

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, 5 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.

10 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 15 (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 20 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, especially in 25 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. Moreover, 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 [16 α ,17 α -d] isoxazolidines" (J. Med. Chem., 25, 1492-1495, 1982).

Some glucocorticoid isoxazolidine derivatives are also described in the co-pending patent application WO 2011/029547.

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

SUMMARY OF THE INVENTION

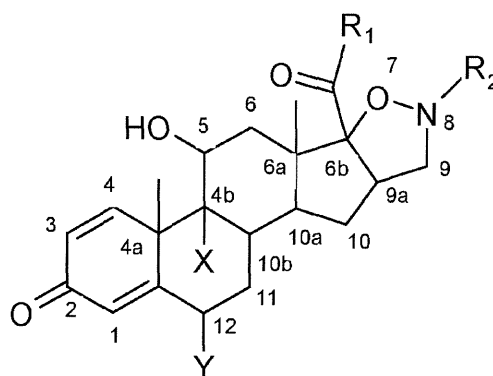
The present invention relates to anti-inflammatory and antiallergic compounds of the glucocorticosteroid series, to processes for their preparation, to compositions comprising them, to therapeutic uses and combinations with other pharmaceutical active ingredients for the treatment of

respiratory disorders, among which beta2-agonists, antimuscarinic agents, corticosteroids, 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) and mucus regulators.

DETAILED DESCRIPTION OF THE INVENTION

In particular, the invention is directed to compounds of general formula

(I)



(I)

wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n and n' are each independently 0, 1 or 2;

Z is a single bond or is selected from $-S-$, $-O-$ and $-OC(R_4R_5)-$;

R_3 is selected from the group consisting of:

- H, halogen, CN, OH, $CONH_2$, (C_1-C_6) alkyl, (C_2-C_4) alkenyl, (C_1-C_6) haloalkyl, (C_2-C_4) alkynyl and (C_1-C_6) alkylsulfonyl and (C_1-C_6) alkylcarbonyl"
- NR_4R_5 , wherein R_4 and R_5 are independently selected from the group consisting of (C_1-C_6) alkyl and (C_1-C_6) alkoxy;
- (C_3-C_8) cycloalkyl, (C_3-C_8) heterocycloalkyl, aryl and heteroaryl, each of which is optionally substituted by one or more halogen atoms or

oxo groups or CN groups; and

R_2 is selected from the group consisting of:

- linear or branched (C_1-C_8) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, optionally substituted by one or more CN groups or halogen atoms;
- 5 - $-(CH_2)_mR_6$, wherein R_6 is selected from the group consisting of (C_3-C_8) cycloalkyl, (C_3-C_8) heterocycloalkyl, aryl, (C_1-C_6) arylalkyl, aryloxy, arylthio and heteroaryl, each of which optionally substituted by one or more substituents selected from the group consisting of oxo, OH, halogen, CN, NH_2 , $CONH_2$, NO_2 , $NHC(O)H$,
- 10 linear or branched (C_1-C_6) alkyl, linear or branched (C_1-C_6) haloalkyl, linear or branched (C_1-C_6) alkoxy, linear or branched (C_1-C_6) haloalkoxy, (C_1-C_6) hydroxyalkoxy, (C_1-C_6) haloalkoxy, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarboxyl, (C_1-C_6) alkylsulfonyl and (C_1-C_6) alkylsulfanyl, (C_1-C_6) alkyloxysulfonyl,
- 15 (C_1-C_6) haloalkylsulfonyloxy, aminosulfonyl, (C_3-C_8) cycloalkyl, (C_3-C_6) heterocycloalkyl and heteroaryl wherein m is 0 or an integer from 1 to 3 and

X and Y are independently H or halogen and

pharmaceutically acceptable salts thereof,

- 20 with the proviso that when R_1 is a group $-CH_2OH$ and R_2 is (C_1-C_6) alkyl or (C_3-C_8) cycloalkyl, then X and Y are fluorine atoms.

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

The expressions "linear" and "straight" have the same meaning.

- 25 The term " (C_1-C_6) alkyl", " (C_1-C_8) alkyl" or " (C_1-C_{15}) alkyl" refers to straight or branched chain alkyl groups wherein the number of carbon atoms is from 1 to 6, 1 to 8 or 1 to 15 respectively. 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 and the like.

The expression “(C₂-C₆)alkenyl” refers to straight or branched carbon chains with one or more double bonds, wherein the number of carbon atoms is
5 from 2 to 6. Examples of said groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like.

The expression “(C₂-C₆)alkynyl” refers to straight or branched carbon chains with one or more triple bonds, wherein the number of carbon atoms is from 1 to 6. Examples of said groups comprise ethynyl, propynyl, butynyl,
10 pentynyl, hexynyl and the like.

The expression “(C₁-C₆)alkylcarboxyl” refers to alkyl-COO groups.

The term “(C₁-C₆)alkoxy” refers to alkyl-oxy (e.g. alkoxy) groups, being the alkyl portion as above defined. Examples of said groups may thus comprise methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-
15 butoxy, tert-butoxy, pentoxy, hexoxy and the like.

The expressions “(C₁-C₆)alkoxycarbonyl” and “(C₁-C₆) hydroxyalkoxy” refer respectively to alkoxy-CO- and (OH)alkoxy- groups.

The expressions “(C₁-C₆)haloalkyl” and “(C₁-C₆)haloalkoxy” refer to the above “(C₁-C₆)alkyl” and “(C₁-C₆)alkoxy” groups wherein one or more
20 hydrogen atoms are replaced by one or more halogen atoms, which can be the same or different from each other.

Examples of said (C₁-C₆)haloalkyl and (C₁-C₆)haloalkoxy groups may thus include halogenated, poly-halogenated and fully halogenated alkyl and alkoxy groups wherein all of the hydrogen atoms are replaced by halogen
25 atoms, e.g. trifluoromethyl or trifluoromethoxyl groups.

The expression “(C₃-C₈)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 "(C₃-C₈)heterocycloalkyl" refers to (C₃-C₈)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).

- 5 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.

The expression "(C₁-C₆)arylalkyl" refers to (C₁-C₆)alkyl groups further substituted by aryl.

- 10 The expressions "aryloxy" and "arylthio" refer respectively to aryl-oxy- and aryl-S- groups, being the aryl portion as above defined.

The expressions "(C₁-C₆)alkylsulfanyl" and "(C₁-C₆)alkylsulfonyl" refer respectively to alkyl-S- and alkyl-SO₂- groups.

- 15 The term "(C₁-C₆)haloalkylsulfonyloxy" refers to haloalkyl-SO₂(O)- groups.

The expression "aminosulfonyl" refers to NH₂S(O₂)-.

- 20 The expression "heteroaryl" refers to mono, bi- or tri-cyclic ring systems with 5 to 20 ring atoms, preferably from 5 to 15, in which at least one ring is aromatic and in which at least one carbon ring atom is a heteroatom or heteroaromatic group (e.g. N, NH, S or O).

Examples of suitable aryl or heteroaryl monocyclic systems include, for instance, thiophene, benzene, pyrrole, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridine, imidazolidine, furan radicals and the like.

- 25 Examples of suitable aryl or heteroaryl bicyclic systems include naphthalene, biphenylene, purine, pteridine, benzothiazole, quinoline, isoquinoline, indole, isoindole, benzothiophene, dihydrobenzo dioxin, dihydrobenzo dioxepine, thiazole, benzo oxazine radicals and the like.

Examples of suitable aryl or heteroaryl tricyclic systems include

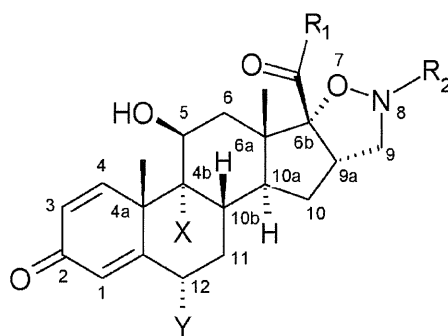
fluorene radicals as well as benzocondensed derivatives of the aforementioned heteroaryl bicyclic systems.

The expressions “linear” and “straight” have the same meaning.

It will be apparent to those skilled in the art that compounds of general
5 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.

10 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 R₁ and R₂ 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
20 (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 those of

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,
 5 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.

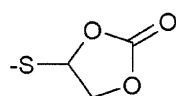
These salts may be prepared from compounds of formula (I) or (I') by known salt-forming procedures.

10 In a preferred embodiment, in the compounds of the invention at least one of **X** and **Y** is a halogen atom, **m** is zero and **R₆** is optionally substituted aryl, (C₃-C₈)cycloalkyl or heteroaryl. In a more preferred embodiment, both **X** and **Y** are independently halogen atoms and **m** is zero and **R₆** is optionally substituted aryl, (C₃-C₈)cycloalkyl or heteroaryl. In a still more preferred
 15 embodiment, both **X** and **Y** are fluorine and **m** is zero and **R₆** is optionally substituted aryl, (C₃-C₈)cycloalkyl or heteroaryl.

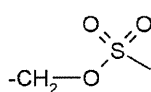
In a preferred embodiment, in the compounds of the invention **m** is zero, **R₆** is optionally substituted aryl, (C₃-C₈)cycloalkyl or heteroaryl, **R₁** is -(CH₂)_n-Z-(CH₂)_{n'}-**R₃**, wherein **n** is 1, **Z** is a single bond, **n'** is 0 and **R₃** is—
 20 OH, or **R₁** is -(CH₂)_n-Z-(CH₂)_{n'}-**R₃**, wherein **n** is 0, **Z** is -S-, **n'** is 1, and **R₃** is an halogen atom, or **R₁** is -(CH₂)_n-Z-(CH₂)_{n'}-**R₃**, wherein **n** is 0, **Z** is a bond, **n'** is 1, and **R₃** is selected from the group consisting of an halogen atom, CN, CONH₂, (C₁-C₆)haloalkyl and (C₁-C₆)alkylcarbonyl. In a more preferred embodiment, **R₁** is -(CH₂)_n-Z-(CH₂)_{n'}-**R₃**, wherein **n** is 0, **Z** is -S-, **n'** is 1, and
 25 **R₃** is an halogen atom, or **R₁** is -(CH₂)_n-Z-(CH₂)_{n'}-**R₃**, wherein **n** is 0, **Z** is a bond, **n'** is 1 and **R₃** is an halogen atom.

In a preferred embodiment, in the compounds of the invention, **R₁** is selected from the group consisting of methyl, hydroxy, hydroxymethyl,

N-methoxy-N-methylamino, N-methyl-N-cyanomethyl, chloromethyl, fluoromethyl, fluoromethoxy, fluoroethoxy, chloromethoxy, cyanomethyl, methylsulfanyl, methylsulfanylmethyl, cyclopropylmethoxy, fluoroethylsulfanyl, trifluoroethylsulfanyl, cyclobutylsulfanyl, cyanomethoxy
 5 and a group of formula (h), (h'), (h'''), (i), (i'), (l), (l'), (l'') or (l''') below



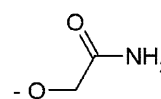
(h)



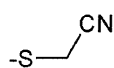
(i)



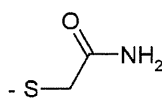
(l)



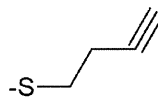
(l')



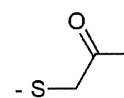
(l'')



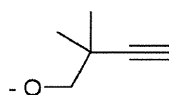
(l''')



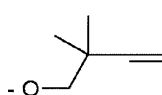
(h')



(h'')



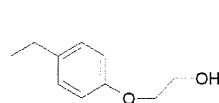
(h''')



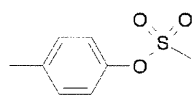
(i')

15 In a preferred embodiment, in the compounds of the invention, **R₂** is selected from the group consisting of cyclohexyl, ethyl-butyl, phenyl-propyl, phenoxy-ethyl, amino-carbonyl-phenyl, amino-sulfonyl-phenyl, bromo-phenyl, cyano-phenyl, cyclopropyl-phenyl, methoxy-benzyl, propyl-butyl, methyl-butyl, tert-butyl-benzyl, methyl-benzyl, dichloro-phenyl, chloro-furan-2-yl-
 20 methyl, chloro-thiophen-2-yl-methyl, phenylsulfanyl-ethyl, cyclohexyl, cyclopentylmethyl, ethyl-2-methyl-propyl, 4-chloro-3-trifluoromethyl-phenyl, 4-chloro-3-methyl-phenyl, trifluoro-propyl, 3,3-dimethyl-butyl, fluoro-benzyl, thiophen-2-ylmethyl, furan-2-ylmethyl, ethyl-methyl-propyl, ethyl-butyl, methoxy-carbonyl-phenyl, methoxy-carbonyl-benzyl, cyclohexylmethyl,
 25 cyclohexylphenyl, methylsulfanyl-benzyl, methylsulfanylmethyl, sec-butyl, cyclopentylmethyl, tert-butoxy-benzyl, tert-butoxy-carbonyl-benzyl, pyridin,

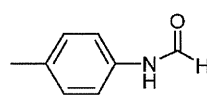
thiazol-4-yl, thiazol-2-yl-methyl, oxazol-2-yl, imidazol-1-yl-ethyl, cyclohexyl-ethyl, pyridin-3-yl-propyl, furan-3-yl, 1H-indol-3-ylmethyl, 1-methyl-1H-indol-3-ylmethyl, quinolin-7-ylmethyl, benzothiazol-2-ylmethyl, bicyclo[2.2.1]hept-2-yl, propylbenzyl, quinolin-5-ylmethyl, benzofuran-3-yl, benzo[1,3]dioxol-5-yl,
 5 methyl-1H-indol-2-yl, methyl-1H-indol-3-ylmethyl, methyl-sulfonyl-phenyl, methyl-1H-imidazol-4-ylmethyl, 1H-imidazol-2-ylmethyl, chloro-phenyl, tolyl, chloro-benzyl, hydroxy-benzyl, thiophen-2-ylmethyl, furan-2-ylmethyl, methyl-benzyl, methoxy-benzyl, butoxy-benzyl, cyclopentylmethyl, chloro-thiophen-2-ylmethyl, methyl-thiophen-2-yl-methyl, bicycloheptyl, imidazolylethyl, 4-
 10 piperidin-4-yl-methyl-phenyl and a group of formula (t), (t'), (t'') or (t''') below



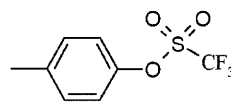
(t)



(t')



(t'')



(t''')

Preferred compounds of general formula (I) or (I') have the formula
 15 **(IA)**, wherein **X** and **Y** are fluorine, **n** is 0 or 1, **n'** is 0 or 1; **Z** is a single bond, or is selected from -S-, -O- and -OC(R₄R₅); **R₃** is selected from the groups consisting of H, halogen, OH, -CN, CONH₂, -NR₄R₅, (C₁-C₆) alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylcarbonyl and an optionally substituted monocyclic(C₃-C₈)heterocycloalkyl; and the groups **R₂**,
 20 **R₄**, **R₅** are as above defined for compounds of formula (I).

Other preferred compounds of general formula (I) or (I') have formula
(IB), wherein **X** and **Y** are fluorine, **R₁** is -(CH₂)_n-Z-(CH₂)_{n'}-R₃, wherein **n** is 1, **Z** is a single bond, **n'** is 0 and **R₃** is -OH; and the group **R₂** is as above defined for compounds of formula (I).

25 Preferred compounds of general formula (I) or (I') have formula **(IC)**, wherein **X** and **Y** are fluorine, **m** is zero and **R₆** is an optionally substituted aryl or heteroaryl, such that **R₂** represents an optionally substituted aryl or

heteroaryl; and **R**₁ is as above defined for compounds of formula (I).

In a preferred embodiment, in the compounds of formula (IC), **R**₂ is optionally substituted phenyl.

In another preferred embodiment, in the compounds of formula (IC), **R**₂
5 is an optionally substituted heteroaryl.

According to analogous procedures and methods described in the present application, the following compounds of formula (IC) may be obtained:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-pyridin-3-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
10 tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid
S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-thiazol-4-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid
15 S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-8-oxazol-2-yl-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]phenanthrene-6b-carbothioic acid
S-fluoromethyl ester;

20 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-furan-3-
yl-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]phenanthrene-6b-carbothioic acid
S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzofuran-3-yl-4b,12-
25 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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

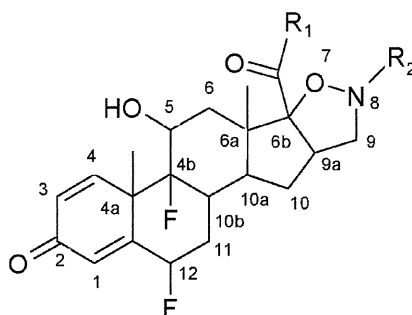
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzo[1,3]dioxol-5-yl-

- 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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
- 5 4a,6a-dimethyl-8-(1-methyl-1H-indol-2-yl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-phenyl)-4b,12-
difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-
- 10 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-p-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid
- 15 S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
8-(4-methoxy-phenyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
- 20 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-o-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid
S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Chloro-phenyl)-4b,12-
- 25 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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-

4a,6a-dimethyl-2-oxo-8-m-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(3-methoxy-phenyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester.

In a preferred embodiment, the invention is directed to compounds of general formula (ID)



(ID)

wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n and n' are each independently 0, 1 or 2;

Z is a single bond or is selected from $-S-$ and $-O-$;

R_3 is selected from the group consisting of:

- H, halogen, CN, $CONH_2$, OH, straight or branched (C_1-C_{15}) alkyl, (C_1-C_6) haloalkyl and (C_1-C_6) alkylsulfonyl;
- NR_4R_5 , wherein R_4 and R_5 are independently selected from the group consisting of (C_1-C_6) alkyl and (C_1-C_6) alkoxy;
- (C_3-C_8) cycloalkyl, (C_3-C_8) heterocycloalkyl, aryl and heteroaryl, each of which is optionally substituted by one or more halogen atoms or oxo groups;

R_2 is selected from the group consisting of:

- straight or branched (C₁-C₈)alkyl;
- -(CH₂)_mR₆, wherein R₆ is (C₃-C₈)cycloalkyl, wherein m is 0 or an integer from 1 to 3 and

pharmaceutically acceptable salts thereof.

5 Examples of compounds of formula (ID) include:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-cyclopentylmethyl-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-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

10 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-cyclohexyl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

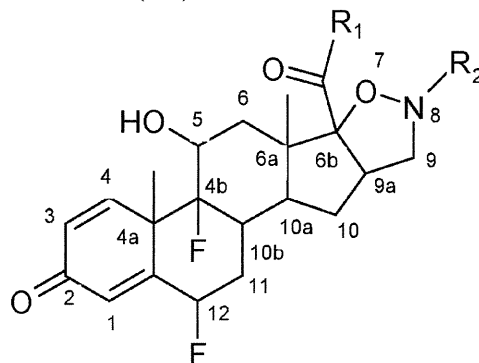
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-cyclohexyl-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester.

15 According to analogous procedures and methods described in the present application, the following compounds of formula (ID) may be obtained:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-cyclohexyl-ethyl)-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-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

25 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-bicyclo[2.2.1]hept-2-yl-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-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester.

In a further preferred embodiment, the invention is directed to compounds of general formula (IE)



(IE)

5 wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n and n' are each independently 0, 1 or 2;

Z is a single bond or is selected from $-S-$ and $-O-$;

R_3 is selected from the group consisting of:

- 10
- H, halogen, CN, OH, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl and (C_1-C_6) alkylsulfonyl;
 - NR_4R_5 , wherein R_4 and R_5 are independently selected from the group consisting of (C_1-C_6) alkyl and (C_1-C_6) alkoxy;
 - (C_1-C_6) alkyl;
 - 15 - (C_3-C_8) cycloalkyl, (C_3-C_8) heterocycloalkyl, aryl and heteroaryl, each of which is optionally substituted by one or more halogen atoms or oxo groups;

and

R_2 is linear or branched (C_1-C_8) alkyl and
20 pharmaceutically acceptable salts thereof.

Examples of compounds of formula (IE) include:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-4b,12-difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-

- 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(1-propyl-butyl)-
- 5 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-butyl)-2-oxo-
- 10 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-methyl-butyl)-
- 15 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-propyl-butyl)-
- 20 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(1-propyl-butyl)-
- 25 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-(1-Ethyl-2-methyl-propyl)-4b,12-difluoro-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-

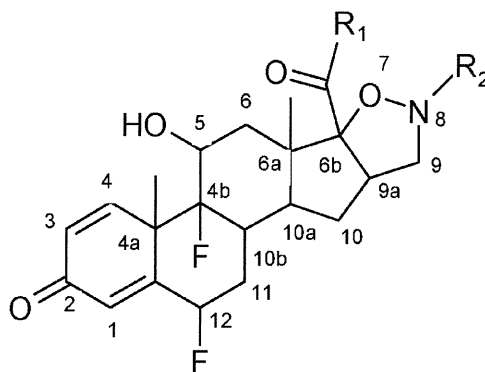
- 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-butyl)-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid;
- 5 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-propyl-butyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-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]phenanthrene-6b-carboxylic acid;
- 10 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(1-Ethyl-2-methyl-propyl)-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]phenanthrene-6b-carboxylic acid;
- 15 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-butyl)-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]phenanthrene-6b-carboxylic acid;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-butyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
- 20 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-propyl-butyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
- 25 (4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-((S)-1-Ethyl-2-methyl-propyl)-

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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester.

According to analogous procedures and methods described in the
present application, the following compounds of the invention of formula (IE)
may be obtained:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(1-Ethyl-2-methyl-
propyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester.

In a preferred embodiment, the invention is directed to compounds of
general formula (IF)



(IF)

wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_n-R_3$ wherein n is 1 and n' is zero;

- Z is a single bond;
- R_3 is a fluorine atom;

R_2 is selected from the group consisting of:

- linear or branched (C_1-C_8) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, optionally substituted by one or more CN groups;
- $-(CH_2)_mR_6$, wherein R_6 is selected from the group consisting of (C_3-C_8) cycloalkyl, (C_3-C_8) heterocycloalkyl, aryl, aryloxy, arylthio

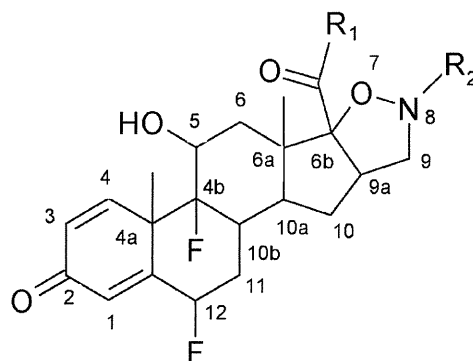
and heteroaryl, each of which optionally substituted by one or more substituents selected from the group consisting of oxo, OH, halogen, CN, NH₂, NO₂, linear or branched (C₁-C₆)alkyl, (C₁-C₆)alkoxy, aryl, (C₁-C₆)hydroxyalkoxy, (C₁-C₆)haloalkoxy, straight or branched (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylcarboxyl, arylthio, and (C₁-C₆)alkylsulfanyl, wherein **m** is 0 or an integer from 1 to 3;

with the proviso that **R**₂ is not 4-chloro-benzyl;

and pharmaceutically acceptable salts thereof.

In particular, the invention is directed to compounds of general formula

(IG)



(IG)

wherein

R₁ is -(CH₂)_n-Z-(CH₂)_{n'}-**R**₃ wherein **n** is 1 and **n'** is zero;

- **Z** is a single bond;
- **R**₃ is a fluorine atom;

R₂ is selected from the group consisting of:

- linear or branched (C₁-C₈)alkyl;
- -(CH₂)_m**R**₆, wherein **R**₆ is selected from the group consisting of (C₃-C₈)cycloalkyl, aryl and heteroaryl, each of which optionally substituted by one or more substituents selected from the group consisting of halogen, linear or branched (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl and (C₁-C₆)alkylsulfanyl

wherein **m** is 0 or an integer from 1 to 3;
with the proviso that **R₂** is not 4-chloro-benzyl;
and pharmaceutically acceptable salts thereof.

In a preferred embodiment, in the compounds of formula (**IG**), **R₂** is
5 (C₁-C₈)alkyl or -(CH₂)_m**R₆**, where **m** is 1 and **R₆** is optionally substituted
heteroaryl.

Other compounds of formula (**IG**) which were obtained with analogous
procedures to those described in the examples, are the following:

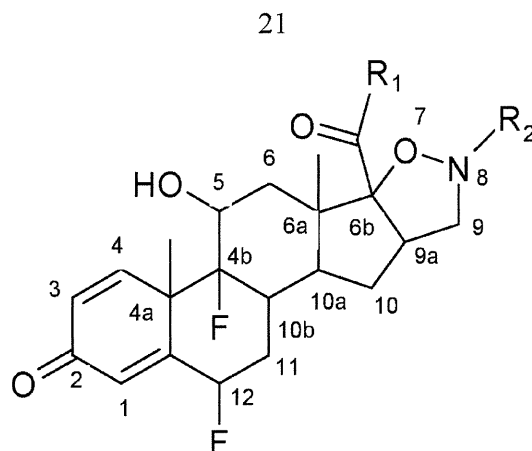
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-6b-(2-fluoro-
10 acetyl)-5-hydroxy-4a,6a-dimethyl-8-(4-methyl-benzyl)-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-4b,12-
difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl
15 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-6b-(2-fluoro-
acetyl)-5-hydroxy-4a,6a-dimethyl-8-phenyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
20 pentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-phenyl)-4b,12-
difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthren-2-one.

25 In a preferred embodiment, the invention is directed to
compounds of general formula (**IH**)



(IH)

wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n is zero and n' is 1;

- Z is $-S-$;
- R_3 is a fluorine atom;

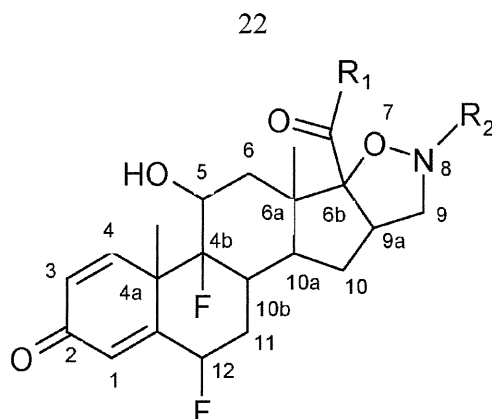
R_2 is selected from the group consisting of:

- linear or branched (C_1-C_8) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, optionally substituted by one or more CN groups or halogen atoms;
- $-(CH_2)_m R_6$, wherein R_6 is selected from the group consisting of (C_3-C_8) cycloalkyl, (C_3-C_8) heterocycloalkyl, aryl, aryloxy, arylthio and heteroaryl, each of which optionally substituted by one or more substituents selected from the group consisting of oxo, OH, halogen, CN, NH_2 , NO_2 , linear or branched (C_1-C_6) alkyl, linear or branched (C_1-C_6) haloalkyl, linear or branched (C_1-C_6) alkoxy, aryl, (C_1-C_6) hydroxyalkoxy, (C_1-C_6) haloalkoxy, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarboxyl, arylthio, and (C_1-C_6) alkylsulfanyl, wherein m is 0 or an integer from 1 to 3;

with the proviso that R_2 is neither 4-chloro-benzyl nor propyl-benzene;

and pharmaceutically acceptable salts thereof.

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



(II)

wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n is zero and n' is 1;

- 5 - Z is $-S-$;
 - R_3 is a fluorine atom;

R_2 is selected from the group consisting of:

- linear or branched (C_1-C_8) alkyl optionally substituted by one or more halogen atoms;
 10 - $-(CH_2)_mR_6$, wherein R_6 is selected from the group consisting of (C_3-C_8) cycloalkyl, aryl, aryloxy, arylthio and heteroaryl, each of which optionally substituted by one or more substituents selected from the group consisting of halogen, linear or branched (C_1-C_6) alkyl, linear or branched (C_1-C_6) haloalkyl, linear or branched (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl and (C_1-C_6) alkylsulfanyl
 15 wherein m is 0 or an integer from 1 to 3;

with the proviso that R_2 is neither 4-chloro-benzyl nor propyl-benzene; and pharmaceutically acceptable salts thereof.

In a preferred embodiment, in the compounds of formula (II), R_2 is
 20 $-(CH_2)_mR_6$, m is 1 and R_6 is optionally substituted aryl or heteroaryl.

Other compounds obtained with analogous procedures to those described in the examples, are the following:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-

- 4a,6a-dimethyl-2-oxo-8-(5-methyl-thiophen-2-yl-methyl)-
2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
- 5 8-(4-methoxy-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
- 10 4a,6a-dimethyl-8-(3-methyl-butyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclopentylmethyl-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-
- 15 pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-(4-propyl-benzyl)-
2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
- 20 (4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-
dimethyl-8-(3-methyl-benzyl)-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]phenanthrene-6b-carbothioic acid
S-((S)-fluoromethyl) ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
- 25 4a,6a-dimethyl-2-oxo-8-(5-chloro-thiophen-2-yl-methyl)-
2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-

- 4a,6a-dimethyl-8-(4-methyl-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-benzyl)-
- 5 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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-(2-phenylsulfanyl-ethyl)-
- 10 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-(1-propyl-butyl)-
- 15 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-(2-phenoxy-ethyl)-
- 20 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-(5-chloro-furan-2-yl-methyl)-
- 25 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclohexyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-

4a,6a-dimethyl-2-oxo-8-(5-methyl-thiophen-2-yl-methyl)-
2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-
a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(4-
5 methoxy-benzyl)-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]phenanthrene-6b-carbothioic acid S-
fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-8-(3-methyl-butyl)-2-oxo-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
10 tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-
fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclopentylmethyl-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]phenanthrene-6b-carbothioic acid S-
15 fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-(4-propyl-benzyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-
fluoromethyl ester;

(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-
20 dimethyl-8-(3-methyl-benzyl)-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]phenanthrene-6b-carbothioic acid S-
((S)-fluoromethyl) ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
25 4a,6a-dimethyl-2-oxo-8-(5-chloro-thiophen-2-yl-methyl)-
2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-
a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-

4a,6a-dimethyl-8-(4-methyl-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(2-phenylsulfanyl-ethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-propyl-butyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(2-phenoxy-ethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(5-chloro-furan-2-yl-methyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclohexyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butoxy-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Butoxy-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(5-methyl-furan-2-ylmethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-(5-methylsulfanyl-thiophen-2-ylmethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-((S)-1-Ethyl-2-methyl-propyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(3,3,3-trifluoro-propyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclopropylmethyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Cyclohexyl-ethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Bicyclo[2.2.1]hept-2-yl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-((S)-1-methyl-1H-indol-3-ylmethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-m-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-o-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-p-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(4-fluoro-phenyl)-
 5 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]phenanthrene-6b-carbothioic acid S-((S)-fluoromethyl) ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
 4a,6a-dimethyl-2-oxo-8-pyridin-3-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
 10 tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(3-fluoro-phenyl)-
 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]phenanthrene-6b-carbothioic acid S-
 15 ((S)-fluoromethyl) ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
 4a,6a-dimethyl-2-oxo-8-(4-trifluoromethyl-phenyl)-
 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester.

20 According to analogous procedures and methods described in the present application, the following compounds may be obtained:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(1-ethyl-2-methyl-propyl)-
 4b,

12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-
 25 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
 4a,6a-dimethyl-2-oxo-8-propyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-

tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid
S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-pyridin-3-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
5 tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid
S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-thiazol-4-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-
tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid
10 S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-8-oxazol-2-yl-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]phenanthrene-6b-carbothioic acid
S-fluoromethyl ester;

15 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-thiazol-2-ylmethyl-
2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-8-
20 (2-imidazol-1-yl-ethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Cyclohexyl-ethyl)-
4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-
25 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-
4a,6a-dimethyl-2-oxo-8-(3-pyridin-3-yl-propyl)-

- 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-furan-3-yl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(1H-indol-3-ylmethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-quinolin-7-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzothiazol-2-ylmethyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Bicyclo[2.2.1]hept-2-yl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-quinolin-5-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-quinolin-2-ylmethyl-

- 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzofuran-3-yl-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-
- 5 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzo[1,3]dioxol-5-yl-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-
- 10 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(1-methyl-1H-indol-2-yl)-2-oxo-
- 15 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-methyl-1H-indol-3-ylmethyl)-
- 20 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-methyl-1H-imidazol-4-ylmethyl)-
- 25 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-p-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(4-methoxy-phenyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-o-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-m-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-8-(3-methoxy-phenyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester.

Other compounds obtained with analogous procedures to those described in the examples, are the following:

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(1-propyl-butyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

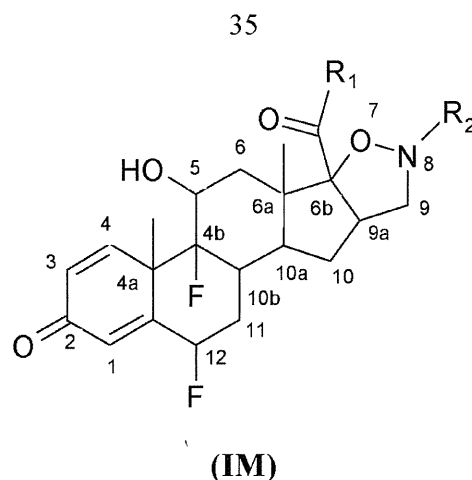
5 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-benzyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-10 6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-propyl-benzyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclohexyl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-15 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-methyl-butyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one. 20

In a preferred embodiment, the invention is directed to compounds of general formula **(IM)**



wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n is zero and n' is 1;

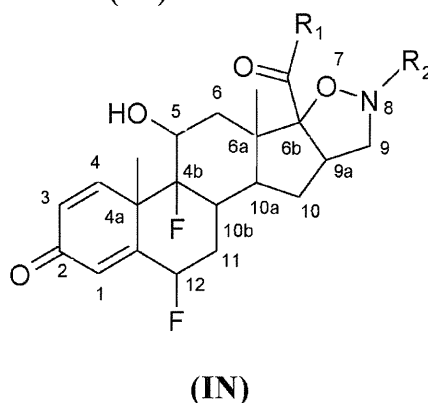
5 Z is a single bond;

R_3 is $-OH$;

R_2 is selected from the group consisting of:

- linear or branched (C_1-C_8) alkyl;
 - $-(CH_2)_mR_6$, wherein R_6 is selected from the group consisting of
- 10 (C_3-C_8) cycloalkyl, wherein m is 0 or an integer from 1 to 3 and pharmaceutically acceptable salts thereof.

In a preferred embodiment, the invention is directed to compounds of general formula (IN)



wherein

R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n is zero and n' is 1;

Z is a single bond;

R_3 is $-OH$;

R_2 is $-(CH_2)_mR_6$, wherein R_6 is aryl optionally substituted by one or more substituents selected from the group consisting of halogen, CN, $CONH_2$, $NHC(O)H$, linear or branched (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonyl, linear or branched (C_1-C_6) haloalkyl, linear or branched (C_1-C_6) haloalkoxy, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkoxysulfonyl, (C_1-C_6) haloalkylsulfonyloxy, (C_3-C_8) cycloalkyl, (C_3-C_6) heterocycloalkyl, aminosulfonyl, heteroaryl and m is 0 and pharmaceutically acceptable salts thereof.

Other compounds obtained with analogous procedures to those described in the examples, are the following:

10 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(1-propyl-butyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclohexyl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-15 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-methyl-butyl)-20 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-p-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one; 25

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-m-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-

- pentaleno[2,1-aphenanthren-2-one;
(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(4-fluoro-phenyl)-
5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- 5 pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Chloro-phenyl)-4b,12-
difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- 10 pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-
(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-trifluoromethyl-phenyl)-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(3-fluoro-phenyl)-
- 15 5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-
(2-hydroxy-acetyl)-4a,6a-dimethyl-8-o-tolyl-
- 20 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-3-methyl-phenyl)-
4b,12-difluoro-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- 25 pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-3-trifluoromethyl-
phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-

- pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,4-Dichloro-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- 5 pentaleno[2,1-a]phenanthren-2-one;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Bromo-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- pentaleno[2,1-a]phenanthren-2-one;
10 4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS)-4b-Fluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzonitrile;
4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- 15 pentaleno[2,1-a]phenanthren-8-yl]-benzamide;
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-trifluoromethoxy-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- 20 pentaleno[2,1-a]phenanthren-2-one;
Methanesulfonic acid 4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- pentaleno[2,1-a]phenanthren-8-yl]-phenyl ester;
25 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Cyclohexyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
- pentaleno[2,1-a]phenanthren-2-one;

- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-thiophen-2-yl-phenyl)
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 5 4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzoic acid methyl ester;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-(4-methanesulfonyl-phenyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 10 3-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzonitrile;
- 15 4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzene sulfonamide;
- 20 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Cyclopropyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 25 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

N-{4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-8-yl]-phenyl}-formamide;

5 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-trifluoromethyl-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-
10 (2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-trifluoromethoxy-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Bromo-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-
15 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

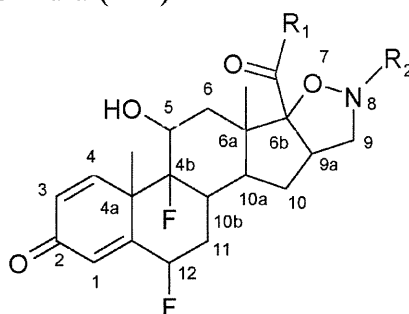
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzothiazol-6-yl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-(4-hydroxy-phenyltrifluoromethanesulfonate)-4a,6a-dimethyl-
4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

25 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Cyclopropyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-piperidin-4-ylmethyl-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one.

- 5 In a preferred embodiment, the invention is directed to compounds of general formula (IN')



(IN')

wherein

- 10 **R₁** is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n is zero and n' is 1;
Z is a single bond;
R₃ is $-OH$;
R₂ is $-(CH_2)_mR_6$, wherein **R₆** is heteroaryl and **m** is 0 and pharmaceutically acceptable salts thereof.

- 15 Other compounds which were obtained with analogous procedures to those described in the examples, are the following:

- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-quinolin-6-yl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

- 20 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-pyridin-3-yl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzothiazol-6-yl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one.

5 It is to be understood that the present invention covers all combinations of particular and preferred groups and embodiments described hereinabove.

Hereinafter, compounds of formula (I), (I'), (IA), (IB), (IC), (ID), (IF), (IG), (IH), (IL), (IM), (IN) and their pharmaceutically acceptable salts and solvates are referred to as "compounds of the invention".

10 Examples of preferred compounds of the invention are:

Compound	Chemical Name
10	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,3-dimethyl-butyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
11	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-(4-fluoro-benzyl)-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
12	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-thiophen-2-ylmethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
13	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-furan-2-ylmethyl-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
14	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-ethyl-butyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

15	3-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-ylmethyl]-benzoic acid methyl ester
16	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-cyclohexylmethyl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
17	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-methylsulfanyl-benzyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
18	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-((R,S)-sec-butyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
19	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-cyclopentylmethyl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
20	4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-ylmethyl]-benzoic acid tert-butyl ester
21	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-benzyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
23	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(1-propyl-butyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
24	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-benzyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
25	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-propyl-benzyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

26	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclohexyl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
27	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-methyl-butyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
28	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(5-methylsulfanyl-thiophen-2-ylmethyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
29	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-(1-Ethyl-2-methyl-propyl)-4b,12-difluoro-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
30	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Butoxy-benzyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
31	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Cyclohexyl-ethyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
32	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-8-(1-methyl-1H-indol-3-ylmethyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
33	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Bicyclo[2.2.1]hept-2-yl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
34	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-pyridin-3-yl-propyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
35	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3,3,3-trifluoro-propyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
36	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-(2-imidazol-1-yl-ethyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

37	(4aS,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b-(R)-Fluoro-12-fluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-quinolin-5-ylmethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
38	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-thiazol-2-ylmethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
39	Methanesulfonic acid 2-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-benzyl)-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	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-6b-acetyl-8-(4-chloro-benzyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
41	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-benzyl)-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]phenanthrene-6b-carboxylic acid
42	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,3-dimethyl-butyl)-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]phenanthrene-6b-carboxylic acid
43	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-(4-fluoro-benzyl)-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]phenanthrene-6b-carboxylic acid
44	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-thiophen-2-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
45	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-furan-2-ylmethyl-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]phenanthrene-6b-carboxylic acid
46	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(5-methyl-thiophen-2-ylmethyl)-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]phenanthrene-6b-carboxylic acid

(continued)

47	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(4-methoxy-benzyl)-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]phenanthrene-6b-carboxylic acid
48	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-butyl)-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]phenanthrene-6b-carboxylic acid
49	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclopentylmethyl-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]phenanthrene-6b-carboxylic acid
50	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(4-propyl-benzyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
51	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-benzyl)-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]phenanthrene-6b-carboxylic acid
52	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(5-Chloro-thiophen-2-ylmethyl)-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]phenanthrene-6b-carboxylic acid
53	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(4-methyl-benzyl)-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]phenanthrene-6b-carboxylic acid
54	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-benzyl)-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]phenanthrene-6b-carboxylic acid
55	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(2-phenylsulfanyl-ethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
56	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-propyl-butyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
57	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(2-phenoxy-ethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid

(continued)

58	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(5-Chloro-furan-2-ylmethyl)-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]phenanthrene-6b-carboxylic acid
59	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclohexyl-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]phenanthrene-6b-carboxylic acid
60	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-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]phenanthrene-6b-carboxylic acid
61	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butoxy-benzyl)-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]phenanthrene-6b-carboxylic acid
62	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Butoxy-benzyl)-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]phenanthrene-6b-carboxylic acid
63	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(5-methyl-furan-2-ylmethyl)-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]phenanthrene-6b-carboxylic acid
64	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(5-methylsulfanyl-thiophen-2-ylmethyl)-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]phenanthrene-6b-carboxylic acid
65	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(1-Ethyl-2-methyl-propyl)-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]phenanthrene-6b-carboxylic acid
66	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(3,3,3-trifluoro-propyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
67	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclopropylmethyl-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]phenanthrene-6b-carboxylic acid
68	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Cyclohexyl-ethyl)-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]phenanthrene-6b-carboxylic acid

(continued)

69	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Bicyclo[2.2.1]hept-2-yl-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]phenanthrene-6b-carboxylic acid
70	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(1-methyl-1H-indol-3-ylmethyl)-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]phenanthrene-6b-carboxylic acid
71	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-benzyl)-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]phenanthrene-6b-carbothioic acid S-(2-oxo-[1,3]dioxolan-4-yl) ester
72	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-benzyl)-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]phenanthrene-6b-carboxylic acid methoxymethyl-amide
73	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-thiophen-2-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid fluoromethyl ester
74	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-(4-fluoro-benzyl)-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]phenanthrene-6b-carboxylic acid fluoromethyl ester
75	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-(4-fluoro-benzyl)-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]phenanthrene-6b-carboxylic acid cyanomethyl ester
76	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-thiophen-2-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid cyanomethyl ester
77	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-furan-2-ylmethyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(continued)

78	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-8-(4-fluoro-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
79	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-thiophen-2-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
80	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,3-dimethyl-butyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
81	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(5-methyl-thiophen-2-yl-methyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
82	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(4-methoxy-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
83	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-butyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
84	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclopentylmethyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
85	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(4-propyl-benzyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(continued)

86	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(3-methyl-benzyl)-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]phenanthrene-6b-carbothioic acid S-((S)-fluoromethyl) ester
87	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(5-chloro-thiophen-2-yl-methyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
88	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(4-methyl-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
89	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
90	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(2-phenylsulfanyl-ethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
91	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-propyl-butyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
92	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(2-phenoxy-ethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
93	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(5-chloro-furan-2-yl-methyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
94	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclohexyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(continued)

95	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
96	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butoxy-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
97	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Butoxy-benzyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
98	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(5-methyl-furan-2-ylmethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
99	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-(5-methylsulfanyl-thiophen-2-ylmethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
100	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-((S)-1-Ethyl-2-methyl-propyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
101	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(3,3,3-trifluoro-propyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
102	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Cyclopropylmethyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
103	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Cyclohexyl-ethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(continued)

104	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Bicyclo[2.2.1]hept-2-yl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
105	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-((S)-1-methyl-1H-indol-3-yl-methyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
107	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-8-(4-methyl-benzyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
108	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-8-thiophen-2-ylmethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
109	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-6b-(2-fluoro-acetyl)-8-(4-fluoro-benzyl)-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
110	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-6b-(2-fluoro-acetyl)-8-furan-2-ylmethyl-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
111	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-8-(4-methoxy-benzyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
112	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-cyclopentylmethyl-4b,12-difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
113	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,3-dimethyl-butyl)-4b,12-difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

114	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(5-chloro-thiophen-2-ylmethyl)-4b,12-difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
116	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-[4-(2-hydroxy-ethoxy)-benzyl]-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
122	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-phenyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
123	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
124	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-p-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
125	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-quinolin-6-yl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
126	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-pyridin-3-yl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
127	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-m-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
128	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(4-fluoro-phenyl)-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
129	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Chloro-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

130	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-trifluoromethyl-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
131	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(3-fluoro-phenyl)-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
132	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-o-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
133	(4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-3-methyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
134	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-3-trifluoromethyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
135	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,4-Dichloro-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
136	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Bromo-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
137	4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS)-4b-Fluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzonitrile
138	4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzamide
139	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-trifluoromethoxy-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

140	Methanesulfonic acid 4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-phenyl ester
141	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Cyclohexyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
142	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-thiophen-2-yl-phenyl) 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
143	4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzoic acid methyl ester
144	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-(4-methanesulfonyl-phenyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
145	3-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzonitrile
146	4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzene sulfonamide
147	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Cyclopropyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
148	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
149	N-{4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-phenyl}-formamide
150	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-trifluoromethyl-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

151	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-trifluoromethoxy-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
152	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Bromo-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
153	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzothiazol-6-yl-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
154	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-(4-hydroxy-phenyltrifluoromethansulfonate)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
155	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Cyclopropyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
156	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-piperidin-4-ylmethyl-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
158	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-phenyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
159	(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]phenanthrene-6b-carboxylic acid
160	(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]phenanthrene-6b-carboxylic acid
161	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-m-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid

(continued)

162	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-o-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
163	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-p-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
164	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-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]phenanthrene-6b-carboxylic acid
165	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(4-fluoro-phenyl)-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]phenanthrene-6b-carboxylic acid
166	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-pyridin-3-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
167	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(3-fluoro-phenyl)-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]phenanthrene-6b-carboxylic acid
168	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(4-trifluoromethyl-phenyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid
169	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-phenyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
170	(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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
171	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-m-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(continued)

172	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-o-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
173	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-p-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
174	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
175	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(4-fluoro-phenyl)-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]phenanthrene-6b-carbothioic acid S-((S)-fluoromethyl) ester
176	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-pyridin-3-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
177	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(3-fluoro-phenyl)-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]phenanthrene-6b-carbothioic acid S-((S)-fluoromethyl) ester
178	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(4-trifluoromethyl-phenyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
179	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-8-phenyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
180	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-phenyl)-4b,12-difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one

(continued)

181	Methanesulfonic 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
182	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-6b-(2-Chloro-acetyl)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
183	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-6b-(2-methylsulfanyl-acetyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
184	(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]phenanthrene-6b-carboxylic acid chloromethyl thioester
185	(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]phenanthrene-6b-carboxylic acid cyclopropylmethyl ester
186	(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]phenanthrene-6b-carboxylic acid cyanomethyl ester
187	(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]phenanthrene-6b-carboxylic acid carbamoylmethyl ester
188	(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]phenanthrene-6b-carboxylic acid 2,2,2-trifluoro-ethyl ester
189	(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]phenanthrene-6b-carboxylic acid 2-fluoro-ethyl ester

(continued)

190	(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]phenanthrene-6b-carbothioic acid S-cyanomethyl ester
191	(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]phenanthrene-6b-carbothioic acid S-(2-fluoro-ethyl) ester
192	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]phenanthrene-6b-carbothioic acid S-(2,2,2-trifluoro-ethyl) ester
193	(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]phenanthrene-6b-carbothioic acid S-carbamoylmethyl ester
194	(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]phenanthrene-6b-carbothioic acid S-prop-2-ynyl ester
195	(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]phenanthrene-6b-carbothioic acid S-cyclobutyl ester
196	(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]phenanthrene-6b-carbothioic acid S-(2-oxo-propyl) ester
197	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]phenanthrene-6b-carboxylic acid methyl ester
198	(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]phenanthrene-6b-carboxylic acid cyanomethyl-methyl-amide

(continued)

199	(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]phenanthrene-6b-carbothioic acid S-methyl ester
201	(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-6b-Acetyl-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
202	(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]phenanthrene-6b-carboxylic acid 1,1-dimethyl-prop-2-ynyl ester
203	(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]phenanthrene-6b-carboxylic acid 1,1-dimethyl-allyl ester

Other preferred compounds of general formula (I), which were obtained with analogous procedures to those described in the examples, are the following:

Chemical name
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(3-phenyl-propyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid dimethylamide
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,3-Dimethyl-butyl)-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]phenanthrene-6b-carboxylic acid cyanomethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(2-Ethyl-butyl)-4b,12-Difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(3-phenyl-propyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid cyanomethyl ester

According to analogous procedures and methods described in the present application, preferred compounds of the invention from the list below reported, may be obtained:

Chemical name
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-propyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-pyridin-3-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-thiazol-4-yl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-oxazol-2-yl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-thiazol-2-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(2-imidazol-1-yl-ethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(3-pyridin-3-yl-propyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-furan-3-yl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(1H-indol-3-ylmethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-quinolin-7-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzothiazol-2-ylmethyl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-quinolin-5-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-quinolin-2-ylmethyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-Benzofuran-3-yl-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
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(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-8-(1-methyl-1H-indol-2-yl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-methyl-1H-indol-3-ylmethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-(1-methyl-1H-imidazol-4-ylmethyl)-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(1H-imidazol-2-ylmethyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

(continued)

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-p-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(4-methoxy-phenyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-o-tolyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester
(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-8-(3-methoxy-phenyl)-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]phenanthrene-6b-carbothioic acid S-fluoromethyl ester

The present 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.

5 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, corticosteroids, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase
10 subunit beta (IKK2) inhibitors, human neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs) and mucus regulators.

 The present invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a
15 β2-agonist selected from the group consisting of carmoterol, GSK-642444, indacaterol, milveterol, arformoterol, formoterol, salbutamol, levalbuterol, terbutaline, AZD-3199, BI-1744-CL, LAS-100977, bambuterol, isoproterenol, procaterol, clenbuterol, reproterol, fenoterol and ASF-1020 and salts thereof.

The present 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, ipratropium, trospium, glycopyrronium and oxitropium salts.

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

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

20 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, prolactin C and prolactin inhaled.

25 The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, 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, either as such or as pharmaceutically acceptable salt, with a NSAID selected from the group consisting of ibuprofen and ketoprofen.

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

The present 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 present 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 present 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, 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 present 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 present 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.

- 5 The present 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.

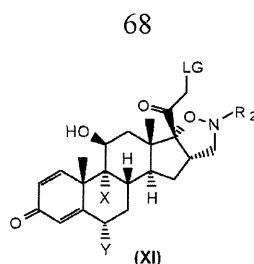
- 10 The invention is also directed to a device which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler or a nebulizer, in particular a soft mist nebulizer comprising a compound of the invention.

- The invention is also directed to a kit comprising the pharmaceutical compositions of compounds of the invention alone or in combination with or
15 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 present invention may be prepared according to a variety of synthetic steps which are carried out according to conventional
20 methods and techniques or which are hereinbelow described.

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

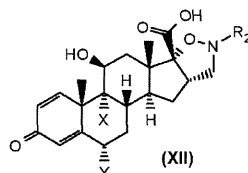
- The present invention is also directed to a process for the preparation of a compound of general formula (I'), wherein $\mathbf{R}_1 = -(\text{CH}_2)_n - \mathbf{Z} - (\text{CH}_2)_{n'} - \mathbf{R}_3$, $\mathbf{n}$ and
25 $\mathbf{n}' = 0$, $\mathbf{Z}$ and $\mathbf{R}_3$ are as defined above, which comprises the conversion of the hydroxyl group of 2-hydroxy acetyl moiety at position 6b of compounds of general formula (VI) into a leaving group (LG) of compounds of general formula (XI)



wherein the LG may be displaced by a nucleophile or wherein, after introduction of the LG on the C21 hydroxy moiety, a redox reaction can be performed, to afford the corresponding methyl ketone.

5 The present invention is also directed to a process for the preparation of compounds of general formula (I'), wherein $\mathbf{R}_1 = -(\text{CH}_2)_n\text{-Z-(CH}_2)_{n'}\text{-R}_3$, $\mathbf{n}$ and $\mathbf{n}' = 0$, $\mathbf{Z}$ and $\mathbf{R}_3$ are as defined above, which comprises:

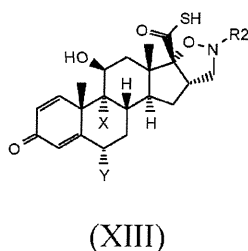
- the reaction of a compound of formula (VI) to obtain a compound of general formula (XII)



- the treatment of compound of formula (XII) with one or more equivalents of an acid activating agent and then with a nucleophile.

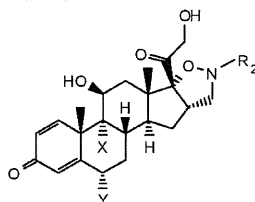
The present invention is also directed to a process for the preparation of compounds of general formula (I') wherein $\mathbf{R}_1 = -(\text{CH}_2)_n\text{-Z-(CH}_2)_{n'}\text{-R}_3$ wherein $\mathbf{n} = \mathbf{n}' = 0$, $\mathbf{Z} = \text{S}$ and $\mathbf{R}_3$ is as defined above, which comprises:

- the reaction of compounds of formula (VI) under oxidizing conditions to obtain the intermediates of general formula (XII)
- its conversion into compounds of general formula (XIII)



- the alkylation of compound of formula (XIII).

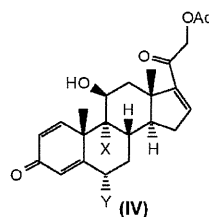
The present invention is also directed to a process for the preparation of compounds of general formula (VI)



(VI)

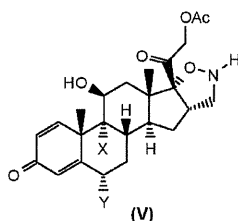
5 which comprises:

- the reaction of a compound of general formula (IV)



(IV)

with N-tetrahydropyranyl hydroxylamine (HO-NH-THP), to prepare a
10 compound of formula (V)

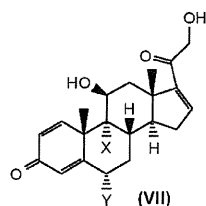


(V)

- the optional further functionalization of compound of formula (V) and
- the deprotection.

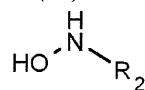
The present invention is also directed to a process for the preparation of
15 a compound of general formula (VI), which comprises:

- the reaction of a compound of formula (VII)



(VII)

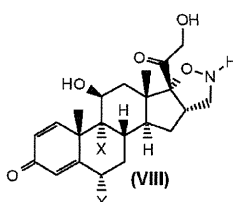
with a compound of formula (X)



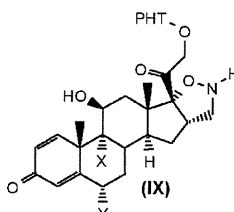
(X)

The present invention is also directed to a process for the preparation of
5 a compound of general formula (VI), which comprises:

- reaction of a compound of formula (VII) with N-tetrahydropyranyl hydroxylamine (HO-NH-THP) to obtain compound of formula (VIII)



- 10 - protection of a compound of formula (VIII) to obtain compound of formula (IX)



- 15 - optional further functionalization of a compound of formula (IX) and
- deprotection.

The present invention is also directed to a process for the preparation of compounds of general formula (I'), wherein $\mathbf{R}_1 = -(\text{CH}_2)_n - \mathbf{Z} - (\text{CH}_2)_{n'} - \mathbf{R}_3$, n and $n' = 0$, $\mathbf{Z} = \text{O}$ and $\mathbf{R}_3 = \text{Ac}$, which comprises the reaction of the intermediates of general formula (IV) with hydroxylamines of formula (X).

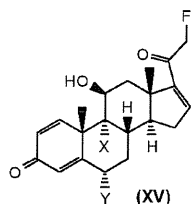
20 The present invention is also directed to a process for the reparation of compounds of general formula (I'), wherein $\mathbf{R}_1 = -(\text{CH}_2)_n - \mathbf{Z} - (\text{CH}_2)_{n'} - \mathbf{R}_3$, $n = 0$, $n' = 1$, $\mathbf{R}_3 = \text{F}$, which comprises

- reaction of compound (VII) with mesyl chloride and DIPEA in dry

acetonitrile;

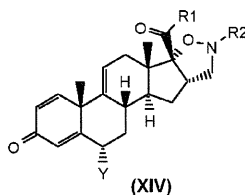
- in situ addition of tetra-n-butylammonium fluoride (TBAF) and KI and
- cycloaddition reaction of the obtained intermediate (XV)

5



with HO-NH-THP.

The present invention is also directed to a process for the preparation of compounds of general formula (I') wherein $R_1 = -(CH_2)_n - Z - (CH_2)_{n'} - R_3$ wherein $n=1$, $n'=0$, $Z=O$, $R_3=H$ and $X=Cl$ as reported in scheme, by reacting the compounds of formula (I') wherein $n=1$, $n'=0$, $Z=O$, $R_3=Ac$ and $X=H$ with methanesulfonyl chloride in the presence of a base to obtain compounds of formula (XIV)



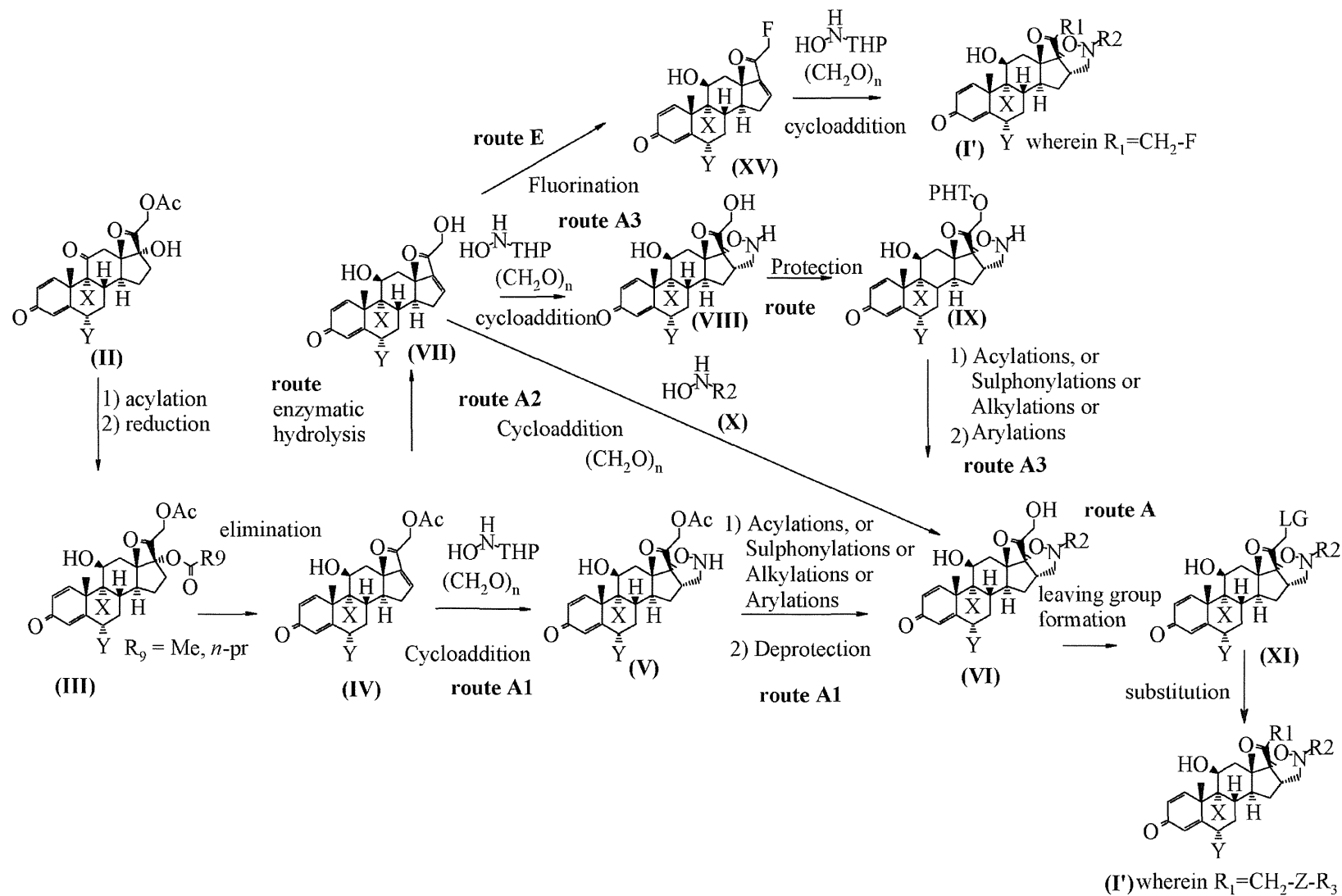
15 which react with a chlorinating agent and, after hydrolysis of the acetyl ester by treatment of a base, affords the aforementioned compounds of general formula (I').

In preferred embodiment of the invention, all the processes herein described are performed with compounds and intermediates where X and Y are fluorine.

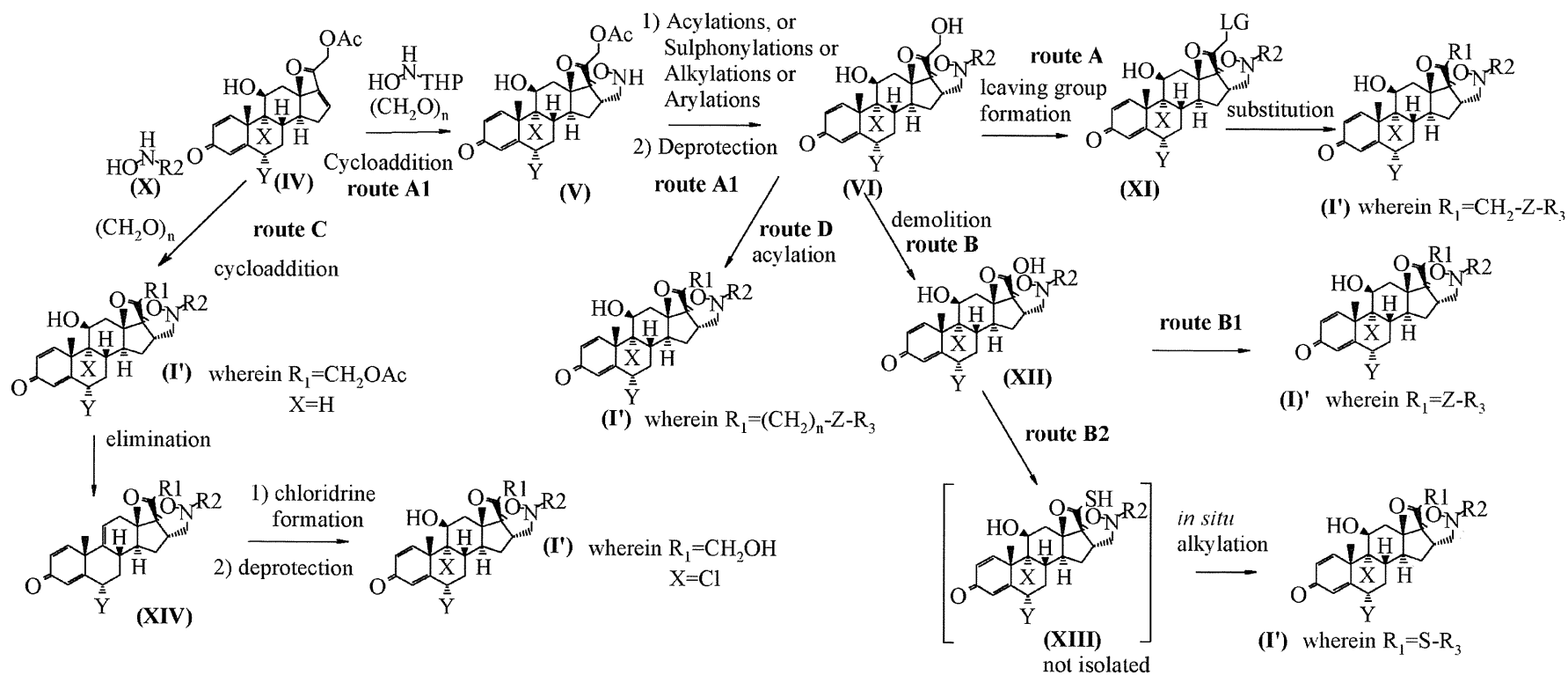
20 From all of the above, it is clear to the person skilled in the art that by selecting the starting material with a proper stereochemical configuration, any of the possible stereoisomers of formula (I) can be obtained.

Some of the processes used for the preparation of the compounds of formula (I'), as described in Scheme 1, may also be applied to compounds of formula (I).

Scheme 1



Scheme 2



Procedure for the preparation of the compounds of the invention

According to particular embodiments, the compounds of the invention may be prepared according to different routes described in scheme 1, depending on the nature of the substituents R_1 and R_2 .

5 **Route A1** - the reaction of compounds of general formula (IV) with N-tetrahydropyranyl hydroxylamine (HO-NH-THP), to prepare a compound of formula (V), can be conveniently conducted in a protic solvent such as EtOH at a temperature ranging from 80 to 100 °C. The THP protecting group is directly cleaved in the reaction conditions.

10 These compounds may be further functionalized with alkyl halides, acyl halides, isocyanates, carbamoyl chlorides or sulphonyl chlorides using conventional methods (J. Med. Chem., 379-388, 1995; J. C. S. Chem. Comm., 256-257, 1985), to give compounds of general formula (VI). These reactions are usually carried out in a solvent such as dichloromethane (DCM) or
15 tetrahydrofuran (THF) and proceed at a temperature range from room temperature (RT) to reflux. A base such as triethylamine or diisopropylethylamine may be required to promote the reaction. The reaction with aryl halides may be performed under the known copper catalyzed N-arylation of isoxazolidine (Bioorg. Med. Chem. Lett., 2834, 2005). The acetyl
20 ester may be easily hydrolyzed using standard conditions for the deacetylation of alcohols, treating for example the compound with a base such as sodium or potassium hydroxide or potassium carbonate in a suitable solvent (e.g. methanol or ethanol). This reaction usually proceeds at RT over a period of 1 to 5 hours leading to compounds of general formula (VI).

25 Compounds of general 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 dimethylformamide (DMF) and typically proceeds at a temperature range from 80 to 110°C, over a period of 0.5 to 4 hours.

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

Route A2 - alternatively, the compounds of general formula (VI) may be prepared starting from the reaction of a compound of formula (VII) with a compound of formula (X) in the presence of paraformaldehyde, using known
10 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 (X) are either commercially available or may be easily prepared using procedures well known for those skilled in the
15 art, 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).

The compounds of formula (VII) may be prepared hydrolyzing the
20 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).

Route A3 - compounds of general formula (VIII) may be prepared
25 starting from the reaction of a compound of formula (VII) with HO-NH-THP. This reaction may be conveniently conducted in dioxane or in a protic solvent such as EtOH at a temperature ranging from 80 to 100°C. The THP protecting group is directly cleaved in the reaction conditions. The obtained (VIII) can be

conveniently and selectively protected by treatment with dihydropyran in a suitable solvent such as DCM or THF, at temperature from 0°C to RT, to obtain compound of formula (IX). The reaction is complete in time ranging from 0.5 to 3 hours. Compounds of formula (IX) may be further
5 functionalized with alkyl halides, acyl halides, isocyanates, carbamoyl chlorides or sulphonyl chlorides as described in Route A1. The THP protecting group can be easily removed by treating the protected intermediate with HCl in a suitable solvent, such as THF or dioxane. This reaction usually proceeds at RT over a period of 1 to 15 hours leading to compounds of general
10 formula (VI).

Route A - conversion of the hydroxyl group of 2-hydroxy acetyl moiety at position 6b of compounds of general formula (VI) into a leaving group (LG) of compounds of general formula (XI) can be carried out by treating compounds of formula (VI) with methanesulfonyl chloride or
15 p-toluenesulphonyl chloride (March's, "Advanced Organic Chemistry", Wiley-Interscience), in a suitable solvent, such as pyridine. This reaction is usually performed at RT over a period of 1 to 5 hours.

The LG of compounds of general formula (XI) may be easily displaced by nucleophiles such as halide anions, alcohols, thiols, thioacids, amines, amides and carbanions (J. Org. Chem., 1042, 1999; J.Steroid.Biochem.13, 311-322, 1980), to obtain compounds of general formula (I) and (I') wherein $R_1 = -(CH_2)_n - Z - (CH_2)_{n'} - R_3$, n and $n' = 0$, Z and R_3 are as defined above. The reaction is usually performed in a suitable solvent, such as DCM, THF or DMF, in a range of temperature from 0 to 80°C over a period of 1-5 h and
25 may be promoted by a base such as sodium or potassium carbonate or sodium hydride. After introduction of the LG (for example mesylate) on the C21 hydroxy moiety, an oxidoreduction reaction can be performed, for example by means of an excess of sodium iodide, to afford the corresponding methyl

ketone. The obtained product may be further functionalized modifying the moiety introduced by the described nucleophilic substitution reaction.

Route B - reaction of compounds of formula (VI) under well known oxidation conditions to obtain the intermediates of general formula (XII). This reaction is usually performed in open air at RT over a period of 12 to 48 hours, in a suitable solvent such as THF in the presence of aqueous solution of an inorganic base, such as sodium or potassium hydroxide.

Route B1 - conversion of the intermediates of formula (XII) into compounds of general formula (I) and (I') wherein $R_1 = -(CH_2)_n-Z-(CH_2)_{n'}-R_3$, n and $n'=0$, Z and R_3 are as defined above, by treating the acid (XII) with one or more equivalents of an acid activating agent such as carbonyldiimidazole or HATU. The reaction is usually performed in a suitable polar solvent such as DMF, in a range of temperature from 0 to 80°C over a period of 1-2 hours. The activated acid may be reacted with a nucleophile, such as alcohols, thiols, thioacids and amines. The reaction may be promoted by a base such as sodium or potassium carbonate, sodium hydride and proceeds at a temperature ranging from 0 to 20°C over a period of 1 to 24 hours.

Alternatively, the intermediates of formula (XII) may be converted into the corresponding acyl chloride under well known conditions, using oxalyl chloride in a suitable solvent such as DCM. The activated intermediate may be reacted with a nucleophile such as alcohols, thiols, thioacids, amines and carbanions such as alkyl, aryl and heteroaryl cuprates or other metallorganic compounds reported in the literature, to be suitable for the conversion of acyl chlorides into the corresponding ketones.

Intermediates of formula (XII) may be also converted into compounds of general formula (I) and (I') wherein $R_1 = -(CH_2)_n-Z-(CH_2)_{n'}-R_3$, n and $n'=0$, $Z = O$ and R_3 is as defined above, by treating the acid (XII) with a base such as potassium sodium or cesium carbonate and triethylamine, in a suitable

solvent such as DMF or acetonitrile, at a temperature ranging from 0 to 20°C. Sometimes these alkylation reactions may be promoted by copper salts such as copper iodide, in the presence of KI. The obtained products may be further functionalized modifying the moiety introduced by the described nucleophilic substitution reaction.

Route B2 - conversion of intermediates of formula (XII) into compounds of general formula (XIII), derived from reaction of acid (XII) with carbonyldiimidazole or HATU, followed by reaction with the sodium salt of thioacetic acid and/or anhydrous hydrogen sulfide. The reaction is usually performed adding the solution of the preformed salt in the reaction solvent to the solution of the activated acid at a temperature ranging from 0 to 20°C or directly adding the solid anhydrous sodium hydrogen sulfide. The thioacid intermediate (XIII) readily formed is in situ reacted with an alkylating reagent, such as bromoalkanes, leading to thioesters of general formula (I) and (I') wherein $R_1 = -(CH_2)_n - Z - (CH_2)_{n'} - R_3$, n and $n' = 0$, $Z = S$ and R_3 is as defined above. The choice of suitable bromoalkane, such as bromo-chloromethane, may allow the preparation of compounds of formula (I) and (I') wherein $R_1 = -(CH_2)_n - Z - (CH_2)_{n'} - R_3$, n and $n' = 0$, $Z = S$ and R_3 is as defined above, that may be further modified. For example, the reaction of these compounds in which R_3 is chloromethyl with potassium iodide, followed by treatment with silver fluoride, may allow the preparation of compounds of formula (I) and (I') in which $R_3 = \text{fluoromethyl}$. These reactions are well known to those skilled in the art (J. Med. Chem., 37, 3717-3729, 1994). Alternatively, the thioacid intermediate (XIII) may be in situ reacted with a DMF solution of bromofluoromethane affording smoothly compounds of formula (I) and (I') in which $R_3 = \text{fluoromethyl}$.

Route C - reaction of the intermediates of general formula (IV) with hydroxylamines of formula (X) in the presence of paraformaldehyde using

known procedures for the isoxazolidine formation by cycloaddition of nitrones. The reaction is conveniently performed in a protogenic solvent, such as ethanol. The reaction is conveniently carried out at high temperature, for example from 60 to 85°C and leads to compounds of general formula (I) and (I') wherein $\mathbf{R}_1 = -(\text{CH}_2)_n - \text{Z} - (\text{CH}_2)_{n'} - \mathbf{R}_3$, wherein $n=1$, $n'=0$, $\mathbf{Z}=\text{O}$ and $\mathbf{R}_3=\text{Ac}$.

The intermediates of general formula (XIV) may be prepared by treating compounds of general formula (I) and (I') wherein $\mathbf{R}_1 = -(\text{CH}_2)_n - \text{Z} - (\text{CH}_2)_{n'} - \mathbf{R}_3$, wherein $n=1$, $n'=0$, $\mathbf{Z}=\text{O}$, $\mathbf{R}_3=\text{Ac}$ and $\mathbf{X}=\text{H}$, with methanesulfonyl chloride in a suitable solvent, such as DMF, in the presence of a base, such as pyridine. The reaction proceeds at a temperature ranging from 80 to 100°C over a period of 1 to 5 hours.

Reacting compounds of formula (XIV) under well known conditions for the preparation of chlorohydrine starting from the corresponding alkene, compounds of general formula (I') wherein $\mathbf{R}_1 = -(\text{CH}_2)_n - \text{Z} - (\text{CH}_2)_{n'} - \mathbf{R}_3$, wherein $n=1$, $n'=0$, $\mathbf{Z}=\text{O}$, $\mathbf{R}_3=\text{H}$ and $\mathbf{X}=\text{Cl}$, are obtained. The reaction involves the use of a chlorinating agent, such as N-chlorosuccinimide or dichloro-5,5-dimethylhydantoin, and is promoted by an acid such as perchloric acid. The reaction is usually carried out in a polar solvent such as THF, in a range of temperature from 0 to 20°C over a period of 1 to 4 hours. The acetyl ester of compounds of formula (XIV) may be easily hydrolyzed using standard conditions for the deacetylation of alcohols, treating for example the compound with a base such as sodium or potassium carbonate in a solvent such as methanol or ethanol. This reaction usually proceeds at low temperature, ranging from 0 to 20°C, over a period of 0.5 to 2 hours.

Route D – reaction of the intermediates of general formula (VI) with acyl chlorides, using known procedures. The reaction is conveniently performed in DCM as solvent in the presence of a base such as triethylamine, at room temperatures over a period of 20 to 50 hours. This procedure provides

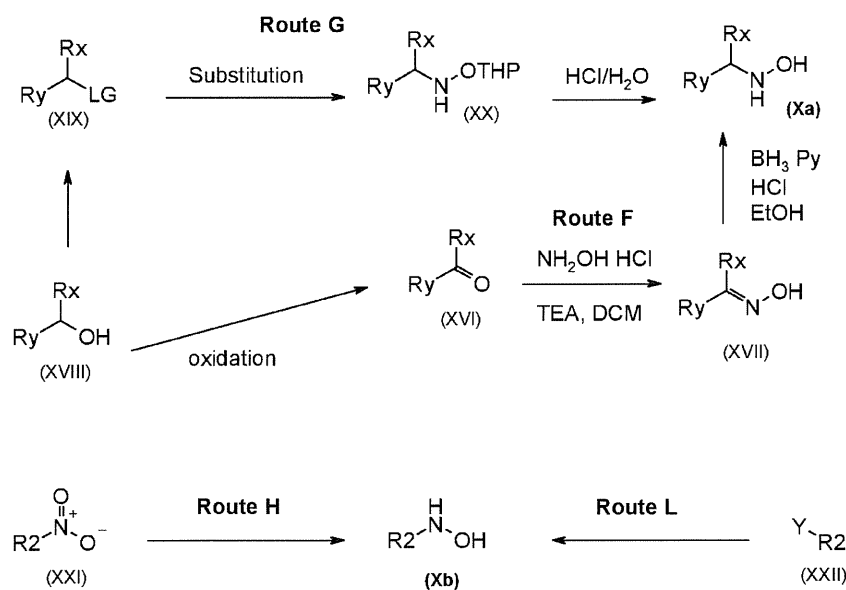
compounds of formula (I') wherein $R_1 = -(CH_2)_n-Z-(CH_2)_{n'}-R_3$, $n=1$, $n'=0$, $Z=O$, R_3 are as defined above.

Route E – reaction of compound (VII) with mesyl chloride and N,N-diisopropylethylamine (DIPEA) in dry acetonitrile. Then, the introduction of fluorine atom can be conveniently performed by in situ addition of tetra-n-butylammonium fluoride (TBAF) and KI and heating over a period of 8 to 20 hours. Cycloaddition reaction of the obtained intermediate (XV) with hydroxylamines of formula (X) in the presence of paraformaldehyde, under the known conditions described in Route C, affords compounds of general formula (I'), wherein $R_1 = -(CH_2)_n-Z-(CH_2)_{n'}-R_3$, $n=0$, $n'=1$, $R_3=F$ and R_2 as defined above.

Hydroxylamines of formula (X) are either commercially available or may be prepared according to different synthetic routes, some of which are well known to those skilled in the art.

In one aspect of the present invention, synthetic routes for the preparation of Hydroxylamines of formula (X) are provided as described in Scheme 3.

Scheme 3



Route F - reaction of compounds of general formula (XVI) with hydroxylamine hydrochloride ($\text{NH}_2\text{OH HCl}$) in presence of triethyl amine, to prepare an oxime of formula (XVII) can be conveniently conducted in DCM as solvent at a temperature ranging from RT to 50 °C.

5 These compounds [oximes of general formula (XVII)] may be reduced to hydroxylamines of general formula (Xa), wherein R_x and R_y may have different meanings within the scope of the instant invention, with a reducing agent such as, for example, borane pyridine complex and HCl in polar protic solvents such as ethanol at RT (*Tetrahedron* **1992**, Vol. 47, N° 17, 3557-3570;
10 *J. Med. Chem.* **1997**, 40, 1955-1968). Compounds of general formula (XVI) are commercially available or can be obtained by oxidation of compounds of general formula (XVIII) by well known procedures (for example Swern oxidation: *J.A.C.S.*, **2005**, 127, 29, 10396).

Route G - Alternatively, the compounds of general formula (Xa) may
15 be prepared by the reaction of an activated compound of general formula (XIX), where LG is a suitable leaving group, such as for example an halide (Cl, Br or I), a mesylate, a tosylate or another leaving group, with O-tetrahydropyranyl hydroxylamine (NH_2OTHP) to generate an intermediate of formula (XX), using well known procedures (*J.A.C.S.* **2000**, 122, 18, 4522;
20 *Tetrahedron* **1999**, 55, 41, 12069), and subsequent deprotection of the THP protective group. The substitution reaction is conveniently carried out in DMF, ethanol or acetonitrile as solvents, in the presence of different kind of bases such as K_2CO_3 or DIPEA and at temperatures ranging from RT to 80°C. Compounds of general formula (XIX) may be commercially available or may
25 be prepared starting from an alcohol of general formula (XVIII) and converting the hydroxyl group into the suitable leaving group by procedures well known to those skilled in the art. For example, mesylates can be conveniently obtained from alcohols (XVIII) with mesyl chloride and TEA in

DCM (*Organic Letters* **2002**, vol. 4, N° 15, 2485).

Route H –Hydroxylamines of general formula (Xb), wherein R2 is optionally substituted aryl or heteroaryl, may be prepared starting from the corresponding nitro-aryl or nitro-heteroaryl compounds. For example, nitro compounds (XXI) can be conveniently reduced to hydroxylamines (*Synthetic Communications* **1997**, Vol. 27, N° 20, 3497-3504) with BiCl₃ and KBH₄ in polar protic solvents, such as ethanol at RT. Alternatively, aryl or heteroaryl hydroxylamines (Xb) may be conveniently obtained by reduction of nitro compounds (XXI) with hydrazine in the presence of Raney nickel in an appropriate mixture of solvents, such as ethanol and dichloromethane (*Synthesis* **1984**, 11, 938-941). It is necessary, in this procedure, to control the temperature between 0 and 10°C. Finally, another convenient reductive method to afford compounds of general formula (Xb), entails the reduction of compounds (XXI) with Zn and NH₄Cl (*Tetrahedron Letters* **2005**, Vol.46, N° 35, 5913-5918; *Joc* **1982**, 47, 7, 1171), in different polar solvents such as acetone or ethanol.

Route L – Alternatively, aryl or heteroaryl hydroxylamines of general formula (Xb) as above defined, may be prepared by nucleophilic aromatic substitution from aryl or heteroaryl electron-poor chlorides or fluorides with hydroxylamine, using methods readily apparent for those skilled in the art. For example, reaction of a compound of general formula (XXII), wherein Y is a suitable leaving group such as chlorine or fluorine, with aqueous hydroxylamine in ethanol (*J. Med. Chem.* **2009**, 52, 19, 5974) may give hydroxylamines of general formula (Xb). The reaction is conducted at reflux in time ranging from 6 to 10 hours. Different methods (WO2006/74187; (**2006**); (A2) English) entail reaction of the suitable aryl or heteroaryl electron-poor chlorides or fluorides with hydroxylamine hydrochloride in polar protic solvents, such as isopropanol. The reaction can be conveniently conducted under microwave heating at a temperature of 130°C, in time

ranging from 15 to 25 hours.

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.

5 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
10 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.

15 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
20 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;
25 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.

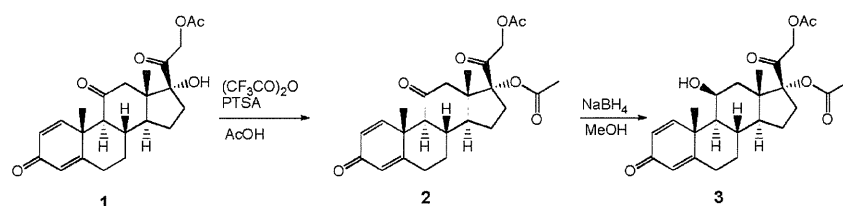
Preferably the compounds of the invention may be administered for the

prevention and/or treatment of respiratory diseases such as from mild to acute severe conditions of asthma and COPD.

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

5 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.

10 **Example 1**



Preparation of acetic acid (8S,9S,10R,13S,14S,17R)-17-(2-acetoxy-acetyl)-10,13-dimethyl-3,11-dioxo-6,7,8,9,10,11,12,13,14,15,16,17-
15 dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester (intermediate 2)

To a suspension of acetic acid 2-((10R,13S,17R)-17-hydroxy-10,13-dimethyl-3,11-dioxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl)-2-oxo-ethyl ester (intermediate 1) (2 g, 4.99 mmol) and p-toluene sulphonic acid (PTSA) (200 mg, 1.051 mmol) in
 20 acetic acid (5 ml), at 0°C, trifluoroacetic anhydride (5 ml, 35.4 mmol) was slowly added over 10 minutes. After stirring at 0°C for 20 min, the reaction mixture was stirred at RT for 3 hr.

The reaction mixture was poured in ice/water (130 ml) and the resulting mixture was extracted with DCM (2 x 100 ml) and AcOEt (2 x 100 ml). The
 25 combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by flash chromatography on

silica gel, in gradient elution from DCM to DCM AcOEt 50: 50 to give the title compound (2.64 g, quantitative yield).

LC-MS (ESI POS): 445.2 (MH⁺)

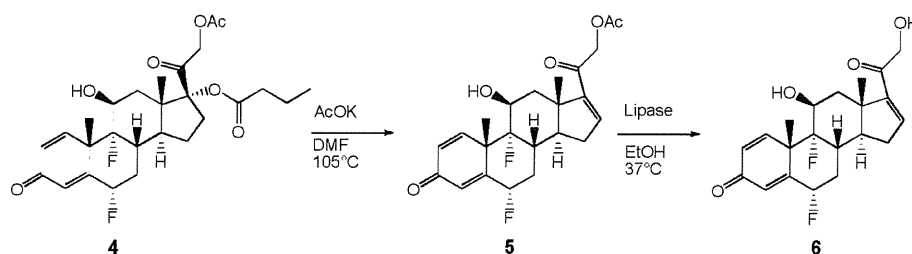
**Preparation of acetic acid (8S,9S,10R,13S,14S,17R)-17-(2-acetoxy-
5 acetyl)-11-hydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-
dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester (intermediate 3)**

To an ice cooled solution of intermediate 2 (2.64 g, 5.97 mmol) in THF (15 ml) and MeOH (15.00 ml), sodium borohydride (221 mg, 5.84 mmol) was added in portions over a period of 2.5 hr. The reaction mixture was poured in
10 1 N HCl and ice (150 ml). The formed precipitate was extracted with AcOEt (3 x 100 ml) and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude material was purified by flash chromatography on silica gel, in gradient elution from DCM to DCM/AcOEt 40: 60 to afford the title compound (1.21 g, 45.6% yield).

15 ¹H NMR (300 MHz, CHLOROFORM-d) ppm 7.28 (d, 1 H), 6.30 (dd, 1 H), 6.05 (t, 1 H), 4.92 (d, 1 H), 4.69 (d, 1 H), 4.48 - 4.58 (m, 1 H), 2.75 - 2.91 (m, 1 H), 2.61 (m, 1 H), 2.37 (ddd, 1 H), 2.18 - 2.21 (m, 3 H), 2.09 - 2.28 (m, 3 H), 2.07 (s, 3 H), 1.74 - 1.98 (m, 3 H), 1.51 - 1.70 (m, 1 H), 1.48 (s, 3 H), 1.26 - 1.39 (m, 2 H), 1.11 - 1.19 (m, 1 H), 1.05 (s, 3 H)

20 LC-MS (ESI POS): 445.2 (MH⁺)

Example 2



**Preparation of acetic acid 2-((6S,8S,9R,10S,11S,13S,14S)-6,9-
25 difluoro-11-hydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15-**

**decahydro-3H-cyclopenta[a]phenanthren-17-yl)-2-oxo-ethyl ester
(intermediate 5)**

To a solution of butyric acid (9R,10S,11S,13S,17R)-17-(2-acetoxy-acetyl)-9-chloro-11-hydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester (intermediate 4) (2.48 g, 4.88 mmol) in anhydrous DMF (60 ml), under nitrogen atmosphere, potassium acetate (3.83 g, 39.0 mmol) was added and the reaction mixture was stirred at 100°C for 1.5 hr. The cooled reaction mixture was poured into ice and brine (200 ml) and the aqueous layer was extracted with AcOEt (3 x 150 ml). The combined organic extracts were washed with water and brine, dried over Na₂SO₄ and concentrated to afford 2.55 g of crude title compound which was used in the next step without further purification.

¹H NMR (300 MHz, DMSO-*d*₆): ppm 7.29 (dd, 1 H), 6.99 (dd, 1 H), 6.29 (dd, 1 H), 5.98 - 6.15 (m, 1 H), 5.68 (dddd, 1 H), 5.56 (dd, 1 H), 5.10 (d, 1 H), 4.92 (d, 1 H), 3.98 - 4.23 (m, 1 H), 2.56 - 2.83 (m, 1 H), 2.26 - 2.44 (m, 3 H), 2.14 - 2.26 (m, 1 H), 2.09 (s, 3 H), 1.71 - 1.87 (m, 1 H), 1.55 - 1.65 (m, 2 H), 1.53 (s, 3 H), 1.15 (s, 3 H).

LC-MS (ESI POS): 421.97 (MH⁺)

Preparation of (6S,8S,9R,10S,11S,13S,14S)-6,9-difluoro-11-hydroxy-17-(2-hydroxy-acetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15-decahydro-cyclopenta[a]phenanthren-3-one (intermediate 6)

To a solution of (intermediate 5) (2.55 g, 6.06 mmol) in ethanol (100 ml), *Candida Antarctica* Lipase (2 U/mg) (510 mg, 6.06 mmol) was added and the reaction mixture was stirred at 37°C overnight. The reaction mixture was filtered, washing with methanol, and the residue was purified by flash chromatography on silica gel, in gradient elution from DCM/AcOEt 90:10 to DCM/AcOEt 50:50, to afford 1.62 g of title compound (70.6% yield).

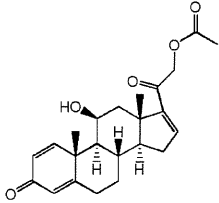
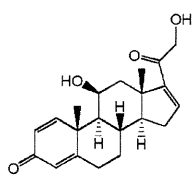
¹H NMR (300 MHz, DMSO-*d*₆): ppm 7.29 (dd, 1 H), 6.87 (dd, 1 H),

6.29 (dd, 1 H), 6.09 - 6.17 (m, 1 H), 5.67 (dddd, 1 H), 5.53 (dd, 1 H), 4.77 (t, 1 H), 4.44 (dd, 1 H), 4.26 (dd, 1 H), 4.04 - 4.15 (m, 1 H), 2.56 - 2.79 (m, 1 H), 2.39 (dd, 1 H), 2.25 - 2.35 (m, 2 H), 2.09 - 2.25 (m, 1 H), 1.76 (td, 1 H), 1.55 - 1.66 (m, 2 H), 1.53 (s, 3 H), 1.17 (s, 3 H).

5 LC-MS (ESI POS): 379.99 (MH⁺)

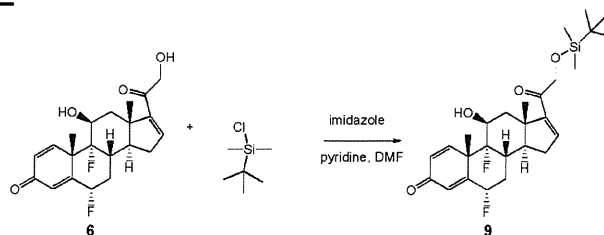
Intermediates 7 and 8 listed in Table 1 were prepared as previously described for intermediates 5 and 6, starting from intermediate 3.

Table 1

Intermediate	Structure	Yield	Analytical
7		50%	LC-MS (ESI POS): 385.45 (MH ⁺) ¹ H NMR (300 MHz, CHLOROFORM-d) ppm 7.32 (d, 1 H), 6.74 (dd, 1 H), 6.29 (dd, 1 H), 6.03 (t, 1 H), 5.02 (d, 1 H), 4.88 (d, 1 H), 4.36 - 4.51 (m, 1 H), 2.55 - 2.73 (m, 1 H), 2.21 - 2.54 (m, 5 H), 2.19 (s, 3 H), 2.05 - 2.18 (m, 1 H), 1.66 (dd, 1 H), 1.51 (s, 3 H), 1.28 (s, 3 H), 1.04 - 1.44 (m, 4 H)
8		94%	LC-MS (ESI POS): 343.2 (MH ⁺) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.34 (d, 1 H), 6.83 (dd, 1 H), 6.16 (dd, 1 H), 5.92 (t, 1 H), 4.80 (d, 1 H), 4.74 (t, 1 H), 4.42 (dd, 1 H), 4.23 (dd, 1 H), 4.15 - 4.23 (m, 1 H), 2.53 - 2.67 (m, 1 H), 2.43 (dd, 1 H), 1.94 - 2.39 (m, 5 H), 1.42 - 1.48 (m, 1 H), 1.39 (dd, 1 H), 1.17 (s, 3 H), 0.74 - 1.33 (m, 5 H)

10

Example 3



Preparation of (6S,8S,9R,10S,11S,13S,14S)-17-(2-(tert-

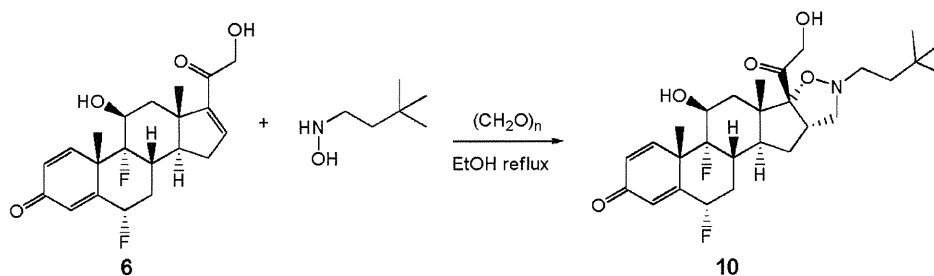
butyldimethylsilyloxy)acetyl)-6,9-difluoro-11-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15-decahydro-3H-cyclopenta[a]phenanthren-3-one (intermediate 9)

To a solution of 6 (300 mg, 0.793 mmol) in dry DMF (12 ml), imidazole (135 mg, 1.982 mmol) and pyridine (0.321 ml, 3.96 mmol) were added, followed by tert-butylchlorodimethylsilane (263 mg, 1.744 mmol). The reaction was stirred at room temperature for 2hs. The conversion was complete.

The reaction was diluted with AcOEt and washed with water, the aqueous layer was extracted twice with AcOEt, and then the combined extracts were dried over sodium sulphate and evaporated. Crude was purified *via* chromatographic column over silica gel (DCM, DCM/AcOEt 8 : 1) to give 365 mg (93% yield).

LC-MS (ESI POS): 493.1 (MH⁺)

Example 4



15

Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-8-(3,3-dimethyl-butyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one (compound 10)

A mixture of 6 (1.3 g, 3.44 mmol), N-(3, 3-dimethylbutyl) hydroxylamine (826 mg, 7.05 mmol) and paraformaldehyde (0.650 g, 21.64 mmol) in ethanol (50 ml) was stirred at reflux overnight. The solvent was evaporated and the crude was purified by silica gel chromatography (DCM/MeOH 98: 2) to give compound 9 (1.56 g, 3.07 mmol, 89% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H) 6.29 (dd, 1 H) 6.11 (s, 1

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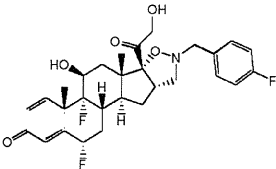
H) 5.49 - 5.79 (m, 1 H) 5.44 (d, 1 H) 4.77 (t, 1 H) 4.48 (dd, 1 H) 4.12 - 4.24 (m, 1 H) 4.12 (dd, 1 H) 3.43 - 3.60 (m, 1 H) 3.31 - 3.43 (m, 1 H) 2.54 - 2.72 (m, 3 H) 2.08 - 2.34 (m, 2 H) 1.80 - 2.01 (m, 2 H) 1.51 - 1.71 (m, 3 H) 1.49 (s, 3 H) 1.18 - 1.46 (m, 3 H) 0.86 (s, 9 H) 0.81 (s, 3 H)

- 5 LC-MS (ESI POS): 508.26 MH⁺
 $[\alpha]_{\text{D}}^{25} = +131.4$ (c 0.213; CHCl₃)

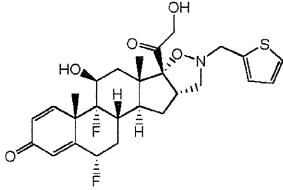
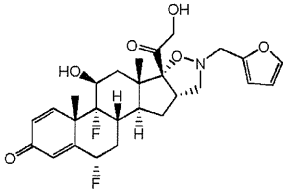
The compounds listed in Table 2 were prepared as previously described for compound 10, by cycloaddition of intermediate 6, 8 or 9 with suitable hydroxylamine or hydroxylamine hydrochloride.

- 10 Final compounds were purified by silica gel column chromatography or preparative HPLC.

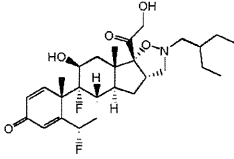
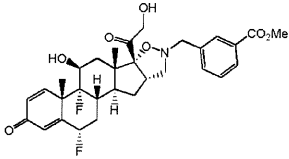
Table 2

Compound	Structure	Yield	Analytical
11		88%	LC-MS (ESI POS): 532.03 (MH⁺) $[\alpha]_{\text{D}}^{25} = +175.3$ (c=0.22, CHCl₃) ¹H NMR (300 MHz, DMSO-<i>d</i>₆) ppm 7.28 - 7.37 (m, 2 H), 7.26 (dd, 1 H), 7.01 - 7.18 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.50 - 5.78 (m, 1 H), 5.43 (dd, 1 H), 4.57 - 4.77 (m, 1 H), 3.99 - 4.26 (m, 2 H), 3.89 (d, 1 H), 3.83 - 3.95 (m, 1 H), 3.75 (d, 1 H), 3.43 - 3.60 (m, 1 H), 3.34 - 3.43 (m, 1 H), 2.57 - 2.69 (m, 1 H), 2.04 - 2.36 (m, 3 H), 1.78 - 1.99 (m, 1 H), 1.52 - 1.72 (m, 3 H), 1.49 (s, 3 H), 1.38 - 1.48 (m, 1 H), 0.80 (s, 3 H)

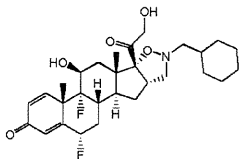
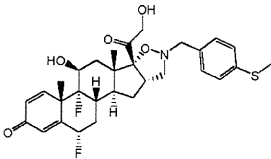
(continued)

12		43%	LC-MS (ESI POS): 519.98 (MH⁺) $[\alpha]_D^{25} = + 129.9^\circ$ (c = 0.63, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.40 - 7.47 (m, 1 H), 7.26 (dd, 1 H), 6.83 - 7.03 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.49 - 5.80 (m, 1 H), 5.45 (dd, 1 H), 4.72 (br. s., 1 H), 4.33 (dd, 1 H), 4.09 - 4.24 (m, 2 H), 3.88 - 4.07 (m, 2 H), 3.43 - 3.60 (m, 1 H), 3.34 - 3.43 (m, 1 H), 2.55 - 2.70 (m, 1 H), 2.04 - 2.39 (m, 3 H), 1.90 - 2.03 (m, 1 H), 1.51 - 1.71 (m, 3 H), 1.49 (s, 3 H), 1.37 - 1.47 (m, 1 H), 0.81 (s, 3 H)
13		59%	LC-MS (ESI POS): 504.02 (MH⁺) $[\alpha]_D^{25} = + 133.1^\circ$ (c = 0.30, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.55 (dd, 1 H), 7.26 (dd, 1 H), 6.40 (dd, 1 H), 6.22 - 6.35 (m, 2 H), 6.12 (s, 1 H), 5.49 - 5.78 (m, 1 H), 5.43 (d, 1 H), 4.71 (s br, 1H), 4.27 (d, 1 H), 3.99 (d, 1 H), 3.92 (d, 1 H), 3.82 (d, 1 H), 3.35 - 3.54 (m, 3 H), 2.55 - 2.71 (m, 1 H), 2.01 - 2.31 (m, 3 H), 1.84 - 1.98 (m, 1 H), 1.51 - 1.68 (m, 3 H), 1.49 (s, 3 H), 1.42 (dd, 1 H), 0.81 (s, 3 H)

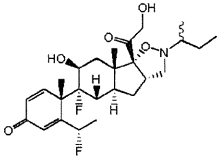
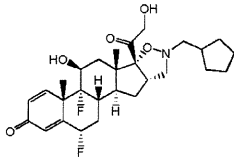
(continued)

14		10%	LC-MS (ESI POS): 508.45 MH⁺ $[\alpha]_D^{25} = + 126.4$ (c 0.135, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.49 - 5.81 (m, 1 H), 5.44 (dd, 1 H), 4.81 (t, 1 H), 4.45 (dd, 1 H), 4.15 - 4.24 (m, 1 H), 4.12 (dd, 1 H), 3.42 - 3.60 (m, 1 H), 3.33 - 3.43 (m, 1 H), 2.55 - 2.70 (m, 1 H), 2.06 - 2.34 (m, 2 H), 1.83 - 2.06 (m, 2 H), 1.50 - 1.71 (m, 3 H), 1.49 (s, 3 H), 1.12 - 1.46 (m, 8 H), 0.62 - 0.92 (m, 9 H)
15		41%	LC-MS (ESI POS): 572.42 MH⁺ $[\alpha]_D^{25} = + 148.3$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.90 (s, 1 H), 7.87 (dt, 1 H), 7.55 (dt, 1 H), 7.47 (t, 1 H), 7.26 (dd, 1 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.48 - 5.81 (m, 1 H), 5.43 (dd, 1 H), 4.67 (br. s., 1 H), 3.84 - 4.26 (m, 5 H), 3.83 (s, 3 H), 3.45 - 3.60 (m, 1 H), 3.34 - 3.45 (m, 1 H), 2.56 - 2.71 (m, 1 H), 2.05 - 2.36 (m, 3 H), 1.81 - 1.97 (m, 1 H), 1.51 - 1.70 (m, 3 H), 1.49 (s, 3 H), 1.36 - 1.46 (m, 1 H), 0.80 (s, 3 H)

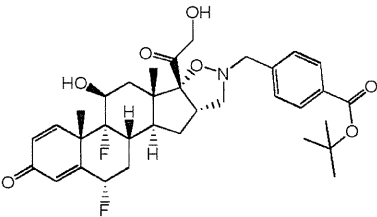
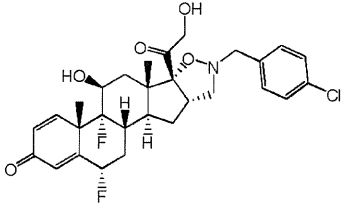
(continued)

16		71%	LC-MS (ESI POS): 520.45 MH⁺ $[\alpha]_D^{25} = + 150.2$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.49 – 5.82 (m, 1 H), 5.44 (dd, 1 H), 4.80 (t, 1 H), 4.45 (dd, 1 H), 4.16 – 4.25 (m, 1 H), 4.12 (dd, 1 H), 3.40 – 3.56 (m, 1 H), 3.32 – 3.40 (m, 1 H), 2.56 – 2.71 (m, 1 H), 2.05 – 2.33 (m, 2 H), 1.85 – 2.05 (m, 2 H), 1.75 (dd, 1 H), 1.51 – 1.70 (m, 7 H), 1.49 (s, 3 H), 1.41 (dd, 1 H), 1.03 – 1.31 (m, 5 H), 0.83 – 1.00 (m, 3 H), 0.81 (s, 3 H)
17		70%	LC-MS (ESI POS): 560.3 MH⁺ $[\alpha]_D^{25} = + 203.5$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.07 – 7.36 (m, 5 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.48 – 5.77 (m, 1 H), 5.43 (d, 1 H), 4.48 – 4.82 (m, 1 H), 4.02 – 4.29 (m, 2 H), 3.87 – 3.98 (m, 1 H), 3.86 (d, 1 H), 3.73 (d, 1 H), 3.32 – 3.54 (m, 2 H), 2.55 – 2.67 (m, 1 H), 2.45 (s, 3 H), 2.01 – 2.31 (m, 3 H), 1.91 (d, 1 H), 1.48 (s, 3 H), 1.33 – 1.73 (m, 4 H), 0.80 (s, 3 H)

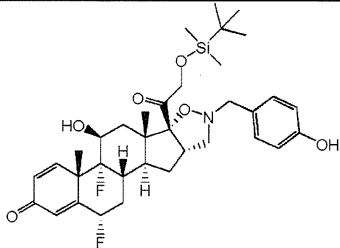
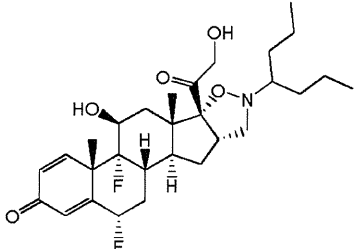
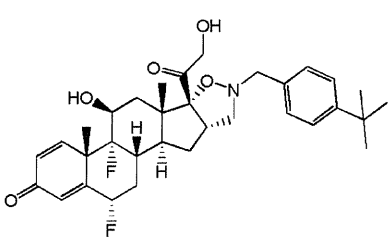
(continued)

18		23%	LC-MS (ESI POS): 480.34 MH⁺ $[\alpha]_D^{25} = + 84.1$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.04 - 6.19 (m, 1 H), 5.49 - 5.77 (m, 1 H), 5.37 - 5.49 (m, 1 H), 4.47 (d, 1 H), 4.16 - 4.21 (m, 1 H), 4.12 (d, 1 H), 3.25 - 3.42 (m, 2 H), 2.57 - 2.68 (m, 1 H), 1.87 - 2.25 (m, 4 H), 1.50 - 1.69 (m, 3 H), 1.49 (s, 3 H), 1.22 - 1.47 (m, 4 H), 0.90 and 1.05 (d, 3 H), 0.76 - 0.87 (m, 6 H)
19		82%	LC-MS (ESI POS): 506.25 MH⁺ $[\alpha]_D^{25} = + 151.5$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.48 - 5.75 (m, 1 H), 5.38 - 5.46 (m, 1 H), 4.71 - 4.86 (m, 1 H), 4.48 (dd, 1 H), 4.15 - 4.23 (m, 1 H), 4.11 (dd, 1 H), 3.42 - 3.58 (m, 1 H), 3.32 - 3.42 (m, 1 H), 2.57 (d, 2 H), 2.35 - 2.45 (m, 1 H), 1.86 - 2.19 (m, 6 H), 1.51 - 1.78 (m, 6 H), 1.49 (s, 3 H), 1.34 - 1.45 (m, 2 H), 1.03 - 1.22 (m, 3 H), 0.82 (s, 3 H)

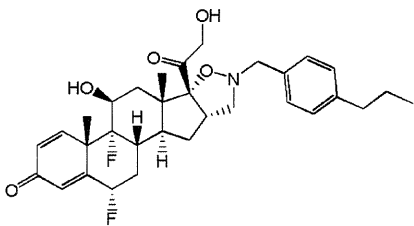
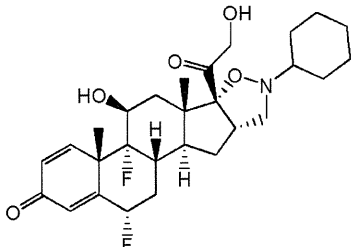
(continued)

20		LC-MS (ESI POS): 614.29 MH⁺ $[\alpha]_D^{25} = +208.5$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-<i>d</i>₆) ppm 7.76 - 7.90 (m, 2 H), 7.32 - 7.48 (m, 2 H), 7.25 (dd, 1 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.48 - 5.82 (m, 1 H), 5.42 (dd, 1 H), 4.63 - 4.77 (m, 1 H), 4.10 - 4.22 (m, 1 H), 3.71 - 4.10 (m, 4 H), 3.46 - 3.62 (m, 1 H), 3.35 - 3.46 (m, 1 H), 2.57 - 2.70 (m, 1 H), 2.06 - 2.36 (m, 2 H), 1.79 - 1.96 (m, 1 H), 1.57 - 1.67 (m, 4 H), 1.54 (s, 9 H), 1.49 (s, 3 H), 1.36 - 1.51 (m, 1 H), 0.80 (s, 3 H) 39%
21		LC-MS (ESI POS): 547.99 (MH⁺) ¹H NMR (300 MHz, DMSO-<i>d</i>₆) ppm 7.20 - 7.43 (m, 5 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.50 - 5.81 (m, 1 H), 5.43 (dd, 1 H), 4.54 - 4.78 (m, 1 H), 4.00 - 4.23 (m, 2 H), 3.81 - 3.97 (m, 2 H), 3.74 (d, 1 H), 3.33 - 3.59 (m, 2 H), 2.55 - 2.63 (m, 1 H), 2.01 - 2.35 (m, 3 H), 1.77 - 1.96 (m, 1 H), 1.51 - 1.69 (m, 3 H), 1.49 (s, 3 H), 1.35 - 1.46 (m, 1 H), 0.80 (s, 3 H) 84%

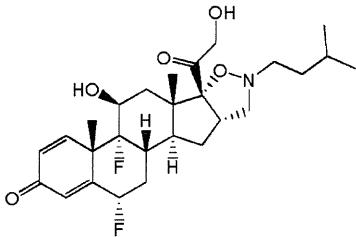
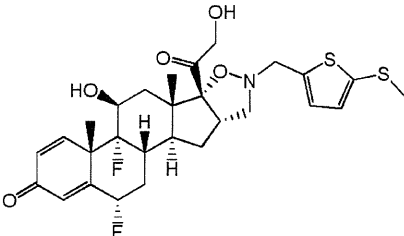
(continued)

22		86%	LC-MS (ESI POS): 644.0 (MH ⁺)
23		40%	LC-MS (ESI POS): 522.13 MH ⁺ $[\alpha]_D^{25} = +133.6$ (c 0.2 MeOH) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.26 (dd, 1 H), 6.29 (dd, 1 H), 6.07 - 6.17 (m, 1 H), 5.48 - 5.79 (m, 1 H), 5.43 (dd, 1 H), 4.79 (t, 1 H), 4.44 (dd, 1 H), 4.16 - 4.22 (m, 1 H), 4.12 (dd, 1 H), 3.31 - 3.49 (m, 2 H), 2.55 - 2.66 (m, 1 H), 2.41 - 2.47 (m, 1 H), 1.83 - 2.32 (m, 5 H), 1.50 - 1.70 (m, 3 H), 1.49 (s, 3 H), 1.11 - 1.46 (m, 8 H), 0.85 (t, 6 H), 0.81 (s, 3 H)
24		68%	LC-MS (ESI POS): 570.18 MH ⁺ $[\alpha]_D^{25} = +122.4$ (C 0.149, CHCl ₃) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.28 - 7.34 (m, 2 H), 7.26 (dd, 1 H), 7.15 - 7.22 (m, 2 H), 6.30 (dd, 1 H), 6.11 (s, 1 H), 5.48 - 5.79 (m, 1 H), 5.43 (dd, 1 H), 4.57 - 4.82 (m, 1 H), 4.29 (dd, 1 H), 4.11 - 4.22 (m, 1 H), 3.98 (dd, 1 H), 3.87 (d, 1 H), 3.79 (d, 1 H), 3.31 - 3.51 (m, 2 H), 2.55 - 2.68 (m, 1 H), 2.01 - 2.32 (m, 3 H), 1.82 - 1.98 (m, 1 H), 1.51 - 1.74 (m, 2 H), 1.48 (s, 3 H), 1.29 - 1.44 (m, 2 H), 1.25 (s, 9 H), 0.80 (s, 3 H)

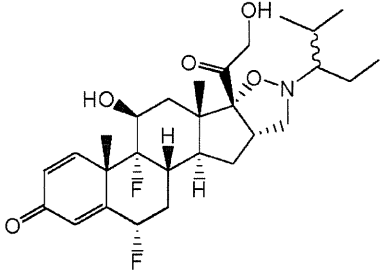
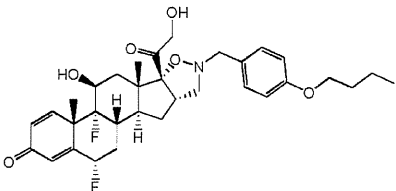
(continued)

25		LC-MS (ESI POS): 556.25 MH⁺ $[\alpha]_D^{25} = +151.3$ (c 0.147, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (dd, 1 H), 7.14 - 7.20 (m, 2 H), 7.06 - 7.14 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.49 - 5.77 (m, 1 H), 5.43 (dd, 1 H), 4.66 (br. s., 1 H), 4.08 - 4.31 (m, 2 H), 3.92 (d, 1 H), 3.85 (d, 1 H), 3.76 (d, 1 H), 3.33 - 3.51 (m, 2 H), 2.58 - 2.71 (m, 1 H), 2.44 - 2.48 (m, 2 H), 1.99 - 2.33 (m, 3 H), 1.80 - 1.98 (m, 1 H), 1.50 - 1.70 (m, 5 H), 1.47 (s, 3 H), 1.31 - 1.45 (m, 1 H), 0.87 (t, 3 H), 0.80 (s, 3 H) 71%
26		LC-MS (ESI POS): 506.29 MH⁺ $[\alpha]_D^{25} = +97.8$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.49 - 5.74 (m, 1 H), 5.43 (dd, 1 H), 4.76 (t, 1 H), 4.49 (dd, 1 H), 4.13 - 4.22 (m, 1 H), 4.12 (dd, 1 H), 3.41 - 3.61 (m, 1 H), 3.31 - 3.41 (m, 1 H), 2.54 - 2.69 (m, 1 H), 2.31 - 2.44 (m, 1 H), 1.82 - 2.31 (m, 5 H), 1.50 - 1.76 (m, 6 H), 1.49 (s, 3 H), 1.35 - 1.46 (m, 1 H), 0.97 - 1.30 (m, 6 H), 0.81 (s, 3 H) 69%

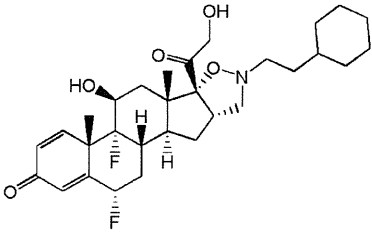
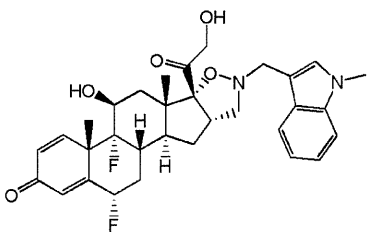
(continued)

27		LC-MS (ESI POS): 494.17 MH⁺ $[\alpha]_D^{25} = +242.2$ (c 0.09, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.48 - 5.80 (m, 1 H), 5.44 (d, 1 H), 4.78 (dd, 1 H), 4.47 (dd, 1 H), 4.11 - 4.22 (m, 1 H), 4.12 (dd, 1 H), 3.41 - 3.58 (m, 1 H), 3.32 - 3.42 (m, 1 H), 2.55 - 2.71 (m, 3 H), 2.03 - 2.37 (m, 2 H), 1.83 - 2.03 (m, 2 H), 1.50 - 1.72 (m, 4 H), 1.49 (s, 3 H), 1.27 - 1.46 (m, 3 H), 0.85 (d, 3 H), 0.85 (d, 3 H), 0.81 (s, 3 H) 77%
28		LC-MS (ESI POS): 566.13 MH⁺ $[\alpha]_D^{25} = +140.2$ (c 0.119, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (dd, 1 H), 6.95 (d, 1 H), 6.85 (d, 1 H), 6.30 (dd, 1 H), 6.11 (s, 1 H), 5.48 - 5.79 (m, 1 H), 5.44 (dd, 1 H), 4.38 (d, 1 H), 4.08 - 4.25 (m, 2 H), 4.03 (d, 1 H), 3.95 (d, 1 H), 3.38 - 3.51 (m, 2 H), 2.56 - 2.68 (m, 1 H), 2.41 (s, 3 H), 2.03 - 2.32 (m, 3 H), 1.89 - 2.04 (m, 1 H), 1.51 - 1.71 (m, 4 H), 1.49 (s, 3 H), 1.34 - 1.45 (m, 1 H), 0.81 (s, 3 H) 66%

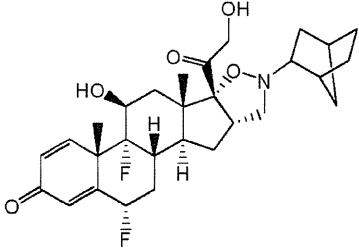
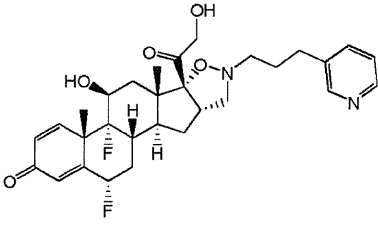
(continued)

29		LC-MS (ESI POS): 508.22 MH⁺ $[\alpha]_D^{25} = +118.8$ (c 0.26, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (d, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.46 - 5.81 (m, 1 H), 5.43 (d, 1 H), 4.81 and 4.83 (t, 1 H), 4.48 (dd, 1 H), 4.13 - 4.25 (m, 1 H), 4.10 and 4.13 (dd, 1 H), 3.31 - 3.53 (m, 2 H), 2.53 - 2.70 (m, 2 H), 2.27 (dt, 2 H), 2.02 - 2.21 (m, 3 H), 1.87 - 2.01 (m, 1 H), 1.68 - 1.87 (m, 1 H), 1.53 (s, 3 H), 1.36 - 1.68 (m, 4 H), 0.88 and 0.95 (t, 3 H), 0.84 and 0.85 (d, 3 H), 0.82 (s, 3 H), 0.75 and 0.82 (d, 3 H) 58%
30		LC-MS (ESI POS): 596.09 MH⁺ $[\alpha]_D^{25} = +154.9$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (dd, 1 H), 7.16 (m, 2 H), 6.84 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.47 - 5.79 (m, 1 H), 5.42 (d, 1 H), 4.50 - 4.77 (m, 1 H), 4.05 - 4.26 (m, 2 H), 3.94 (m, 3 H), 3.59 - 3.86 (m, 2 H), 3.33 - 3.46 (m, 1 H), 1.98 - 2.31 (m, 3 H), 1.93 (d, 1 H), 1.51 - 1.79 (m, 5 H), 1.49 (s, 3 H), 1.36 - 1.47 (m, 3 H), 0.93 (t, 3 H), 0.80 (s, 3 H) 69%

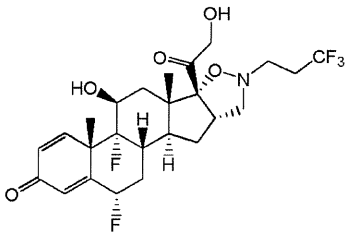
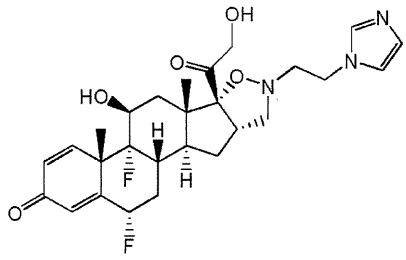
(continued)

31		LC-MS (ESI POS): 534.28 MH⁺ $[\alpha]_D^{25} = +152.3$ (c 0.23, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.48 - 5.78 (m, 1 H), 5.44 (dd, 1 H), 4.78 (t, 1 H), 4.46 (dd, 1 H), 4.12 - 4.24 (m, 1 H), 4.12 (dd, 1 H), 3.42 - 3.57 (m, 1 H), 3.31 - 3.41 (m, 1 H), 2.56 - 2.74 (m, 3 H), 2.02 - 2.33 (m, 2 H), 1.83 - 1.97 (m, 2 H), 1.51 - 1.72 (m, 8 H), 1.49 (s, 3 H), 1.04 - 1.46 (m, 7 H), 0.83 - 0.97 (m, 2 H), 0.81 (s, 3 H) 65%
32		LC-MS (ESI POS): 567.23 M⁺ $[\alpha]_D^{25} = +110$ (c 0.26, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.55 (d, 1 H), 7.38 (d, 1 H), 7.28 (dd, 1 H), 7.22 (s, 1 H), 7.13 (ddd, 1 H), 7.00 (ddd, 1 H), 6.32 (dd, 1 H), 6.14 (s, 1 H), 5.49 - 5.81 (m, 1 H), 5.45 (dd, 1 H), 4.65 (br. s., 1 H), 3.83 - 4.38 (m, 5 H), 3.72 (s, 3 H), 3.30 - 3.49 (m, 2 H), 2.55 - 2.69 (m, 1 H), 1.95 - 2.36 (m, 4 H), 1.52 - 1.71 (m, 3 H), 1.50 (s, 3 H), 1.41 (dd, 1 H), 0.82 (s, 3 H) 8%

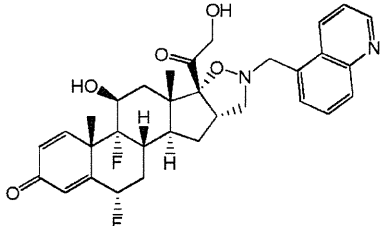
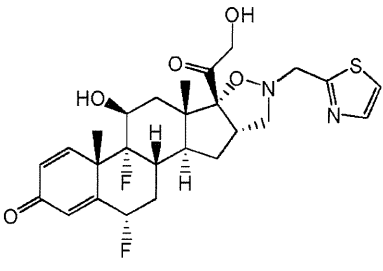
(continued)

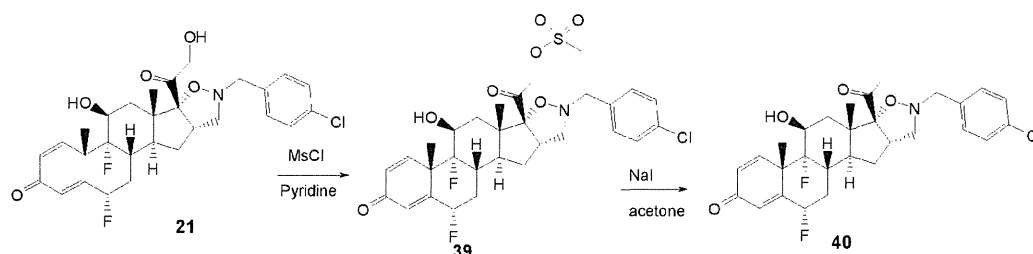
33		80% LC-MS (ESI POS): 518.11 MH⁺ $[\alpha]_D^{25} = +108.5$ (c 0.24, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (d, 1 H), 6.29 (dt, 1 H), 6.11 (s, 1 H), 5.48 - 5.86 (m, 1 H), 5.43 (d, 1 H), 4.76 and 4.83 (t, 1 H), 4.30 - 4.67 (m, 1 H), 4.05 - 4.24 (m, 1 H), 4.08 (dd, 1 H), 3.35 - 3.60 (m, 2 H), 2.55 - 2.75 (m, 2 H), 2.18 - 2.37 (m, 1 H), 2.10 (br. s., 2 H), 1.81 - 2.05 (m, 2 H), 1.32 - 1.68 (m, 5 H), 1.48 (s, 3 H), 1.12 - 1.32 (m, 4 H), 0.93 - 1.12 (m, 3 H), 0.79 and 0.82 (s, 3 H), 0.58 - 0.90 and 0.84 - 0.96 (m, 1 H)
34		34% LC-MS (ESI POS): 543.24 MH⁺ $[\alpha]_D^{25} = +136.9$ (c 0.3, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 8.33 - 8.48 (m, 2 H), 7.60 (dt, 1 H), 7.29 (ddd, 1 H), 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.49 - 5.80 (m, 1 H), 5.44 (dd, 1 H), 4.83 (t, 1 H), 4.51 (dd, 1 H), 4.14 - 4.23 (m, 1 H), 4.13 (dd, 1 H), 3.44 - 3.57 (m, 1 H), 3.33 - 3.44 (m, 1 H), 2.57 - 2.81 (m, 5 H), 2.06 - 2.33 (m, 2 H), 1.86 - 2.03 (m, 2 H), 1.69 - 1.85 (m, 2 H), 1.51 - 1.69 (m, 3 H), 1.49 (s, 3 H), 1.42 (dd, 1 H), 0.82 (s, 3 H)

(continued)

35		16% LC-MS (ESI POS): 520.17 MH⁺ $[\alpha]_D^{25} = +123.8$ (c 0.27, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.50 - 5.80 (m, 1 H), 5.45 (dd, 1 H), 4.81 (t, 1 H), 4.43 (dd, 1 H), 4.14 - 4.24 (m, 1 H), 4.14 (dd, 1 H), 3.47 - 3.64 (m, 1 H), 3.33 - 3.47 (m, 1 H), 2.89 - 3.10 (m, 1 H), 2.76 - 2.89 (m, 1 H), 2.58 - 2.70 (m, 2 H), 2.38 - 2.46 (m, 1 H), 1.85 - 2.35 (m, 4 H), 1.53 - 1.72 (m, 3 H), 1.49 (s, 3 H), 1.43 (dd, 1 H), 0.82 (s, 3 H)
36		62% LC-MS (ESI POS): 518.25 MH⁺ $[\alpha]_D^{25} = +122.2$ (c 0.1435; MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.57 (s, 1 H), 7.26 (dd, 1 H), 7.12 (t, 1 H), 6.83 (s, 1 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.50 - 5.83 (m, 1 H), 5.45 (dd, 1 H), 4.86 (t, 1 H), 4.45 (dd, 1 H), 4.01 - 4.24 (m, 4 H), 3.35 - 3.51 (m, 2 H), 3.03 - 3.21 (m, 1 H), 2.87 - 3.03 (m, 1 H), 2.58 - 2.71 (m, 1 H), 1.86 - 2.30 (m, 4 H), 1.52 - 1.76 (m, 3 H), 1.49 (s, 3 H), 1.42 (dd, 1 H), 0.82 (s, 3 H)

(continued)

37		LC-MS (ESI POS): 565.27 MH⁺ $[\alpha]_D^{25} = +193.2$ (c 0.25, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 8.89 (dd, 1 H), 8.55 (dt, 1 H), 7.97 (d, 1 H), 7.70 (dd, 1 H), 7.54 (dd, 1 H), 7.49 (dd, 1 H), 7.27 (dd, 1 H), 6.32 (dd, 1 H), 6.14 (s, 1 H), 5.49 - 5.80 (m, 1 H), 5.42 (dd, 1 H), 4.53 (br. s., 1 H), 4.38 (d, 1 H), 4.29 (d, 1 H), 4.09 - 4.22 (m, 1 H), 3.66 - 3.91 (m, 2 H), 3.53 (br. s., 1 H), 3.37 (br. s., 1 H), 2.54 - 2.70 (m, 1 H), 2.15 - 2.35 (m, 3 H), 1.83 - 1.97 (m, 1 H), 1.52 - 1.72 (m, 3 H), 1.49 (s, 3 H), 1.39 - 1.46 (m, 1 H), 0.78 (s, 3 H) 18%
38		LC-MS (ESI POS): 521.22 MH⁺ $[\alpha]_D^{25} = +172.7$ (c 0.33, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.73 (d, 1 H), 7.69 (d, 1 H), 7.26 (dd, 1 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.49 - 5.79 (m, 1 H), 5.44 (dd, 1 H), 4.81 (t, 1 H), 4.38 (dd, 1 H), 4.07 - 4.23 (m, 1 H), 4.06 - 4.39 (m, 2 H), 3.99 (dd, 1 H), 3.53 - 3.74 (m, 1 H), 3.41 - 3.53 (m, 1 H), 2.56 - 2.71 (m, 1 H), 2.07 - 2.36 (m, 3 H), 1.82 - 1.97 (m, 1 H), 1.51 - 1.69 (m, 3 H), 1.49 (s, 3 H), 1.38 - 1.47 (m, 1 H), 0.81 (s, 3 H) 29%

Example 5**Preparation of Methanesulfonic acid 2-**

5 [(4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-8-(4-chloro-benzyl)-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-azapentaleno[2,1-*a*]phenanthren-6b-yl]-2-oxo-ethyl ester (compound 39)

To a solution of 21 (200 mg, 0.365 mmol) in dry pyridine (8 ml) under
10 nitrogen atmosphere, methanesulfonyl chloride (0.057 ml, 0.730 mmol) was added. After 3 hr stirring, further methanesulfonyl chloride (0.057 ml, 0.730 mmol) was added. The reaction mixture was stirred at room temperature for further 1 hr.

The reaction mixture was poured into 2 N HCl (80 ml) and ice and the
15 formed precipitate was filtered and washed with cold 1 N HCl and water; then, the filtered solid was dissolved in DCM. The obtained organic phase was dried over anhydrous sodium sulphate and concentrated to afford 222 mg of the desired compound 74 (97% yield).

LC-MS (ESI POS): 626.3 (MH⁺)

20 **Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-6b-Acetyl-8-(4-chloro-benzyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-*a*]phenanthren-2-one (compound 40)**

Compound 39 (308 mg, 0.492 mmol) was dissolved in acetone (12 ml)
25 and sodium iodide (738 mg, 4.92 mmol) was added. The reaction mixture was

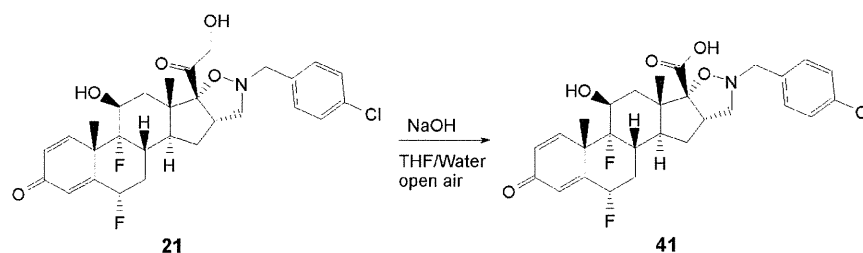
stirred at 65°C overnight. The reaction mixture was diluted with AcOEt (80 ml), washed with sat Na₂S₂O₃ until disappearance of the iodine, then with sat NaHCO₃. Organic layer was dried over Na₂SO₄ and evaporated, to give 224 mg of crude material, which was purified by preparative HPLC, to afford 65 mg of pure compound 75 (25% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.33 - 7.42 (m, 2 H), 7.28 - 7.33 (m, 2 H), 7.26 (d, 1 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.48 - 5.80 (m, 1 H), 5.43 (br. s., 1 H), 4.07 - 4.27 (m, 1 H), 3.93 (d, 1 H), 3.74 (d, 1 H), 3.44 - 3.57 (m, 1 H), 3.34 - 3.44 (m, 1 H), 2.56 - 2.76 (m, 1 H), 2.05 - 2.36 (m, 3 H), 1.91 - 2.04 (m, 1 H), 1.88 (s, 3 H), 1.52 - 1.69 (m, 3 H), 1.49 (s, 3 H), 1.43 (dd, 1 H), 0.79 (s, 3 H)

LC-MS (ESI POS): 532.28 (MH⁺)

[α]_D²⁵ = + 285.8 (c 0.11, CHCl₃)

Example 6



Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-benzyl)-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-azapentaleno[2,1-a]phenanthrene-6b-carboxylic acid (compound 41)

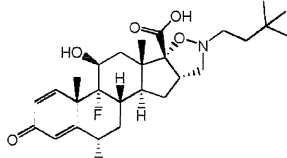
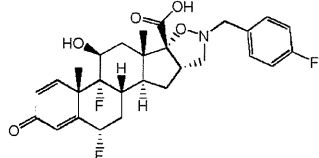
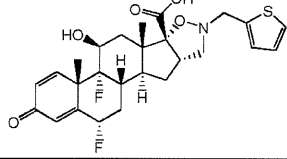
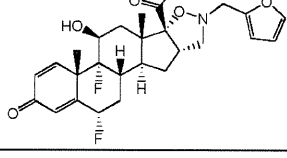
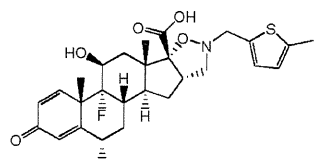
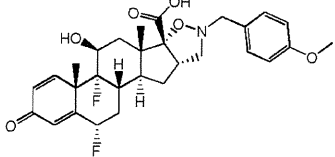
To a solution of compound 21 (1.55 g, 2.83 mmol) in tetrahydrofuran (60 ml) and water (30.0 ml) at 0°C, 6 N sodium hydroxide (1.414 ml, 8.49 mmol) was dropped and the reaction mixture was stirred at 0°C for 10 min and at room temperature for 56 hrs. Tetrahydrofuran was evaporated, the aqueous layer was acidified to pH 1 and extracted with AcOEt (100 ml x 3).

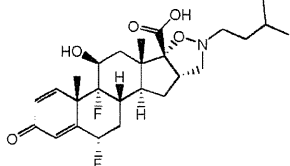
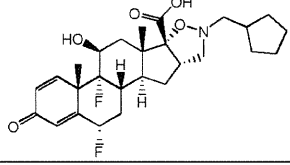
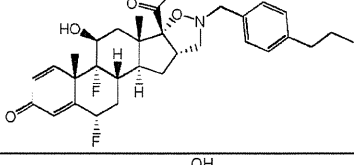
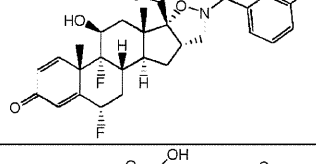
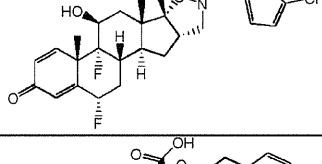
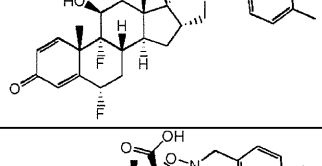
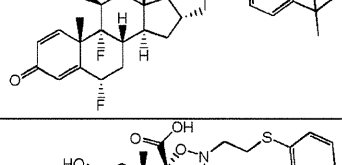
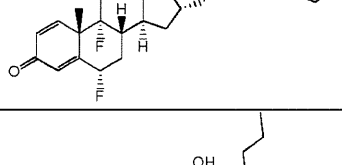
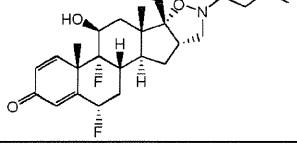
The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Crude was purified by silica gel flash chromatography in DCM/AcOEt/ HCO_2H 60: 39.5: 0.5, to afford 1.11 g of pure compound (R_f = 0.34 in DCM/AcOEt/ HCO_2H 50: 49.5 : 0.5).

5 LC-MS (ESI POS): 534.2 (MH⁺)

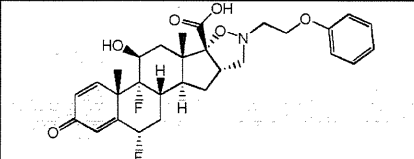
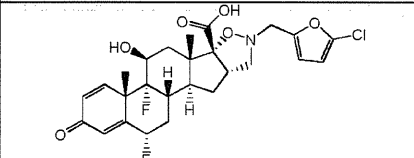
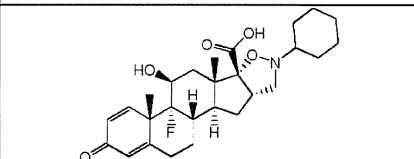
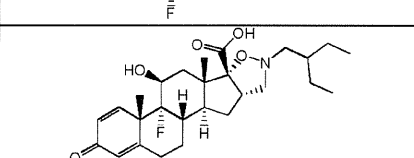
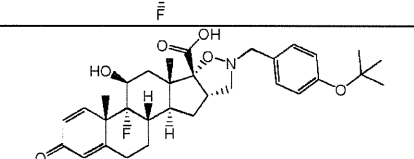
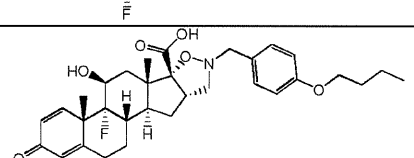
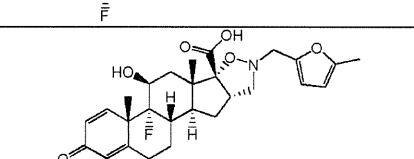
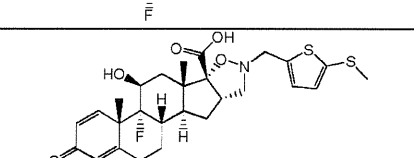
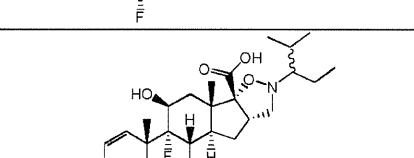
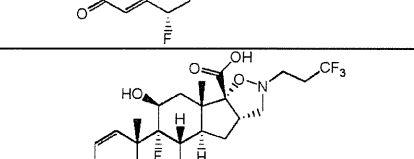
Compounds listed in Table 3 were prepared as previously described for compound 41:

Table 3

Compound	Structure	Yield	Analytical
42		89%	LC_MS (ESI POS): 494.2 (MH ⁺)
43		62%	LC_MS (ESI POS): 518.1 (MH ⁺)
44		55%	LC_MS (ESI POS): 506.1 (MH ⁺)
45		41%	LC_MS (ESI POS): 490.1 (MH ⁺)
46		20%	LC_MS (ESI POS): 520.1 (MH ⁺)
47		99%	LC_MS (ESI POS): 530.1 (MH ⁺)

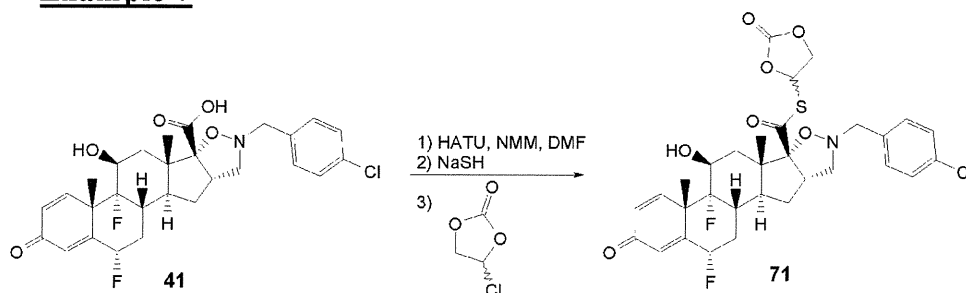
48		96%	LC_MS (ESI POS): 480.1 (MH ⁺)
49		71%	LC_MS (ESI POS): 492.1 (MH ⁺)
50		43%	LC_MS (ESI POS): 542.1 (MH ⁺)
51		98%	LC_MS (ESI POS): 514.1 (MH ⁺)
52		97%	LC_MS (ESI POS): 540.0 (MH ⁺)
53		97%	LC_MS (ESI POS): 514.2 (MH ⁺)
54		50%	LC_MS (ESI POS): 556.2 (MH ⁺)
55		59%	LC_MS (ESI POS): 546.1 (MH ⁺)
56		78%	LC_MS (ESI POS): 508.1 (MH ⁺)

(continued)

57		99%	LC-MS (ESI POS): 530.1 (MH ⁺)
58		31%	LC-MS (ESI POS): 524.0 (MH ⁺)
59		63%	LC-MS (ESI POS): 492.1 (MH ⁺)
60		68%	LC-MS (ESI POS): 494.1 (MH ⁺)
61		44%	LC-MS (ESI POS): 572.2 (MH ⁺)
62		79%	LC-MS (ESI POS): 572.2 (MH ⁺)
63		91%	LC-MS (ESI POS): 504.0 (MH ⁺)
64		95%	LC-MS (ESI POS): 552.1 (MH ⁺)
65		99%	LC-MS (ESI POS): 494.1 (MH ⁺)
66		60%	LC-MS (ESI POS): 506.0 (MH ⁺)

(continued)

67		88%	LC_MS (ESI POS): 464.1 (MH ⁺)
68		72%	LC_MS (ESI POS): 520.2 (MH ⁺)
69		97%	LC_MS (ESI POS): 504.1 (MH ⁺)
70		96%	LC_MS (ESI POS): 553.2 (MH ⁺)

Example 7

Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-benzyl)-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-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-(2-oxo-[1,3]dioxolan-4-yl) ester (compound 71)

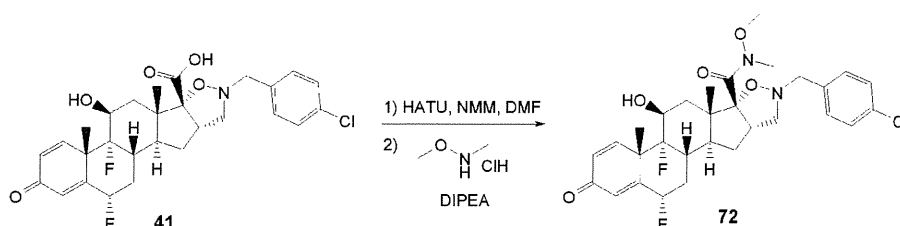
To a solution of compound 41 (300 mg, 0.562 mmol) in dry DMF (11.2 ml), kept under nitrogen, HATU (235 mg, 0.618 mmol) was added, followed by N-methylmorpholine (0.062 ml, 0.562 mmol). The reaction mixture was heated at 65°C for 40 min, after which time conversion into the activate ester was complete. The mixture was cooled down to room temperature and NaSH (94 mg, 1.685 mmol) was added portion wise. The

solution, turned deep green, was stirred at room temperature for 20 min, then 4-chloro-1,3-dioxolan-2-one (206 mg, 1.685 mmol) was then added dropwise, followed by KI (46.6 mg, 0.281 mmol), and mixture stirred at room temperature overnight. AcOEt (70 ml) was added and the mixture washed with
 5 brine; the aqueous layer was extracted with AcOEt (2 x 70 ml) and the combined organic extracts were washed with 1N HCl solution and brine. Organic phase was dried over Na₂SO₄ and evaporated, affording 940 mg of crude, which was purified *via* chromatographic column on silica gel in gradient elution from DCM/AcOEt 30 : 1 to DCM/AcOEt 5 : 1, to afford
 10 320 mg of the desired compound. It was further purified *via* preparative HPLC (mobile phase: water/ACN without acidic additive) to afford 140 mg of a solid (39% yield). ¹H-NMR analysis reveals the presence of the aldehyde arising from hydrolysis of the carbonate.

¹H NMR (300 MHz, DMSO-d₆) ppm 7.18 - 7.42 (m, 5 H), 6.26 - 6.38 (m, 2 H), 6.13 (s, 1 H), 5.45 - 5.80 (m, 2 H), 4.88 and 4.92 (t, 1 H), 4.33 and 4.42 (dd, 1 H), 4.09 - 4.24 (m, 1 H), 3.99 and 4.02 (d, 1 H), 3.84 and 3.85 (d, 1 H), 3.45 - 3.60 (m, 1 H), 3.34 - 3.45 (m, 1 H), 2.56 - 2.70 (m, 1 H), 1.97 - 2.34 (m, 4 H), 1.52 - 1.91 (m, 4 H), 1.48 and 1.49 (s, 3 H), 0.90 and 0.92 (s, 3 H)

LC-MS (ESI POS): 636.35 (MH⁺)

20 Example 8



**Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-8-(4-chloro-benzyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-
 25 2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthrene-6b-carboxylic acid methoxy-methyl-amide**

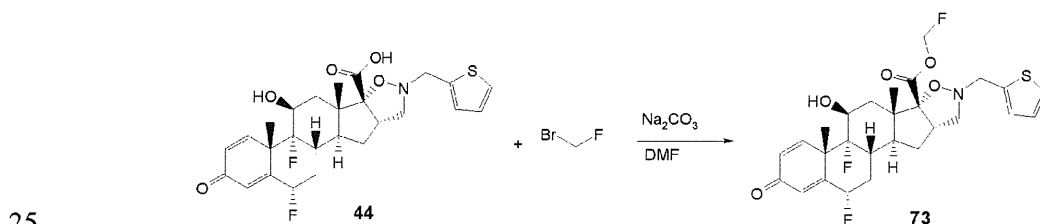
(compound 72)

To a solution of compound 41 (300 mg, 0.562 mmol) in dry DMF (10.6 ml), kept under nitrogen atmosphere, HATU (235 mg, 0.618 mmol) is added, followed by N-methylmorpholine (0.062 ml, 0.562 mmol). Mixture is stirred at 70°C for 40 min, after which time conversion into the activated ester is complete. Reaction is cooled down to room temperature and N, O-dimethyl hydroxylamine hydrochloride (164 mg, 1.685 mmol) is added, followed by TEA (0.313 ml, 2.247 mmol). Mixture is stirred at room temperature overnight. Further addition of N, O-dimethyl hydroxylamine hydrochloride (164 mg, 1.685 mmol) and TEA (0.313 ml, 2.247 mmol) is done, and mixture heated at 65°C for 5h. Conversion is complete. Mixture is diluted with AcOEt (60 ml) and washed with brine (60 ml). Aqueous layer is extracted with AcOEt (2 x 60 ml), and then organic extracts are washed with 1N HCl solution, dried over Na₂SO₄ and evaporated. Crude (700 mg) is purified *via* preparative HPLC (neutral mobile phase), obtaining 96 mg of pure solid (30% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 - 7.39 (m, 4 H), 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.12 (s, 1 H), 5.46 - 5.75 (m, 1 H), 5.36 (d, 1 H), 4.02 - 4.21 (m, 1 H), 3.72 - 3.97 (m, 3 H), 3.38 - 3.63 (m, 1 H), 3.29 (s, 3 H), 2.98 (br. s., 3 H), 2.56 - 2.66 (m, 1 H), 2.03 - 2.34 (m, 3 H), 1.69 - 2.01 (m, 2 H), 1.51 - 1.68 (m, 2 H), 1.49 (s, 3 H), 1.31 - 1.46 (m, 1 H), 0.87 (s, 3 H)

LC-MS (ESI POS): 577.29 MH⁺

[α]_D²⁵ = + 122.1 (c 0.134, CHCl₃)

Example 9

Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-

**Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-thiophen-2-ylmethyl-
2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-
pentaleno[2,1-a]phenanthrene-6b-carboxylic acid fluoromethyl ester
(compound 73)**

5 To a solution of compound 44 (150 mg, 0.297 mmol) in dry DMF (3 ml) under nitrogen atmosphere, sodium carbonate (157 mg, 1.483 mmol) was added. After stirring at room temperature for 20 min the mixture was cooled to 0°C and bromofluoromethane (0.371 ml, 0.742 mmol) was added. The reaction mixture was stirred at 0°C for 15 min and at RT for 1 hr; then, further 2 M solution of
10 bromofluoromethane (0.371 ml, 0.742 mmol) in DMF was added and the mixture was stirred at RT for 46 hr. The reaction mixture was poured into a cooled HCl solution (1 ml of 1 N HCl and 19 ml of water) and the aqueous phase was extracted with AcOEt (3 x 40 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated. The crude material (162 mg) was purified by silica
15 gel flash chromatography in gradient elution from DCM/AcOEt 97 : 3 to DCM/AcOEt 84 : 16 to afford 92 mg of pure compound (58% yield; R_f = 0.39 in AcOEt/DCM 20 : 80).

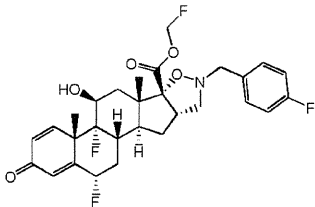
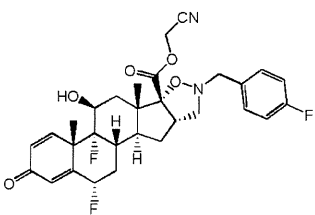
¹H NMR (300 MHz, DMSO-d₆) ppm 7.39 (dd, 1 H), 7.26 (dd, 1 H), 6.76 - 7.02 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.76 (dd, 1 H), 5.89 (dd, 3 H), 5.53 -
20 5.73 (m, 1 H), 5.50 (d, 1 H), 4.12 - 4.28 (m, 1 H), 4.10 (br. s., 2 H), 3.48 - 3.65 (m, 2 H), 2.56 - 2.70 (m, 1 H), 2.04 - 2.33 (m, 2 H), 1.83 - 2.04 (m, 1 H), 1.54 - 1.83 (m, 2 H), 1.50 (s, 3 H), 1.35 - 1.48 (m, 1 H), 0.94 (s, 3 H)

LC-MS (ESI POS): 538.28 MH⁺

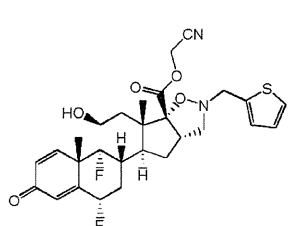
[α]_D²⁵ = + 46.49 (c 0.111; CHCl₃)

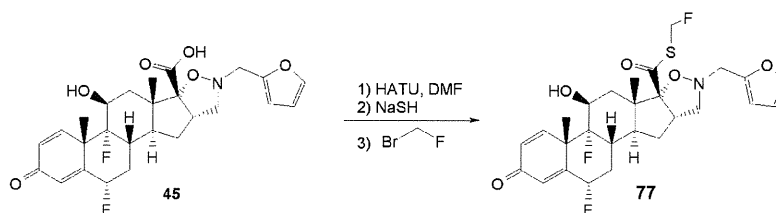
25 The compounds listed in Table 4 were prepared as previously described for compound 73 utilizing the suitable alkylating agent:

Table 4

Compound	Structure	Yield	Analytical
74		64%	LC-MS (ESI POS): 550.31MH+ $[\alpha]_D^{25} = + 222.5$ (c 0.064; CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 - 7.35 (m, 2 H), 7.25 (dd, 1 H), 6.98 - 7.16 (m, 2 H), 6.29 (dd, 1 H), 6.12 (s, 1 H), 5.86 (dd, 1 H), 5.80 (dd, 1 H), 5.52 - 5.76 (m, 1 H), 5.50 (dd, 1 H), 4.09 - 4.24 (m, 1 H), 3.92 (d, 1 H), 3.84 (d, 1 H), 3.42 - 3.69 (m, 2 H), 2.55 - 2.71 (m, 1 H), 2.05 - 2.36 (m, 2 H), 1.77 - 1.92 (m, 1 H), 1.53 - 1.77 (m, 4 H), 1.49 (s, 3 H), 1.39 - 1.47 (m, 1 H), 0.94 (s, 3 H)
75		75%	LC-MS (ESI POS): 557.3 MH+ $[\alpha]_D^{25} = + 112.3$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.20 - 7.39 (m, 3 H), 7.09 (t, 2 H), 6.29 (dd, 1 H), 6.12 (s, 1 H), 5.54 - 5.79 (m, 1 H), 5.52 (d, 1 H), 5.11 (d, 1 H), 5.05 (d, 1 H), 4.08 - 4.22 (m, 1 H), 3.93 (d, 1 H), 3.82 (d, 1 H), 3.51 - 3.59 (m, 1 H), 2.53 - 2.63 (m, 1 H), 2.36 - 2.45 (m, 1 H), 2.22 - 2.36 (m, 2 H), 2.04 - 2.21 (m, 1 H), 1.59 - 1.91 (m, 3 H), 1.33 - 1.59 (m, 2 H), 1.49 (s, 3 H), 0.93 (s, 3 H)

(continued)

76		37%	LC-MS (ESI POS): 545.04 MH⁺ $[\alpha]_D^{25} = + 74.80$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.35 - 7.42 (m, 1 H), 7.26 (dd, 1 H), 6.84 - 6.99 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.55 - 5.80 (m, 1 H), 5.50 - 5.55 (m, 1 H), 5.06 (s, 2 H), 4.12 - 4.28 (m, 1 H), 3.93 - 4.12 (m, 2 H), 3.45 - 3.68 (m, 2 H), 2.55 - 2.63 (m, 1 H), 2.02 - 2.33 (m, 3 H), 1.81 - 2.02 (m, 1 H), 1.59 - 1.81 (m, 2 H), 1.49 (s, 3 H), 1.32 - 1.47 (m, 2 H), 0.93 (s, 3 H)
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Example 10

Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-furan-2-ylmethyl-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-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester (compound 77)

A mixture of compound 45 (453 mg, 0.925 mmol), HATU (387 mg, 1.018 mmol) and N-methylmorpholine (0.102 ml, 0.925 mmol) in dry DMF (15 ml) was stirred under nitrogen atmosphere at 70°C for 1.5 hrs and LC-MS showed the formation of the desired activated ester (93% conversion). The solution was cooled to RT and sodium hydrogen sulfide, anhydrous (156 mg, 2.78 mmol) was added. The mixture was stirred at RT for 25 min, then 2 M

solution of bromofluoromethane (1.388 ml, 2.78 mmol) in DMF was added and the mixture was stirred at Room Temperature for 2 hrs. Further bromofluoromethane (0.463 ml, 0.925 mmol) was added and the reaction mixture stirred at RT overnight.

5 The reaction mixture was diluted with AcOEt (130 ml) and the organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated. The obtained crude mixture (561 mg) was purified by flash chromatography on silica gel in gradient elution from AcOEt/petroleum ether 5 : 95 to AcOEt/petroleum ether 30 : 70 and then with DCM to afford 184 mg of the
10 title compound (37% yield; $R_f = 0.79$ in AcOEt/DCM 30 : 70).

^1H NMR (300 MHz, DMSO-d_6) ppm 7.54 (dd, 1 H), 7.25 (dd, 1 H), 6.26 - 6.41 (m, 3 H), 6.12 (s, 1 H), 5.88 (dd, 1 H), 5.78 (dd, 1 H), 5.51 - 5.75 (m, 1 H), 5.50 (dd, 1 H), 4.10 - 4.26 (m, 1 H), 3.95 (s, 2 H), 3.42 - 3.55 (m, 1 H), 3.33 - 3.42 (m, 1 H), 2.56 - 2.69 (m, 1 H), 2.02 - 2.37 (m, 3 H), 1.90 (dt, 1
15 H), 1.50 - 1.77 (m, 3 H), 1.49 (s, 3 H), 1.40 - 1.48 (m, 1 H), 0.88 (s, 3 H)

LC-MS (ESI POS): 538.4 (MH⁺)

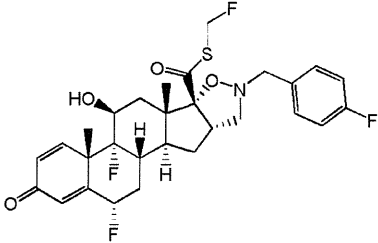
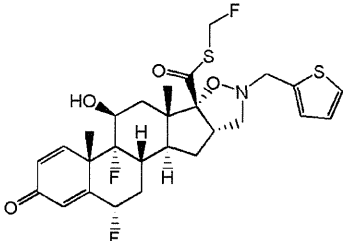
$[\alpha]_D^{25} = +112.4$ (c 0.145; CHCl_3)

The compounds listed in Table 5 were prepared as previously described for compound 77, starting from the suitable acid derivative:

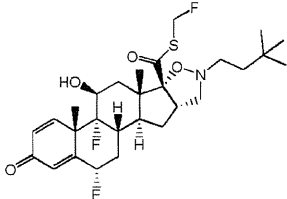
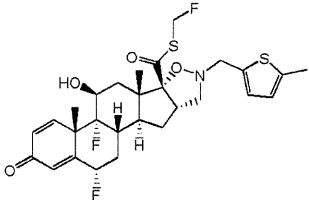
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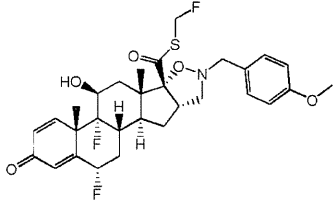
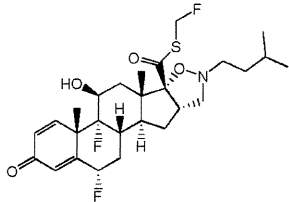
Table 5

Compound	Structure	Yield	Analytical
78		86%	LC-MS (ESI POS): 566.46 MH⁺ $[\alpha]_D^{25} = +163.3$ (c 0.174, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.29 - 7.39 (m, 2 H), 7.24 (dd, 1 H), 7.04 - 7.16 (m, 2 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.86 (dd, 1 H), 5.76 (dd, 1 H), 5.52 - 5.74 (m, 1 H), 5.50 (dd, 1 H), 4.07 - 4.28 (m, 1 H), 3.95 (d, 1 H), 3.86 (d, 1 H), 3.46 - 3.61 (m, 1 H), 3.33 - 3.46 (m, 1 H), 2.56 - 2.76 (m, 1 H), 2.04 - 2.31 (m, 3 H), 1.78 - 1.95 (m, 1 H), 1.51 - 1.74 (m, 4 H), 1.49 (s, 3 H), 0.88 (s, 3 H)
79		39%	LC-MS (ESI POS): 554.42 MH⁺ $[\alpha]_D^{25} = +123.9$ (c 0.108, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.42 (dd, 1 H), 7.25 (dd, 1 H), 6.99 (dd, 1 H), 6.95 (dd, 1 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.88 (dd, 1 H), 5.78 (dd, 1 H), 5.53 - 5.76 (m, 1 H), 5.51 (dd, 1 H), 4.18 - 4.21 (m, 1 H), 4.19 (d, 1 H), 4.12 (d, 1 H), 3.44 - 3.58 (m, 1 H), 3.35 - 3.44 (m, 1 H), 2.58 - 2.75 (m, 1 H), 2.03 - 2.37 (m, 3 H), 1.86 - 2.03 (m, 1 H), 1.52 - 1.79 (m, 3 H), 1.49 (s, 3 H), 1.38 - 1.48 (m, 1 H), 0.89 (s, 3 H)

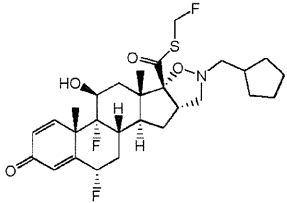
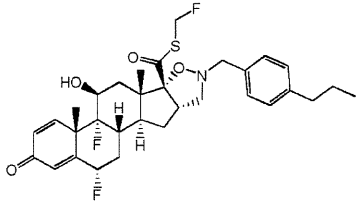
(continued)

80		LC-MS (ESI POS): 542.37 MH⁺ $[\alpha]_D^{25} = + 134.9$ (0.23, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (d, 1 H), 6.29 (dd, 1 H), 6.12 (s, 1 H), 5.89 (dd, 1 H), 5.81 (dd, 1 H), 5.53 - 5.73 (m, 1 H), 5.50 (dd, 1 H), 4.07 - 4.24 (m, 1 H), 3.46 - 3.67 (m, 1 H), 3.32 - 3.45 (m, 1 H), 2.55 - 2.78 (m, 3 H), 1.95 - 2.33 (m, 3 H), 1.82 - 1.95 (m, 1 H), 1.51 - 1.80 (m, 4 H), 1.49 (s, 3 H), 1.29 - 1.47 (m, 2 H), 0.89 (s, 3 H), 0.86 (s, 9 H) 16%
81		LC-MS (ESI POS): 568.14 MH⁺ $[\alpha]_D^{25} = + 57.09$ (c 0.27, DMF) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.75 (d, 1 H), 6.61 (dq, 1 H), 6.30 (dd, 1 H), 6.09 - 6.14 (m, 1 H), 5.89 (dd, 1 H), 5.79 (dd, 1 H), 5.51 - 5.75 (m, 1 H), 5.49 (dd, 1 H), 4.14 - 4.26 (m, 1 H), 4.10 (d, 1 H), 4.04 (d, 1 H), 3.31 - 3.50 (m, 2 H), 2.56 - 2.70 (m, 1 H), 2.34 (d, 3 H), 2.02 - 2.30 (m, 3 H), 1.90 - 2.02 (m, 1 H), 1.72 (d, 1 H), 1.51 - 1.67 (m, 1 H), 1.49 (s, 3 H), 1.31 - 1.48 (m, 2 H), 0.89 (s, 3 H) 11%

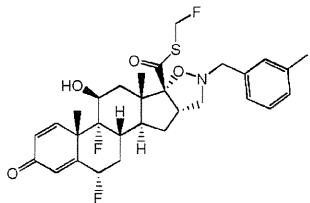
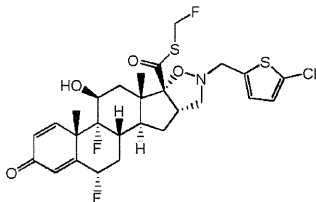
(continued)

82		LC-MS (ESI POS): 578.11 MH⁺ $[\alpha]_D^{25} = +131.6$ (c 0.25, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 7.14 - 7.22 (m, 2 H), 6.75 - 6.90 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.87 (dd, 1 H), 5.77 (dd, 1 H), 5.51 - 5.73 (m, 1 H), 5.49 (dd, 1 H), 4.08 - 4.28 (m, 1 H), 3.89 (d, 1 H), 3.83 (d, 1 H), 3.71 (s, 3 H), 3.39 - 3.52 (m, 1 H), 3.32 - 3.41 (m, 1 H), 2.55 - 2.71 (m, 1 H), 2.03 - 2.37 (m, 3 H), 1.82 - 1.97 (m, 1 H), 1.52 - 1.75 (m, 3 H), 1.49 (s, 3 H), 1.40 - 1.48 (m, 1 H), 0.88 (s, 3 H) 20%
83		LC-MS (ESI POS): 528.2 MH⁺ $[\alpha]_D^{25} = +132.9$ (c 0.1145 CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.08 - 6.18 (m, 1 H), 5.89 (dd, 1 H), 5.81 (dd, 1 H), 5.51 - 5.73 (m, 1 H), 5.49 (dd, 1 H), 4.05 - 4.26 (m, 1 H), 3.45 - 3.66 (m, 1 H), 3.31 - 3.45 (m, 1 H), 2.55 - 2.81 (m, 3 H), 2.19 - 2.36 (m, 1 H), 1.95 - 2.19 (m, 2 H), 1.79 - 1.93 (m, 1 H), 1.67 - 1.77 (m, 1 H), 1.51 - 1.67 (m, 3 H), 1.49 (s, 3 H), 1.43 - 1.48 (m, 1 H), 1.40 (q, 2 H), 0.89 (s, 3 H), 0.84 (d, 3 H), 0.84 (d, 3 H) 37%

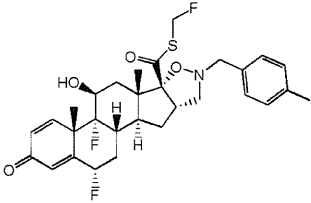
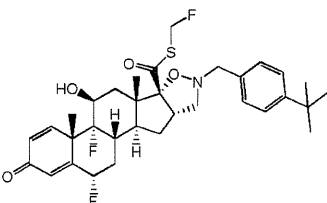
(continued)

84		LC-MS (ESI POS): 540.2 MH⁺ $[\alpha]_D^{25} = +149.8$ (C 0.145, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (d, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.89 (dd, 1 H), 5.82 (dd, 1 H), 5.55 (m, 1 H), 5.49 (dd, 1 H), 3.99 - 4.28 (m, 1 H), 3.44 - 3.65 (m, 1 H), 3.37 (m, 1 H), 2.56 - 2.70 (m, 1 H), 2.54 - 2.70 (m, 2 H), 2.19 - 2.34 (m, 1 H), 1.98 - 2.19 (m, 3 H), 1.82 - 1.98 (m, 1 H), 1.56 - 1.82 (m, 4 H), 1.37 - 1.56 (m, 6 H), 1.48 (s, 3 H), 0.98 - 1.24 (m, 2 H), 0.89 (s, 3 H) 10%
85		LC-MS (ESI POS): 590.18 MH⁺ $[\alpha]_D^{25} = +84.95$ (c 0.109, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 7.14 - 7.21 (m, 2 H), 7.05 - 7.14 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.88 (dd, 1 H), 5.77 (dd, 1 H), 5.50 - 5.74 (m, 1 H), 5.48 (dd, 1 H), 4.08 - 4.24 (m, 1 H), 3.90 (s, 2 H), 3.32 - 3.51 (m, 2 H), 2.55 - 2.71 (m, 1 H), 2.43 - 2.48 (m, 2 H), 2.01 - 2.33 (m, 3 H), 1.82 - 1.94 (m, 1 H), 1.69 (d, 1 H), 1.50 - 1.65 (m, 4 H), 1.48 (s, 3 H), 1.36 - 1.46 (m, 1 H), 0.88 (s, 3 H), 0.86 (t, 3 H) 43%

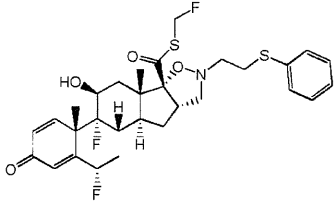
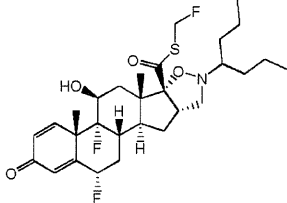
(continued)

86		14% LC-MS (ESI POS): 562.15 MH⁺ $[\alpha]_D^{25} = +181.2$ (c 0.37, DMF) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 7.16 (t, 1 H), 7.11 - 7.15 (m, 1 H), 6.98 - 7.10 (m, 2 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.89 (dd, 1 H), 5.80 (dd, 1 H), 5.51 - 5.76 (m, 1 H), 5.49 (dd, 1 H), 4.07 - 4.28 (m, 1 H), 3.90 (s, 2 H), 3.42 - 3.54 (m, 1 H), 3.34 - 3.45 (m, 1 H), 2.56 - 2.71 (m, 1 H), 2.25 (s, 3 H), 2.02 - 2.24 (m, 3 H), 1.79 - 1.94 (m, 1 H), 1.51 - 1.73 (m, 4 H), 1.49 (s, 3 H), 0.89 (s, 3 H)
87		31% LC-MS (ESI POS): 588.11 MH⁺ $[\alpha]_D^{25} = +155.6$ (c 0.43, DMF) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.94 (d, 1 H), 6.86 (d, 1 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.88 (dd, 1 H), 5.79 (dd, 1 H), 5.53 - 5.76 (m, 1 H), 5.51 (dd, 1 H), 4.16 - 4.25 (m, 1 H), 4.18 (d, 1 H), 4.02 (d, 1 H), 3.45 - 3.61 (m, 1 H), 3.35 - 3.46 (m, 1 H), 2.56 - 2.70 (m, 1 H), 2.05 - 2.31 (m, 3 H), 1.85 - 1.98 (m, 1 H), 1.68 - 1.78 (m, 1 H), 1.53 - 1.68 (m, 2 H), 1.49 (s, 3 H), 1.39 - 1.47 (m, 1 H), 0.89 (s, 3 H)

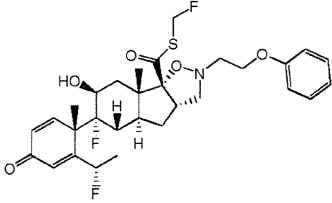
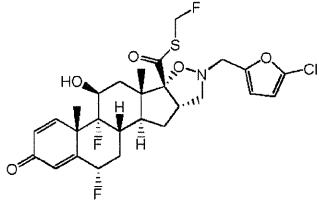
(continued)

88		LC-MS (ESI POS): 562.16 MH⁺ $[\alpha]_D^{25} = +145.2$ (c 0.34, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 7.15 - 7.21 (m, 2 H), 7.02 - 7.13 (m, 2 H), 6.30 (dd, 1 H), 6.09 - 6.15 (m, 1 H), 5.88 (dd, 1 H), 5.78 (dd, 1 H), 5.51 - 5.76 (m, 1 H), 5.49 (dd, 1 H), 4.09 - 4.23 (m, 1 H), 3.91 (d, 1 H), 3.85 (d, 1 H), 3.41 - 3.54 (m, 1 H), 3.34 - 3.42 (m, 1 H), 2.55 - 2.70 (m, 1 H), 2.26 (s, 3 H), 2.01 - 2.25 (m, 3 H), 1.79 - 1.96 (m, 1 H), 1.49 (s, 3 H), 1.41 - 1.76 (m, 4 H), 0.88 (s, 3 H) 10%
89		LC-MS (ESI POS): 604.18 MH⁺ $[\alpha]_D^{25} = +94.6$ (c 0.0905, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 - 7.35 (m, 2 H), 7.24 (d, 1 H), 7.16 - 7.22 (m, 2 H), 6.30 (dd, 1 H), 6.11 (s, 1 H), 5.90 (dd, 1 H), 5.79 (dd, 1 H), 5.52 - 5.69 (m, 1 H), 4.07 - 4.28 (m, 1 H), 3.93 (s, 2 H), 3.31 - 3.52 (m, 2 H), 2.54 - 2.70 (m, 1 H), 1.81 - 2.37 (m, 5 H), 1.69 (d, 1 H), 1.53 - 1.65 (m, 1 H), 1.48 (s, 3 H), 1.34 - 1.46 (m, 2 H), 1.23 (s, 9 H), 0.88 (s, 3 H) 5%

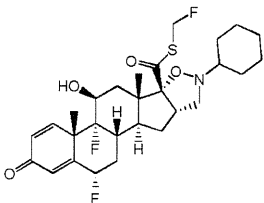
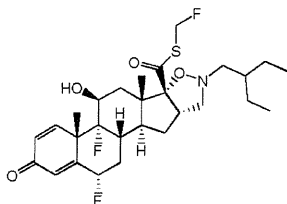
(continued)

90		LC-MS (ESI POS): 594.2 MH⁺ $[\alpha]_D^{25} = +80.97$ (c 0.103, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.05 - 7.41 (m, 6 H), 6.30 (dd, 1 H), 6.11 (s, 1 H), 5.91 (dd, 1 H), 5.82 (dd, 1 H), 5.53 - 5.73 (m, 1 H), 5.52 (dd, 1 H), 4.01 - 4.36 (m, 1 H), 3.46 - 3.63 (m, 1 H), 3.33 - 3.46 (m, 1 H), 3.13 - 3.23 (m, 1 H), 3.03 - 3.13 (m, 1 H), 2.94 - 3.03 (m, 1 H), 2.80 - 2.94 (m, 1 H), 2.55 - 2.68 (m, 1 H), 2.01 - 2.36 (m, 3 H), 1.81 - 2.01 (m, 1 H), 1.53 - 1.81 (m, 3 H), 1.49 (s, 3 H), 1.38 - 1.48 (m, 1 H), 0.90 (s, 3 H) 38%
91		LC-MS (ESI POS): 556.26 MH⁺ $[\alpha]_D^{25} = +137.9$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.90 (dd, 1 H), 5.81 (dd, 1 H), 5.51 - 5.71 (m, 1 H), 5.49 (dd, 0 H), 4.04 - 4.27 (m, 1 H), 3.42 - 3.59 (m, 1 H), 3.32 - 3.42 (m, 1 H), 2.56 - 2.70 (m, 2 H), 1.97 - 2.32 (m, 4 H), 1.82 - 1.96 (m, 1 H), 1.69 - 1.80 (m, 1 H), 1.51 - 1.69 (m, 3 H), 1.49 (s, 3 H), 1.13 - 1.47 (m, 8 H), 0.88 (s, 3 H), 0.85 (t, 3 H), 0.83 (t, 3 H) 15%

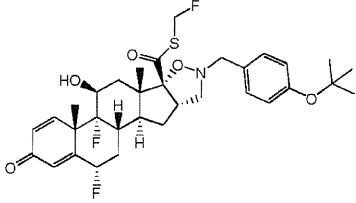
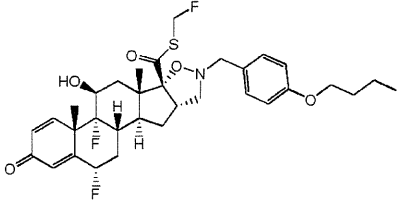
(continued)

92		LC-MS (ESI POS): 578.2 MH⁺ $[\alpha]_D^{25} = +131.1$ (c 0.28, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.17 - 7.34 (m, 3 H), 6.82 - 7.01 (m, 3 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.86 (dd, 1 H), 5.73 (dd, 1 H), 5.53 - 5.74 (m, 1 H), 5.51 (dd, 1 H), 4.15 - 4.31 (m, 1 H), 4.14 (t, 2 H), 3.51 - 3.71 (m, 1 H), 3.33 - 3.51 (m, 1 H), 3.13 - 3.24 (m, 1 H), 2.96 - 3.13 (m, 1 H), 2.55 - 2.76 (m, 1 H), 2.04 - 2.35 (m, 3 H), 1.82 - 1.97 (m, 1 H), 1.51 - 1.80 (m, 4 H), 1.49 (s, 3 H), 0.90 (s, 3 H) 14%
93		LC-MS (ESI POS): 572.13 MH⁺ $[\alpha]_D^{25} = +148.7$ (c 0.33, DMF) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.42 (d, 1 H), 6.37 (d, 1 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.87 (dd, 1 H), 5.77 (dd, 1 H), 5.51 - 5.76 (m, 1 H), 5.49 (dd, 1 H), 4.07 - 4.27 (m, 1 H), 3.96 (d, 1 H), 3.86 (d, 1 H), 3.45 - 3.58 (m, 1 H), 3.34 - 3.45 (m, 1 H), 2.57 - 2.71 (m, 1 H), 1.98 - 2.32 (m, 3 H), 1.83 - 1.94 (m, 1 H), 1.49 (s, 3 H), 1.42 - 1.76 (m, 4 H), 0.88 (s, 3 H) 32%

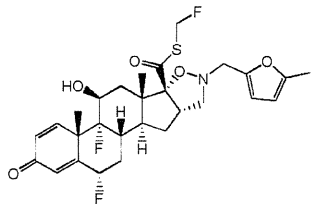
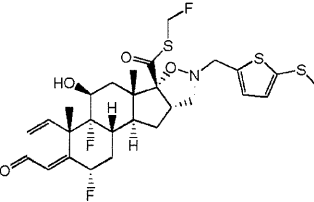
(continued)

94		LC-MS (ESI POS): 540.27 MH⁺ $[\alpha]_D^{25} = +126.8$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.89 (dd, 1 H), 5.79 (dd, 1 H), 5.51 - 5.75 (m, 1 H), 5.49 (dd, 1 H), 4.01 - 4.26 (m, 1 H), 3.43 - 3.64 (m, 1 H), 3.31 - 3.42 (m, 1 H), 2.55 - 2.71 (m, 2 H), 2.19 - 2.35 (m, 1 H), 1.95 - 2.19 (m, 3 H), 1.81 - 1.95 (m, 1 H), 1.52 - 1.78 (m, 7 H), 1.49 (s, 3 H), 1.40 - 1.48 (m, 1 H), 1.01 - 1.36 (m, 5 H), 0.89 (s, 3 H) 21%
95		LC-MS (ESI POS): 542.05 MH⁺ $[\alpha]_D^{25} = +167.0$ (c 0.2, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.89 (dd, 1 H), 5.82 (dd, 1 H), 5.50 - 5.72 (m, 1 H), 5.49 (dd, 1 H), 4.08 - 4.26 (m, 1 H), 3.43 - 3.59 (m, 1 H), 3.33 - 3.43 (m, 1 H), 2.61 - 2.70 (m, 1 H), 2.58 (t, 2 H), 1.98 - 2.36 (m, 3 H), 1.80 - 1.94 (m, 1 H), 1.51 - 1.77 (m, 5 H), 1.49 (s, 3 H), 1.39 - 1.48 (m, 1 H), 1.13 - 1.36 (m, 3 H), 0.89 (s, 3 H), 0.81 (t, 3 H), 0.78 (t, 3 H) 23%

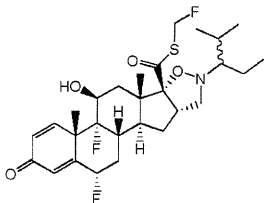
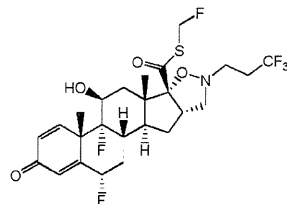
(continued)

96		LC-MS (ESI POS): 620.19 MH⁺ $[\alpha]_D^{25} = +128.8$ (c 0.105, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 7.13 - 7.21 (m, 2 H), 6.81 - 6.90 (m, 2 H), 6.30 (dd, 1 H), 6.11 (s, 1 H), 5.86 (dd, 1 H), 5.75 (dd, 1 H), 5.49 - 5.75 (m, 1 H), 5.48 (dd, 1 H), 4.10 - 4.24 (m, 1 H), 3.94 (d, 1 H), 3.87 (d, 1 H), 3.31 - 3.50 (m, 2 H), 2.54 - 2.72 (m, 1 H), 1.95 - 2.32 (m, 3 H), 1.82 - 1.95 (m, 1 H), 1.51 - 1.75 (m, 3 H), 1.48 (s, 3 H), 1.34 - 1.46 (m, 1 H), 1.24 (s, 9 H), 0.88 (s, 3 H) 16%
97		LC-MS (ESI POS): 620.24 MH⁺ $[\alpha]_D^{25} = +142.4$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 7.12 - 7.21 (m, 2 H), 6.76 - 6.87 (m, 2 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.88 (dd, 1 H), 5.77 (dd, 1 H), 5.51 - 5.75 (m, 1 H), 5.49 (dd, 1 H), 4.09 - 4.26 (m, 1 H), 3.91 (t, 2 H), 3.89 (br. s., 1 H), 3.83 (d, 1 H), 3.32 - 3.50 (m, 2 H), 2.56 - 2.71 (m, 1 H), 2.01 - 2.35 (m, 3 H), 1.81 - 1.98 (m, 1 H), 1.53 - 1.77 (m, 5 H), 1.49 (s, 3 H), 1.34 - 1.47 (m, 3 H), 0.93 (t, 3 H), 0.88 (s, 3 H) 27%

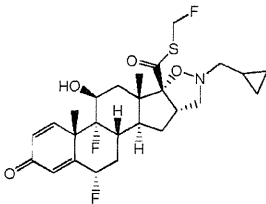
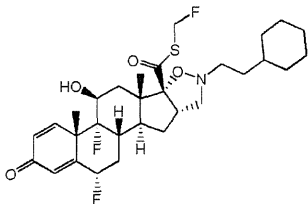
(continued)

98		LC-MS (ESI POS): 552.2 MH⁺ $[\alpha]_D^{25} = +104.3$ (c 0.6, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.30 (dd, 1 H), 6.18 (d, 1 H), 6.12 (s, 1 H), 5.96 (dq, 1 H), 5.88 (dd, 1 H), 5.79 (dd, 1 H), 5.51 - 5.76 (m, 1 H), 5.49 (dd, 1 H), 4.09 - 4.26 (m, 1 H), 3.92 (d, 1 H), 3.85 (d, 1 H), 3.40 - 3.52 (m, 1 H), 3.33 - 3.42 (m, 1 H), 2.57 - 2.70 (m, 1 H), 2.20 - 2.26 (m, 1 H), 2.18 (d, 3 H), 2.01 - 2.16 (m, 2 H), 1.83 - 1.96 (m, 1 H), 1.52 - 1.77 (m, 3 H), 1.49 (s, 3 H), 1.37 - 1.48 (m, 1 H), 0.88 (s, 3 H) 18%
99		LC-MS (ESI POS): 599.88 MH⁺ $[\alpha]_D^{25} = +115.9$ (c 0.162, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.95 (d, 1 H), 6.87 (d, 1 H), 6.30 (dd, 1 H), 6.11 (s, 1 H), 5.89 (dd, 1 H), 5.79 (dd, 1 H), 5.52 - 5.72 (m, 1 H), 5.50 (dd, 1 H), 4.19 (d, 1 H), 4.15 - 4.21 (m, 1 H), 4.08 (d, 1 H), 3.33 - 3.52 (m, 2 H), 2.54 - 2.70 (m, 1 H), 2.37 (s, 3 H), 2.04 - 2.30 (m, 3 H), 1.89 - 2.03 (m, 1 H), 1.68 - 1.79 (m, 1 H), 1.52 - 1.68 (m, 1 H), 1.49 (s, 3 H), 1.35 - 1.47 (m, 2 H), 0.89 (s, 3 H) 16%

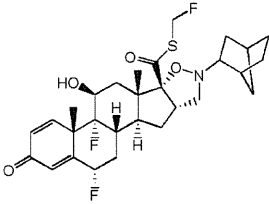
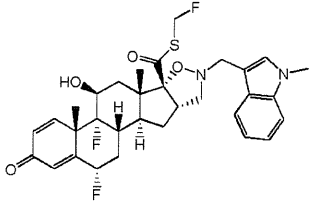
(continued)

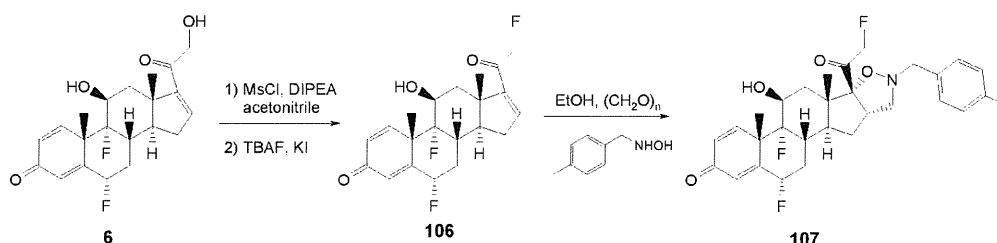
100		19% LC-MS (ESI POS): 542.18 MH⁺ $[\alpha]_D^{25} = +143.9$ (c 0.25, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.79 - 6.03 (m, 1 H), 5.71 - 5.94 (m, 1 H), 5.51 - 5.73 (m, 1 H), 5.49 (dd, 1 H), 4.18 (dd, 1 H), 3.51 (t, 1 H), 3.32 - 3.45 (m, 1 H), 2.58 - 2.70 (m, 1 H), 2.01 - 2.35 (m, 5 H), 1.83 - 2.01 (m, 1 H), 1.56 - 1.83 (m, 4 H), 1.49 (s, 3 H), 1.43 - 1.56 (m, 2 H), 0.97 (t, 3 H), 0.80 - 0.93 (m, 7 H), 0.75 (d, 2 H)
101		18% LC-MS (ESI POS): 554.02 MH⁺ $[\alpha]_D^{25} = +129.0$ (c 0.111, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.12 (s, 1 H), 5.90 (dd, 1 H), 5.82 (dd, 1 H), 5.56 (m, 1 H), 5.51 (m, 1 H), 3.98 - 4.30 (m, 1 H), 3.49 - 3.73 (m, 1 H), 3.34 - 3.47 (m, 1 H), 2.96 - 3.17 (m, 1 H), 2.76 - 2.93 (m, 1 H), 2.55 - 2.69 (m, 1 H), 2.21 - 2.32 (m, 2 H), 2.02 - 2.20 (m, 2 H), 1.89 (dt, 1 H), 1.54 - 1.80 (m, 4 H), 1.43 - 1.53 (m, 1 H), 1.49 (s, 3 H), 0.90 (s, 3 H)

(continued)

102		LC-MS (ESI POS): 512.12 MH⁺ $[\alpha]_D^{25} = +129.6$ (c 0.25, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (d, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.90 (dd, 1 H), 5.80 (dd, 1 H), 5.51 - 5.77 (m, 1 H), 5.49 (dd, 1 H), 4.16 (d, 1 H), 3.46 - 3.66 (m, 1 H), 3.31 - 3.46 (m, 1 H), 2.60 - 2.80 (m, 2 H), 2.60 - 2.75 (m, 1 H), 2.19 - 2.36 (m, 1 H), 2.01 - 2.19 (m, 2 H), 1.81 - 1.96 (m, 1 H), 1.55 - 1.81 (m, 2 H), 1.49 (s, 3 H), 1.34 - 1.55 (m, 2 H), 0.78 - 0.99 (m, 1 H), 0.90 (s, 3 H), 0.27 - 0.59 (m, 2 H), -0.06 - 0.27 (m, 2 H) 17%
103		LC-MS (ESI POS): 568.23 MH⁺ $[\alpha]_D^{25} = +172.6$ (c 0.21, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.89 (dd, 1 H), 5.81 (dd, 1 H), 5.51 - 5.71 (m, 1 H), 5.49 (dd, 1 H), 4.02 - 4.26 (m, 1 H), 3.45 - 3.66 (m, 1 H), 3.31 - 3.45 (m, 1 H), 2.55 - 2.82 (m, 3 H), 2.17 - 2.33 (m, 1 H), 1.95 - 2.17 (m, 2 H), 1.81 - 1.94 (m, 1 H), 1.52 - 1.78 (m, 8 H), 1.49 (s, 3 H), 1.26 - 1.47 (m, 4 H), 1.00 - 1.24 (m, 3 H), 0.89 (s, 3 H), 0.70 - 0.86 (m, 2 H) 29%

(continued)

104		19% LC-MS (ESI POS): 552.22 MH⁺ $[\alpha]_D^{25} = +150.4$ (c 0.24, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (d, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.91 (dd, 1 H), 5.83 (dd, 1 H), 5.51 - 5.75 (m, 1 H), 5.50 (dd, 1 H), 3.51 - 3.69 (m, 1 H), 3.41 (q, 1 H), 2.54 - 2.87 (m, 2 H), 1.51 - 2.36 (m, 11 H), 1.49 (s, 3 H), 0.95 - 1.46 (m, 7 H), 0.87 (s, 3 H), 0.51 - 0.75 (m, 1 H)
105		7% LC-MS (ESI POS): 601.08 MH⁺ $[\alpha]_D^{25} = +76.63$ (c 0.16 DMF) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.55 (dt, 1 H), 7.37 (d, 1 H), 7.20 - 7.30 (m, 2 H), 7.12 (ddd, 1 H), 6.98 (ddd, 1 H), 6.32 (dd, 1 H), 6.13 (s, 1 H), 5.91 (dd, 1 H), 5.81 (dd, 1 H), 5.53 - 5.77 (m, 1 H), 5.51 (dd, 1 H), 4.10 - 4.38 (m, 2 H), 3.84 - 4.03 (m, 1 H), 3.71 (s, 3 H), 3.33 - 3.41 (m, 2 H), 2.55 - 2.68 (m, 1 H), 2.10 - 2.34 (m, 3 H), 1.92 - 2.03 (m, 1 H), 1.53 - 1.86 (m, 3 H), 1.50 (s, 3 H), 1.38 - 1.48 (m, 1 H), 0.90 (s, 3 H)

Example 11

Preparation of (6S,8S,9R,10S,11S,13S,14S)-6,9-difluoro-17-(2-fluoro-acetyl)-11-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15-decahydro-cyclopenta[a]phenanthren-3-one (intermediate 106)

To a solution of compound 6 (0.5 g, 1.321 mmol) in dry acetonitrile (20 ml), under nitrogen atmosphere, DIPEA (0.396 ml, 2.246 mmol) and Ms-Cl (0.155 ml, 1.982 mmol) are added and the reaction mixture is stirred at room temperature for 1 hour. Then, TBAF (2.64 ml, 2.64 mmol) 1 M in THF and potassium fluoride (0.077 g, 1.321 mmol) are added and the mixture is heated at reflux overnight. The mixture was diluted with AcOEt and the organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. Crude was purified by flash chromatography on silica gel, in gradient elution from petroleum ether/AcOEt 8: 2 to AcOEt, to afford the title compound (98% yield).

LC-MS (ESI POS): 381.3 MH

Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-8-(4-methyl-benzyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one (compound 107)

Compound 107 is obtained in 48% yield reacting intermediate 40 with N-(4-Methyl-benzyl)-hydroxylamine, as previously described for compound 10 (Example 4).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 (dd, 1 H), 7.03 - 7.22 (m, 4

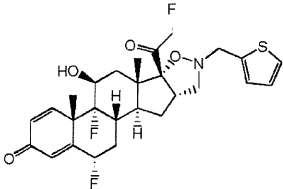
H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.49 - 5.79 (m, 1 H), 5.45 (d, 1 H), 4.89 (d, 2 H), 4.07 - 4.29 (m, 1 H), 3.87 (d, 1 H), 3.76 (d, 1 H), 3.40 - 3.61 (m, 1 H), 3.31 - 3.40 (m, 1 H), 2.55 - 2.68 (m, 1 H), 2.28 (s, 3 H), 2.02 - 2.27 (m, 3 H), 1.74 - 1.96 (m, 1 H), 1.51 - 1.73 (m, 3 H), 1.49 (s, 3 H), 1.46 (dd, 1 H),
 5 0.84 (s, 3 H)

LC-MS (ESI POS): 530.25 MH+

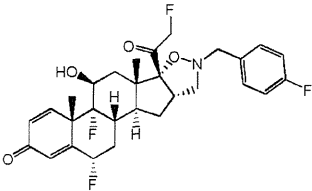
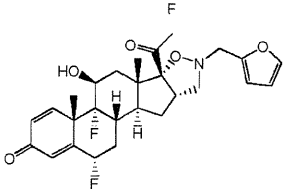
$[\alpha]_D^{25} = +176.3$ (c = 0.1715, CHCl₃)

The compounds listed in Table 6 were prepared as previously described for compound 41 107, by cycloaddition of intermediate 106 with suitable
 10 hydroxylamine or hydroxylamine hydrochloride.

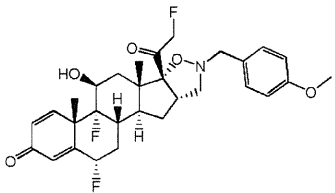
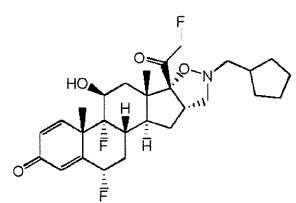
Table 6

Compound	Structure	Yield	Analytical
108		43%	LC-MS (ESI POS): 506.19 MH+ $[\alpha]_D^{25} = +180.8$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.59 (dd, 1 H), 7.27 (dd, 1 H), 6.41 (dd, 1 H), 6.25 - 6.35 (m, 2 H), 6.12 (s, 1 H), 5.49 - 5.80 (m, 1 H), 5.46 (dd, 1 H), 5.00 (d, 2 H), 4.09 - 4.26 (m, 1 H), 3.98 (d, 1 H), 3.84 (d, 1 H), 3.41 - 3.61 (m, 1 H), 3.31 - 3.41 (m, 1 H), 2.56 - 2.70 (m, 1 H), 2.03 - 2.33 (m, 3 H), 1.79 - 1.96 (m, 1 H), 1.50 - 1.70 (m, 3 H), 1.49 (s, 3 H), 1.44 (dd, 1 H), 0.85 (s, 3 H)

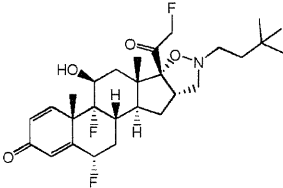
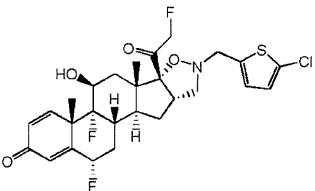
(continued)

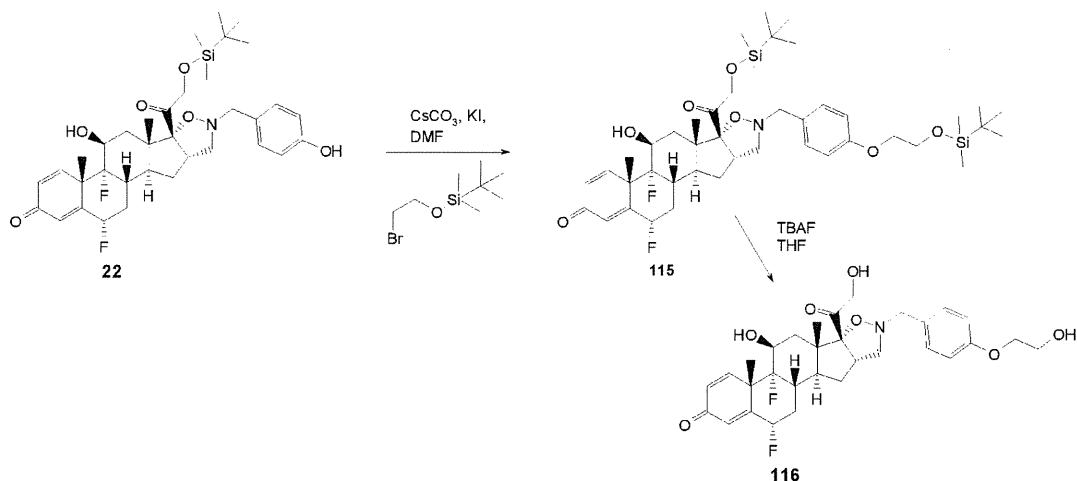
109		30%	LC-MS (ESI POS): 534.27 MH⁺ $[\alpha]_D^{25} = + 157.4$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.30 - 7.38 (m, 2 H), 7.27 (dd, 1 H), 7.07 - 7.21 (m, 2 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.48 - 5.83 (m, 1 H), 5.45 (m, 1 H), 4.90 (dd, 1 H), 4.80 (dd, 1 H), 4.16 (m, 1 H), 3.93 (d, 1 H), 3.79 (d, 1 H), 3.44 - 3.60 (m, 1 H), 3.25 - 3.43 (m, 1 H), 2.56 - 2.70 (m, 1 H), 2.10 - 2.32 (m, 3 H), 1.79 - 1.97 (m, 1 H), 1.52 - 1.71 (m, 3 H), 1.49 (s, 3 H), 1.40 - 1.47 (m, 1 H), 0.84 (s, 3 H)
110		79%	LC-MS (ESI POS): 506.19 MH⁺ $[\alpha]_D^{25} = + 180.8$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.59 (dd, 1 H), 7.27 (dd, 1 H), 6.41 (dd, 1 H), 6.25 - 6.35 (m, 2 H), 6.12 (s, 1 H), 5.49 - 5.80 (m, 1 H), 5.46 (dd, 1 H), 5.00 (d, 2 H), 4.09 - 4.26 (m, 1 H), 3.98 (d, 1 H), 3.84 (d, 1 H), 3.41 - 3.61 (m, 1 H), 3.31 - 3.41 (m, 1 H), 2.56 - 2.70 (m, 1 H), 2.03 - 2.33 (m, 3 H), 1.79 - 1.96 (m, 1 H), 1.50 - 1.70 (m, 3 H), 1.49 (s, 3 H), 1.44 (dd, 1 H), 0.85 (s, 3 H)

(continued)

111		54%	LC-MS (ESI POS): 546.23 MH⁺ $[\alpha]_D^{25} = + 189.2$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 (dd, 1 H), 7.12 - 7.24 (m, 2 H), 6.79 - 6.94 (m, 2 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.50 - 5.79 (m, 1 H), 5.45 (dd, 1 H), 4.89 (d, 2 H), 4.12 - 4.25 (m, 1 H), 3.85 (d, 1 H), 3.73 (s, 3 H), 3.75 (d, 1 H), 3.39 - 3.54 (m, 1 H), 3.30 - 3.38 (m, 1 H), 2.55 - 2.68 (m, 1 H), 2.04 - 2.33 (m, 3 H), 1.80 - 1.96 (m, 1 H), 1.51 - 1.71 (m, 3 H), 1.49 (s, 3 H), 1.45 (dd, 1 H), 0.84 (s, 3 H)
112		33%	LC-MS (ESI POS): 508.3 MH⁺ $[\alpha]_D^{25} = + 147.6$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.49 - 5.82 (m, 1 H), 5.45 (dd, 1 H), 5.29 (dd, 1 H), 5.17 (dd, 1 H), 4.00 - 4.28 (m, 1 H), 3.53 (dt, 1 H), 3.31 - 3.43 (m, 1 H), 2.56 - 2.68 (m, 3 H), 1.83 - 2.43 (m, 6 H), 1.51 - 1.77 (m, 6 H), 1.49 (s, 3 H), 1.35 - 1.47 (m, 3 H), 1.06 - 1.29 (m, 2 H), 0.86 (s, 3 H)

(continued)

113		27%	LC-MS (ESI POS): 510.31 MH⁺ $[\alpha]_D^{25} = + 118.3$ (c 0.25, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (dd, 1 H), 6.29 (dd, 1 H), 6.11 (s, 1 H), 5.49 - 5.79 (m, 1 H), 5.46 (d, 1 H), 5.30 (dd, 1 H), 5.17 (dd, 1 H), 4.04 - 4.29 (m, 1 H), 3.54 (t, 1 H), 3.31 - 3.40 (m, 1 H), 2.55 - 2.86 (m, 3 H), 2.06 - 2.34 (m, 2 H), 1.82 - 2.03 (m, 2 H), 1.52 - 1.75 (m, 2 H), 1.49 (s, 3 H), 1.39 - 1.48 (m, 3 H), 1.22 - 1.38 (m, 1 H), 0.86 (s, 9 H), 0.86 (s, 3 H)
114		42%	LC-MS (ESI POS): 556.14 MH⁺ $[\alpha]_D^{25} = + 185.0$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 (dd, 1 H), 6.97 (d, 1 H), 6.87 (d, 1 H), 6.30 (dd, 1 H), 6.12 (s, 1 H), 5.50 - 5.79 (m, 1 H), 5.47 (d, 1 H), 5.15 (dd, 1 H), 5.04 (dd, 1 H), 4.15 - 4.21 (m, 1 H), 4.19 (d, 1 H), 3.96 (d, 1 H), 3.44 - 3.58 (m, 1 H), 3.31 - 3.44 (m, 1 H), 2.55 - 2.67 (m, 1 H), 2.05 - 2.25 (m, 3 H), 1.84 - 1.98 (m, 1 H), 1.63 - 1.73 (m, 1 H), 1.51 - 1.63 (m, 1 H), 1.49 (s, 3 H), 1.38 - 1.47 (m, 2 H), 0.85 (s, 3 H)

Example 12

Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-4b,12-Difluoro-5-hydroxy-6b-(2-tert-butyl-dimethyl-sililoxy-acetyl)-8-[4-(2-tert-butyl-dimethyl-sililoxy-ethoxy)-benzyl]-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one (intermediate 115)

To a solution of compound 22 (200 mg, 0.311 mmol) in dry DMF (8 ml), under nitrogen atmosphere, cesium carbonate (223 mg, 0.683 mmol), (2-bromoethoxy)(tert-butyl)dimethylsilane (135 μ l, 0.621 mmol) and potassium iodide (10 mg, 0.066 mmol) were added. The reaction mixture was heated at 50°C overnight, and further cesium carbonate (0.056 g, 0.171 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (0.033 ml, 0.155 mmol) were added. The mixture was then further stirred at 50°C for 8 hrs. The reaction mixture was diluted with AcOEt and the organic phase was washed with water, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, in gradient elution from DCM to DCM/AcOEt 7:3 affording 256 mg, (92% yield).

LC-MS (ESI POS): 802.4 (MH⁺)

Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-4b,12-

Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-[4-(2-hydroxy-ethoxy)-benzyl]-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one (compound 116)

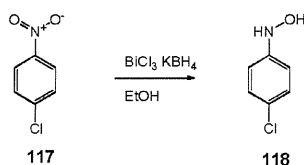
5 To a solution of compound 115 (0.256 g, 0.319 mmol) in dry THF (8 ml), at 0°C under nitrogen atmosphere, tetrabutylammonium fluoride (0.670 ml, 0.670 mmol) was added and the mixture was stirred at 0°C for 1 hr and at room temperature for 1.5 hrs. Solvent was evaporated and the crude (535 mg) was purified by flash chromatography on silica gel, in gradient elution from
10 DCM/AcOEt 9: 1 to AcOEt/EtOH 9: 1. Repurification of the obtained product by flash chromatography on silica gel, in gradient elution from DCM/AcOEt 6: 4 to AcOEt/EtOH 97: 3 afforded 46 mg of the title compound (25% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (dd, 1 H), 7.11 - 7.22 (m, 2 H), 6.76 - 6.91 (m, 2 H), 6.30 (dd, 1 H), 6.13 (s, 1 H), 5.50 - 5.74 (m, 1 H),
15 5.43 (dd, 1 H), 4.80 (t, 1 H), 4.65 (s, 1 H), 4.04 - 4.25 (m, 1 H), 3.92 - 4.01 (m, 2 H), 3.60 - 3.90 (m, 5 H), 3.32 - 3.56 (m, 2 H), 2.56 - 2.68 (m, 1 H), 1.83 - 2.44 (m, 5 H), 1.51 - 1.68 (m, 3 H), 1.49 (s, 3 H), 1.37 - 1.47 (m, 1 H), 0.80 (s, 3 H)

LC-MS (ESI POS): 574.39 (MH⁺)

20 $[\alpha]_D^{25} = +155.8$ (c 0.2 MeOH)

Example 13



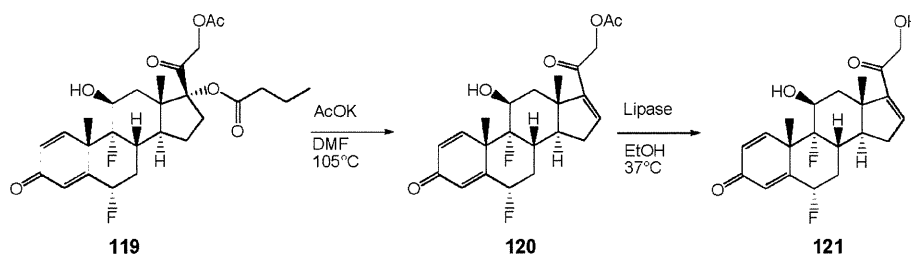
Preparation of N-(4-chlorophenyl) hydroxylamine (intermediate 118)
25

To a dispersion of 1-chloro-4-nitrobenzene 117 (1 g, 6.35 mmol) in

absolute ethanol (32 ml) and water (10.24 ml), bismuth(III)chloride (0.400 g, 1.269 mmol) was added; then, potassium borohydride (0.514 g, 9.52 mmol) was added gradually with stirring in water bath, under nitrogen atmosphere. The mixture turned black and a black precipitate was formed. After 20 minutes stirring at RT, under nitrogen atmosphere, the mixture was acidified with 0.5 N HCl to pH 7 and immediately extracted with ethyl ether. The organic extracts were dried over Na₂SO₄ and concentrated to afford the desired hydroxylamine (959 mg), which was used as such without further purification.

LC-MS (ESI POS): 126.9 (MH⁺)

Example 14



Preparation of acetic acid 2-((6S,9R,10S,11S,13S)-6,9-difluoro-11-hydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15-decahydro-3H-cyclopenta[a]phenanthren-17-yl)-2-oxo-ethyl ester (intermediate 120)

To a solution of butyric acid (9R,10S,11S,13S,17R)-17-(2-acetoxyacetyl)-9-chloro-11-hydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester (intermediate 119) (2.48 g, 4.88 mmol) in anhydrous DMF (60 ml), under nitrogen atmosphere, potassium acetate (3.83 g, 39.0 mmol) is added and the reaction mixture is stirred at 100°C for 1.5 hr. The cooled reaction mixture is poured into ice and brine (200 ml) and the aqueous layer is extracted with AcOEt (3 x 150 ml). The combined organic extracts are washed with water and brine, dried over Na₂SO₄ and concentrated to afford 2.55 g of

crude title compound which is used in the next step without further purification.

¹H NMR (300 MHz, DMSO-*d*₆): ppm 7.29 (dd, 1 H), 6.99 (dd, 1 H), 6.29 (dd, 1 H), 5.98 - 6.15 (m, 1 H), 5.68 (dddd, 1 H), 5.56 (dd, 1 H), 5.10 (d, 1 H), 4.92 (d, 1 H), 3.98 - 4.23 (m, 1 H), 2.56 - 2.83 (m, 1 H), 2.26 - 2.44 (m, 3 H), 2.14 - 2.26 (m, 1 H), 2.09 (s, 3 H), 1.71 - 1.87 (m, 1 H), 1.55 - 1.65 (m, 2 H), 1.53 (s, 3 H), 1.15 (s, 3 H).

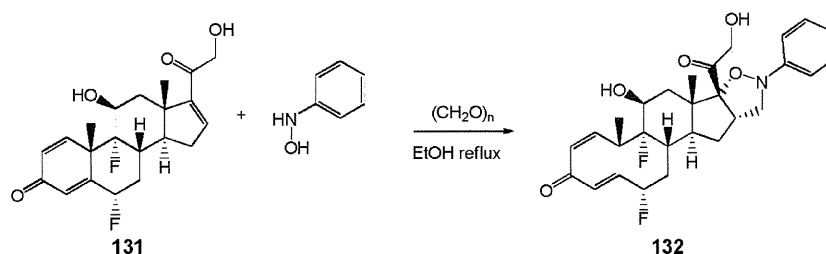
LC-MS (ESI POS): 421.97 (MH⁺)

Preparation of (6S,9R,10S,11S,13S)-6,9-Difluoro-11-hydroxy-17-(2-hydroxy-acetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15-decahydro-cyclopenta[a]phenanthren-3-one (intermediate 121)

To a solution of (intermediate 120) (2.55 g, 6.06 mmol) in ethanol (100 ml), *Candida Antarctica* Lipase (2 U/mg) (510 mg, 6.06 mmol) is added and the reaction mixture is stirred at 37°C overnight. The reaction mixture is filtered, washing with methanol, and the residue is purified by flash chromatography on silica gel, in gradient elution from DCM/AcOEt 90:10 to DCM/AcOEt 50:50, to afford 1.62 g of title compound (70.6% yield).

¹H NMR (300 MHz, DMSO-*d*₆): ppm 7.29 (dd, 1 H), 6.87 (dd, 1 H), 6.29 (dd, 1 H), 6.09 - 6.17 (m, 1 H), 5.67 (dddd, 1 H), 5.53 (dd, 1 H), 4.77 (t, 1 H), 4.44 (dd, 1 H), 4.26 (dd, 1 H), 4.04 - 4.15 (m, 1 H), 2.56 - 2.79 (m, 1 H), 2.39 (dd, 1 H), 2.25 - 2.35 (m, 2 H), 2.09 - 2.25 (m, 1 H), 1.76 (td, 1 H), 1.55 - 1.66 (m, 2 H), 1.53 (s, 3 H), 1.17 (s, 3 H).

LC-MS (ESI POS): 379.99 (MH⁺)

Example 15

Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-phenyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one (compound 122)

A mixture of 121, N-phenyl hydroxylamine (57.7 mg, 0.529 mmol) and paraformaldehyde (47.6 mg, 1.586 mmol) in Ethanol (6 ml) was stirred at 100°C for 19 hr. The reaction was not complete. N-phenyl hydroxylamine (20 mg, 0.183 mmol) and paraformaldehyde (27 mg, 0.899 mmol) were added and the mixture was heated at 100°C for further 3 hr. The solvent was evaporated and the residue was purified by silica gel flash chromatography in gradient elution from DCM to AcOEt/MeOH/DCM 9.8 : 0.2 : 90, to AcOEt/MeOH/DCM 29.8 : 0.2 : 70, affording 83 mg of pure compound (63% yield; $R_f = 0.24$ in AcOEt/MeOH/DCM 29 : 1 : 70).

^1H NMR (300 MHz, DMSO- d_6) ppm 7.19 - 7.36 (m, 3 H), 6.90 - 7.04 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.79 (m, 1 H), 5.51 (dd, 1 H), 4.92 (t, 1 H), 4.51 (dd, 1 H), 4.29 (dd, 1 H), 4.17 - 4.24 (m, 1 H), 4.13 (t, 1 H), 3.50 - 3.66 (m, 1 H), 2.61 - 2.71 (m, 1 H), 2.57 (dd, 1 H), 2.01 - 2.35 (m, 3 H), 1.51 - 1.82 (m, 4 H), 1.50 (s, 3 H), 0.91 (s, 3 H)

LC-MS (ESI POS): 500.17 MH $^+$

$[\alpha]_D^{25} = +71.09$ (c 0.092; CHCl_3)

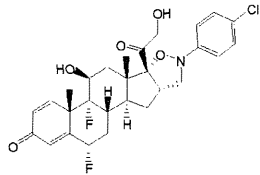
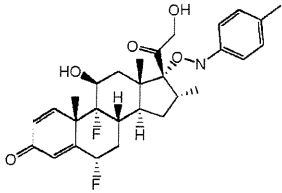
Compounds listed in Table 7 were prepared as previously described for compound 122, by cycloaddition of intermediate 121 with suitable

hydroxylamine, hydroxylamine hydrochloride or protected hydroxylamine. In the last case, deprotection reaction was carried out on the final compound.

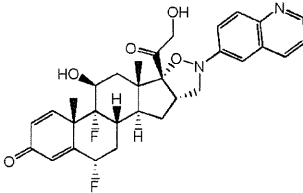
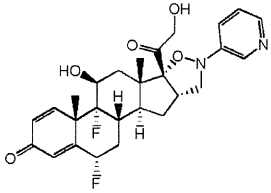
Final compounds were purified by silica gel column chromatography or preparative HPLC.

5

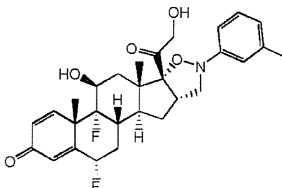
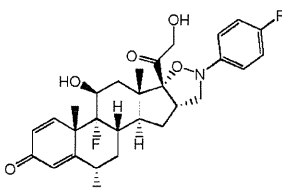
Table 7

Compound	Structure	Yield	Analytical
123		83%	LC-MS (ESI POS): 534.19 MH ⁺ $[\alpha]_D^{25} = +72.74$ (c 0.19; CHCl ₃) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.29 - 7.38 (m, 2 H), 7.25 (dd, 1 H), 6.93 - 7.05 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.77 (m, 1 H), 5.51 (d, 1 H), 4.94 (t, 1 H), 4.48 (dd, 1 H), 4.28 (dd, 1 H), 4.17 - 4.24 (m, 1 H), 4.13 (t, 1 H), 3.59 (q, 1 H), 2.60 - 2.69 (m, 1 H), 2.59 (dd, 1 H), 2.00 - 2.32 (m, 3 H), 1.51 - 1.83 (m, 4 H), 1.49 (s, 3 H), 0.90 (s, 3 H)
124		60%	LC-MS (ESI POS): 514.22 MH ⁺ $[\alpha]_D^{25} = +81.8$ (c 0.125, CHCl ₃) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.26 (d, 1 H), 7.09 (m, 2 H), 6.87 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.51 - 5.78 (m, 1 H), 5.31 - 5.52 (m, 1 H), 4.39 - 4.60 (m, 1 H), 4.14 - 4.36 (m, 2 H), 4.07 (t, 1 H), 3.57 (q, 1 H), 2.65 (m, 1 H), 2.23 (s, 3 H), 1.97 - 2.34 (m, 4 H), 1.59 - 1.85 (m, 2 H), 1.49 (s, 3 H), 1.39 - 1.59 (m, 3 H), 0.90 (s, 3 H)

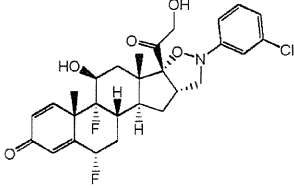
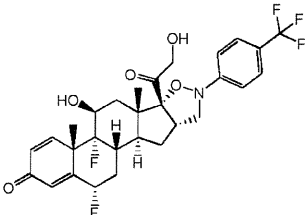
(continued)

125		51%	LC-MS (ESI POS): 551.22 MH⁺ $[\alpha]_D^{25} = + 57.3$ (c 0.3, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 8.74 (dd, 1 H), 8.26 (dd, 1 H), 7.93 (d, 1 H), 7.50 (dd, 1 H), 7.46 (dd, 1 H), 7.40 (d, 1 H), 7.26 (dd, 1 H), 6.28 (dd, 1 H), 6.07 (s, 1 H), 5.53 - 5.78 (m, 1 H), 5.53 (dd, 1 H), 4.97 (t, 1 H), 4.58 (dd, 1 H), 4.35 (dd, 1 H), 4.28 (t, 1 H), 4.14 - 4.25 (m, 1 H), 3.57 - 3.77 (m, 1 H), 2.72 - 2.85 (m, 1 H), 2.56 - 2.70 (m, 1 H), 2.10 - 2.31 (m, 3 H), 1.54 - 1.90 (m, 4 H), 1.50 (s, 3 H), 0.94 (s, 3 H)
126		10%	LC-MS (ESI POS): 501.14 MH⁺ $[\alpha]_D^{25} = + 78.05$ (c 0.0925; CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 8.29 (dd, 1 H), 8.21 (dd, 1 H), 7.38 (ddd, 1 H), 7.31 (ddd, 1 H), 7.26 (dd, 1 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.53 - 5.74 (m, 1 H), 5.51 (dd, 1 H), 4.95 (t, 1 H), 4.50 (dd, 1 H), 4.30 (dd, 1 H), 4.12 - 4.24 (m, 2 H), 3.53 - 3.71 (m, 1 H), 2.55 - 2.75 (m, 2 H), 1.98 - 2.33 (m, 3 H), 1.51 - 1.86 (m, 4 H), 1.49 (s, 3 H), 0.91 (s, 3 H)

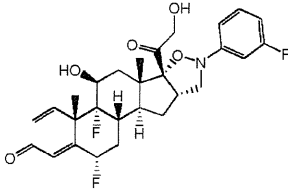
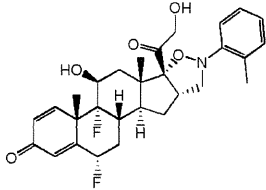
(continued)

127		79%	LC-MS (ESI POS): 514.09 MH⁺ $[\alpha]_D^{25} = +70.69$ (c 0.26, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (d, 1 H), 7.15 (t, 1 H), 6.58 - 6.95 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.82 (m, 1 H), 5.50 (d, 1 H), 4.91 (t, 1 H), 4.50 (dd, 1 H), 4.28 (dd, 1 H), 4.16 - 4.28 (m, 1 H), 4.10 (t, 1 H), 3.58 (dd, 1 H), 2.54 - 2.68 (m, 2 H), 2.27 (s, 3 H), 2.03 - 2.34 (m, 3 H), 1.62 - 1.90 (m, 2 H), 1.49 (s, 3 H), 1.37 - 1.62 (m, 2 H), 0.90 (s, 3 H)
128		5%	LC-MS (ESI POS): 518.12 MH⁺ $[\alpha]_D^{25} = +87.67$ (c 0.24, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 7.07 - 7.20 (m, 2 H), 6.91 - 7.07 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.76 (m, 1 H), 5.51 (dd, 1 H), 4.93 (t, 1 H), 4.49 (dd, 1 H), 4.27 (dd, 1 H), 4.16 - 4.27 (m, 1 H), 4.10 (t, 1 H), 3.59 (q, 1 H), 2.54 - 2.71 (m, 2 H), 2.10 - 2.33 (m, 2 H), 1.99 - 2.10 (m, 1 H), 1.49 (s, 3 H), 1.42 - 1.81 (m, 4 H), 0.90 (s, 3 H)

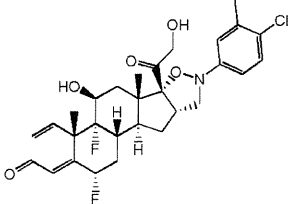
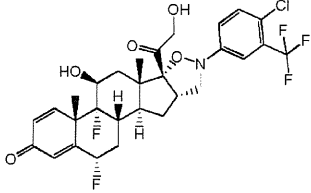
(continued)

129		87%	LC-MS (ESI POS): 534.1 MH⁺ $[\alpha]_D^{25} = +69.70$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.30 (t, 1 H), 7.26 (dd, 1 H), 6.98 - 7.06 (m, 2 H), 6.93 (ddd, 1 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.55 - 5.81 (m, 1 H), 5.52 (dd, 1 H), 4.95 (t, 1 H), 4.47 (dd, 1 H), 4.29 (dd, 1 H), 4.18 - 4.25 (m, 1 H), 3.51 - 3.69 (m, 1 H), 2.54 - 2.70 (m, 2 H), 2.02 - 2.34 (m, 3 H), 1.62 - 1.88 (m, 3 H), 1.51 - 1.62 (m, 2 H), 1.49 (s, 3 H), 0.90 (s, 3 H)
130		68%	LC-MS (ESI POS): 568.21 MH⁺ $[\alpha]_D^{25} = +49.5$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.53 - 7.74 (m, 2 H), 7.26 (dd, 1 H), 7.03 - 7.20 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.55 - 5.85 (m, 1 H), 5.52 (dd, 1 H), 4.97 (t, 1 H), 4.47 (dd, 1 H), 4.30 (dd, 1 H), 4.16 - 4.25 (m, 2 H), 3.56 - 3.73 (m, 1 H), 2.55 - 2.71 (m, 2 H), 2.04 - 2.30 (m, 3 H), 1.64 - 1.86 (m, 2 H), 1.51 - 1.64 (m, 2 H), 1.50 (s, 3 H), 0.92 (s, 3 H)

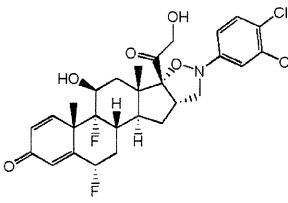
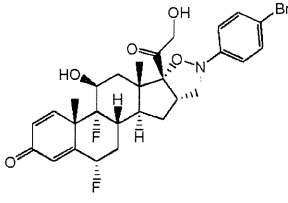
(continued)

131		95%	LC-MS (ESI POS): 518.2 MH⁺ $[\alpha]_D^{25} = +69.15$ (c = 0.26, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.28 - 7.40 (m, 1 H), 7.26 (dd, 1 H), 6.73 - 6.92 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.54 - 5.77 (m, 1 H), 5.51 (dd, 1 H), 4.94 (t, 1 H), 4.47 (dd, 1 H), 4.29 (dd, 1 H), 4.18 - 4.24 (m, 1 H), 4.16 (t, 1 H), 3.51 - 3.66 (m, 1 H), 2.63 (dd, 1 H), 2.55 - 2.70 (m, 1 H), 2.02 - 2.26 (m, 3 H), 1.63 - 1.86 (m, 2 H), 1.51 - 1.61 (m, 2 H), 1.49 (s, 3 H), 0.91 (s, 3 H)
132		24%	LC-MS (ESI POS): 514.23 MH⁺ $[\alpha]_D^{25} = +54.83$ (c 0.24, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.30 (dd, 1 H), 7.28 (dd, 1 H), 7.11 - 7.24 (m, 2 H), 7.05 (td, 1 H), 6.31 (dd, 1 H), 6.12 (s, 1 H), 5.53 - 5.84 (m, 1 H), 5.50 (dd, 1 H), 4.88 (t, 1 H), 4.39 (dd, 1 H), 4.19 - 4.30 (m, 1 H), 4.14 (dd, 1 H), 3.85 (t, 1 H), 3.53 - 3.72 (m, 1 H), 2.58 - 2.70 (m, 1 H), 2.41 (dd, 1 H), 2.23 - 2.38 (m, 2 H), 2.15 (s, 3 H), 2.03 - 2.13 (m, 1 H), 1.70 - 1.84 (m, 1 H), 1.53 - 1.73 (m, 3 H), 1.51 (s, 3 H), 0.90 (s, 3 H)

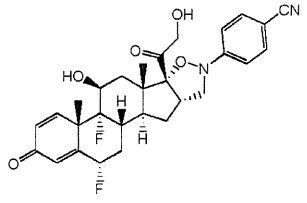
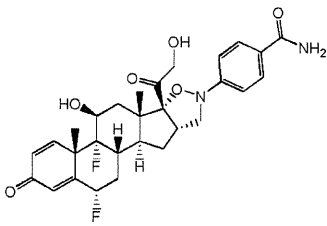
(continued)

133		38% LC-MS (ESI POS): 548.21 MH⁺ $[\alpha]_D^{25} = + 54.96$ (c 0.25, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.30 (d, 1 H), 7.26 (dd, 1 H), 6.96 (d, 1 H), 6.82 (dd, 1 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.78 (m, 1 H), 5.51 (d, 1 H), 4.93 (t, 1 H), 4.49 (dd, 1 H), 4.28 (dd, 1 H), 4.16 - 4.27 (m, 1 H), 4.11 (t, 1 H), 3.59 (q, 1 H), 2.54 - 2.69 (m, 2 H), 1.97 - 2.36 (m, 3 H), 2.29 (s, 3 H), 1.41 - 1.81 (m, 4 H), 1.49 (s, 3 H), 0.90 (s, 3 H)
134		36% LC-MS (ESI POS): 602.17 MH⁺ $[\alpha]_D^{25} = + 48.8$ (c 0.25, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.62 (d, 1 H), 7.11 - 7.40 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.55 - 5.76 (m, 1 H), 5.53 (dd, 1 H), 4.98 (t, 1 H), 4.46 (dd, 1 H), 4.30 (dd, 1 H), 4.14 - 4.28 (m, 2 H), 3.52 - 3.72 (m, 1 H), 2.73 (dd, 1 H), 2.56 - 2.67 (m, 1 H), 2.01 - 2.34 (m, 3 H), 1.63 - 1.87 (m, 2 H), 1.51 - 1.63 (m, 2 H), 1.49 (s, 3 H), 0.91 (s, 3 H)

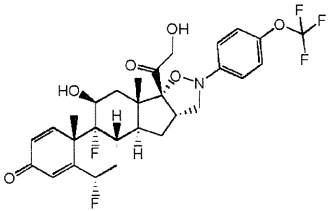
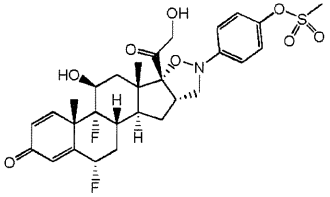
(continued)

135		68% LC-MS (ESI POS): 568.18 MH⁺ $[\alpha]_D^{25} = +53.21$ (c 0.28, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.52 (d, 1 H), 7.26 (dd, 1 H), 7.20 (d, 1 H), 6.98 (dd, 1 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.54 - 5.74 (m, 1 H), 5.52 (d, 1 H), 4.96 (t, 1 H), 4.46 (dd, 1 H), 4.29 (dd, 1 H), 4.19 - 4.24 (m, 1 H), 4.18 (t, 1 H), 3.50 - 3.68 (m, 1 H), 2.65 (dd, 1 H), 2.54 - 2.61 (m, 1 H), 2.01 - 2.31 (m, 3 H), 1.62 - 1.84 (m, 2 H), 1.51 - 1.62 (m, 2 H), 1.49 (s, 3 H), 0.90 (s, 3 H)
136		52% LC-MS (ESI POS): 578.19 MH⁺ $[\alpha]_D^{25} = +56.2$ (c 0.2, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.39 - 7.50 (m, 2 H), 7.25 (dd, 1 H), 6.86 - 7.02 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.53 - 5.77 (m, 1 H), 5.51 (dd, 1 H), 4.95 (t, 1 H), 4.47 (dd, 1 H), 4.27 (dd, 1 H), 4.17 - 4.23 (m, 1 H), 4.14 (t, 1 H), 3.59 (q, 1 H), 2.54 - 2.68 (m, 2 H), 2.01 - 2.25 (m, 3 H), 1.61 - 1.85 (m, 2 H), 1.50 - 1.61 (m, 2 H), 1.49 (s, 3 H), 0.90 (s, 3 H)

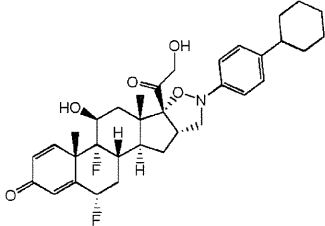
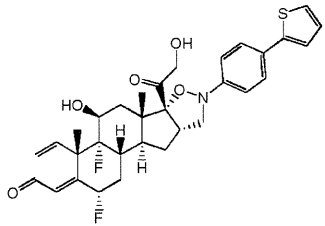
(continued)

137		LC-MS (ESI POS): 525.32 MH⁺ $[\alpha]_D^{25} = +19.35$ (c 0.55, DMF) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.59 - 7.86 (m, 2 H), 7.26 (dd, 1 H), 6.99 - 7.18 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.54 (dd, 1 H), 5.46 - 5.75 (m, 1 H), 4.99 (t, 1 H), 4.44 (dd, 1 H), 4.29 (dd, 1 H), 4.24 (t, 1 H), 4.13 - 4.23 (m, 1 H), 3.55 - 3.73 (m, 1 H), 2.77 (dd, 1 H), 2.54 - 2.71 (m, 1 H), 2.00 - 2.25 (m, 3 H), 1.65 - 1.90 (m, 2 H), 1.51 - 1.65 (m, 2 H), 1.49 (s, 3 H), 0.91 (s, 3 H) 39%
138		LC-MS (ESI POS): 543.35 MH⁺ $[\alpha]_D^{25} = +52.38$ (c 0.21, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.78 - 7.89 (m, 2 H), 7.78 (br. s., 1 H), 7.26 (d, 1 H), 7.15 (br. s., 1 H), 6.89 - 7.04 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.54 - 5.77 (m, 1 H), 5.52 (d, 1 H), 4.95 (t, 1 H), 4.49 (dd, 1 H), 4.30 (dd, 1 H), 4.13 - 4.25 (m, 2 H), 3.50 - 3.72 (m, 1 H), 2.57 - 2.76 (m, 2 H), 1.98 - 2.39 (m, 3 H), 1.64 - 1.91 (m, 2 H), 1.52 - 1.64 (m, 2 H), 1.50 (s, 3 H), 0.91 (s, 3 H) 18%

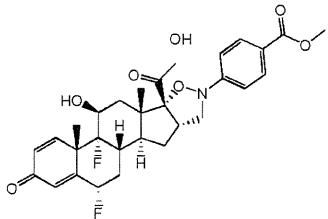
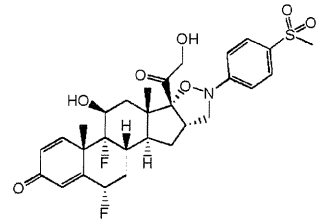
(continued)

139		15% LC-MS (ESI POS): 584.26 MH⁺ $[\alpha]_D^{25} = +63.04$ (c 0.25, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 (m, 3 H), 7.07 (d, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.49 - 5.78 (m, 1 H), 5.52 (dd, 1 H), 4.94 (t, 1 H), 4.49 (dd, 1 H), 4.28 (dd, 1 H), 4.11 - 4.23 (m, 1 H), 4.16 (t, 1 H), 3.48 - 3.75 (m, 1 H), 2.56 - 2.70 (m, 2 H), 1.99 - 2.25 (m, 3 H), 1.60 - 1.82 (m, 2 H), 1.49 (s, 3 H), 1.28 - 1.60 (m, 2 H), 0.91 (s, 3 H)
140		52% LC-MS (ESI POS): 594.18 MH⁺ $[\alpha]_D^{25} = +50.7$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.16 - 7.35 (m, 3 H), 6.93 - 7.11 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.54 - 5.87 (m, 1 H), 5.51 (dd, 1 H), 4.94 (t, 1 H), 4.49 (dd, 1 H), 4.29 (dd, 1 H), 4.17 - 4.23 (m, 1 H), 4.16 (t, 1 H), 3.50 - 3.69 (m, 1 H), 3.32 (s, 3 H), 2.56 - 2.71 (m, 2 H), 2.02 - 2.27 (m, 3 H), 1.63 - 1.86 (m, 2 H), 1.51 - 1.63 (m, 2 H), 1.50 (s, 3 H), 0.91 (s, 3 H)

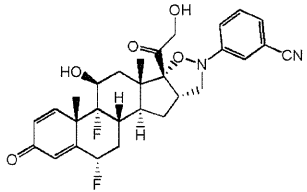
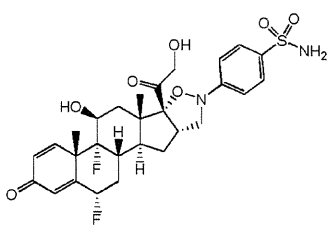
(continued)

141		LC-MS (ESI POS): 582.34 MH⁺ $[\alpha]_D^{25} = +64.4$ (c 0.2, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 7.06 - 7.16 (m, 2 H), 6.81 - 6.93 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.83 (m, 1 H), 5.50 (dd, 1 H), 4.90 (t, 1 H), 4.51 (dd, 1 H), 4.27 (dd, 1 H), 4.15 - 4.23 (m, 1 H), 4.07 (t, 1 H), 3.50 - 3.64 (m, 1 H), 2.55 - 2.71 (m, 2 H), 2.33 - 2.45 (m, 1 H), 2.02 - 2.30 (m, 3 H), 1.51 - 1.88 (m, 8 H), 1.49 (s, 3 H), 1.12 - 1.44 (m, 6 H), 0.90 (s, 3 H) 61%
142		LC-MS (ESI POS): 582.22 MH⁺ $[\alpha]_D^{25} = +12.6$ (c 0.4, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.52 - 7.62 (m, 2 H), 7.46 (dd, 1 H), 7.38 (dd, 1 H), 7.26 (dd, 1 H), 7.09 (dd, 1 H), 6.94 - 7.05 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.54 - 5.77 (m, 1 H), 5.52 (dd, 1 H), 4.95 (t, 1 H), 4.52 (dd, 1 H), 4.30 (dd, 1 H), 4.20 - 4.25 (m, 1 H), 4.16 (t, 1 H), 3.52 - 3.69 (m, 1 H), 2.55 - 2.71 (m, 2 H), 1.99 - 2.32 (m, 3 H), 1.62 - 1.89 (m, 2 H), 1.52 - 1.62 (m, 2 H), 1.50 (s, 3 H), 0.92 (s, 3 H) 15%

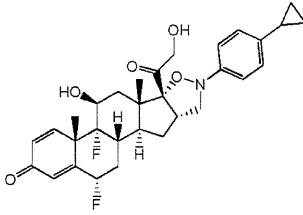
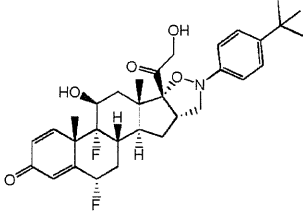
(continued)

143		30% LC-MS (ESI POS): 558.33 MH⁺ $[\alpha]_D^{25} = +49.3$ (c 0.2 MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.73 - 7.96 (m, 2 H), 7.26 (dd, 1 H), 6.93 - 7.11 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.54 - 5.81 (m, 1 H), 5.52 (dd, 1 H), 4.98 (t, 1 H), 4.47 (dd, 1 H), 4.30 (dd, 1 H), 4.17 - 4.26 (m, 2 H), 3.81 (s, 3 H), 3.54 - 3.70 (m, 1 H), 2.55 - 2.85 (m, 2 H), 2.01 - 2.26 (m, 3 H), 1.64 - 1.87 (m, 2 H), 1.51 - 1.64 (m, 2 H), 1.49 (s, 3 H), 0.92 (s, 3 H)
144		50% LC-MS (ESI POS): 578.32 MH⁺ $[\alpha]_D^{25} = +44.0$ (c 0.2, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.72 - 7.87 (m, 2 H), 7.26 (dd, 1 H), 7.06 - 7.19 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.53 (dd, 1 H), 5.46 - 5.85 (m, 1 H), 4.91 - 5.05 (m, 1 H), 4.47 (dd, 1 H), 4.31 (dd, 1 H), 4.26 (t, 1 H), 4.15 - 4.24 (m, 1 H), 3.56 - 3.72 (m, 1 H), 3.12 (s, 3 H), 2.77 (dd, 1 H), 2.58 - 2.69 (m, 1 H), 2.02 - 2.32 (m, 3 H), 1.64 - 1.86 (m, 2 H), 1.52 - 1.64 (m, 2 H), 1.50 (s, 3 H), 0.92 (s, 3 H)

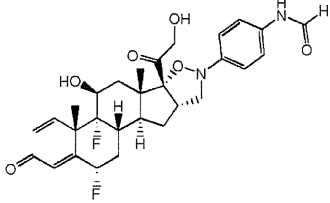
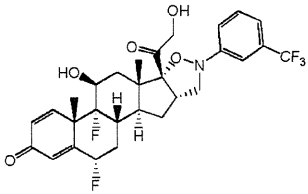
(continued)

145		LC-MS (ESI POS): 525.16 MH⁺ $[\alpha]_D^{25} = +90.32$ (c 0.25; DCM) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.49 (t, 1 H), 7.37 - 7.45 (m, 2 H), 7.30 (ddd, 1 H), 7.26 (dd, 1 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.74 (m, 1 H), 5.52 (dd, 1 H), 4.95 (t, 1 H), 4.48 (dd, 1 H), 4.31 (dd, 1 H), 4.20 - 4.27 (m, 1 H), 4.21 (t, 1 H), 3.49 - 3.71 (m, 1 H), 2.67 (dd, 1 H), 2.56 - 2.63 (m, 1 H), 1.98 - 2.27 (m, 3 H), 1.63 - 1.88 (m, 2 H), 1.51 - 1.63 (m, 2 H), 1.50 (s, 3 H), 0.91 (s, 3 H) 16%
146		LC-MS (ESI POS): 579.25 MH⁺ $[\alpha]_D^{25} = +45.41$ (c 0.0925; MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.60 - 7.79 (m, 2 H), 7.26 (dd, 1 H), 7.17 (s, 2 H), 7.01 - 7.12 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.80 (m, 1 H), 5.52 (dd, 1 H), 4.47 (d, 1 H), 4.30 (d, 1 H), 4.21 (t, 1 H), 4.12 - 4.23 (m, 1 H), 3.56 - 3.71 (m, 1 H), 2.67 - 2.78 (m, 1 H), 2.55 - 2.67 (m, 1 H), 2.01 - 2.33 (m, 3 H), 1.63 - 1.87 (m, 2 H), 1.51 - 1.63 (m, 2 H), 1.50 (s, 3 H), 0.92 (s, 3 H) 25%

(continued)

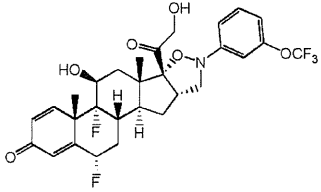
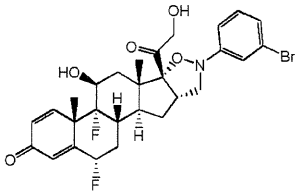
147		68%	LC-MS (ESI POS): 540.28 MH⁺ $[\alpha]_D^{25} = +78.53$ (c 0.3; MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 (dd, 1 H), 6.94 - 7.07 (m, 2 H), 6.76 - 6.93 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.79 (m, 1 H), 5.50 (d, 1 H), 4.90 (t, 1 H), 4.50 (dd, 1 H), 4.27 (dd, 1 H), 4.14 - 4.21 (m, 1 H), 4.06 (t, 1 H), 3.44 - 3.68 (m, 1 H), 2.53 - 2.70 (m, 2 H), 1.97 - 2.30 (m, 3 H), 1.79 - 1.92 (m, 1 H), 1.60 - 1.79 (m, 2 H), 1.51 - 1.60 (m, 1 H), 1.49 (s, 3 H), 1.42 - 1.49 (m, 1 H), 0.90 (s, 3 H), 0.78 - 0.88 (m, 2 H), 0.50 - 0.65 (m, 2 H)
148		41%	LC-MS (ESI POS): 556.38 MH⁺ $[\alpha]_D^{25} = +71.25$ (c 0.4, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 - 7.33 (m, 2 H), 7.26 (d, 1 H), 6.78 - 6.98 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.53 - 5.75 (m, 1 H), 5.51 (dd, 1 H), 4.90 (t, 1 H), 4.51 (dd, 1 H), 4.28 (dd, 1 H), 4.16 - 4.23 (m, 1 H), 4.08 (t, 1 H), 3.49 - 3.69 (m, 1 H), 2.55 - 2.70 (m, 2 H), 1.98 - 2.32 (m, 3 H), 1.61 - 1.84 (m, 2 H), 1.52 - 1.61 (m, 1 H), 1.49 (s, 3 H), 1.40 - 1.48 (m, 1 H), 1.24 (s, 9 H), 0.90 (s, 3 H)

(continued)

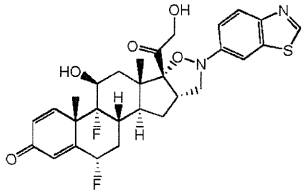
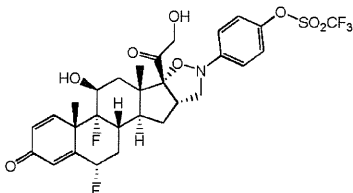
149		17%	LC-MS (ESI POS): 543.24 MH⁺ $[\alpha]_D^{25} = +32.5$ (c 0.0415; MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 10.04 (s, 1 H), 8.20 (d, 1 H), 7.50 (d, 2 H), 7.26 (d, 1 H), 6.78 - 7.02 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.51 - 5.79 (m, 1 H), 5.50 (d, 1 H), 4.92 (t, 1 H), 4.51 (dd, 1 H), 4.27 (dd, 1 H), 4.15 - 4.26 (m, 1 H), 4.07 (t, 1 H), 3.44 - 3.67 (m, 1 H), 2.60 - 2.71 (m, 2 H), 1.96 - 2.32 (m, 3 H), 1.60 - 1.81 (m, 2 H), 1.41 - 1.58 (m, 2 H), 1.49 (s, 3 H), 0.90 (s, 3 H)
150		34%	LC-MS (ESI POS): 568.23 MH⁺ $[\alpha]_D^{25} = +57.8$ (c 0.2, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.43 - 7.64 (m, 1 H), 7.12 - 7.39 (m, 4 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.44 - 5.79 (m, 1 H), 5.53 (d, 1 H), 4.96 (t, 1 H), 4.48 (dd, 1 H), 4.31 (dd, 1 H), 4.15 - 4.31 (m, 2 H), 3.62 (q, 1 H), 2.55 - 2.79 (m, 3 H), 1.96 - 2.25 (m, 2 H), 1.63 - 1.93 (m, 2 H), 1.50 (s, 3 H), 1.27 - 1.63 (m, 2 H), 0.92 (s, 3 H)

(continued)

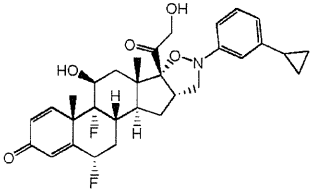
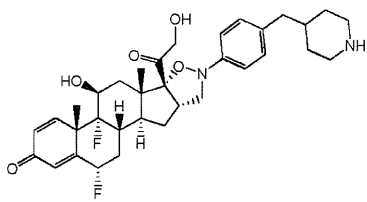
154

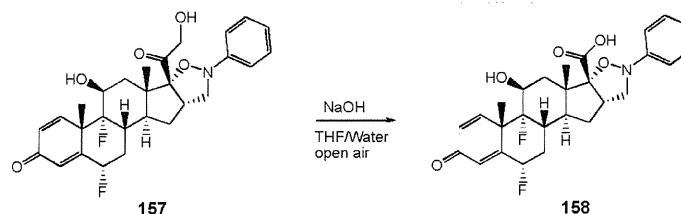
151		15% LC-MS (ESI POS): 584.2 MH⁺ $[\alpha]_D^{25} = +76.6$ (c 0.22, DCM) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.41 (t, 1 H), 7.26 (dd, 1 H), 6.90 - 7.02 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.50 - 5.77 (m, 1 H), 5.50 - 5.54 (m, 1 H), 4.92 - 4.98 (m, 1 H), 4.46 (dd, 1 H), 4.29 (dd, 1 H), 4.20 (t, 1 H), 4.07 - 4.24 (m, 1 H), 3.61 (q, 1 H), 2.67 (dd, 2 H), 2.04 - 2.28 (m, 3 H), 1.65 - 1.82 (m, 2 H), 1.50 (s, 3 H), 1.55 (dd, 2 H), 0.91 (s, 3 H)
152		71% LC-MS (ESI POS): 578.04 MH⁺ $[\alpha]_D^{25} = +65.8$ (c 0.0900, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.19 - 7.33 (m, 2 H), 7.10 - 7.19 (m, 2 H), 6.97 (ddd, 1 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.53 - 5.78 (m, 1 H), 5.52 (dd, 1 H), 4.95 (t, 1 H), 4.46 (dd, 1 H), 4.29 (dd, 1 H), 4.18 - 4.26 (m, 1 H), 4.17 (t, 1 H), 3.47 - 3.75 (m, 1 H), 2.63 (dd, 1 H), 2.55 - 2.70 (m, 1 H), 1.98 - 2.37 (m, 3 H), 1.60 - 1.88 (m, 2 H), 1.51 - 1.60 (m, 2 H), 1.49 (s, 3 H), 0.90 (s, 3 H)

(continued)

153		LC-MS (ESI POS): 557.1 MH⁺ $[\alpha]_D^{25} = +71.16$ (c 0.6, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 9.21 (s, 1 H), 7.98 (d, 1 H), 7.75 (d, 1 H), 7.26 (dd, 1 H), 7.21 (dd, 1 H), 6.28 (dd, 1 H), 6.07 (s, 1 H), 5.54 - 5.77 (m, 1 H), 5.52 (dd, 1 H), 4.95 (t, 1 H), 4.55 (dd, 1 H), 4.33 (dd, 1 H), 4.20 - 4.27 (m, 1 H), 4.22 (t, 1 H), 3.51 - 3.79 (m, 1 H), 2.69 (dd, 1 H), 2.54 - 2.65 (m, 1 H), 2.02 - 2.31 (m, 3 H), 1.64 - 1.89 (m, 2 H), 1.52 - 1.63 (m, 2 H), 1.50 (s, 3 H), 0.92 (s, 3 H)
154		LC-MS (ESI POS): 647.97 MH⁺ $[\alpha]_D^{25} = +56.0$ (c 0.24, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.31 - 7.52 (m, 2 H), 7.26 (dd, 1 H), 6.95 - 7.18 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.44 - 5.77 (m, 1 H), 5.52 (dd, 1 H), 4.95 (t, 1 H), 4.48 (dd, 1 H), 4.29 (dd, 1 H), 4.11 - 4.24 (m, 1 H), 4.18 (t, 1 H), 3.62 (q, 1 H), 2.55 - 2.72 (m, 2 H), 1.98 - 2.30 (m, 3 H), 1.44 - 1.83 (m, 4 H), 1.49 (s, 3 H), 0.91 (s, 3 H)

(continued)

155		LC-MS (ESI POS): 540.1 MH⁺ $[\alpha]_D^{25} = +43.6$ (c 0.3; MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (dd, 1 H), 7.14 (t, 1 H), 6.75 (ddd, 1 H), 6.55 - 6.70 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.54 - 5.79 (m, 1 H), 5.51 (dd, 1 H), 4.91 (t, 1 H), 4.50 (dd, 1 H), 4.28 (dd, 1 H), 4.17 - 4.23 (m, 1 H), 4.11 (t, 1 H), 3.49 - 3.66 (m, 1 H), 2.60 - 2.69 (m, 1 H), 2.56 (dd, 1 H), 2.00 - 2.25 (m, 3 H), 1.88 (tt, 1 H), 1.61 - 1.81 (m, 2 H), 1.51 - 1.59 (m, 2 H), 1.50 (s, 3 H), 0.91 - 0.97 (m, 2 H), 0.90 (s, 3 H), 0.49 - 0.71 (m, 2 H) 19%
156		LC-MS (ESI POS): 597.16 MH⁺ $[\alpha]_D^{25} = +54.6$ (c 0.29; MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 (d, 1 H), 7.05 (m, 2 H), 6.88 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.37 - 5.82 (m, 1 H), 5.51 (br. s., 1 H), 4.74 - 5.03 (m, 1 H), 4.51 (dd, 1 H), 4.21 (m, 1 H), 4.27 (dd, 1 H), 4.07 (t, 1 H), 3.57 (q, 1 H), 2.77 - 2.98 (m, 2 H), 2.56 - 2.70 (m, 2 H), 2.13 - 2.43 (m, 7 H), 2.03 - 2.12 (m, 1 H), 1.59 - 1.87 (m, 2 H), 1.38 - 1.59 (m, 5 H), 1.49 (s, 3 H), 0.80 - 1.08 (m, 2 H), 0.90 (s, 3 H) 21%

Example 16

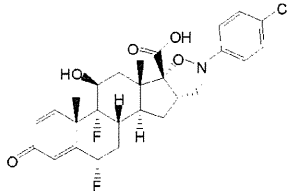
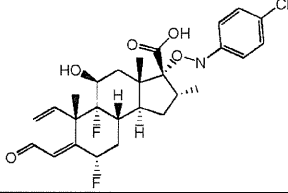
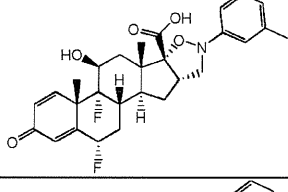
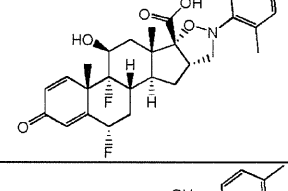
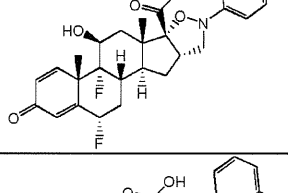
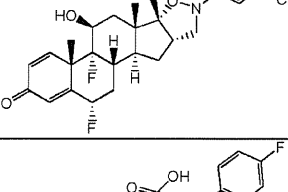
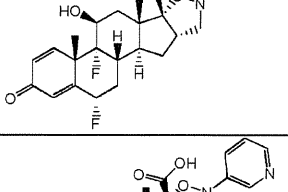
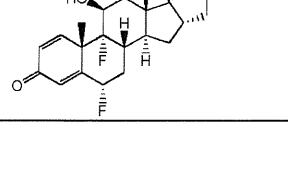
Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-phenyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-*a*]phenanthrene-6b-carboxylic acid (compound 158)

To a solution of 157 (733 mg, 1.461 mmol) in Tetrahydrofuran (12 ml), at 0°C, air was bubbled for 15 minutes; then, 6 N sodium hydroxide (0.974 ml, 5.85 mmol) was slowly dropped and air was bubbled for further 5 minutes at 0°C. The reaction mixture was left to warm up to RT and it was stirred at RT overnight. The reaction mixture was acidified to pH 1 and tetrahydrofuran was evaporated. The aqueous layer was extracted with AcOEt (100 ml x 3). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated. Crude was purified by silica gel flash chromatography in DCM/AcOEt/HCO₂H 39.5: 0.5: 50, affording 396 mg of the title compound (56%).

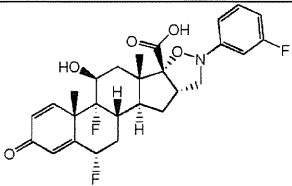
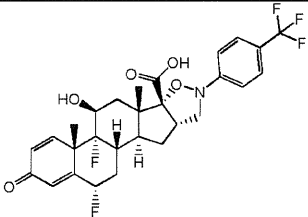
LC-MS (ESI POS): 486.1 (MH⁺)

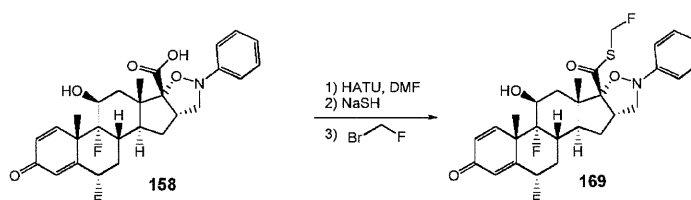
Compounds in Table 8 were prepared as previously described for compound 58 158:

Table 8

Compound	Structure	Yield	Analytical
159		90%	LC_MS (ESI POS): 519.9 (MH ⁺)
160		60%	LC_MS (ESI POS): 520.0 (MH ⁺)
161		53%	LC_MS (ESI POS): 500.1 (MH ⁺)
162		97%	LC_MS (ESI POS): 500.1 (MH ⁺)
163		16%	LC_MS (ESI POS): 500.2 (MH ⁺)
164		84%	LC_MS (ESI POS): 520.0 (MH ⁺)
165		93%	LC_MS (ESI POS): 504.1 (MH ⁺)
166		Used as crude	LC_MS (ESI POS): 487.0 (MH ⁺)

(continued)

167		93%	LC_MS (ESI POS): 504.1 (MH ⁺)
168		46%	LC_MS (ESI POS): 534.1 (MH ⁺)

Example 17

Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-4a,6a-dimethyl-2-oxo-8-phenyl-2,4a,4b,5,6,6a,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-fluoromethyl ester (compound 169)

A mixture of compound 158 (396 mg, 0.816 mmol), HATU (341 mg, 0.897 mmol) and N-methylmorpholine (90 μ l, 0.816 mmol) in dry DMF (5 ml) was stirred under nitrogen atmosphere at 70°C for 4 hrs and LC-MS showed the formation of the desired activated ester. The solution was cooled to RT and anhydrous sodium hydrogen sulfide (137 mg, 2.447 mmol) was added. The mixture was stirred at RT for 25 min, then 2 M solution of bromofluoromethane (1.223 ml, 2.447 mmol) in DMF was added and the mixture was stirred at RT for 2 hrs overnight.

Water (20 ml) was added to the reaction mixture and the formed precipitate was filtered. The collected precipitate was purified by flash chromatography on silica gel in gradient elution from AcOEt/DCM 5 : 95 to

AcOEt/DCM 10 : 90 and then preparative HPLC to afford 39 mg of the title compound (9% yield).

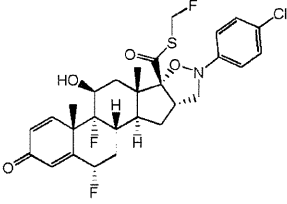
¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 – 7.36 (m, 2 H), 7.24 (dd, 1 H), 6.93 – 7.09 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.92 (dd, 1 H), 5.84 (dd, 1 H), 5.56 (dd, 1 H), 5.47 – 5.74 (m, 1 H), 4.22 (t, 1 H), 4.14 – 4.23 (m, 1 H), 3.59 (q, 1 H), 2.64 (dd, 1 H), 2.54 – 2.71 (m, 1 H), 2.07 – 2.33 (m, 2 H), 1.94 – 2.07 (m, 1 H), 1.84 (d, 1 H), 1.68 – 1.80 (m, 1 H), 1.52 – 1.66 (m, 2 H), 1.50 (s, 3 H), 0.98 (s, 3 H)

LC-MS (ESI POS): 534.17 (MH⁺)

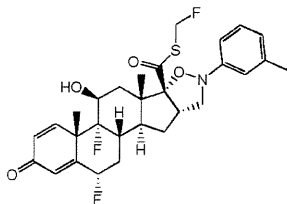
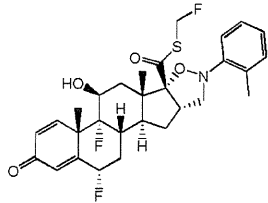
$[\alpha]_D^{25} = + 87.4$ (c 0.114; CHCl₃)

Compounds in Table 9 were prepared as previously described for compound 169, starting from the suitable acid derivative:

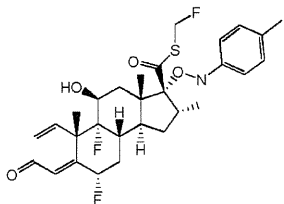
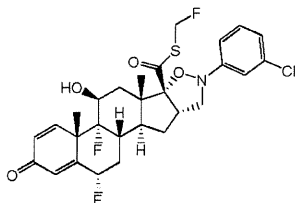
Table 9

Compound	Structure	Yield	Analytical
170		42%	LC-MS (ESI POS): 568.09 MH⁺ $[\alpha]_D^{25} = + 55.80$ (c 0.157; CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.29 – 7.43 (m, 2 H), 7.24 (dd, 1 H), 6.89 – 7.11 (m, 2 H), 6.28 (dd, 1 H), 6.09 (s, 1 H), 5.92 (dd, 1 H), 5.84 (dd, 1 H), 5.54 – 5.62 (m, 1 H), 5.47 – 5.74 (m, 1 H), 4.04 – 4.34 (m, 2 H), 3.50 – 3.68 (m, 1 H), 2.65 (t, 2 H), 2.05 – 2.31 (m, 2 H), 1.92 – 2.05 (m, 1 H), 1.68 – 1.89 (m, 2 H), 1.52 – 1.66 (m, 2 H), 1.49 (s, 3 H), 0.98 (s, 3 H)

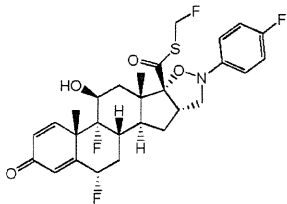
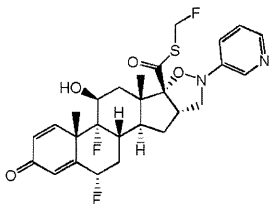
(continued)

171		50%	LC-MS (ESI POS): 548.23 MH⁺ $[\alpha]_D^{25} = +64.0$ (c 0.24, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 7.17 (t, 1 H), 6.74 – 6.89 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.92 (dd, 1 H), 5.84 (dd, 1 H), 5.56 (dd, 1 H), 5.46 – 5.74 (m, 1 H), 4.17 – 4.29 (m, 1 H), 4.19 (t, 1 H), 3.58 (q, 1 H), 2.55 – 2.67 (m, 2 H), 2.27 (s, 3 H), 1.95 – 2.25 (m, 3 H), 1.83 (d, 1 H), 1.68 – 1.79 (m, 1 H), 1.52 – 1.66 (m, 2 H), 1.49 (s, 3 H), 0.98 (s, 3 H)
172		37%	LC-MS (ESI POS): 547.91 MH⁺ $[\alpha]_D^{25} = +77.1$ (c 0.2 dmsO) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.35 (dd, 1 H), 7.27 (dd, 1 H), 7.17 – 7.24 (m, 1 H), 7.12 – 7.17 (m, 1 H), 7.07 (td, 1 H), 6.31 (dd, 1 H), 6.09 – 6.19 (m, 1 H), 5.90 (dd, 1 H), 5.81 (dd, 1 H), 5.57 – 5.79 (m, 1 H), 5.56 (dd, 1 H), 4.15 – 4.35 (m, 1 H), 3.92 (t, 1 H), 3.54 – 3.66 (m, 1 H), 2.22 – 2.47 (m, 4 H), 2.16 (s, 3 H), 1.95 – 2.10 (m, 1 H), 1.55 – 1.87 (m, 4 H), 1.51 (s, 3 H), 0.98 (s, 3 H)

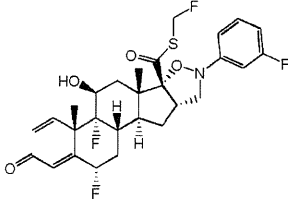
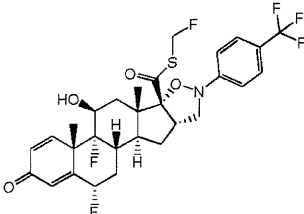
(continued)

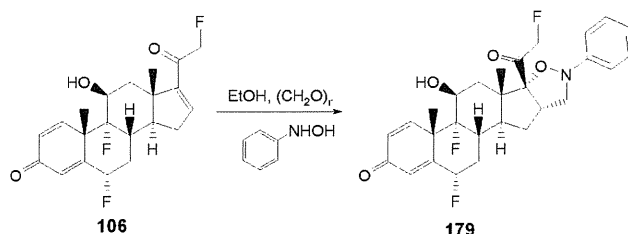
173		14%	LC-MS (ESI POS): 548.11 MH⁺ $[\alpha]_D^{25} = +66.4$ (c 0.103, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 7.04 – 7.16 (m, 2 H), 6.82 – 7.02 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.92 (dd, 1 H), 5.84 (dd, 1 H), 5.55 (dd, 1 H), 5.49 – 5.73 (m, 1 H), 4.17 – 4.29 (m, 1 H), 4.16 (t, 1 H), 3.58 (q, 1 H), 2.62 – 2.79 (m, 1 H), 2.53 – 2.62 (m, 1 H), 2.23 (s, 3 H), 1.93 – 2.22 (m, 3 H), 1.67 – 1.88 (m, 2 H), 1.50 – 1.66 (m, 2 H), 1.49 (s, 3 H), 0.97 (s, 3 H)
174		29%	LC-MS (ESI POS): 568.07 MH⁺ $[\alpha]_D^{25} = +55.0$ (c 0.2, CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.33 (t, 1 H), 7.24 (dd, 1 H), 7.01 – 7.09 (m, 2 H), 6.97 (ddd, 1 H), 6.28 (dd, 1 H), 6.07 – 6.12 (m, 1 H), 5.92 (dd, 1 H), 5.85 (dd, 1 H), 5.57 (dd, 1 H), 5.48 – 5.72 (m, 1 H), 4.27 (t, 1 H), 4.14 – 4.25 (m, 1 H), 3.48 – 3.68 (m, 1 H), 2.56 – 2.71 (m, 2 H), 1.94 – 2.24 (m, 4 H), 1.52 – 1.93 (m, 3 H), 1.49 (s, 3 H), 0.98 (s, 3 H)

(continued)

175		24%	LC-MS (ESI POS): 552.15 MH⁺ $[\alpha]_D^{25} = +76.56$ (c 0.25, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.24 (dd, 1 H), 7.10 – 7.20 (m, 2 H), 7.00 – 7.10 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.93 (dd, 1 H), 5.85 (dd, 1 H), 5.56 (dd, 1 H), 5.41 – 5.73 (m, 1 H), 4.11 – 4.31 (m, 2 H), 3.52 – 3.69 (m, 1 H), 2.57 – 2.72 (m, 2 H), 2.06 – 2.34 (m, 2 H), 1.93 – 2.05 (m, 1 H), 1.67 – 1.89 (m, 2 H), 1.52 – 1.67 (m, 2 H), 1.49 (s, 3 H), 0.98 (s, 3 H)
176		12%	LC-MS (ESI POS): 535.1 MH⁺ $[\alpha]_D^{25} = +29.84$ (c 0.0925; MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 8.33 (d, 1 H), 8.24 (dd, 1 H), 7.42 (ddd, 1 H), 7.35 (dd, 1 H), 7.24 (dd, 1 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.93 (dd, 1 H), 5.85 (dd, 1 H), 5.55 – 5.60 (m, 1 H), 5.47 – 5.75 (m, 1 H), 4.30 (t, 1 H), 4.10 – 4.25 (m, 1 H), 3.55 – 3.71 (m, 1 H), 2.66 – 2.78 (m, 1 H), 2.59 – 2.66 (m, 1 H), 2.02 – 2.35 (m, 3 H), 1.52 – 1.90 (m, 4 H), 1.50 (s, 3 H), 0.99 (s, 3 H)

(continued)

177		24% LC-MS (ESI POS): 552.11 MH⁺ $[\alpha]_D^{25} = +68.31$ (c 0.26, DCM) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.29 - 7.49 (m, 1 H), 7.24 (dd, 1 H), 6.69 - 6.91 (m, 3 H), 6.28 (dd, 1 H), 6.09 (s, 1 H), 5.92 (dd, 1 H), 5.85 (dd, 1 H), 5.57 (dd, 1 H), 5.49 - 5.74 (m, 1 H), 4.25 (t, 1 H), 4.14 - 4.22 (m, 1 H), 3.50 - 3.67 (m, 1 H), 2.57 - 2.81 (m, 2 H), 2.07 - 2.34 (m, 2 H), 1.95 - 2.07 (m, 1 H), 1.68 - 1.92 (m, 2 H), 1.53 - 1.68 (m, 2 H), 1.50 (s, 3 H), 0.98 (s, 3 H)
178		35% LC-MS (ESI POS): 602.21 MH⁺ $[\alpha]_D^{25} = +42.6$ (c 0.2, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.53 - 7.84 (m, 2 H), 7.24 (dd, 1 H), 7.08 - 7.21 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.92 (dd, 1 H), 5.85 (dd, 1 H), 5.58 (dd, 1 H), 5.42 - 5.74 (m, 1 H), 4.35 (t, 1 H), 4.07 - 4.29 (m, 1 H), 3.50 - 3.76 (m, 1 H), 2.59 - 2.86 (m, 2 H), 1.96 - 2.35 (m, 3 H), 1.69 - 1.94 (m, 2 H), 1.53 - 1.69 (m, 2 H), 1.50 (s, 3 H), 1.00 (s, 3 H)

Example 18

Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-4b,12-Difluoro-6b-(2-fluoro-acetyl)-5-hydroxy-4a,6a-dimethyl-8-phenyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one (compound 179)

A mixture of 106 (150 mg, 0.394 mmol), N-phenyl hydroxylamine (86 mg, 0.789 mmol) and paraformaldehyde (71.0 mg, 2.366 mmol) in ethanol (13 ml) was stirred at 100°C for 20 hr. N-phenyl hydroxylamine (47.3 mg, 0.434 mmol) and paraformaldehyde (52.1 mg, 1.735 mmol) were further added and the mixture was heated at 100°C for 3 hr. The solvent was evaporated and the residue was purified by silica gel flash chromatography in gradient elution from AcOEt/MeOH/DCM 4.8 : 0.2 : 95, to AcOEt/MeOH/DCM 9.8 : 0.2 : 90, affording 144 mg of desired compound (R_f = 0.22 in AcOEt/MeOH/DCM 9.8 : 0.2 : 90). The compound was further purified by silica gel flash chromatography in gradient elution from DCM, to DCM/AcOEt 87 : 13 to afford 122 mg of the title compound (62% yield).

^1H NMR (300 MHz, DMSO- d_6) ppm 7.27 - 7.34 (m, 2 H), 7.27 (dd, 1 H), 6.93 - 7.07 (m, 3 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 (d, 1 H), 5.49 - 5.74 (m, 1 H), 5.37 (dd, 1 H), 5.30 (dd, 1 H), 4.17 - 4.27 (m, 1 H), 4.19 (t, 1 H), 3.56 (q, 1 H), 2.60 - 2.71 (m, 1 H), 2.59 (dd, 1 H), 2.11 - 2.32 (m, 2 H), 2.07 (ddd, 1 H), 1.80 (d, 1 H), 1.63 - 1.77 (m, 1 H), 1.51 - 1.62 (m, 2 H), 1.50 (s, 3 H), 0.95 (s, 3 H)

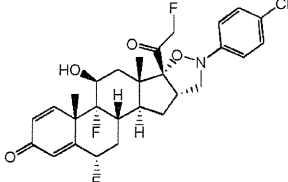
LC-MS (ESI POS): 502.15 MH⁺

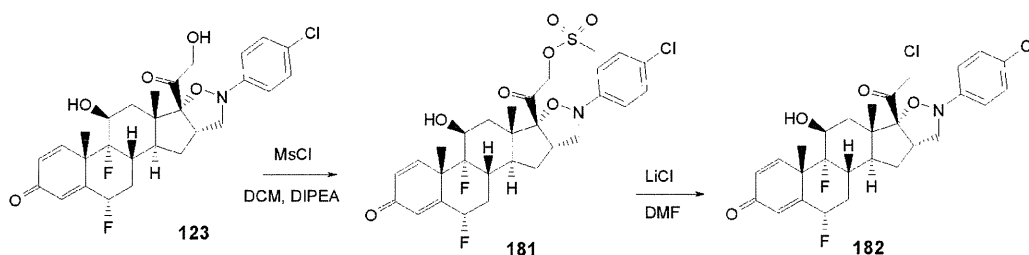
$[\alpha]_D^{25} = +68.72$ (c 0.094; CHCl₃)

The compounds listed in Table 10 were prepared as previously described for compound 179, by cycloaddition of intermediate 106 with suitable hydroxylamine or hydroxylamine hydrochloride.

Table 10

5

Compound	Structure	Yield	Analytical
180		65%	LC-MS (ESI POS): 536.07 MH⁺ $[\alpha]_D^{25} = +50.85$ (c 0.0885; CHCl₃) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.30 - 7.43 (m, 2 H), 7.26 (dd, 1 H), 6.93 - 7.08 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 (d, 1 H), 5.47 - 5.80 (m, 1 H), 5.36 (dd, 1 H), 5.29 (dd, 1 H), 4.14 - 4.25 (m, 1 H), 4.19 (t, 1 H), 3.44 - 3.65 (m, 1 H), 2.58 - 2.73 (m, 1 H), 2.60 (dd, 1 H), 1.97 - 2.30 (m, 3 H), 1.63 - 1.87 (m, 2 H), 1.51 - 1.61 (m, 2 H), 1.49 (s, 3 H), 0.94 (s, 3 H)

Example 20**Preparation of Methanesulfonic acid 2-**

10 [(4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-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 181)

Methanesulfonyl chloride (79 μ L, 1.011 mmol) was added at 0°C under nitrogen atmosphere to a solution of 123 (450 mg, 0.843 mmol) and DIPEA (221 μ L, 1.264 mmol) in DCM (dried over CaCl_2 , 20 ml). The mixture was
5 stirred at RT for 2h.

The mixture was diluted with DCM, and washed with 2.5% aqueous NaHCO_3 . The aqueous phase was extracted with DCM, and the combined organics were washed with brine, dried over Na_2SO_4 and filtered. The solvent was evaporated.

10 LC-MS (ESI POS): 612.2 (MH⁺)

Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-6b-(2-Chloro-acetyl)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one (compound 182)

15 A mixture of compound 181 (195 mg, 0.319 mmol) and lithium chloride (162 mg, 3.82 mmol) in dry DMF (6 ml) was stirred under nitrogen at 70°C for 2h.

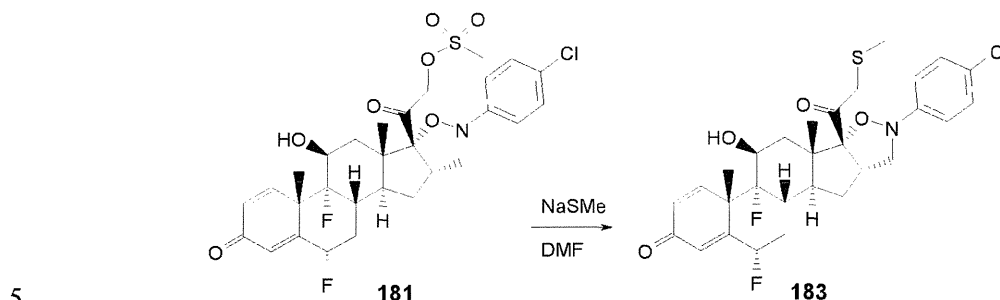
The mixture was partitioned between AcOEt and brine, and then the aqueous phase was extracted with AcOEt. The combined organics were
20 washed with brine, dried over Na_2SO_4 and filtered. The solvent was evaporated and the crude was purified by silica gel flash chromatography (eluent: DCM: MeOH 99: 1). A solid was obtained, which was triturated with Et_2O /EtOH (95:5) to give the title compound (33% yield).

¹H NMR (300 MHz, DMSO- d_6) ppm 7.30 - 7.41 (m, 2 H), 7.27 (dd, 1
25 H), 6.95 - 7.12 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.33 - 5.80 (m, 1 H), 5.52 (d, 1 H), 4.70 (s, 2 H), 3.96 - 4.33 (m, 2 H), 3.60 (q, 1 H), 2.55 - 2.70 (m, 2 H), 2.00 - 2.36 (m, 3 H), 1.83 (d, 1 H), 1.63 - 1.78 (m, 1 H), 1.28 - 1.63 (m, 2 H), 1.49 (s, 3 H), 0.92 (s, 3 H)

LC-MS (ESI POS): 552.21 (MH⁺)

$[\alpha]_D^{25} = +81.85$ (c 0.26, CHCl₃)

Example 21



Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-8-(4-Chlorophenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-6b-(2-methylsulfonyl-acetyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one (compound 183)

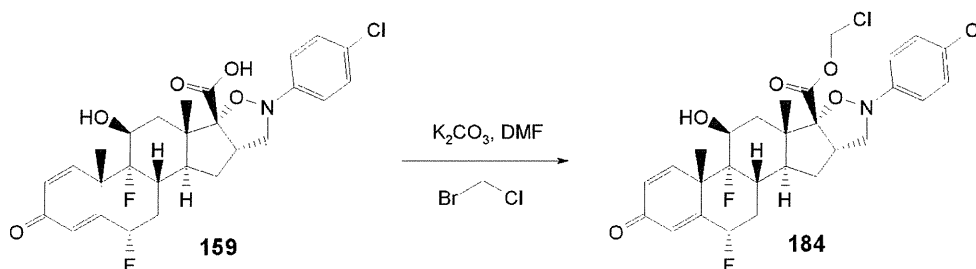
10 A mixture of compound 181 (175 mg, 0.286 mmol) and sodium methanethiolate (24.05 mg, 0.343 mmol) in DMF dry (4 ml) was stirred at RT under nitrogen atmosphere for 3h. The mixture was partitioned between AcOEt and brine, and the aqueous phase was extracted with AcOEt. The combined organics were washed with brine, dried over Na₂SO₄ and filtered.

15 The solvent was evaporated and the residue was triturated with acetonitrile. The obtained crude was purified by silica gel flash chromatography (DCM: MeOH 99: 1) and then it was triturated with Et₂O to afford the desired compound (16% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.29 - 7.48 (m, 2 H), 7.26 (dd, 1 H),
20 6.89 - 7.10 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.53 - 5.78 (m, 1 H), 5.51 (dd, 1 H), 4.17 - 4.30 (m, 1 H), 4.13 (t, 1 H), 3.70 (d, 1 H), 3.62 (d, 1 H), 3.54 - 3.63 (m, 1 H), 2.61 (dd, 1 H), 2.55 - 2.71 (m, 1 H), 2.06 - 2.25 (m, 3 H), 2.04 (s, 3 H), 1.88 (d, 1 H), 1.63 - 1.81 (m, 1 H), 1.51 - 1.62 (m, 2 H), 1.50 (s, 3 H), 0.93 (s, 3 H)

LC-MS (ESI POS): 564.24 (MH⁺)

$$[\alpha]_D^{25} = + 85.92 \text{ (c 0.24, CHCl}_3\text{)}$$

Example 22

- 5 **Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-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-azapentaleno[2,1-a]phenanthrene-6b-carboxylic acid chloromethyl thioester (compound 184)**

- 10 Compound 159 was dissolved in DMF (4 ml) in a nitrogen atmosphere; potassium carbonate (106 mg, 0.769 mmol) and bromochloromethane (0.125 ml, 1.923 mmol) were added and the mixture was stirred at room temperature for 4 hours. The reaction mixture was partitioned between water and AcOEt. The organic phase was separated and the solvent was removed.
- 15 The crude was purified by silica gel flash chromatography (eluent DCM/AcOEt 95/5 to 9/1) affording a solid that was further triturated in Et₂O, affording the title compound (23% yield).

- 20 ¹H NMR (300 MHz, DMSO-*d*₆) ppm 7.28 - 7.35 (m, 2 H), 7.25 (dd, 1 H), 6.83 - 7.04 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.95 (d, 1 H), 5.93 (d, 1 H), 5.61 (dd, 1 H), 5.47 - 5.78 (m, 1 H), 4.20 - 4.35 (m, 1 H), 4.16 (t, 1 H), 3.63 - 3.81 (m, 1 H), 2.77 (dd, 1 H), 2.61 - 2.72 (m, 1 H), 1.96 - 2.26 (m, 3 H), 1.68 - 1.93 (m, 2 H), 1.52 - 1.62 (m, 2 H), 1.50 (s, 3 H), 1.02 (s, 3 H)

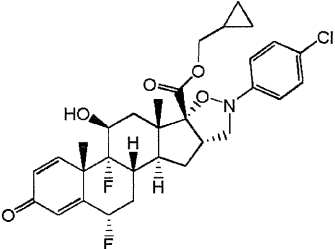
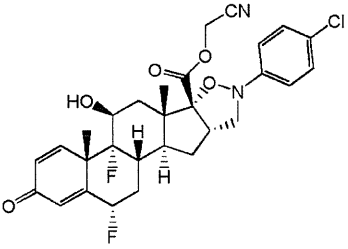
LC-MS (ESI POS): 568.17 (MH⁺)

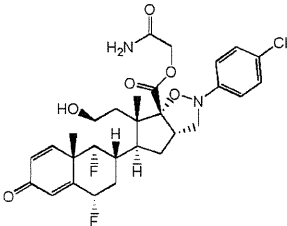
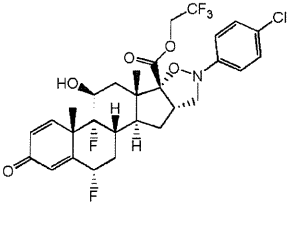
$$[\alpha]_D^{25} = + 56.2 \text{ (c 0.3, MeOH)}$$

- 25 The compounds in Table 11 were prepared as previously described for

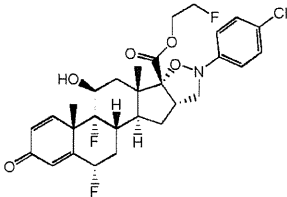
compound 184, starting from acid 159, the suitable alkylating agent and a base such as Na₂CO₃, K₂CO₃ or triethylamine with the suitable solvent:

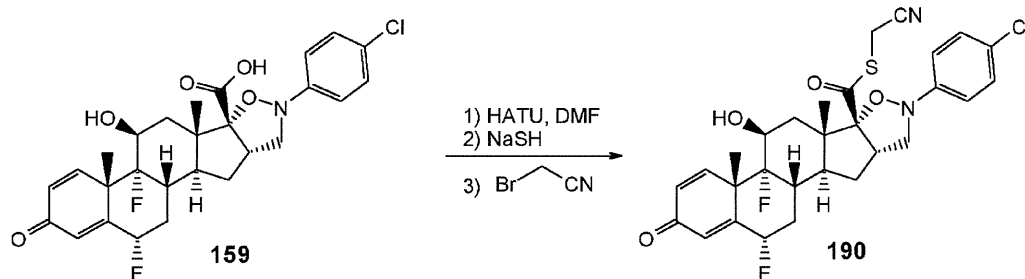
Table 11

Compound	Structure	Yield	Analytical
185		33%	LC-MS (ESI POS): 574.3 MH⁺ $[\alpha]_D^{25} = +59.5$ (c 0.2, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 - 7.33 (m, 2 H), 7.26 (dd, 1 H), 6.89 - 7.01 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.55 (d, 1 H), 5.48 - 5.77 (m, 1 H), 4.16 - 4.34 (m, 1 H), 4.11 (t, 1 H), 3.95 (dd, 1 H), 3.87 (dd, 1 H), 3.60 - 3.75 (m, 1 H), 2.81 (dd, 1 H), 2.55 - 2.71 (m, 1 H), 1.95 - 2.31 (m, 3 H), 1.82 - 1.94 (m, 1 H), 1.66 - 1.82 (m, 1 H), 1.52 - 1.61 (m, 2 H), 1.50 (s, 3 H), 1.04 - 1.22 (m, 1 H), 1.00 (s, 3 H), 0.43 - 0.60 (m, 2 H), 0.20 - 0.37 (m, 2 H)
186		25%	LC-MS (ESI POS): 559.14 MH⁺ $[\alpha]_D^{25} = +78.96$ (c 0.25, DCM) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.28 - 7.36 (m, 2 H), 7.26 (dd, 1 H), 6.87 - 7.03 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.61 (dd, 1 H), 5.43 - 5.78 (m, 1 H), 5.11 (d, 1 H), 5.05 (d, 1 H), 4.19 - 4.38 (m, 1 H), 4.18 (t, 1 H), 3.66 - 3.81 (m, 1 H), 2.78 (dd, 1 H), 2.56 - 2.70 (m, 1 H), 1.96 - 2.26 (m, 3 H), 1.66 - 1.88 (m, 2 H), 1.52 - 1.64 (m, 2 H), 1.50 (s, 3 H), 1.01 (s, 3 H)

187		LC-MS (ESI POS): 577.13 MH⁺ $[\alpha]_D^{25} = + 51.0$ (c 0.22, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.25 - 7.40 (m, 2 H), 7.23 - 7.29 (m, 1 H), 7.14 - 7.23 (m, 2 H), 6.85 - 7.07 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.47 - 5.80 (m, 1 H), 5.56 (d, 1 H), 4.46 (s, 2 H), 4.16 - 4.26 (m, 1 H), 4.11 (t, 1 H), 3.60 - 3.82 (m, 1 H), 2.82 (dd, 1 H), 2.56 - 2.69 (m, 1 H), 1.86 - 2.25 (m, 4 H), 1.65 - 1.86 (m, 1 H), 1.50 (s, 3 H), 1.33 - 1.63 (m, 2 H), 1.06 (s, 3 H) 24%
188		LC-MS (ESI POS): 602.26 MH⁺ $[\alpha]_D^{25} = + 57.6$ (c 0.3, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.29 - 7.37 (m, 2 H), 7.26 (dd, 1 H), 6.90 - 7.03 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.64 (d, 1 H), 5.46 - 5.81 (m, 1 H), 4.71 - 4.96 (m, 2 H), 4.18 - 4.26 (m, 1 H), 4.16 (t, 1 H), 3.50 - 3.81 (m, 1 H), 2.79 (dd, 1 H), 2.59 - 2.68 (m, 1 H), 1.94 - 2.25 (m, 3 H), 1.66 - 1.85 (m, 2 H), 1.52 - 1.63 (m, 2 H), 1.50 (s, 3 H), 1.00 (s, 3 H) 20%

(continued)

189		LC-MS (ESI POS): 566.18 MH ⁺ $[\alpha]_D^{25} = +55$ (c 0.21, MeOH) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.19 - 7.37 (m, 3 H), 6.86 - 7.04 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.56 (dd, 1 H), 5.43 - 5.81 (m, 1 H), 4.63 (dt, 2 H), 4.02 - 4.49 (m, 4 H), 3.55 - 3.76 (m, 1 H), 2.82 (dd, 1 H), 2.55 - 2.68 (m, 1 H), 1.96 - 2.35 (m, 3 H), 1.86 (d, 1 H), 1.68 - 1.81 (m, 1 H), 1.51 - 1.64 (m, 2 H), 1.50 (s, 3 H), 0.99 (s, 3 H)
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Example 23

Preparation of (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-azapentaleno[2,1-a]phenanthrene-6b-carbothioic acid S-cyanomethyl ester (compound 190)

Compound 159 (218 mg, 0.419 mmol) was dissolved in DMF (5 ml) in a nitrogen atmosphere; HATU (175 mg, 0.461 mmol) and 4-methylmorpholine (50.9 mg, 0.503 mmol) were added and the mixture was stirred at room temperature for 1 hour. Then sodium hydrogen sulfide (47.0 mg, 0.839 mmol) was added and the mixture turned into dark green. The resulting mixture was stirred at RT for 1 hour, 2-bromoacetonitrile (0.117 ml, 1.677 mmol) was added and the solution was stirred in closed vessel at RT overnight. The

reaction mixture was diluted with AcOEt and the organic layer was washed with water and brine, dried (Na₂SO₄) and concentrated. The crude was purified by silica gel flash chromatography (eluent DCM/AcOEt 95/5 to 9/1) affording a solid that was further triturated with Et₂O, to yield the desired

5 compound (22% yield).

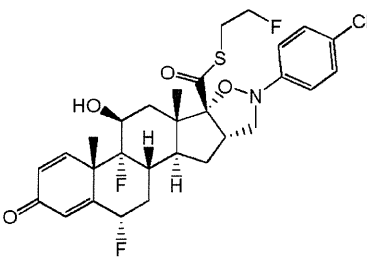
¹H NMR (300 MHz, DMSO-d₆) ppm 7.32 - 7.45 (m, 2 H), 7.24 (dd, 1 H), 6.93 - 7.10 (m, 2 H), 6.28 (dd, 1 H), 6.09 (s, 1 H), 5.62 (dd, 1 H), 5.40 - 5.79 (m, 1 H), 4.24 (t, 1 H), 4.15 - 4.21 (m, 1 H), 4.00 (d, 1 H), 3.92 (d, 1 H), 3.50 - 3.69 (m, 1 H), 2.56 - 2.71 (m, 2 H), 2.04 - 2.25 (m, 2 H), 1.94 - 2.04 (m, 10 1 H), 1.77 - 1.87 (m, 1 H), 1.69 - 1.77 (m, 1 H), 1.52 - 1.66 (m, 2 H), 1.50 (s, 3 H), 1.00 (s, 3 H)

LC-MS (ESI POS): 575.21 (MH⁺)

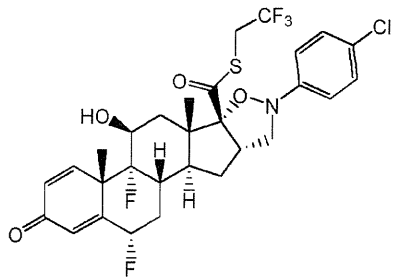
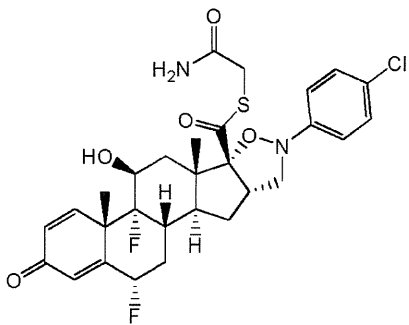
[α]_D²⁵ = + 31.76 (c 0.25, MeOH)

The compounds in Table 12 were prepared as previously described for
15 compound 190, starting from acid 159 and the suitable alkylating:

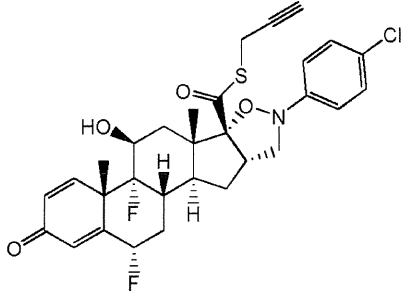
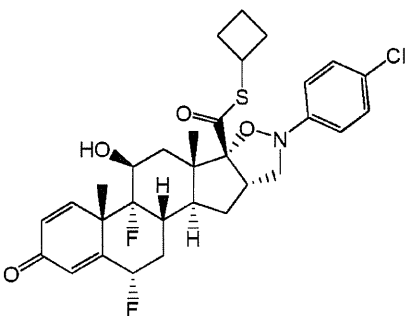
Table 12

Compound	Structure	Yield	Analytical
191		18%	LC-MS (ESI POS): 582.25 MH ⁺ [α] _D ²⁵ = + 40.00 (c 0.2, MeOH) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.30 - 7.42 (m, 2 H), 7.24 (dd, 1 H), 6.90 - 7.12 (m, 2 H), 6.28 (dd, 1 H), 6.00 - 6.15 (m, 1 H), 5.56 (dd, 1 H), 5.40 - 5.86 (m, 1 H), 4.49 (m, 2 H), 4.18 - 4.29 (m, 1 H), 4.20 (t, 1 H), 3.49 - 3.71 (m, 1 H), 2.97 - 3.25 (m, 2 H), 2.55 - 2.70 (m, 2 H), 1.92 - 2.31 (m, 3 H), 1.80 - 1.92 (m, 1 H), 1.65 - 1.80 (m, 1 H), 1.51 - 1.65 (m, 2 H), 1.49 (s, 3 H), 0.96 (s, 3 H)

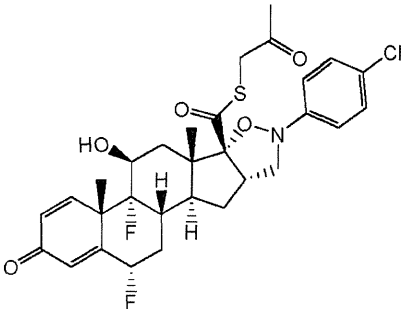
(continued)

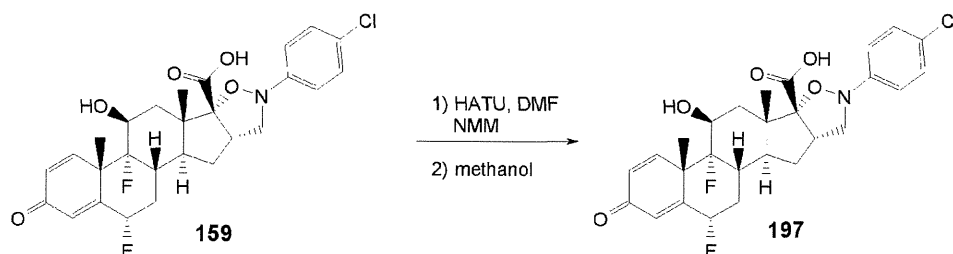
192		LC-MS (ESI POS): 618.16 MH⁺ $[\alpha]_D^{25} = +46.50$ (c 0.2, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.30 - 7.48 (m, 2 H), 7.23 (dd, 1 H), 6.80 - 7.12 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.63 (dd, 1 H), 5.46 - 5.77 (m, 1 H), 4.23 (t, 1 H), 4.12 - 4.32 (m, 1 H), 3.88 (d, 1 H), 3.81 (d, 1 H), 3.58 (q, 1 H), 2.60 - 2.71 (m, 2 H), 1.93 - 2.30 (m, 3 H), 1.67 - 1.89 (m, 2 H), 1.49 (s, 3 H), 1.33 - 1.67 (m, 2 H), 0.96 (s, 3 H) 29%
193		LC-MS (ESI POS): 593.3 MH⁺ $[\alpha]_D^{25} = +45.10$ (c 0.2, DCM) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.48 (br. s., 1 H), 7.35 (d, 2 H), 7.25 (d, 1 H), 7.02 (d, 2 H), 6.90 - 7.15 (m, 1 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.37 - 5.79 (m, 0 H), 5.58 (d, 1 H), 4.03 - 4.34 (m, 2 H), 3.47 - 3.63 (m, 4 H), 2.63 (d, 3 H), 2.22 (d, 1 H), 2.05 - 2.16 (m, 1 H), 1.94 (d, 1 H), 1.64 - 1.84 (m, 1 H), 1.49 (s, 3 H), 1.31 - 1.64 (m, 2 H), 0.96 (s, 3 H) 15%

(continued)

194		LC-MS (ESI POS): 574.2 MH⁺ $[\alpha]_D^{25} = + 56.7$ (c 0.5, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.30 - 7.44 (m, 2 H), 7.24 (dd, 1 H), 6.93 - 7.07 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.58 (dd, 1 H), 5.40 - 5.75 (m, 1 H), 4.21 (t, 1 H), 4.11 - 4.27 (m, 1 H), 3.60 - 3.71 (m, 2 H), 3.50 - 3.62 (m, 1 H), 3.09 (t, 1 H), 2.55 - 2.69 (m, 2 H), 2.17 - 2.31 (m, 1 H), 2.03 - 2.17 (m, 1 H), 1.92 - 2.03 (m, 1 H), 1.80 - 1.90 (m, 1 H), 1.67 - 1.81 (m, 1 H), 1.51 - 1.65 (m, 2 H), 1.49 (s, 3 H), 0.97 (s, 3 H) 28%
195		LC-MS (ESI POS): 622.19 MH⁺ $[\alpha]_D^{25} = + 65$ (c 0.3, MeOH) ¹H NMR (300 MHz, DMSO-d₆) ppm 7.37 (m, 2 H), 7.24 (d, 1 H), 7.07 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.59 (d, 1 H), 5.46 - 5.79 (m, 1 H), 4.23 (t, 1 H), 4.02 - 4.35 (m, 1 H), 3.61 (dq, 2 H), 2.55 - 2.72 (m, 2 H), 2.04 - 2.29 (m, 5 H), 1.67 - 2.04 (m, 5 H), 1.50 (s, 3 H), 1.37 - 1.67 (m, 2 H), 0.97 (s, 3 H) 8%

(continued)

196		LC-MS (ESI POS): 592.19 MH ⁺ $[\alpha]_D^{25} = +31.4$ (c 0.21, MeOH) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.30 - 7.45 (m, 2 H), 7.25 (dd, 1 H), 6.91 - 7.08 (m, 2 H), 6.29 (dd, 1 H), 6.08 (s, 1 H), 5.61 (dd, 1 H), 5.43 - 5.80 (m, 1 H), 4.19 - 4.29 (m, 1 H), 4.18 (t, 1 H), 3.87 (d, 1 H), 3.79 (d, 1 H), 3.54 (q, 1 H), 2.55 - 2.71 (m, 2 H), 2.22 - 2.31 (m, 1 H), 2.20 (s, 3 H), 2.02 - 2.16 (m, 1 H), 1.85 - 2.00 (m, 2 H), 1.64 - 1.80 (m, 1 H), 1.51 - 1.64 (m, 2 H), 1.50 (s, 3 H), 0.95 (s, 3 H)
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Example 24

Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-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-azapentaleno[2,1-a]phenanthrene-6b-carboxylic acid methyl ester (compound 181)

In a nitrogen atmosphere 159 (290 mg, 0.558 mmol) was dissolved in dry DMF, N-methylmorpholine (73.6 μ L, 0.669 mmol) and HATU (233 mg, 0.614 mmol) were added and the mixture was stirred at room temperature for 1 h. Methanol (250 μ L, 6.18 mmol) was added and the mixture was heated at 60°C for 3 hours and at room temperature overnight. Further methanol (400 μ L, 9.86 mmol) was added and the mixture was stirred at 60°C for 4 hours. The reaction mixture was diluted with water and the formed solid was recovered by filtration. The obtained solid was triturated in acetonitrile, then it

was purified by preparative HPLC (acetonitrile/water without TFA) affording the title compound (55 mg, 18.5% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.26 - 7.33 (m, 2 H), 7.26 (dd, 1 H), 6.87 - 7.04 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.52 - 5.78 (m, 1 H),
 5.51 (dd, 1 H), 4.16 - 4.25 (m, 1 H), 4.12 (t, 1 H), 3.69 (t, 1 H), 3.65 (s, 3 H),
 2.80 (dd, 1 H), 2.55 - 2.68 (m, 1 H), 2.18 - 2.26 (m, 1 H), 2.05 - 2.18 (m, 1 H),
 1.94 - 2.05 (m, 1 H), 1.78 - 1.92 (m, 1 H), 1.66 - 1.79 (m, 1 H), 1.52 - 1.64 (m,
 2 H), 1.50 (s, 3 H), 0.96 (s, 3 H)

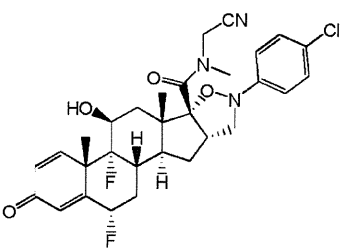
LC-MS (ESI POS): 534.11 (MH⁺)

[α]_D²⁵ = + 35 (c 0.34; MeOH)

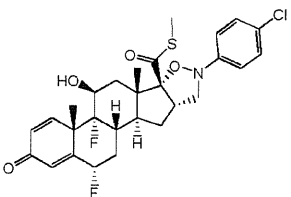
The compounds listed in Table 13 were prepared as previously described for compound 197, starting from acid 159 and the suitable nucleophile, such as alcohol, amine or amine salt, or metal thiolates:

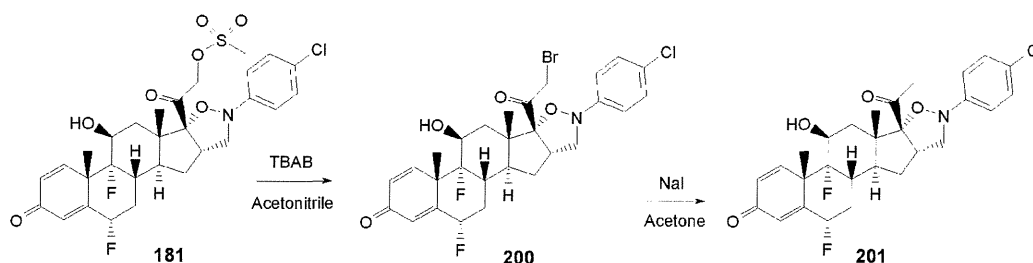
Table 13

15

Compound	Structure	Yield	Analytical
198		13%	LC-MS (ESI POS): 572.28 MH ⁺ [α] _D ²⁵ = + 7.3 (c 0.3, MeOH) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.31 (d, 2 H), 7.26 (d, 1 H), 7.00 (d, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.56 - 5.65 (m, 1 H), 5.45 - 5.80 (m, 1 H), 4.45 (d, 1 H), 4.28 (d, 1 H), 4.18 - 4.27 (m, 1 H), 4.08 (dd, 1 H), 4.02 (q, 1 H), 3.38 (s, 3 H), 2.64 (dd, 2 H), 2.05 - 2.30 (m, 3 H), 1.62 - 1.94 (m, 2 H), 1.50 (s, 3 H), 1.34 - 1.61 (m, 2 H), 0.99 (s, 3 H)

(continued)

199		LC-MS (ESI POS): 550.26 MH ⁺ $[\alpha]_D^{25} = +66.2$ (c 0.2, DCM) ¹ H NMR (300 MHz, DMSO-d ₆) ppm 7.29 - 7.46 (m, 2 H), 7.24 (dd, 1 H), 6.88 - 7.08 (m, 2 H), 6.28 (dd, 1 H), 6.08 (s, 1 H), 5.52 - 5.82 (m, 1 H), 5.50 (dd, 1 H), 4.16 - 4.26 (m, 1 H), 4.17 (t, 1 H), 3.52 - 3.65 (m, 1 H), 2.55 - 2.67 (m, 2 H), 2.22 (s, 3 H), 1.92 - 2.19 (m, 3 H), 1.81 - 1.91 (m, 1 H), 1.65 - 1.81 (m, 1 H), 1.51 - 1.65 (m, 2 H), 1.49 (s, 3 H), 0.95 (s, 3 H)
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Example 25

Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-6b-(2-Bromo-acetyl)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one (compound 200)

Methanesulfonic acid 181 (653 mg, 1.067 mmol) was dissolved in acetonitrile (20 ml), tetrabutylammonium bromide (344 mg, 1.067 mmol) was added and the mixture was heated at 80°C for 6 hours, then at room temperature overnight. Further tetrabutylammonium bromide (344 mg, 1.067 mmol) was added and the mixture was heated at 80°C for further 2 hours. The reaction mixture was partitioned between water and AcOEt. The organic layer was separated, dried over Na₂SO₄ and concentrated. The crude was purified by silica gel flash chromatography (eluent DCM/AcOEt from 8/2

to 7/3) to yield the title compound (630 mg, 1.055 mmol, 99% yield).

LC-MS (ESI POS): 596.0 (MH⁺)

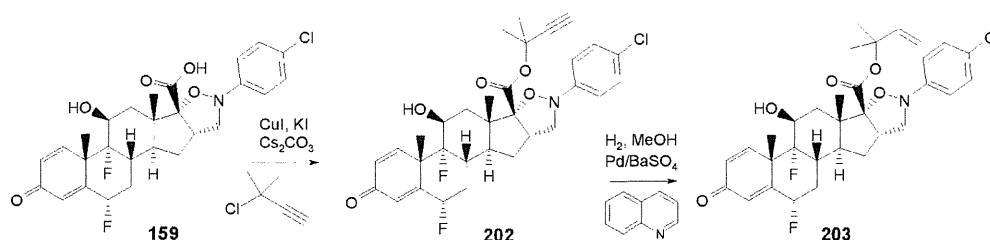
Preparation of (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-6b-Acetyl-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-azapentaleno[2,1-a]phenanthren-2-one (compound 201)

A mixture of 190 (373mg, 0.625 mmol) and sodium iodide (937 mg, 6.25 mmol) in acetone (17 ml) was heated under microwave irradiation at 110°C for 3 hours. More sodium iodide (468 mg, 3.12 mmol) was added and the mixture was heated under microwave irradiation for further 3 hours. The reaction mixture was partitioned between AcOEt and a saturated solution of NaS₂O₃. The organic layer was washed with water, dried over Na₂SO₄ and concentrated. The crude was purified by silica gel flash chromatography (eluent DCM/MeOH =99/1), then by preparative HPLC (CH₃CN/H₂O without TFA) to give the title compound (31 mg, 0.060 mmol, 10% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.29 - 7.43 (m, 2 H), 7.27 (dd, 1 H), 6.94 - 7.08 (m, 2 H), 6.29 (dd, 1 H), 6.09 (s, 1 H), 5.52 - 5.75 (m, 1 H), 5.51 (d, 1 H), 4.16 - 4.30 (m, 1 H), 4.09 (t, 1 H), 3.51 - 3.64 (m, 1 H), 2.62 - 2.70 (m, 1 H), 2.61 (dd, 2 H), 2.20 (s, 3 H), 2.04 - 2.19 (m, 2 H), 1.82 (d, 1 H), 1.59 - 1.74 (m, 1 H), 1.51 - 1.59 (m, 2 H), 1.50 (s, 3 H), 0.89 (s, 3 H)

LC-MS (ESI POS): 518.2 (MH⁺)

$[\alpha]_D^{25} = + 65.2$ (0.072, CHCl₃)

Example 26

Preparation of (4a*S*,4b*R*,5*S*,6a*S*,6b*R*,9a*S*,10a*S*,10b*S*,12*S*)-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-azapentaleno[2,1-a]phenanthrene-6b-carboxylic acid 1,1-dimethyl-prop-2-ynyl ester (compound 202)

To a mixture of 159 (450 mg, 0.865 mmol), Cs₂CO₃ (282 mg, 0.865 mmol), copper(I) iodide (16.48 mg, 0.087 mmol) and KI (230 mg, 1.385 mmol), in dry DMF (4 ml), 3-chloro-3-methylbut-1-yne (178 mg, 1.731 mmol) was added and the reaction mixture was stirred at RT overnight. Ethyl acetate was added and the formed solid was filtered off; water was added and the organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel flash chromatography (eluent: DCM/MeOH, 98/2) and, after evaporation of the solvent, the obtained solid was triturated with Et₂O, filtered and dried under vacuum, to give the title compound (200 mg, 0.341 mmol, 39.4% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.22 - 7.35 (m, 2 H), 7.25 (dd, 1 H), 6.75 - 7.07 (m, 2 H), 6.28 (dd, 1 H), 6.09 (s, 1 H), 5.53 - 5.78 (m, 1 H), 5.51 (d, 1 H), 4.19 (d, 1 H), 4.07 (t, 1 H), 3.55 - 3.80 (m, 1 H), 3.50 (s, 1 H), 2.83 (dd, 1 H), 2.54 - 2.61 (m, 1 H), 2.19 - 2.33 (m, 1 H), 1.82 - 2.18 (m, 3 H), 1.67 - 1.82 (m, 1 H), 1.63 (s, 3 H), 1.58 (s, 3 H), 1.55 (m, 2 H), 1.51 (s, 3 H), 1.03 (s, 3 H)

LC-MS (ESI POS): 586.15 (MH⁺)

$$[\alpha]_D^{25} = + 40.6 \text{ (c 0.2, DCM)}$$

Preparation of (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-azapentaleno[2,1-a]phenanthrene-6b-carboxylic acid 1,1-dimethyl-allyl ester (compound 203)

A mixture of 202 (150 mg, 0.256 mmol), quinoline (9.10 μ L, 0.077 mmol) and 5% Pd /BaSO₄ (15 mg) was hydrogenated for 5 hours at 15 psi. The catalyst was filtered off and the solvent evaporated. The residue was purified by silica gel flash chromatography (eluent: DCM/MeOH, 98/2) then by preparative HPLC (CH₃CN/H₂O without TFA), to afford the title compound (37 mg, 0.063 mmol, 25% yield).

¹H NMR (300 MHz, DMSO-d₆) ppm 7.27 - 7.32 (m, 2 H), 7.25 (dd, 1 H), 6.89 - 7.01 (m, 2 H), 6.28 (dd, 1 H), 6.09 (s, 1 H), 5.99 (dd, 1 H), 5.50 - 5.77 (m, 1 H), 5.48 (dd, 1 H), 5.20 (dd, 1 H), 5.04 (dd, 1 H), 4.12 - 4.26 (m, 1 H), 4.05 (t, 1 H), 3.62 (td, 1 H), 2.82 (dd, 1 H), 2.55 - 2.69 (m, 1 H), 2.18 - 2.26 (m, 1 H), 2.04 - 2.18 (m, 1 H), 1.84 - 2.04 (m, 2 H), 1.63 - 1.80 (m, 1 H), 1.51 - 1.61 (m, 2 H), 1.51 (s, 3 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 1.01 (s, 3 H)

LC-MS (ESI POS): 588.23 (MH⁺)

$$[\alpha]_D^{25} = + 48.4 \text{ (c 0.2, DCM)}$$

Legend

* NMR

s = singlet

d = doublet

25 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

5 THE INVENTION

In vivo studies

Example 27

Lipopolysaccharide (LPS)-induced lung neutrophilia

The potency and duration of action of the compounds described in the
10 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
15 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 μ moles/Kg of body weight) were
administered intratracheally as suspension (0.2%Tween 80 in NaCl 0.9%)
20 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
25 comprised between 0.05 and 0.16 μ moles/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 28

5 **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
10 developed by DiscoverRx (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
15 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 DiscoverRx assay uses EFC of b-galactosidase (b-gal) as an indicator of GR-translocation in engineered CHO-K1 biosensor cells. The
20 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
25 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% CO₂ 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).

5 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
10 at 37°C for two hours. Detection was made by adding the detection buffer from the kit supplied by DiscoverX and incubating at room temperature 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
15 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 0.35 nM and 10 nM.

Example 29

Inhibition of LPS-induced nitric oxide production in RAW 264.7 20 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)
25 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.

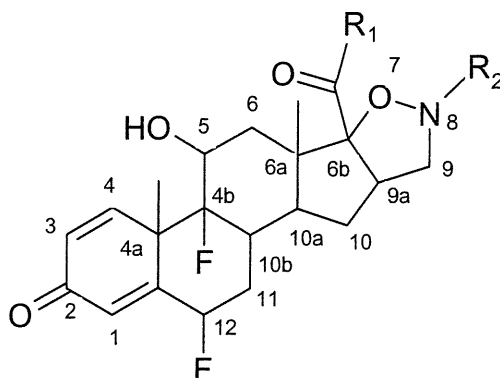
Cells were grown in a culture medium (RPMI supplemented with

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
5 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).

10 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 0.06 and 5.3 nM.

CLAIMS

1. A compound of general formula (IN)



(IN)

wherein

- R_1 is $-(CH_2)_n-Z-(CH_2)_{n'}-R_3$ wherein n is zero and n' is 1;

- Z is a single bond;

- R_3 is $-OH$;

- R_2 is $-(CH_2)_mR_6$, wherein R_6 is phenyl optionally substituted by one or more substituents selected from the group consisting of halogen, CN, $CONH_2$, $NHC(O)H$, linear or branched (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonyl, linear or branched (C_1-C_6) haloalkyl, linear or branched (C_1-C_6) haloalkoxy, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkoxysulfonyl, (C_1-C_6) haloalkylsulfonyloxy, (C_3-C_8) cycloalkyl, (C_3-C_6) heterocycloalkyl, aminosulfonyl;

m is 0;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, which is:

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

- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-chloro-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 5 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-p-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-m-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 10 (4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(4-fluoro-phenyl)-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 15 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Chloro-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-trifluoromethyl-phenyl)-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 20 (4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-8-(3-fluoro-phenyl)-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 25 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-

- hydroxy-acetyl)-4a,6a-dimethyl-8-o-tolyl-4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- (4aS,4bR,5S,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-3-methyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-((S)-2-hydroxy-acetyl)-4a,6a-dimethyl-
- 5 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Chloro-3-trifluoromethyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-
- 10 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3,4-Dichloro-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-
- 15 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Bromo-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-
- 20 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- 4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzamide;
- (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(4-trifluoromethoxy-phenyl)-
- 25 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;
- Methanesulfonic acid 4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-

2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-phenyl ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Cyclohexyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-

5 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzoic acid methyl
10 ester;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-8-(4-methanesulfonyl-phenyl)-4a,6a-dimethyl-

4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

15 3-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzonitrile;

4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-

20 tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-benzene sulfonamide;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-Cyclopropyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-

4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

25 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(4-tert-Butyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-

4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

N-{4-[(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,6b,9,9a,10,10a,10b,11,12-

5 tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-8-yl]-phenyl}-formamide;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-trifluoromethyl-phenyl)-

4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

10 (4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-4b,12-Difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-8-(3-trifluoromethoxy-phenyl)-

4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Bromo-phenyl)-4b,12-difluoro-5-

15 hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-

4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

(4aS,4bR,5S,6aS,6bR,9aS,10aS,10bS,12S)-8-(3-Cyclopropyl-phenyl)-4b,12-difluoro-5-hydroxy-6b-(2-hydroxy-acetyl)-4a,6a-dimethyl-

20 4a,4b,5,6,6a,6b,8,9,9a,10,10a,10b,11,12-tetradecahydro-7-oxa-8-aza-pentaleno[2,1-a]phenanthren-2-one;

or pharmaceutically acceptable salts thereof.

3. A pharmaceutical composition comprising a compound as defined in anyone of the claims 1 or 2, together with one or more pharmaceutically acceptable carriers
25 and/or excipients.

4. A combination of a compound as defined in anyone of the claims 1 or 2 with one or more active ingredients selected from the classes of beta2-agonists,

antimuscarinic agents, corticosteroids, 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) and
5 mucus regulators.

5. A compound as defined in anyone of claims 1 or 2, for use as a medicament.

6. A compound as defined in anyone of claims 1 or 2, for use in the prevention and/or treatment of a disease of the respiratory tract characterized by airway obstruction.

10 7. A compound as defined in anyone of claims 1 or 2 for use in the prevention and treatment of a disease of the respiratory tract according to claim 6, wherein the disease is asthma or COPD.

8. A device comprising the pharmaceutical composition according to claim 3, which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler or
15 soft mist nebulizer.