[0096] 一般而言，可以通过一般反应方案中示例的方法或通过其变型、使用易于得到的原料、试剂和常规的合成操作制备本发明的化合物。在这些反应中，还能够利用本领域技术人员众所周知的变化形式。

[0097] 式 (III) 的化合物易于由已知化合物、通过已知方法、以为式 (II) 的化合物原料制备 (J. Med. Chem. 1982, 25, 1492-1495)。它们也可以商购。

[0098] 式 (IV) 的化合物可以便利地根据文献中报道的标准方法制备。例如，可以通过用碱例如乙酸钾处理式 (III) 的化合物制备它们。该反应通常在适合的极性溶剂例如 DMF 中进行且典型地在 80 — 110℃的温度范围进行 0.5 — 4 小时期限。

[0099] 式 (V) 的化合物可以通过水解式 (IV) 的化合物制备。该反应优选通过使化合物 (IV) 进行酶，例如来自南极假丝酵母 (Candida antarctica) 的固定化脂酶 (Sigma Aldrich) (Tetrahedron, 50, 13165-13172, 1994) 作用进行。

[0100] 式 (VII) 的化合物可以使用用于异噁唑烷形成的已知方法、通过硝酮类的环加成、在低聚甲醛的存在下、从式 (V) 的化合物与式 (VI) 的化合物反应开始制备 (J. Med. Chem., 25, 1492-1495, 1982)。该反应便利地在给质子溶剂例如乙醇中在 80 — 100℃的温度下进行。式 (VI) 的羟基胺是商购的或易于使用公知方法制备，例如通过用还原剂例如硼烷吡啶复合物 (J. Med. Chem., 40, 1955-1968, 1997) 还原肟或通过使 O- 四氢吡喃基羟基胺与适合的烷基化试剂例如烷基卤反应 (Chem. Pharm. Bull., 46, 966-972, 1998) 来制备。

[0101] 按照合成反应路线 (反应路线 A-D) 中所述，通过使式 (VII) 的化合物与式 (VIII)、(IX)、(X)、(XI)、(XII) 或 (XIII) 的化合物反应易于将式 (VII) 的化合物的羟基转化成酯、碳酸酯、氨基甲酸酯或硫代碳酸酯。

[0102] 如果适合，本领域技术人员可以将适合的变化形式引入特别地在实验中描述的条件，以便使合成反应路线适合提供本发明另外的化合物。这样的变化形式可以包括、但不限于应用适合的原料生成不同的化合物，改变反应溶剂和温度，用类似作用的化学物质替代反应剂，在保护 / 脱保护阶段引入或除去对反应条件和反应剂敏感的官能团，以及引入或除去定向于化学平台进一步官能化的特定合成步骤。

[0103] 式 (VII) 的中间体与酰氯 (VIII) 按照反应路线 A 反应，得到式 (I) 的化合物，该反应便利地在 DCM(二氯甲烷) 作为溶剂中在碱例如三乙胺或 DIPEA(N, N- 二异丙基 - 乙胺) 或吡啶的存在下在 RT 进行 4 — 50 小时期限。

[0104] 或者，反应路线 B，式 (VII) 的化合物的羟基转化成氨基甲酸酯易于通过使式 (VII) 的化合物与式 (IX) 的化合物按照已知方法进行。该反应便利地在 DCM 作为溶剂中在碱例如 DMAP 的存在下在 RT 进行 4 — 50 小时期限。

[0105] 按照反应路线 C，式 (VII) 的中间体与 CDI(1, 1'- 羰基二咪唑) 反应，然后添加期望的醇 (X) 或硫醇 (XI) 或胺 (XII)，得到式 (I) 的化合物，该反应便利地在 THF(四氢呋喃) 中在 RT 进行 4 — 50 小时期限。

[0106] 或者，反应路线 D，式 (VII) 的化合物的羟基转化成式 (I) 的化合物可以通过使式 (XIII) 的化合物与 HOBt(羟基苯并三唑) 反应、然后添加式 (VII) 的化合物、EDC(1- 乙基 -3-(3- 二甲基氨基丙基) 碳二亚胺) 和 DMAP(4- 二甲基氨基吡啶) 进行。该反应便利地在 DMF 作为溶剂中在 RT 进行 4 — 50 小时期限。

[0107] 从上述内容中应清楚地表明任意所述的基团可以照此存在或以任意适当被保护

的形式存在。

[0108] 特别地，存在于中间体和化合物上且可能生成不需要的副反应和副产物的官能团需要适当地被保护，然后进行烷基化、酰化、偶合或磺酰化。同样，随后那些相同保护基的脱保护可以在所述反应完成后进行。

[0109] 在本发明中，除非另有指示，否则术语"保护基"表示适合于保护与之结合的基团功能的保护基团。典型地，保护基用于保护氨基、羟基或羧基官能团。适合的保护基由此可以包括，例如苄基、苄氧基羰基、叔丁氧基羰基、烷基或苄基酯类等，它们是本领域技术人员众所周知的[就一般参考文献而言，参见 20T. W. Green ;Protective Groups in Organic Synthesis(Wiley, N. Y. 1981)]。

[0110] 有利地，例如，可以以包含 0.001 — 1000mg/ 天、优选 0.1 — 500mg/ 天的剂量施用本发明的化合物。

[0111] 当通过吸入途径施用它们时，本发明化合物的剂量有利地包含 0.01 — 20mg/ 天，优选 0.1 — 10mg/ 天。

[0112] 优选地，可以单独或与其它活性成分组合施用本发明的化合物以用于预防和 / 或治疗任意的阻塞性呼吸系统疾病，例如哮喘、慢性支气管炎和慢性阻塞性肺疾病 (COPD)。

[0113] 然而，可以施用本发明的化合物以用于预防和 / 或治疗其中涉及炎症细胞数量、活性和运动减少的任意疾病。

[0114] 这样的疾病的实例包括 :相关炎症，例如哮喘和其它过敏性疾病、COPD、急性鼻炎 ;可逆性急性移植物排斥和选择的自体免疫疾病的急性转剧、骨髓移植中的移植物抗宿主病 ;自体免疫疾病，例如类风湿性关节炎和其它关节炎 ;皮肤病，例如系统性红斑狼疮、系统性皮肌炎、银屑病、炎症性眼病、自身免疫性血液病和多发性硬化急性转剧 ;肾、肝、心脏和其它器官移植 ;贝赫切特急性眼综合征、内源性葡萄膜炎、特应性皮炎、炎性肠病和肾病综合征 ;何杰金氏病和非何杰金淋巴瘤、多发性骨髓瘤和慢性淋巴细胞白血病 (CLL) ;自身免疫性溶血性贫血和与 CLL 相关的血小板减少症 ;白血病和恶性淋巴瘤。

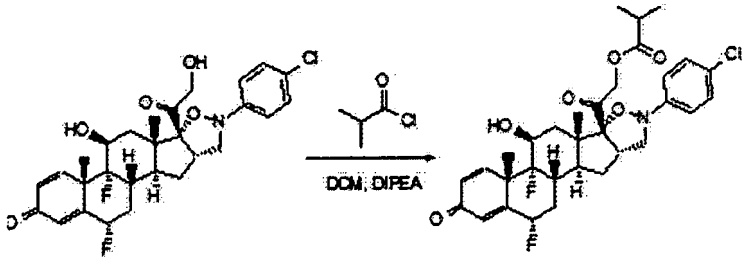
[0115] 优选地，可以施用本发明的化合物以用于预防和 / 或治疗呼吸系统疾病，例如从轻度到急性严重性哮喘病症和 COPD。

[0116] 现在通过下列实施例进一步描述本发明。

[0117] 在报道的实验方法中，可以施用如下缩写 :TEA = 三乙胺 ;DCM = 二氯甲烷 ;RT = 室温 ;AcOEt = 乙酸乙酯 ;DMF = N, N- 二甲基甲酰胺 ;DMSO = 二甲亚砜 ;HATU = O-(7- 氮杂苯并三唑 -1- 基)-N, N, N', N' - 四甲基脲鎓六氟磷酸盐 ;DMAP = 4- 二甲基氨基吡啶 ;DIPEA = 乙基二异丙基胺。

[0118] 实施例 1

[0119]



中间体 2 **化合物 1**

[0120] 异丁酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯(化合物 1)的制备

[0121] 在氮气气氛中在 5 ℃下向搅拌的中间体 2(600mg,1.124mmol)和 DIPEA(0.391ml,2.247mmol)在干二氯甲烷(30ml)中的溶液中加入异丁酰氯(0.235ml,2.247mmol),将该反应化合物在 5℃搅拌 10min 并且在 RT 搅拌 16hr。再加入 DIPEA(0.196ml,1.124mmol)和异丁酰氯(0.118ml,1.124mmol),将该混合物在 RT 搅拌 72h。再加入另一部分 DIPEA(0.196ml,1.124mmol)和异丁酰氯(0.118ml,1.124mmol),将该反应混合物在 RT 搅拌 1hr 并且在 50℃搅拌 1.5hr。

[0122] 用 DCM(100ml)稀释该反应混合物,用 1N HCl、饱和 $NaHCO_3$溶液和盐水洗涤有机层,干燥(Na_2SO_4),浓缩。通过硅胶快速色谱法纯化粗产物,洗脱梯度为 DCM/AcOEt 98:2 — DCM/AcOEt 92:8,得到 481mg 纯化合物(71%收率;Rf = 0.37,在 AcOEt/DCM 10:90 中)。

[0123] ^1H NMR(300MHz,DMSO-d_6)ppm 7.31-7.45(m,2H),7.26(dd,1H),6.98-7.10(m,2H),6.29(dd,1H),6.08(s,1H),5.62(d,1H),5.42-5.78(m,1H),5.06(d,1H),4.90(d,1H),4.18-4.32(m,1H),4.17(t,1H),3.44-3.62(m,1H),2.56-2.71(m,2H),2.63(spt,1H),2.04-2.34(m,3H),1.84-1.96(m,1H),1.63-1.83(m,1H),1.52-1.63(m,2H),1.50(s,3H),1.14(d,3H),1.13(d,3H),0.94(s,3H)

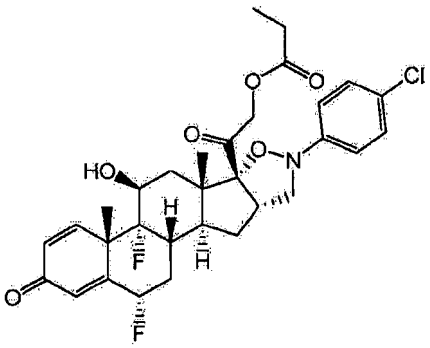
[0124] LC-MS(ESI POS):604.10MH+

[0125] $[\alpha]_D^{25}$= +58.3(c 0.2;MeOH)

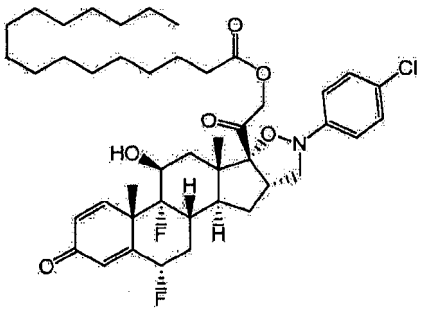
[0126] 如上述对化合物 1 所述、通过用适合的酰氯酰化中间体 2 制备表中列出的化合物:

[0127] 表 1

[0128]

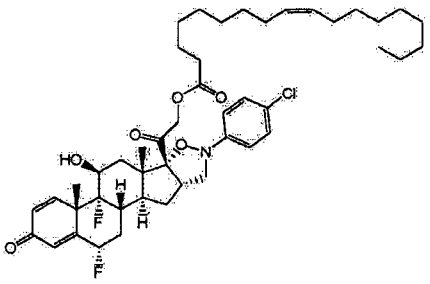
化合物	结构	收率	分析
3		61%	LC-MS (ESI POS): 590.14 MH+ $[\alpha]_D^{25}$ = + 59.7 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.31 - 7.43 (m, 2 H), 7.26 (dd, 1 H), 6.90 - 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (dd, 0 H), 5.45 - 5.73 (m, 1 H), 5.06 (d, 1 H), 4.90 (d, 1 H), 4.19 - 4.31 (m, 1 H), 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

[0129]

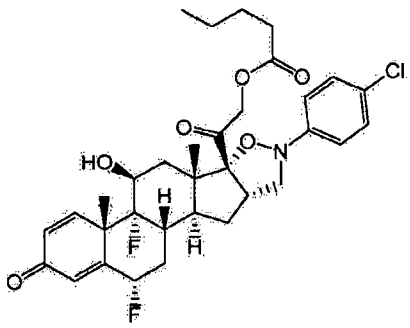
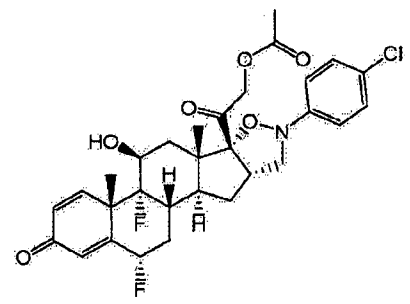
			H), 1.07 (t, 3 H), 0.94 (s, 3 H)
4		70%	LC-MS (ESI POS): 772.6 MH+ $[\alpha]_D^{25}$ = + 65.9 (c 0.2 $CHCl_3$) ^1H NMR (300 MHz, DMSO-d_6) ppm 7.31 - 7.41 (m, 2 H), 7.26 (d, 1 H), 6.98 - 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.62 (d, 1 H), 5.43 - 5.79 (m, 1 H), 5.06 (d, 1 H), 4.89 (d, 1 H), 4.18 - 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)

[0130] （接续）

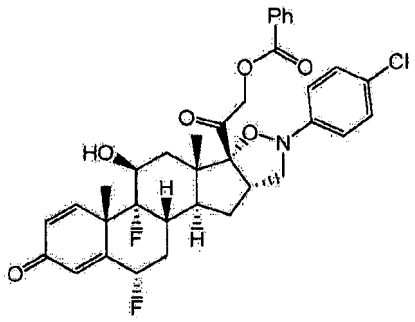
[0131]

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)**

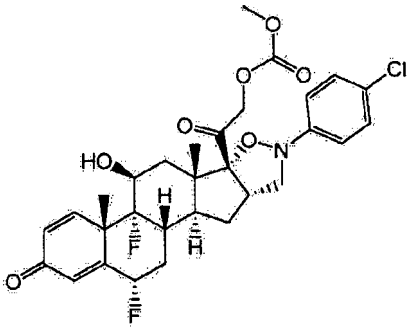
[0132]

6		56%	LC-MS (ESI POS): 618.23 MH+ $[\alpha]_D^{25}$ = + 68.6 (c 0.2 $CHCl_3$) ^1H 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)
7		47%	LC-MS (ESI POS): 576.23 MH+ $[\alpha]_D^{25}$ = + 53.8 (c 0.2 MeOH)

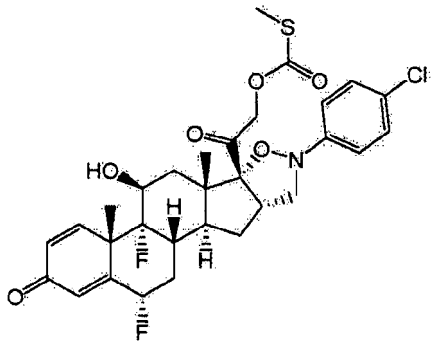
[0133]

			^{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

[0134]

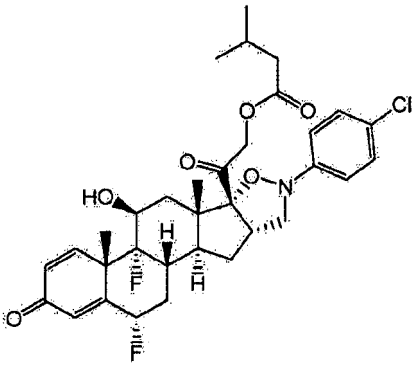
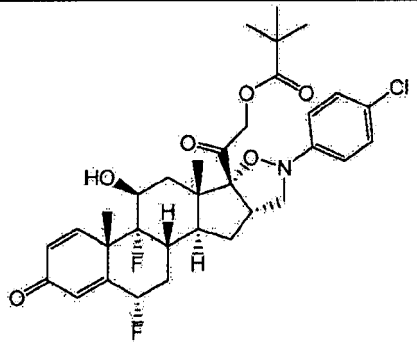
			(m, 2 H), 6.30 (dd, 1 H), 6.09 (s, 1 H), 5.67 (dd, 1 H), 5.49 – 5.85 (m, 1 H), 5.35 (d, 1 H), 5.17 (d, 1 H), 4.23 – 4.32 (m, 1 H), 4.21 (t, 1 H), 3.47 – 3.65 (m, 1 H), 2.56 – 2.69 (m, 2 H), 2.09 – 2.32 (m, 3 H), 1.91 – 2.04 (m, 1 H), 1.66 – 1.83 (m, 1 H), 1.53 – 1.65 (m, 2 H), 1.51 (s, 3 H), 1.00 (s, 3 H)
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

[0135]

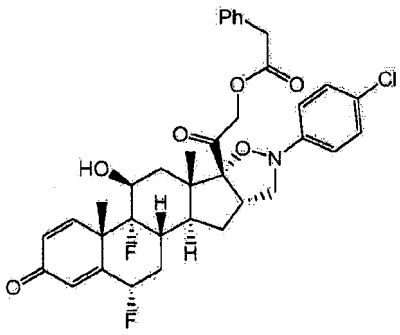
			(m, 1 H), 2.61 (dd, 1 H), 2.04 – 2.29 (m, 3 H), 1.85 (d, 1 H), 1.63 – 1.80 (m, 1 H), 1.51 – 1.63 (m, 2 H), 1.50 (s, 3 H), 0.95 (s, 3 H)
10		66%	LC-MS (ESI POS): 608.08 MH+ $[\alpha]_D^{25}$ = + 50.8 (c 0.2 MeOH) ^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.30 - 7.42 (m, 2 H), 7.26 (d, 1 H), 6.94 - 7.10 (m, 2 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)

[0136] （接续）

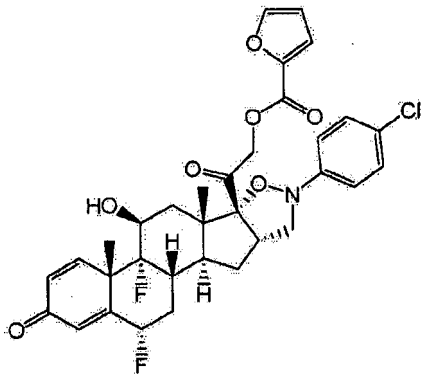
[0137]

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)

[0138]

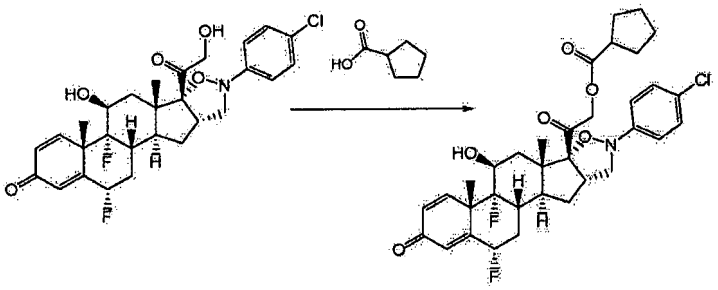
			^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.30 - 7.41 (m, 2 H), 7.26 (dd, 1 H), 6.95 - 7.12 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.61 (d, 1 H), 5.48 - 5.75 (m, 1 H), 5.06 (d, 1 H), 4.91 (d, 1 H), 4.17 (t, 1 H), 4.09 - 4.35 (m, 1 H), 3.53 (q, 1 H), 2.56 - 2.68 (m, 2 H), 2.04 - 2.26 (m, 3 H), 1.89 (d, 1 H), 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)
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 -**

[0139]

			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)**

[0140] 实施例 2

[0141]



中间体 2 化合物 15

[0142] 环戊烷甲酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯(化合物 15)的制备

[0143] 将环戊烷甲酸(137mg,1.2mmol,1.2eq)溶于 DMF(5ml),加入 1-羟基苯并三唑水合物(162mg,1.2mmol,1.2eq),将该反应混合物搅拌 20 分钟。依次加入中间体 2(534mg,1mmol)、4-(二甲基氨基)吡啶(305mg,2.5mmol,2.5eq)和 EDC*HCl(230mg,1.2mmol,1.2eq),将该反应混合物在 RT 搅拌过夜。通过 TLC 分析监测转化(Hex/EtOAc 7/6)。用 HCl 0.6N 使反应停止,用 EtOAc 将产物萃取 2 次。用 $NaHCO_3$饱和溶液、盐水洗涤采集的有机相,用无水 Na_2SO_4干燥。用 NaOH 1N(10ml)、吡啶(用于转移水层中的环戊烷甲酸,2ml)和 EtOAc(30ml)纯化处理粗产物。用水将有机层洗涤 2 次,用硅胶垫过滤。得到化合物 15,为固体,在 50℃真空干燥 2 小时(300mg,收率 47.6%)。

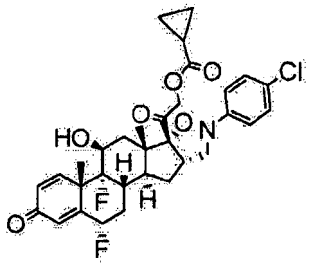
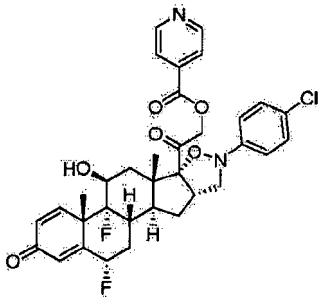
[0144] LC-MS(ESI POS):630.10MH+

[0145] ^1H NMR(400MHz,DMSO-d_6) δ ppm 7.34(d,J = 8.82Hz,2H),7.19-7.28(m,1H),7.04(d,J = 8.82Hz,2H),6.18-6.37(m,1H),5.97-6.13(m,1H),5.46-5.75(m,2H),4.78-5.17(m,2H),4.06-4.31(m,2H),3.42-3.55(m,1H),2.78-2.93(m,1H),2.54-2.74(m,2H),2.09(m,3H),1.49(m,15H),0.93(s,3H).

[0146] 如上述对化合物 15 所述、以相应的羧酸为原料制备表 2 中列出的化合物:

[0147] 表 2

[0148]

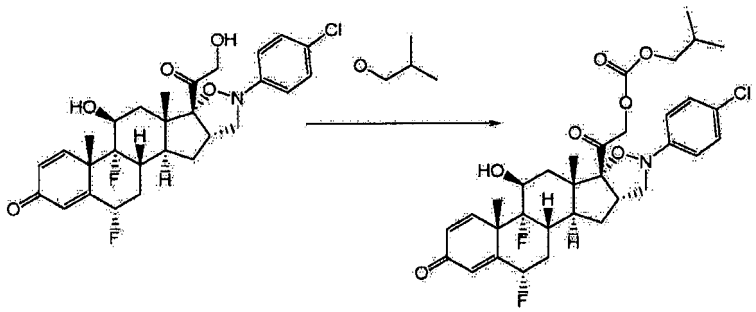
化合物	结构	收率	分析
16		71%	LC-MS (ESI POS): 602.2 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.26 - 7.37 (m, 2 H), 7.14 - 7.24 (m, 1 H), 6.90 - 7.05 (m, 2 H), 6.15 - 6.40 (m, 1 H), 5.99 - 6.06 (m, 1 H), 5.39 - 5.72 (m, 2 H), 4.74 - 5.12 (m, 2 H), 4.03 - 4.22 (m, 2 H), 3.39 - 3.57 (m, 1 H), 2.50 - 2.70 (m, 2 H), 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) ppm 8.76 - 8.95 (m, 2 H), 7.76 - 7.88 (m, 2 H),

[0149]

			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).

[0150] 实施例 3

[0151]



中间体 2 **化合物 18**

[0152] 异丁基甲基碳酸酯 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4-氯-苯基)-4b, 12-二氟-5-羟基-4a, 6a-二甲基-2-氧代-2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2, 1-a]菲-6b-基]-2-氧代-乙酯(化合物 18)的制备

[0153] 在 RT 向在 THF(3ml)中的中间体 2(350mg, 0.66mmol)中分部分加入 CDI(127mg, 0.79mmol, 1.2eq)。将该反应混合物搅拌 1 小时:通过 TLC 分析检测转化率(EtOAc 100%)。在 0℃向该反应混合物中加入异丁醇(1.0ml, 10mmol),在 RT 搅拌 1 小时。观察到痕量的期望的产物。然后将该反应混合物加热至 50℃ 4 小时:转化率增加。在 50℃ 12 小时后,通过 TLC 分析检测转化完成(己烷/EtOAc 3/7)。真空蒸发溶剂,用 EtOAc/H_2O 处理粗产物。用无水 Na_2SO_4 干燥采集的有机层,用硅胶垫纯化粗产物,得到化合物 18(240mg,

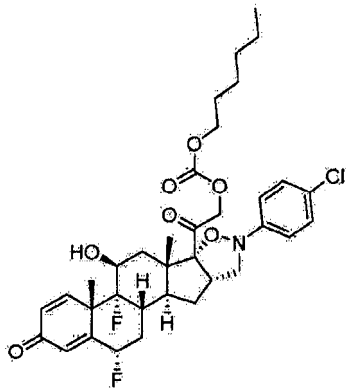
收率58%)。

[0154] LC-MS(ESI POS):634.2LC-MS

[0155] ^{1}H NMR(400MHz,DMSO-d_6) δ ppm 7.34(d,J = 8.82Hz,2H),7.20-7.30(m,1H),7.04(d,J = 8.82Hz,2H),6.21-6.37(m,1H),6.00-6.12(m,1H),5.47-5.72(m,2H),4.83-5.17(m,2H),4.10-4.29(m,2H),3.91(dd,J = 6.62,0.88Hz,2H),3.43-3.60(m,1H),2.55-2.74(m,2H),2.04-2.29(m,3H),1.81-1.99(m,2H),1.64-1.76(m,1H),1.49(m,5H),0.81-0.96(m,9H).

[0156] 如上述对化合物18所述、以己醇为原料制备化合物19:

[0157]

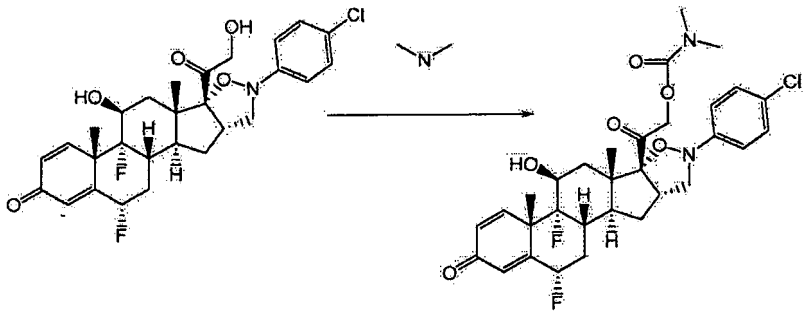
化合物	结构	收率	分析
19		30%	**LC-MS (ESI POS): 662.2 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.33 (s, 2 H), 7.18 - 7.29 (m, 1 H), 7.00 - 7.11 (m, 2 H), 6.22 - 6.37 (m, 1 H), 6.02 - 6.11 (m, 1 H), 5.49 - 5.77 (m, 2 H), 4.79 - 5.17 (m, 2 H), 4.14 - 4.27 (m, 2 H), 4.04 - 4.13 (m, 2 H), 3.44 - 3.62 (m, 1 H), 2.53 - 2.68 (m, 2 H), 2.03**

[0158]

			- 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).

[0159] 实施例4

[0160]



中间体 2 化合物 20

[0161] 二甲基氨基甲酸酯 2-[(4aS, 4bR, 5S, 6aS, 6bR, 9aS, 10aS, 10bS, 12S)-8-(4-氯-苯基)-4b, 12-二氟-5-羟基-4a, 6a-二甲基-2-氧代-2, 4a, 4b, 5, 6, 6a, 8, 9, 9a, 10, 10a, 10b, 11, 12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2, 1-a]菲-6b-基]-2-氧代-乙酯(化合物 20)的制备

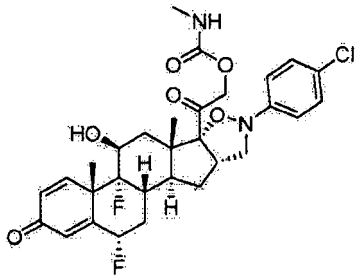
[0162] 在 RT 向在 CH_2Cl_2(3ml)中的中间体 2(310mg, 0.58mmol)中分部分加入 CDI(111mg, 0.70mmol, 1.2eq)。将该反应混合物搅拌 1 小时:通过 TLC 分析检测转化完成(EtOAc 100%)。真空蒸发 CH_2Cl_2,将粗产物溶于 THF(2ml),然后在 0℃加入 2M 二甲胺的 THF 溶液(1.15ml, 2.32mmol),在 RT 搅拌 1 小时。通过 TLC 分析检测转化完成(己烷/EtOAc 2/8)。真空蒸发溶剂,用 CH_2Cl_2/H_2O 处理粗产物。用无水 Na_2SO_4 干燥采集的有机层,用硅胶垫纯化粗产物,然后将得到的黄褐色固体在己烷/乙酸乙酯混合物(8/2, 8ml)中研磨 1 夜。在 50℃真空干燥过滤的固体至恒重,得到化合物 20(200mg, 收率 57%)。

[0163] LC-MS(ESI POS):605.2LC-MS

[0164] ^1H NMR(400MHz, DMSO-d_6) δ ppm 7.31-7.44(m, 2H), 7.21-7.30(m, 1H), 6.99-7.07(m, 2H), 6.20-6.43(m, 1H), 6.01-6.12(m, 1H), 5.47-5.76(m, 2H), 4.69-5.10(m, 2H), 4.08-4.25(m, 2H), 3.43-3.59(m, 1H), 2.80-3.00(m, 6H), 2.55-2.72(m, 2H), 2.03-2.28(m, 3H), 1.83-1.96(m, 1H), 1.65-1.81(m, 1H), 1.49(m, 5H), 0.93(s, 3H).

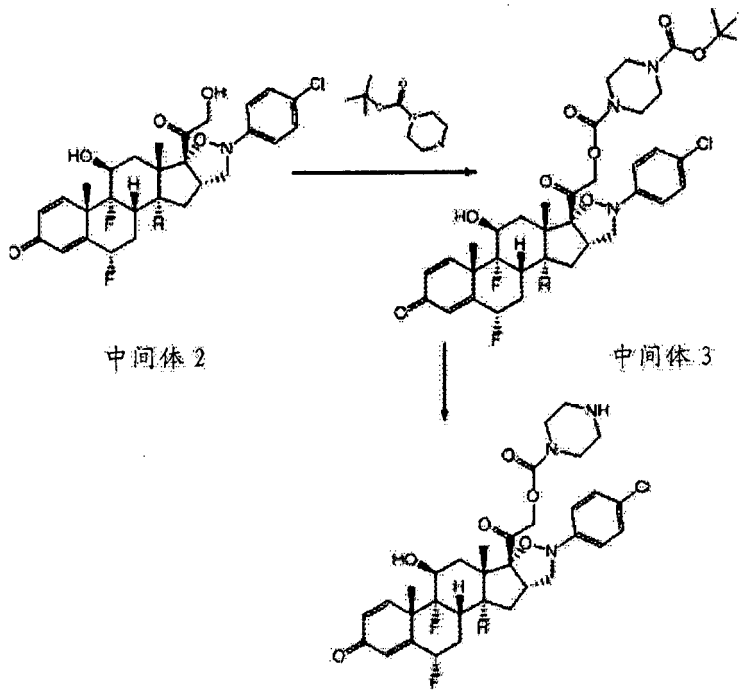
[0165] 如上述对化合物 20 所述、以甲胺为原料制备化合物 21:

[0166]

化合物	结构	收率	分析
21		56.3%	LC-MS (ESI POS): 591.1 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) 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).

[0167] 实施例 5

[0168]



化合物 22

[0169] 哌嗪-1-甲酸 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-氯-苯基)-4b,12-二氟-5-羟基-4a,6a-二甲基-2-氧代-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-十四氢-7-氧杂-8-氮杂-并戊二环烯并[2,1-a]菲-6b-基]-2-氧代-乙酯(化合物 22)的制备

[0170] 在 RT 向在 THF(3.5ml)中的中间体 2(500mg,0.94mmol)中分部分加入 CDI(180mg,1.12mmol,1.2eq)。将该反应混合物搅拌 1 小时:通过 TLC 分析检测完全转化为活化的中间体(己烷:EtOAc 3/7)。将该反应混合物冷却至 10℃,然后加入哌嗪-1-甲酸叔丁酯(174mg,0.94mmol,1.0eq),在 RT 搅拌过夜。通过 TLC 分析检测转化率(己烷/EtOAc 3/7)。真空蒸发溶剂,用 EtOAc/H_2O 处理粗产物。用无水 Na_2SO_4干燥采集的有机层,将粗化合物中间体 3 不经进一步纯化用于下一步(260mg,收率 37%)。

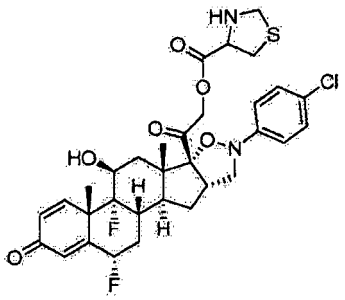
[0171] 将中间体 3(260mg,0.35mmol)在 CH_2Cl_2(5ml)中的溶液冷却至 0℃,向其中滴加三氟甲磺酸三甲基-甲硅烷基酯(63μl,1.0eq,)。将该反应混合物在 0℃搅拌 1 小时,然后用脱矿质水猝灭。用 $NaHCO_3$饱和溶液、然后用去矿质水洗涤有机层,用无水 Na_2SO_4干燥,得到粗化合物,通过硅胶柱色谱法纯化(用 EtOAc/TEA 99:1 洗脱),在 50℃真空干燥至恒重,得到化合物 22(190mg,84%收率)。

[0172] LC-MS(ESI POS):646.4MH+

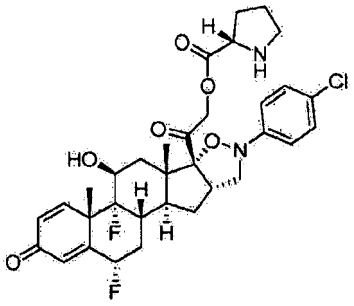
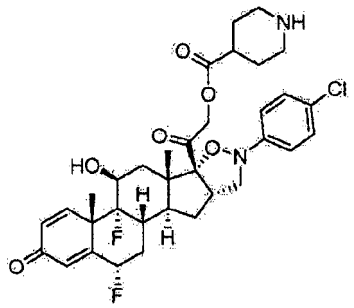
[0173] ^1H NMR(400MHz,DMSO-d_6) δ ppm 7.33(d,J = 8.82Hz,3H),7.03(d,J = 8.82Hz,2H),6.19-6.39(m,1H),6.07(s,1H),5.46-5.76(m,2H),4.76-5.14(m,2H),4.05-4.28(m,2H),3.41-3.60(m,1H),3.18-3.30(m,5H),2.66(m,6H),1.95-2.28(m,3H),1.81-1.95(m,1H),1.57-1.79(m,1H),1.48(m,5H),0.93(s,3H).

[0174] 如上述对化合物 22 所述、以相应的中间体为原料制备下表中列出的化合物:

[0175]

化合物	结构	收率	分析
23		26%	LC-MS (ESI POS): 649.4 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) 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 -

[0176]

			1.78 (m, 1 H), 1.49 (m, 5 H), 0.93 (s, 3 H)
24		27%	LC-MS (ESI POS): 631.2 MH+ ^{1}H NMR (400 MHz, DMSO-d_6) 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) 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),

[0177]

			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)

[0178] 说明

[0179] *NMR

[0180] s =单峰

[0181] d =双峰

[0182] t =三重峰

[0183] q =四重峰

[0184] dd =双组双重峰

[0185] m =多重峰

[0186] br =宽峰

[0187] ESI-POS =电喷雾正电离

[0188] LC-MS =液相色谱法 - 质谱法

[0189] 本发明化合物的药理学活性

[0190] 体内研究

[0191] 实施例 6

[0192] 脂多糖 (LPS)- 诱导的肺中性白细胞增多症

[0193] 按照稍做修改的 Am. J. Respir. Crit. Care Med. 第 162 卷 . pp1455-1461, 2000 中所述的方法，在急性肺部炎症模型中体内评价本发明中所述化合物的效能和作用期限。

[0194] 试验对 Sprague-Dawley 雄性大鼠 (200g) 进行。

[0195] 气管内滴入 LPS 导致 BALF 中嗜中性粒细胞浓度具有统计学显著性增加，即急性进行性肺炎症的标志。

[0196] 对于产生 75％抑制 (ED75 剂量) 的评价试验的糖皮质激素剂量，在 LPS 攻击前 1 小时，在气管内施用作为混悬液 (0.2％ Tween 80 的 NaCl0.9％溶液) 的化合物 (0.01-1μmoles/Kg 体重)。

[0197] 完成测试化合物对 LPS- 诱导的肺中性白细胞增多症的抑制作用的剂量 - 响应曲线，并且在本生物测定中将糖皮质激素的 ED50 剂量取为效能测量值。一些本发明有代表性的化合物的 ED50 剂量值包含 0.05 — 0.16μmoles/Kg 体重。

[0198] 在第二个系列的目的在于作用期限评价的实验中，在 LPS 攻击前 24h，在气管内以

ED75 剂量施用作为混悬液的化合物。在 LPS 攻击前 24 小时施用时，最有意义的化合物具有活性（抑制百分比高于 50%）。

[0199] 体内研究

[0200] 实施例 7

[0201] 糖皮质激素受体 (GR) 易位测定方案

[0202] 根据 ASSAY Drug Devel.Technol.,4(3),263-272,2006，通过由 DiscoveRx(Fremont,CA) 研发的酶片段互补 (Enzyme Fragment Complementation)(EFC) 形式中新的基于细胞的 GR- 易位测定对本发明化合物 GR 的核转位进行定量测定。

[0203] 在没有糖皮质激素存在下，糖皮质激素受体 (GR) 居留在与各种蛋白质包括热激蛋白复合的胞质溶胶中。

[0204] 当糖皮质激素通过细胞膜扩散入细胞质并且结合糖皮质激素受体 (GR) 时，它导致热激蛋白释放并且转位入核，在那里它调节基因转录。

[0205] DiscoveRx 测定使用 b- 半乳糖苷酶 (b-gal) 的 EFC 作为改造的 CHO-K1 生物传感器细胞中 GR- 易位的指示剂。正如所设计的，通过使用专有的组序列添加和修饰，b-gal 的酶受体 (EA) 片段居留于核中。使 b-gal 的小肽酶供体 (ED) 片段直接与 GR 的 C- 末端融合并且在没有受体信号传导的存在下定位于细胞质中。在结合 GR 配体时，该复合物转位于核，其中完整的酶活性因互补被恢复并且检测到 b-gal 活性。

[0206] 在 37℃在包含 5% CO_2 和 95% 空气的加湿气氛中将稳定表达 b-gal 的 NLS- 酶受体片段 (EA) 和 b-gal 的 GR- 酶供体 (ED) 片段的 CHO-K1 细胞维持在 F12 培养基 (Invitrogen,Carlsbad,CA) 中。所述培养基包含 10% FBS、2mM L- 谷氨酰胺、50U/ml 青霉素、50μg/ml 链霉素和 250μg/ml 潮霉素和 500μg/ml G418(Invitrogen)。

[0207] 使用包含细胞膜渗透试剂和 β-gal 底物的 PathHunter 检测试剂盒 (DiscoveRx,Fremont,CA) 测定 GR- 易位。使用 10^{-11} — 10^{-6}M 的不同浓度筛选所有化合物。本测定在 48- 孔 (105 细胞 / 孔) 中进行。与筛选的化合物一起在 37℃温育 2 小时。通过添加来自由 DiscoveRx 提供的试剂盒的检测缓冲液并且在 RT 温育 1 小时进行检测。通过使用 CENTRO LB 960 微量培养板读出器 (Berthold Technologies) 检测发光。

[0208] 通过使用 Prism-3.0 版 Graphpad 软件 (San Diego,CA) 进行统计学分析和 EC50s 测定。

[0209] 使用 GR 易位测定的本发明的一些有代表性的化合物展示出包含 3.2nM — 207nM 的 EC50。

[0210] 实施例 8

[0211] RAW 264.7 巨噬细胞中 LPS- 诱导的一氧化氮产生的抑制

[0212] 基于巨噬细胞鼠细胞 RAW 264.7 系的体外模型用于测试本发明皮质类固醇的抗炎作用。

[0213] 在抗炎过程中，通过 NO 合酶的诱导型同种型 (iNOS) 生成大量一氧化氮 (NO)。细菌脂多糖 (LPS) 常用于实验环境以刺激巨噬细胞中炎症应答。

[0214] 使细胞生长在无酚红的培养基（补充了热灭活的 10% 胎牛血清、2mM 谷氨酰胺、100U/ml 青霉素和 0.1mg/ml 链霉素的 RPMI) 中。通过将细胞与 LPS 一起温育 24 小时至约 100ng/ml 的终浓度引起细胞刺激。在 LPS 暴露前 15 分钟，通过在 DMSO 媒介物中 (0.1% 终

浓度）添加本发明的化合物至这样的化合物的最终期望浓度来进行处理。作为一氧化氮产生指标，通过使用 Griess 比色反应（J. Neuroimmunol.，150，29-36，2004）测定条件培养基中亚硝酸盐浓度。

[0215] 通过使用 Prism- 版 3.0Graphpad 软件（San Diego，CA）进行统计学分析和 IC50s 测定。对本发明一些有代表性的化合物测试的 IC50 值包含 12.2 — 151nM。

[0216] 实施例 9

[0217] 白细胞介素 -8（IL-8）释放测定方案

[0218] 为了评价新吸入的皮质类固醇的抗炎作用，我们评价了这些化合物在抑制 TNF α - 诱导的 IL-8 从人气道平滑肌细胞（ASMCs）中释放中的选择性。

[0219] 暴露于各种炎症介体（肿瘤坏死因子（TNF）- α 或 IL-1 β）的 hASMCs 可以发生表型改变并且分泌趋化因子和细胞因子，它们可以通过活化和募集炎症细胞参与乃至保持粘膜炎症改变（Damera 等人 2009；Howarth 等人，2004；Chung，2000；Koyama 等人，2000）。

[0220] 目前的证据启示由炎症介体诱导的趋化因子和细胞因子分泌被 hASMCs 和肺成纤维细胞中的糖皮质激素抑制（John 等人 1998；Spoelstra 等人，2002；Tobler 等人，1992）。类固醇可以通过活化糖皮质激素受体与活化转录因子之间的直接抑制性相互作用抑制细胞因子 - 诱导的趋化因子分泌，所述转录因子例如为核因子 - κ B 和激活蛋白 -1，它们调节炎症基因表达。此外，糖皮质激素可以通过经 p38MAP 激酶 MKP-1（为类固醇反式激活的基因之一）的有效内源性抑制剂的快速诱导降低 mRNA 稳定性来调节趋化因子表达（King 等人，2009）。

[0221] 初级人气道平滑肌细胞（ASMCs）购自 LONZA（Basel，CH）并且在 37℃在 95％空气和 5％ CO_2 气氛中在补充了 10％胎牛血清、2mM 谷氨酰胺、100U 青霉素和 100 μ g/ml 链霉素（Invitrogen）的 DMEM 培养基中培养。

[0222] 将 ASMC 以 104 细胞 / 孔的密度接种在 48- 孔组织培养板内包含 10％ FBS 的 0.5ml DMEM 中并且使其在 37℃与 5％ CO_2 下生长 24 小时。然后将细胞进行血清饥饿 18 小时，然后用不同浓度的 LAGRA 处理（10-12M-10-6M，最终 DMSO 浓度 0.1％）60min，然后用 TNF α 刺激（0.1ng/ml 作为 ASMCs 的终浓度）。在不含血清的 DMEM 中 18 小时温育后，使用 ELISA 试剂盒（Invitrogen）测定上清液中 IL8 的释放。将化合物效能表示为在用 TNF α 刺激后得到的剂量 - 响应曲线中能够抑制半数最大（50％）IL8 释放 [IC50] 的浓度。

[0223] 全部所述数值为平均值 ± 平均值的标准误差（SEM）。化合物效能（表示为半数最大（50％）抑制浓度 [IC50]）衍生自使用 Prism 软件的 4- 参数非线性迭代曲线 - 拟合分析（Graph Pad Software，San Diego，CA）。通过使用 Prism 软件（Graph Pad Software，San Diego，CA）进行统计学分析、S 形曲线设计和分析。