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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 May 2007 (24.05.2007)

PCT

(10) International Publication Number
WO 2007/057152 A1

(51) International Patent Classification:
C07J 3/00 (2006.01) *A61P 5/44* (2006.01)
A61K 31/56 (2006.01)

(21) International Application Number:
PCT/EP2006/010894

(22) International Filing Date:
13 November 2006 (13.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0523251.7 15 November 2005 (15.11.2005) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BIGGADIKE, Keith** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **NEEDHAM, Deborah** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: **PRITCHARD, Judith**; GlaxoSmithKline, Corporate Intellectual Property, (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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

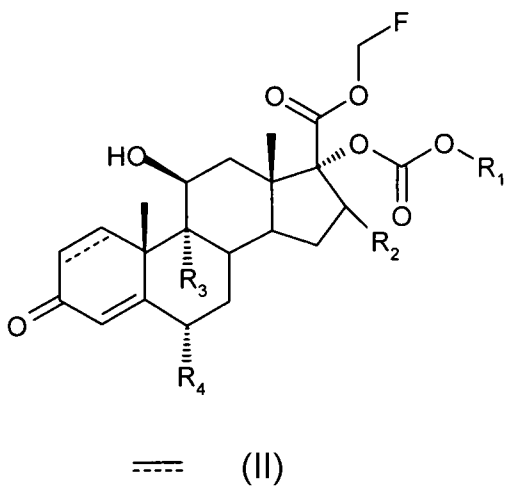
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 17.BETA.-FLUOROMETHOXYCARBONYL-ANDROST-4-EN-3-ONE COMPOUNDS WITH A 17.ALPHA.-CARBONATE SUBSTITUENT



(I)

(II)

(57) Abstract: The present invention is directed to compounds of formula (I) wherein R_1 represents C_4-C_7 branched chain alkyl, C_3-C_8 cycloalkyl optionally substituted by one or more groups independently selected from C_1-C_3 alkyl and methoxy, C_4-C_6 cycloalkylmethyl wherein the methyl group is optionally substituted by a group selected from methyl or ethyl, or a bicycloalkyl group optionally substituted by one or more methyl groups; R_2 represents hydrogen, a methyl group, which may be in either the α or β configuration, or a methylene group; R_3 and R_4 are the same or a different group and each independently represents hydrogen, halogen or a methyl group; and formula (II) represents a single or a double bond; physiologically acceptable solvates thereof, pharmaceutical compositions comprising the compounds, the use of the compounds for the manufacture of medicaments particularly for the treatment of inflammatory and/or allergic conditions, processes for the preparation of the compounds, and chemical intermediates in the processes for the manufacture of the compounds.

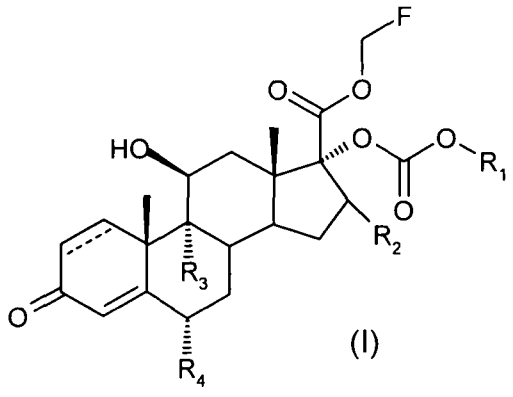
WO 2007/057152 A1

17.BETA.-FLUOROMETHOXYCARBONYL-ANDROST-4-EN-3-ONE COMPOUNDS WITH A 17.ALPHA.-CARBONATE SUBSTITUENT

The present invention relates to compounds which are glucocorticoid receptor agonists of the androstane series and to processes for their preparation. The present invention also relates to pharmaceutical formulations containing the compounds and to therapeutic uses thereof, particularly for the treatment of inflammatory and allergic conditions.

Glucocorticosteroids which have anti-inflammatory properties are known and are widely used for the treatment of inflammatory disorders or diseases such as asthma and rhinitis. Androstane 17α-carbonate compounds said to have anti-inflammatory activity are disclosed in U.S. patent 4,996,335. Drugs of Today 2000, 36(5), 313-320, discloses loteprednol etabonate for the treatment of allergic diseases of the airways. We have identified a novel series of androstane 17α-carbonate derivatives.

Thus, according to one aspect of the invention, there is provided a compound of formula (I)



(I)

wherein

R_1 represents C_4-C_7 branched chain alkyl,

C_3-C_8 cycloalkyl optionally substituted by one or more groups independently selected from C_1-C_3 alkyl and methoxy,

C_4-C_6 cycloalkylmethyl optionally substituted by one or more groups selected from methyl or ethyl,

or a bicycloalkyl group optionally substituted by one or more methyl groups;

R_2 represents hydrogen, a methyl group, which may be in either the α or β configuration, or a methylene group;

R_3 and R_4 are the same or a different group and each independently represents hydrogen, halogen or a methyl group;

and ⎓ represents a single or a double bond;

or a physiologically acceptable solvate thereof.

Examples of solvates include hydrates.

References hereinafter to a compound according to the invention includes both compounds of formula (I) and solvates thereof.

In one embodiment R_1 represents C_4-C_6 branched chain alkyl.

Examples of C_4-C_6 branched alkyl groups which R_1 may represent include a 1,1-dimethylethyl, 1,1-dimethylpropyl, 2-ethylbutyl, 1-ethyl-2-methylpropyl, 1, 2-dimethylpropyl or a 1,2,2-trimethylpropyl Isomer A group.

In one embodiment R_1 represents cyclohexyl optionally substituted by one or more groups independently selected from C_1-C_3 alkyl and methoxy.

In a further embodiment R_1 represents cyclohexyl optionally substituted by one or more groups independently selected from methyl and methoxy.

Examples of cyclohexyl groups which R_1 may represent include a (1*R*, 2*R*)-2-(methyloxy)cyclohexyl, (1*S*, 2*S*)-2-(methyloxy)cyclohexyl or a 3, 3-dimethylcyclohexyl Isomer A group.

In one embodiment R_1 represents cyclopentylmethyl wherein the methyl group is optionally substituted by a group selected from methyl or ethyl.

Examples of optionally substituted cyclopentylmethyl groups which R_1 may represent include a cyclopentylmethyl or a 1-cyclopentylethyl Isomer A group.

In one embodiment R_1 represents a bicycloalkyl group optionally substituted by one or more methyl groups.

Examples of bicycloalkyl groups which R_1 may represent include 1*RS*,2*RS*,4*SR* – bicyclo[2.2.1]hept-2-yl Isomer B, 1*RS*,2*SR*,4*SR* bicyclo [2.2.1]hept-2-yl or a (1*R*, 2*R*, 4*S*)-3, 3-dimethylbicyclo{2.2.1]hept-2-yl group.

In one embodiment R_2 represents a methyl group. In a further embodiment R_2 represents methyl in the α-configuration.

In one embodiment R_3 and R_4, which can be the same or different, each represents hydrogen, methyl, fluorine or chlorine, for example hydrogen or fluorine. In one embodiment R_3 and R_4 are both fluorine.

In one embodiment represents a double bond.

It is to be understood that the present invention covers all combinations of groups referred to hereinabove.

Compounds of formula (I) include:

Fluoromethyl(6α,11β,16α,17α)-17-({[(1,1-dimethylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[2-methyl-1-(1-methylethyl)propyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(2-ethylbutyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*)-2-methylcyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*)-2-methylcyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[4-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*S*,2*S*,4*R*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*R*,2*R*,4*S*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-{[(cycloheptyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-{[(cyclooctyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*S*,3*R*,5*S*)-3,5-dimethylcyclohexyl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*R*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*S*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1-propylbutyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(2,2,3,3-tetramethylcyclopropyl)methyl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[1-(1-methylethyl)butyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(2,2,3,3-tetramethylcyclopropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-{[(cyclopentyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(*cis*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(*trans*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate; and

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate.

In a further embodiment compounds of formula (I) include:

Fluoromethyl(6α,11β,16α,17α)-17-({[(1,1-dimethylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(2-ethylbutyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer B;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*R*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*S*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate Isomer A; and
Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate.

In a further embodiment compounds include:

Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer B;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*R*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*S*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate Isomer A; and Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate.

The compounds of formula (I) have potentially beneficial anti-inflammatory or anti-allergic effects, particularly upon topical administration, demonstrated by, for example, their ability to bind to the glucocorticoid receptor and to illicit a response via that receptor. Hence, the compounds of formula (I) are potentially useful in the treatment of inflammatory and/or allergic disorders.

Examples of disease states in which the compounds of the invention may have utility include skin diseases such as eczema, psoriasis, allergic dermatitis neurodermatitis, pruritis and hypersensitivity reactions; inflammatory conditions of the nose, throat or lungs such as asthma (including allergen-induced asthmatic reactions), rhinitis (including hayfever), nasal polyps, chronic obstructive pulmonary disease, interstitial lung disease, and fibrosis; inflammatory bowel conditions such as ulcerative colitis and Crohn's disease; and auto-immune diseases such as rheumatoid arthritis.

Compounds of the invention may also have use in the treatment of conjunctiva and conjunctivitis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) may be useful in human or veterinary medicine, in particular as anti-inflammatory and anti-allergic agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable solvate thereof for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory and/or allergic conditions.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable solvate thereof for the

manufacture of a medicament for the treatment of patients with inflammatory and/or allergic conditions.

In a further or alternative aspect, there is provided a method for the treatment of a human or animal subject with an inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or physiologically acceptable solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising a compound of formula (I) or physiologically acceptable solvate thereof together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.

Further, there is provided a process for the preparation of such pharmaceutical compositions which comprises mixing the ingredients.

The compounds according to the invention may, for example, be formulated for nasal, oral, buccal, sublingual, parenteral, local or rectal administration, especially local administration.

Local administration as used herein, includes administration by insufflation and inhalation. Examples of various types of preparation for local administration include ointments, lotions, creams, gels, foams, preparations for delivery by transdermal patches, powders, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops), solutions/suspensions for nebulisation, suppositories, pessaries, retention enemas and chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) or liposome or microencapsulation preparations.

Ointments, creams and gels, may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agent and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a solvent such as polyethylene glycol. Thickening agents and gelling agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol,

polyethylene glycols, woolfat, beeswax, carboxypolymethylene and cellulose derivatives, and/or glyceryl monostearate and/or non-ionic emulsifying agents.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents, suspending agents or preservatives.

Spray compositions may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain a compound of formula (I) and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. The aerosol composition may optionally contain additional formulation excipients well known in the art such as surfactants e.g. oleic acid, sorbitan trioleate or lecithin and cosolvents e.g. ethanol.

Advantageously, the formulations of the invention may be buffered by the addition of suitable buffering agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Suitable powders may be formulated with additional excipients, for example, cellobiose octo-acetate and magnesium stearate.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatine, may be formulated containing a powder mix for inhalation of a compound of the invention and a suitable powder base such as lactose or starch. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I). Alternatively, the compound of the invention may be presented without excipients such as lactose.

The proportion of the active compound of formula (I) in the local compositions according to the invention depends on the precise type of formulation to be prepared

but will generally be within the range of from 0.001 to 10% by weight. Generally, however for most types of preparations advantageously the proportion used will be within the range of from 0.005 to 1% and preferably 0.01 to 0.5%. However, in powders for inhalation or insufflation the proportion used will be within the range of from 0.1 to 5%.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains 20μg-2000μg, preferably about 20μg-500μg of a compound of formula (I). Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose with an aerosol will be within the range 100μg-10mg preferably, 200μg-2000μg. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double those with aerosol formulations.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may advantageously be used. Continuous or prolonged delivery may be achieved by an adhesive reservoir system.

For internal administration the compounds according to the invention may, for example, be formulated in conventional manner for oral, parenteral or rectal administration. Formulations for oral administration include syrups, elixirs, powders, granules, tablets and capsules which typically contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, wetting agents, suspending agents, emulsifying agents, preservatives, buffer salts, flavouring, colouring and/or sweetening agents as appropriate. Dosage unit forms are, however, preferred as described below.

Preferred forms of preparation for internal administration are dosage unit forms i.e. tablets and capsules. Such dosage unit forms contain from 0.1mg to 20mg preferably from 2.5 to 10mg of the compounds of the invention.

The compounds according to the invention may in general be given by internal administration in cases where systemic adreno-cortical therapy is indicated.

In general terms preparations, for internal administration may contain from 0.05 to 10% of the active ingredient dependent upon the type of preparation involved. The

daily dose may vary from 0.1mg to 60mg, e.g. 5-30mg, dependent on the condition being treated, and the duration of treatment desired.

Slow release or enteric coated formulations may be advantageous, particularly for the treatment of inflammatory bowel disorders.

The compound and pharmaceutical compositions according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an $M_1/M_2/M_3$ receptor antagonist), β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example another corticosteroid or an NSAID), an anticholinergic agent, a β_2-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. On embodiment of the invention encompasses combinations comprising a compound of formula (I) or a pharmaceutically acceptable solvate or physiologically functional derivative thereof together with a β_2-adrenoreceptor agonist, and/or an anticholinergic, and/or a PDE-4 inhibitor, and/or antihistamine.

One embodiment of the invention encompasses combinations comprising one or two other therapeutic agents.

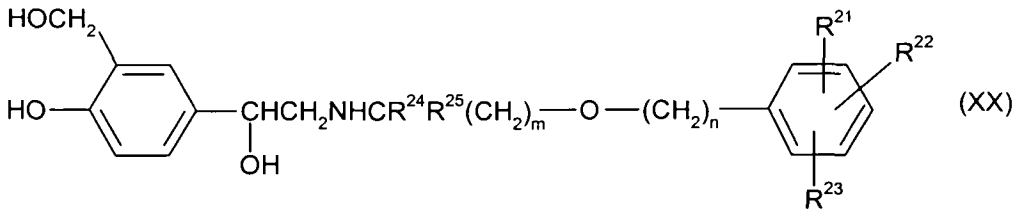
It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

In one embodiment, the invention encompasses a combination comprising a compound of the invention together with a β_2-adrenoreceptor agonist

Examples of β_2-adrenoreceptor agonists include salmeterol (e.g. as racemate or a single enantiomer such as the *R*-enantiomer), salbutamol (e.g. as racemate or a single enantiomer such as the *R*-enantiomer), formoterol (e.g. as racemate or a single diastereomer such as the *R,R*-diastereomer), salmefamol, fenoterol, carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerbuterol, reproterol, bambuterol, indacaterol, terbutaline and salts thereof, for example the xinafoate (1-hydroxy-2-naphthalenecarboxylate) salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. In one embodiment the β_2-adrenoreceptor agonists are long-acting β_2-adrenoreceptor agonists, for example compounds which provide effective bronchodilation for about 12 hours or longer.

Other β_2-adrenoreceptor agonists include those described in WO 02/066422, WO 02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO 2004/022547, WO 2004/037807, WO 2004/037773, WO 2004/037768, WO 2004/039762, WO 2004/039766, WO01/42193 and WO03/042160.

Other β_2-adrenoreceptor agonists include compounds of formula (XX):



(XX)

or a salt or solvate thereof, wherein:
m is an integer of from 2 to 8;
n is an integer of from 3 to 11,
with the proviso that m + n is 5 to 19,
R^{21} is $-XSO_2NR^{26}R^{27}$ wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;
R^{26} and R^{27} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{28}R^{29}$, phenyl, and phenyl (C_{1-4}alkyl)-,
or R^{26} and R^{27}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring, and R^{26} and R^{27} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{28}$, $-SO_2NR^{28}R^{29}$, $-CONR^{28}R^{29}$, $-NR^{28}C(O)R^{29}$, or a 5-, 6- or 7-membered heterocylic ring;

R^{28} and R^{29} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and
p is an integer of from 0 to 6, preferably from 0 to 4;
R^{22} and R^{23} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and
R^{24} and R^{25} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{24} and R^{25} is not more than 4.

Further examples of β_2-adrenoreceptor agonists include:
3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino) hexyl] oxy} butyl) benzenesulfonamide;
3-(3-{[7-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl) phenyl] ethyl}-amino) heptyl] oxy} propyl) benzenesulfonamide;
4-{(1R)-2-[(6-{2-[(2, 6-dichlorobenzyl) oxy] ethoxy} hexyl) amino]-1-hydroxyethyl}-2-(hydroxymethyl) phenol;
4-{(1R)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;
N-[2-hydroxyl-5-[(1*R*)-1-hydroxy-2-[[2-4-[[(2R)-2-hydroxy-2-phenylethyl]amino]phenyl]ethyl]amino]ethyl]phenyl]formamide;
N-2{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine; and
5-[(*R*)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one.

The β_2-adrenoreceptor agonist may be in the form of a salt formed with a pharmaceutically acceptable acid selected from sulphuric, hydrochloric, fumaric, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), cinnamic, substituted cinnamic, triphenylacetic, sulphamic, sulphanilic, naphthaleneacrylic, benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic and 4-phenylbenzoic acid.

Suitable anti-inflammatory agents include corticosteroids. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-

thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester (fluticasone furoate), 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid *S*-cyanomethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide (16α,17-[[(*R*)-cyclohexylmethylene]bis(oxy)]-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione), butixocort propionate, RPR-106541, and ST-126. One embodiment of the invention encompasses corticosteroids including fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3- tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid *S*-cyanomethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester. In one embodiment the corticosteroid is 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Non-steroidal compounds having glucocorticoid agonism that may posess selectivity for transrepression over transactivation and that may be useful in combination therapy include those covered in the following patents: WO03/082827, WO01/10143, WO98/54159, WO04/005229, WO04/009016, WO04/009017, WO04/018429, WO03/104195, WO03/082787, WO03/082280, WO03/059899, WO03/101932, WO02/02565, WO01/16128, WO00/66590, WO03/086294, WO04/026248, WO03/061651, WO03/08277.

Examples of anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAID's).

Examples of NSAID's include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (eg. montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5-lipoxygenase inhibitors. In one embodiment an iNOS (inducible nitric oxide synthase inhibitor) is for oral administration. Examples of iNOS inhibitors include those disclosed in WO93/13055, WO98/30537, WO02/50021, WO95/34534 and WO99/62875. Examples CCR3 inhibitors include those disclosed in WO02/26722.

In one embodiment, the invention provides the use of the compounds of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor, for example in the case of a formulation adapted for inhalation. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family, such as PDE3 and PDE5, as well as PDE4.

Compounds of interest include *cis*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. Also, *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomilast) and its salts, esters, pro-drugs or physical forms, which is described in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference.

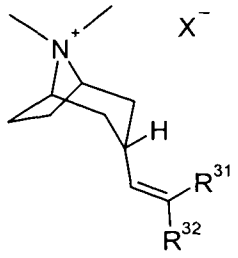
Other compounds of interest include AWD-12-281 from Elbion (Hofgen, N. *et al.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. *et al.* Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23,

Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. *et al.* J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Further compounds of interest are disclosed in the published international patent applications WO04/024728 (Glaxo Group Ltd), PCT/EP2003/014867 (Glaxo Group Ltd) and PCT/EP2004/005494 (Glaxo Group Ltd).

Examples of anticholinergic agents are those compounds that act as antagonists at the muscarinic receptors, in particular those compounds which are antagonists of the M_1 or M_3 receptors, dual antagonists of the M_1/M_3 or M_2/M_3, receptors or pan-antagonists of the $M_1/M_2/M_3$ receptors. Exemplary compounds for administration via inhalation include ipratropium (e.g. as the bromide, CAS 22254-24-6, sold under the name Atrovent), oxitropium (e.g. as the bromide, CAS 30286-75-0) and tiotropium (e.g. as the bromide, CAS 136310-93-5, sold under the name Spiriva). Also of interest are revatropate (e.g. as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO01/04118. Exemplary compounds for oral administration include pirenzepine (CAS 28797-61-7), darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (CAS 5633-20-5, sold under the name Ditropan), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (e.g. as the bromide, CAS 26095-59-0, sold under the name Spasmomen), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare).

Other anticholinergic agents include compounds of formula (XXI), which are disclosed in US patent application 60/487981:



(XXI)

in which the preferred orientation of the alkyl chain attached to the tropane ring is endo;

R^{31} and R^{32} are, independently, selected from the group consisting of straight or branched chain lower alkyl groups having preferably from 1 to 6 carbon atoms, cycloalkyl groups having from 5 to 6 carbon atoms, cycloalkyl-alkyl having 6 to 10 carbon atoms, 2-thienyl, 2-pyridyl, phenyl, phenyl substituted with an alkyl group having not in excess of 4 carbon atoms and phenyl substituted with an alkoxy group having not in excess of 4 carbon atoms;

X^- represents an anion associated with the positive charge of the N atom. X^- may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate, and toluene sulfonate,

including, for example:

(3-*endo*)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

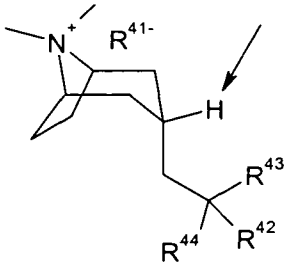
(3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane 4-methylbenzenesulfonate;

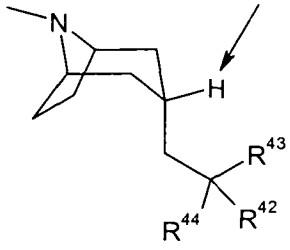
(3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-thienyl)ethenyl]-8-azoniabicyclo[3.2.1]octane bromide; *and/or*

(3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-pyridinyl)ethenyl]-8-azoniabicyclo[3.2.1]octane bromide.

Further anticholinergic agents include compounds of formula (XXII) or (XXIII), which are disclosed in US patent application 60/511009:



(XXII)



(XXIII)

wherein:

the H atom indicated is in the exo position;

R^{41} represents an anion associated with the positive charge of the N atom. R^{41} may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate and toluene sulfonate;

R^{42} and R^{43} are independently selected from the group consisting of straight or branched chain lower alkyl groups (having preferably from 1 to 6 carbon atoms), cycloalkyl groups (having from 5 to 6 carbon atoms), cycloalkyl-alkyl (having 6 to 10 carbon atoms), heterocycloalkyl (having 5 to 6 carbon atoms) and N or O as the heteroatom, heterocycloalkyl-alkyl (having 6 to10 carbon atoms) and N or O as the heteroatom, aryl, optionally substituted aryl, heteroaryl, and optionally substituted heteroaryl;

R^{44} is slected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-heteroaryl, $-OR^{45}$, $-CH_2OR^{45}$, $-CH_2OH$, $-CN$, $-CF_3$, $-CH_2O(CO)R^{46}$, $-CO_2R^{47}$, $-CH_2NH_2$, $-CH_2N(R^{47})SO_2R^{45}$, $-SO_2N(R^{47})(R^{48})$, $-CON(R^{47})(R^{48})$, $-CH_2N(R^{48})CO(R^{46})$, $-CH_2N(R^{48})SO_2(R^{46})$, $-CH_2N(R^{48})CO_2(R^{45})$, $-CH_2N(R^{48})CONH(R^{47})$;

R^{45} is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-heteroaryl;

R^{46} is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-heteroaryl;

R^{47} and R^{48} are, independently, selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl-aryl, and $(C_1\text{-}C_6)$alkyl-heteroaryl, including, for example:

(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;

(Endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;
N-Benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
1-Ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;
(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide;
[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide; and/or
(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

Further compounds include:
(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and/or
(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

Examples of antihistamines (also referred to as H1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H1-receptors, and are safe for human use. First generation antagonists, include derivatives of ethanolamines, ethylenediamines, and alkylamines, e.g diphenylhydramine, pyrilamine, clemastine, chloropheniramine. Second generation antagonists, which are non-sedating, include loratidine, desloratidine,terfenadine,astemizole,acrivastine, azelastine, levocetirizine fexofenadine and cetirizine.

In one embodiment of the invention the anti-histamines include loratidine, desloratidine, fexofenadine and cetirizine.

Further examples include, without limitation, amelexanox, astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, levocetirizine, efletirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine, particularly cetirizine, levocetirizine, efletirizine and fexofenadine. In a further embodiment the invention provides a combination comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof together with an H3 antagonist (and/or inverse agonist). Examples of H3 antagonists include, for example, those compounds disclosed in WO2004/035556 and in WO2006/045416. Other histamine receptor antagonists which may be used in combination with the compounds of the present invention include antagonists (and/or inverse agonists) of the H4 receptor, for example, the compounds disclosed in Jablonowski *et al.*, *J. Med. Chem.* 46:3957-3960 (2003).

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a β_2-adrenorecptor agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a β_2-adrenoreceptor agonist.

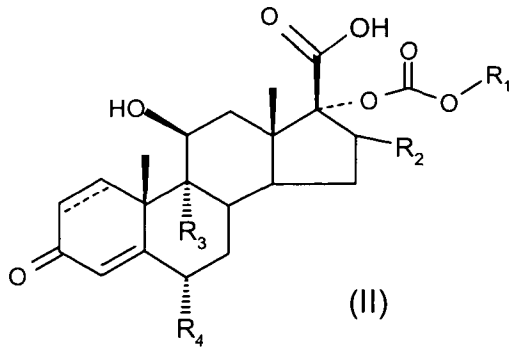
The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Preferably the individual compounds of such combinations may be administered simultaneously in a combined pharmaceutical combination. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

The compounds of formula (I) and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A process according to the invention for preparing a compound of formula (I) comprises reaction of a carboxylic acid of formula (II);



(II)

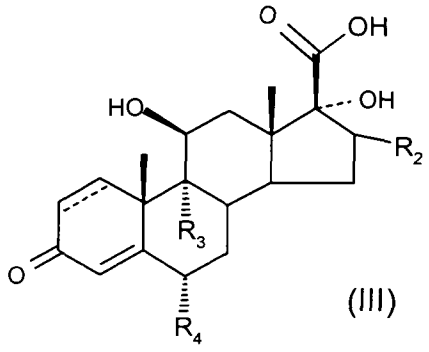
wherein R_1, R_2, R_3, R_4 and ⎓ are as defined above,
with a compound of formula L-CH_2-F wherein L represents a leaving group.

In this process the compound of formula (II) may be reacted with a compound of formula L-CH_2-F wherein L represents a leaving group such as halogen atom or a tosyl or mesyl group or the like, under standard conditions. For example the reaction may be performed in an inert polar organic solvent e.g. N,N-dimethylformamide in the presence of a base e.g. potassium carbonate, sodium carbonate.

Compounds of formula (II) may conveniently be employed as salts when such salts may be prepared in crystalline form, or as solvates.

Compounds of formula L-CH_2-F are either known or may be prepared by known methods.

Compounds of formula (II) may be prepared from the corresponding 17α-hydroxyl derivative of formula (III):



(III)

wherein R_2, R_3, R_4 and ⎓ *are as defined above,*

using for example, methodology similar to that described by G. H. Phillipps *et al.*, to prepare 17α carboxylate esters (Journal of Medicinal Chemistry, (1994), **37**, 3717-3729) and by Druzgala *et al.*, to prepare the 17α carbonate ester loteprednol etabonate (Journal of Steroid Chemistry and Molecular Biology, (1991), **38**, 149-154). The step typically comprises the reaction of the hydoxyacid (III) with a chloroformate R_1OCOCl in the presence of a mild base e.g. triethylamine in a suitable solvent e.g. dichloromethane. In the case of sterically encumbered R_1 groups anhydrides $(R_1OCO)_2O$ may be preferred to the chloroformates.

Generally the chloroformate or anhydride would be employed in at least 2 times molar quantity relative to the compound of formula (III). The second mole of chloroformate or anhydride tends to react with the carboxylic acid moiety in the compound of formula (III) and would need to be removed by reaction with an amine such as diethylamine or 1-methylpiperazine. The chloroformates are either commercially available or are readily prepared by standard methodology e.g. by reaction of the corresponding alcohol R_1OH with phosgene or more preferably triphosgene in the presence of a base e.g. pyridine in a suitable solvent e.g. dichloromethane.

More conveniently, reaction of the 17α-hydroxyl derivative (III) with the chloroformate R_1OCOCl or anhydride $(R_1OCO)_2O$ in pyridine solution often affords the 17α carbonate (II) directly.

Compounds of formula (III) are either known or may be prepared in accordance with procedures generally described by G. H. Phillipps *et al.*, Journal of Medicinal Chemistry, (1994), **37**, 3717-3729.

The following compounds of formula (II) are new and form an aspect of the invention:

(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid;

(6α,11β,16α,17α)-17-{[(cycloheptyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;

(6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;

(6α,11β,16α,17α)-17-{[(cyclooctyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-[({[(1*S*,3*R*,5*S*)-3,5-dimethylcyclohexyl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*RS*,2*RS*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-({[(1-cyclopentylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(2,2,3,3-tetramethylcyclopropyl)methyl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(2,2,3,3-tetramethylcyclopropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid; and
(6α,11β,16α,17α)-17-({[(1-ethyl-2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid.

Compounds of formula (I) and/or solvates thereof demonstrate agonism at the glucocorticoid receptor.

Compounds of formula (I) and/or solvates thereof may demonstrate good anti-inflammatory properties, with predictable pharmacokinetic and pharmacodynamic behaviour. They also may have an attractive side-effect profile, demonstrated, for example, by increased selectivity for the glucocorticoid receptor over the progesterone receptor and/or increased selectivity for glucocorticoid receptor mediated transrepression over transactivation and are likely to be compatible with a convenient regime of treatment in human patients.

The following non-limiting Examples illustrate the invention:

EXAMPLES

General

Abbreviations

DMSO	Dimethylsulphoxide
NMR	Nuclear magnetic resonance
LCMS	Liquid chromatography/mass spectrometry
MeCN	Acetonitrile

Chromatographic purification was performed using pre-packed Bond Elut silica gel cartridges available commercially from Varian.

NMR

^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker DPX 400 working at 400 MHz. The internal standard used was either tetramethylsilane or the residual protonated solvent at 2.50 ppm for DMSO-d_6.

Mass Directed Autopreparative HPLC

Autopreparative HPLC was carried out using a Waters 600 gradient pump, Waters 2767 inject/collector, Waters Reagent Manager, Micromass ZMD mass spectrometer, Gilson Aspec waste collector and Gilson 115 post-fraction UV detector. The column used was typically a Supelco LCABZ++ column with dimension of 20mm internal diameter by 100mm in length. The stationary phase particle size is 5µm. The flow rate was 20ml/min and the runtime was 15 minutes, which comprises a 10-minute gradient followed by a 5 minute column flush and re-equilibration step.

Solvent A: Aqueous solvent = water + 0.1% formic acid.

Solvent B: *Organic solvent = MeCN: water 95:5 +0.05% formic acid*

Specific gradients used were dependent upon the retention time in the analytical system. For 1.5-2.2 min, 0-30% B, 2.0-2.8 min, 5-30% B, 2.5-3.0 min, 15-55% B, 2.8-4.0 min, 30-80% B and 3.8-5.5 min, 50-90% B.

LCMS System
The LCMS system used was as follows:

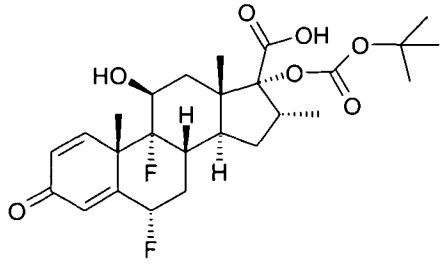
- Column: 3.3cm x 4.6mm ID, 3μm ABZ+PLUS from Supelco
- Flow Rate: 3ml/min
- Injection Volume: 5μl
- Temp: RT
- UV Detection Range: 215 to 330nm

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
B: 95% Acetonitrile + 0.05% Formic Acid

Gradient: Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

Intermediates

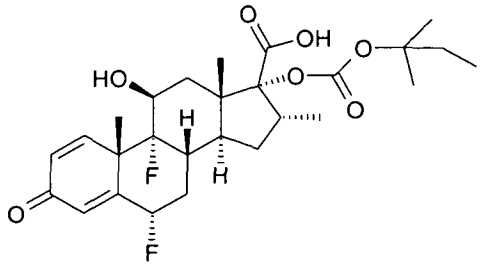
Intermediate 1: (6α,11β,16α,17α)-17-({[(1,1-Dimethylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



Bis(1,1-dimethylethyl) dicarbonate (121mg, 0.56mmol) was added to a stirred solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (G. H. Phillipps *et al.*, (1994) Journal of Medicinal

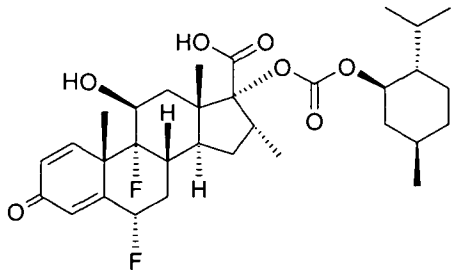
Chemistry, **37**, 3717-3729) (200mg, 0.5mmol) in pyridine (5ml) and the mixture stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the remaining residue stirred with 2M hydrochloric acid (20ml). The resulting precipitate was collected by filtration, washed with water and dried *in vacuo* at 60 °C to give the title compound: LCMS retention time 3.27 min.

Intermediate 2: (6α,11β,16α,17α)-17-({[(1,1-Dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



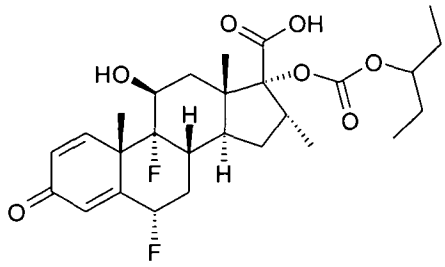
Prepared from bis(1,1-dimethylpropyl) dicarbonate using a method similar to that described for Intermediate 1. LCMS retention time 3.38 min.

Intermediate 3: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid



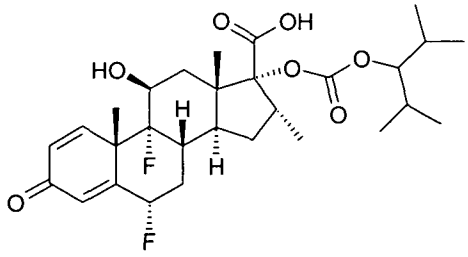
(1*R*)-(-)-Menthyl chloroformate (149 µl, 0.69mmol) was added to a stirred solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (250mg, 0.63mmol) in pyridine (5ml) and the mixture was stirred at room temperature for 3.5 hours. The reaction was poured into 6M hydrochloric acid (30ml) and the resulting precipitate was collected by filtration, washed with water (2 x 15ml) and dried *in vacuo* at 40 °C to give the title compound (385mg): LCMS retention time 3.92 min.

Intermediate 4: (6α,11β,16α,17α)-17-({[(1-Ethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



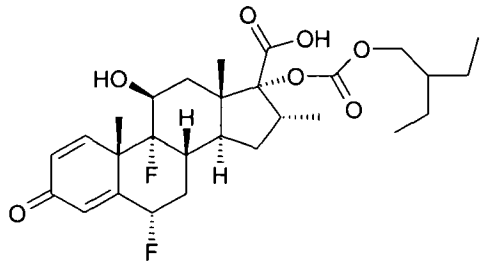
A solution of 3-pentanol (108 µl, 1mmol) and pyridine (81µl, 1mmol) in anhydrous dichloromethane (2ml) was added portionwise over 10 min to a stirred and cooled (ice) solution of triphosgene (98mg, 0.33mmol) in anhydrous dichloromethane (4ml) under nitrogen. After 1h, approximately half of the resulting chloroformate solution was added to a solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (200mg, 0.5mmol) in pyridine (2ml) and the mixture stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the remaining residue stirred with 2M hydrochloric acid. The resulting precipitate was collected by filtration and dried *in vacuo* to give the title compound as a white solid (246mg): LCMS retention time 3.42 min.

Intermediate 5: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-17-[({[2-methyl-1-(1-methylethyl)propyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid



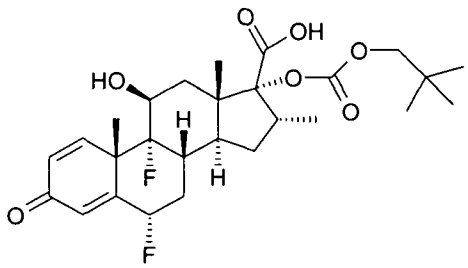
Prepared from 2, 4-dimethyl-3-pentanol using a method similar to that described for Intermediate 4. LCMS retention time 3.58 min.

Intermediate 6: (6α,11β,16α,17α)-17-({[(2-Ethylbutyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



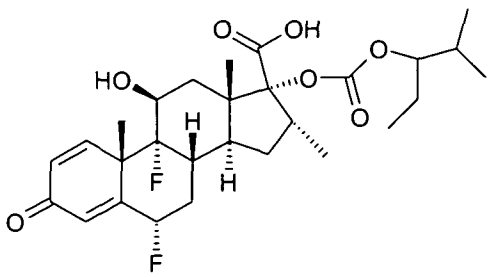
Prepared from 2-ethyl-1-butanol using a method similar to that described for Intermediate 4. LCMS retention time 3.63 min.

Intermediate 7: (6α,11β,16α,17α)-17-({[(2,2-Dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



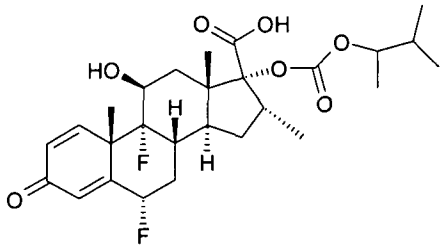
Prepared from 2,2-dimethyl-1-propanol using a method similar to that described for Intermediate 4. LCMS retention time 3.47 min.

Intermediate 8: (6α,11β,16α,17α)-17-({[(1-Ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



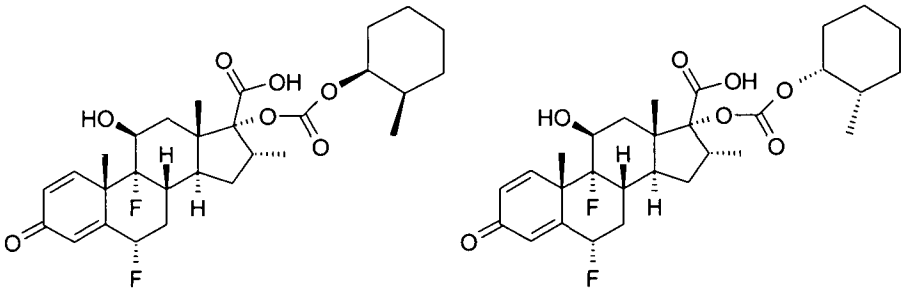
Prepared from 2-methyl-3-pentanol using a method similar to that described for Intermediate 4. LCMS retention time 3.54 min.

Intermediate 9: (6α,11β,16α,17α)-17-({[(1,2-Dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



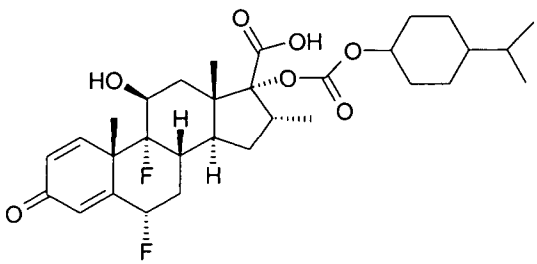
Prepared from 3-methyl-2-butanol using a method similar to that described for Intermediate 4. LCMS retention time 3.43 min.

Intermediate 10: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-17-[({[(1*SR*,2*RS*)-2-methylcyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid



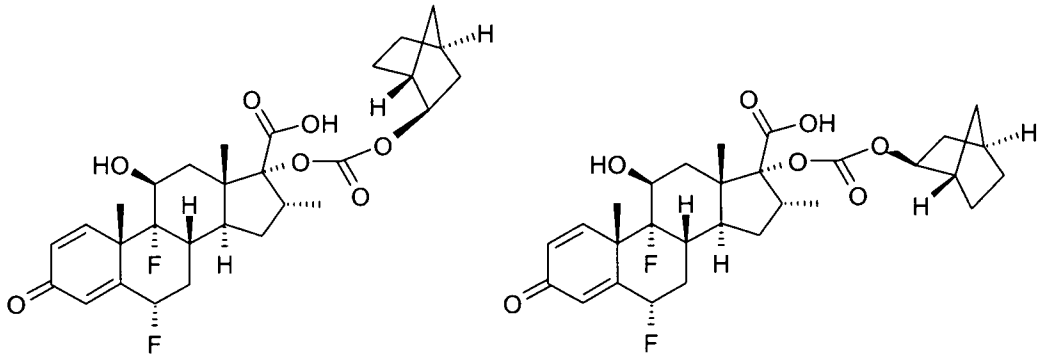
Prepared from racemic *cis*-2-methylcyclohexanol using a method similar to that described for Intermediate 4. LCMS retention time 3.59 min.

Intermediate 11: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-17-[({[4-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid



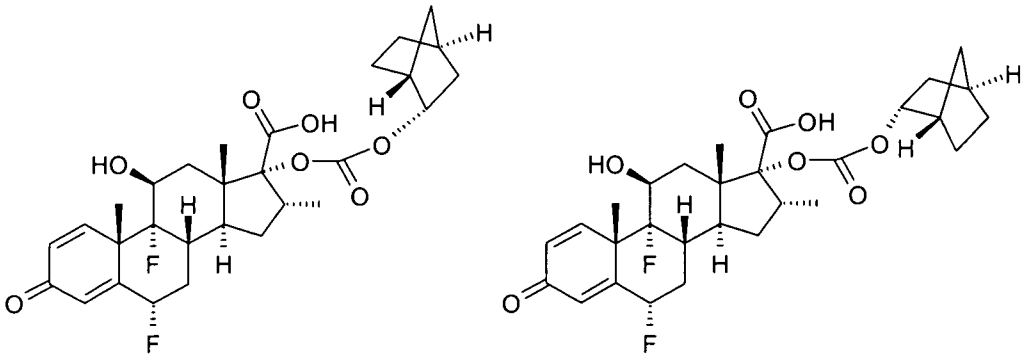
Prepared from *cis/trans*-4-(1-methylethyl)cyclohexanol using a method similar to that described for Intermediate 4. LCMS retention time 3.87 min.

Intermediate 12: (6α,11β,16α,17α)-17-({[(1*RS*,2*RS*,4*SR*)-Bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



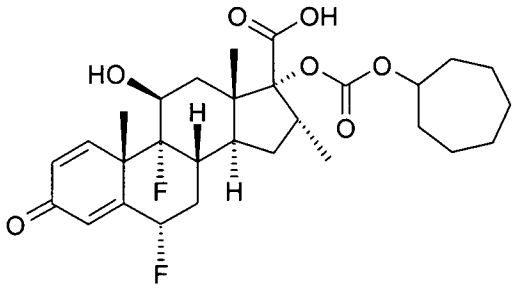
A solution of racemic *exo*-2-norborneol (113mg, 1mmol) and pyridine (81μl, 1mmol) in anhydrous dichloromethane (2ml) was added portionwise over 10 min to a stirred and cooled (ice) solution of triphosgene (98mg, 0.33mmol) in anhydrous dichloromethane (4ml) under nitrogen. After 1h, approximately half of the resulting chloroformate solution was added to a solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (200mg, 0.5mmol) in pyridine (2ml) and the mixture stirred at room temperature overnight. The remainder of the chloroformate solution was then added and after 2 hours the solvent was evaporated *in vacuo* and the remaining residue stirred with 2M hydrochloric acid. The resulting precipitate was collected by filtration and dried *in vacuo* to give the title compound as a white solid (254mg): LCMS retention time 3.54 min.

Intermediate 13: (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-Bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



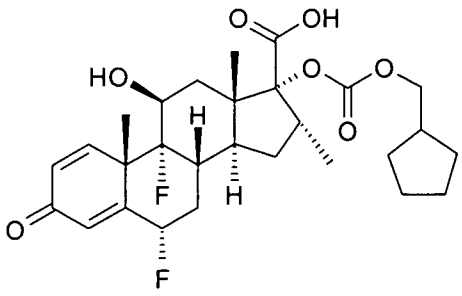
Prepared from racemic *endo*-2-norborneol using a method similar to that described for Intermediate 4. LCMS retention time 3.54 min.

Intermediate 14: (6α,11β,16α,17α)-17-{[(Cycloheptyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



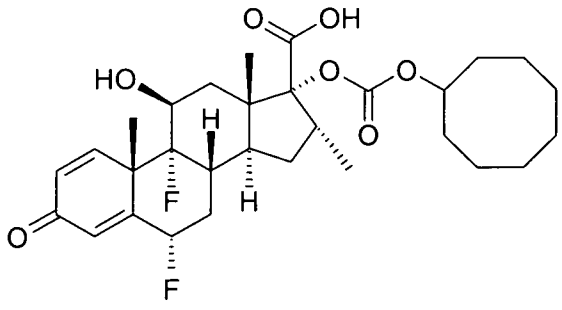
A solution of cycloheptanol (152µl, 1.26mmol) and pyridine (102µl, 1.26mmol) in anhydrous dichloromethane (2.5ml) was added portionwise over 10 min to a stirred and cooled (ice) solution of triphosgene (125mg, 0.42mmol) in anhydrous dichloromethane (6ml) under nitrogen. The ice bath was removed and after 1h approximately half of the resulting chloroformate solution was added to a solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (250mg, 0.63mmol) in pyridine (2ml) and the mixture stirred at room temperature for approximately 3 hours. The remainder of the chloroformate solution was then added and after overnight stirring the reaction was partitioned between 5M hydrochloric acid and ethyl acetate. The organic layer was separated, washed with 1:1 brine:water and evaporated *in vacuo* to give the title compound as a white solid (341mg): LCMS retention time 3.61 min.

Intermediate 15: (6α,11β,16α,17α)-17-({[(Cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



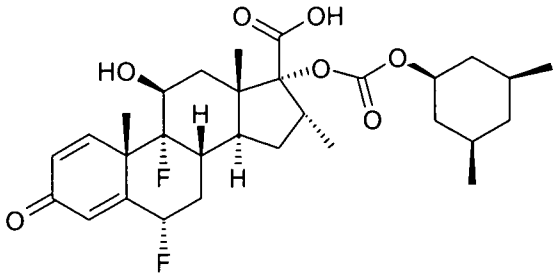
A solution of cyclopentanemethanol (108μl, 1mmol) and pyridine (81μl, 1mmol) in anhydrous dichloromethane (2ml) was added portionwise over 10 min to a stirred and cooled (ice) solution of triphosgene (98mg, 0.33mmol) in anhydrous dichloromethane (4ml) under nitrogen. After 1h, approximately half of the resulting chloroformate solution was added to a solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (200mg, 0.5mmol) in pyridine (2ml) and the mixture stirred at room temperature for 3 hours. The remainder of the chloroformate solution was then added and after overnight stirring the solvent was evaporated *in vacuo* and the remaining residue stirred with 2M hydrochloric acid. The resulting precipitate was collected by filtration and dried *in vacuo* to give the title compound as a white solid (205mg): LCMS retention time 3.52 min.

Intermediate 16: (6α,11β,16α,17α)-17-{[(Cyclooctyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



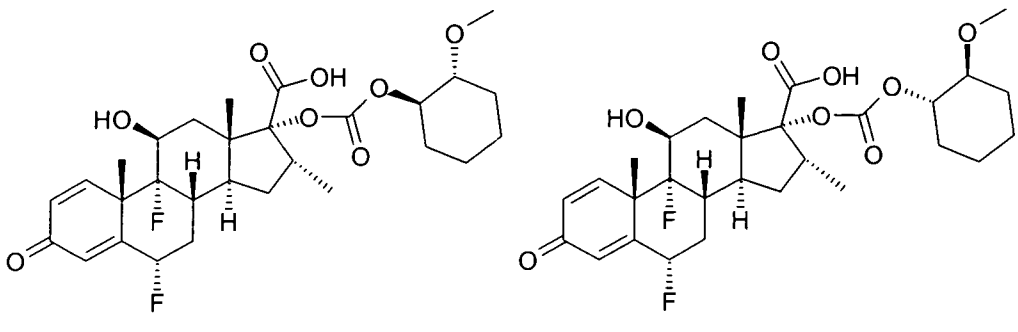
Prepared from cyclooctanol using a method similar to that described for Intermediate 15. LCMS retention time 3.71 min.

Intermediate 17: (6α,11β,16α,17α)-17-[({[(1*S*,3*R*,5*S*)-3,5-Dimethylcyclohexyl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



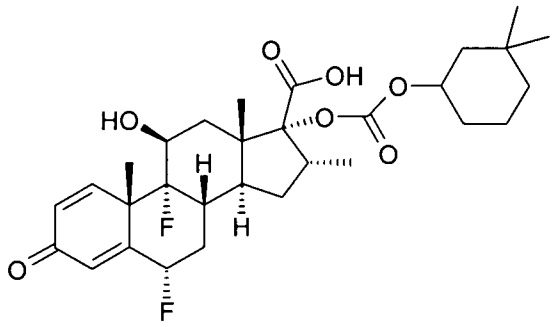
A solution of *cis,cis,cis*-3,5-dimethylcyclohexanol (144 µl, 1mmol) and pyridine (81µl, 1mmol) in anhydrous dichloromethane (2ml) was added portionwise over 10 min to a stirred and cooled (ice) solution of triphosgene (98mg, 0.33mmol) in anhydrous dichloromethane (4ml) under nitrogen. After 1h, approximately half of the resulting chloroformate solution was added to a solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (200mg, 0.5mmol) in pyridine (2ml) and the mixture stirred at room temperature overnight. The remainder of the chloroformate solution was then added, followed by addition of a further two equivalents (1mmol) of freshly prepared chloroformate solution. After 3 hours the solvent was evaporated *in vacuo* and the remaining residue stirred with 2M hydrochloric acid. The resulting precipitate was collected by filtration and dried *in vacuo* to give the title compound as a white solid (313mg): LCMS retention time 3.76 min.

Intermediate 18: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-17-[({[(1*RS*,2*RS*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid



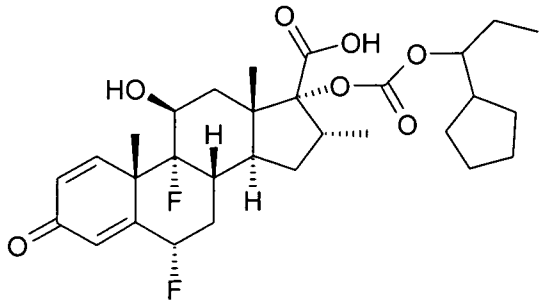
Prepared from racemic *trans*-2-methoxy-cyclohexanol (G. H. Posner et al., (1975) Tetrahedron Letters, **16**, Issue 42, 3589-3600) using a method similar to that described for Intermediate 12. LCMS retention time 3.28 min. and 3.36 min.

Intermediate 19: (6α,11β,16α,17α)-17-({[(3,3-Dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



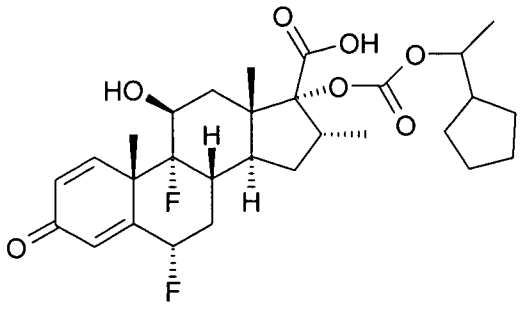
Prepared from 3,3-dimethylcyclohexanol using a method similar to that described for Intermediate 4. LCMS retention time 3.71 min.

Intermediate 20: (6α,11β,16α,17α)-17-({[(1-Cyclopentylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



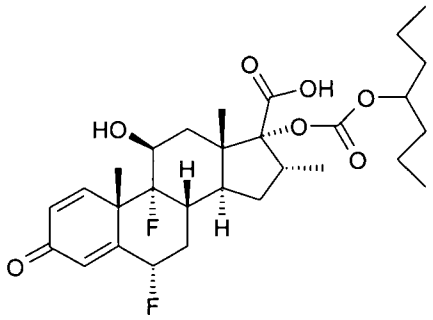
Prepared from 1-cyclopentyl-1-propanol using a method similar to that described for Intermediate 4. LCMS retention time 3.71 min. and 3.73 min.

Intermediate 21: (6α,11β,16α,17α)-17-({[(1-Cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



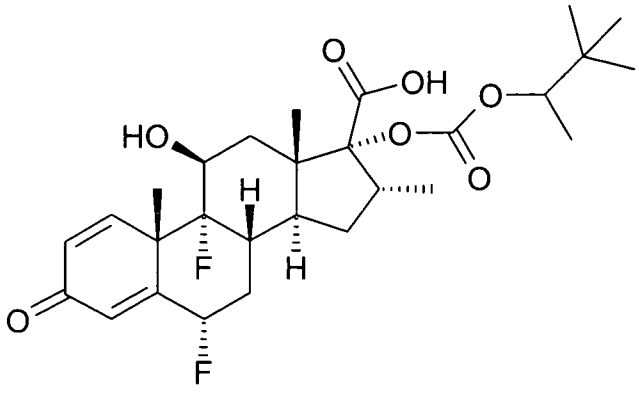
Prepared from 1-cyclopentylethanol using a method similar to that described for Intermediate 4. LCMS retention time 3.61 min. and 3.64 min.

Intermediate 22: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1-propylbutyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid



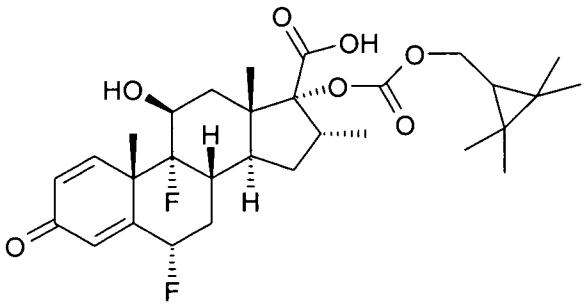
Prepared from 4-heptanol using a method similar to that described for Intermediate 4. LCMS retention time 3.65 min.

Intermediate 23: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid



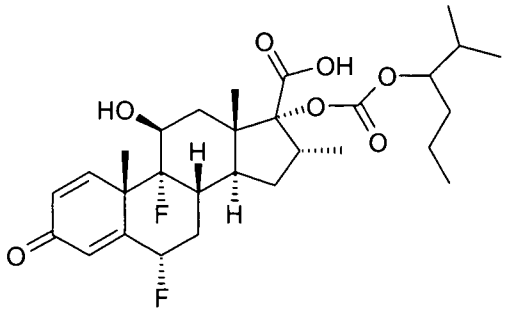
Prepared from 3,3-dimethyl-2-butanol using a method similar to that described for Intermediate 4. LCMS retention time 3.44 min. and 3.54 min.

Intermediate 24: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(2,2,3,3-tetramethylcyclopropyl)methyl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid



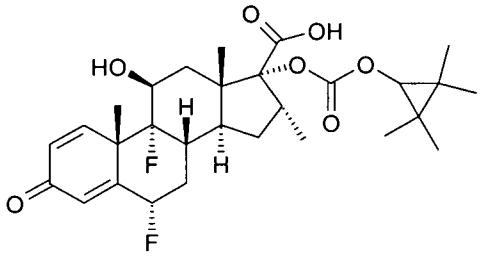
A solution of (2,2,3,3-tetramethylcyclopropyl) methanol (P. S. Wharton et al., (1965) Journal of Organic Chemistry, **30**, 1681-1684) (128mg, 1mmol) and pyridine (81μl, 1mmol) in anhydrous dichloromethane (2ml) was added to a stirred and cooled (ice) solution of triphosgene (98mg, 0.33mmol) in anhydrous dichloromethane (4ml) under nitrogen. After 1h, approximately half of the resulting chloroformate solution was added to a solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (200mg, 0.5mmol) in pyridine (2ml) and the mixture stirred at room temperature for 3 hours. The remainder of the chloroformate solution was then added and after overnight stirring a further two equivalents (1mmol) of freshly prepared chloroformate solution was added. After stirring for 72 hours the solvent was evaporated *in vacuo* and the remaining residue stirred with 2M hydrochloric acid. The resulting precipitate was collected by filtration to give the title compound as a white solid (180mg): LCMS retention time 3.68 min.

Intermediate 25: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-17-[({[1-(1-methylethyl)butyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid



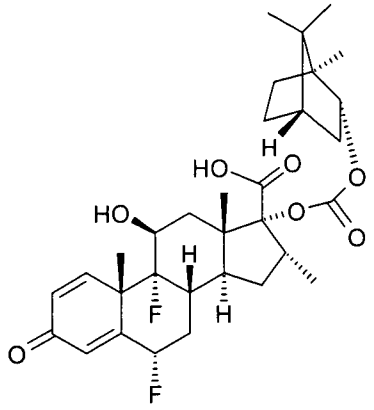
Prepared from 2-methyl-3-hexanol using a method similar to that described for Intermediate 4. LCMS retention time 3.66 min.

Intermediate 26: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(2,2,3,3-tetramethylcyclopropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid



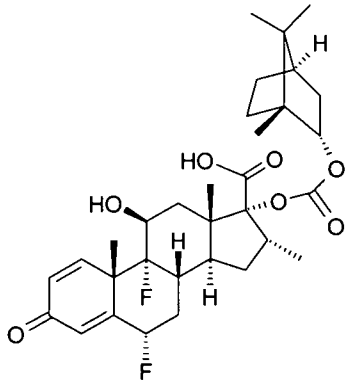
A solution of 2,2,3,3-tetramethylcyclopropanol (114mg, 1mmol) and pyridine (162µl, 2mmol) in anhydrous dichloromethane (2ml) was added portionwise over 5 min to a stirred and cooled (ice) solution of triphosgene (105mg, 0.35mmol) in anhydrous dichloromethane (3ml) under nitrogen. After 1h the resulting chloroformate solution was added to an ice cooled solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (200mg, 0.5mmol) in pyridine (2ml) and the mixture stirred at room temperature overnight. The reaction was then evaporated *in vacuo* and partitioned between 2M hydrochloric acid and ethyl acetate. The organic layer was separated, filtered through a hydrophobic frit and evaporated *in vacuo*. The crude product was purified on a 5g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient to give the title compound as a pale yellow foam (240mg): LCMS retention time 3.65 min.

Intermediate 27: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid



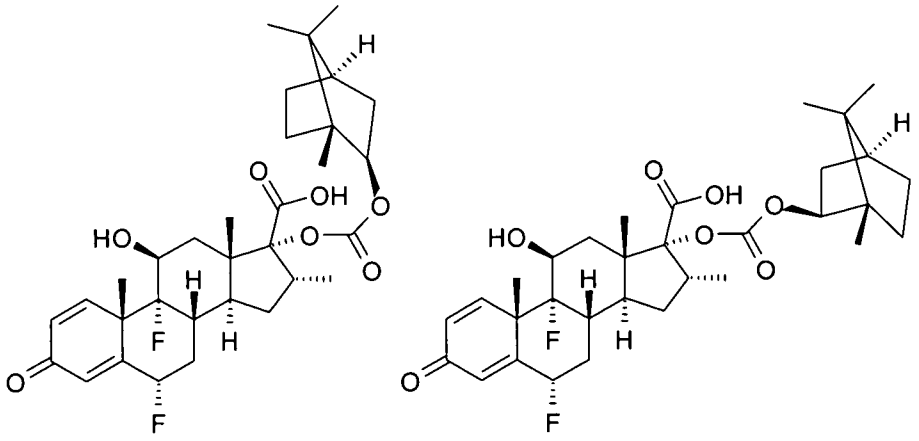
Prepared from (-) Borneol using a method similar to that described for Intermediate 4. LCMS retention time 3.87 min.

Intermediate 28: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid



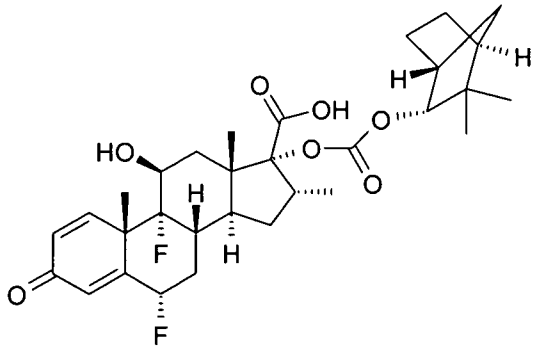
Prepared from (+) Borneol using a method similar to that described for Intermediate 4. LCMS retention time 3.81 min.

Intermediate 29: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*RS*,2*RS*,4*RS*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid



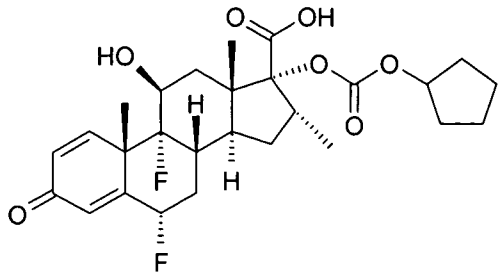
Prepared from (+/-) Isoborneol using a method similar to that described for Intermediate 12. LCMS retention time 3.85 min.

Intermediate 30: (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-Dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



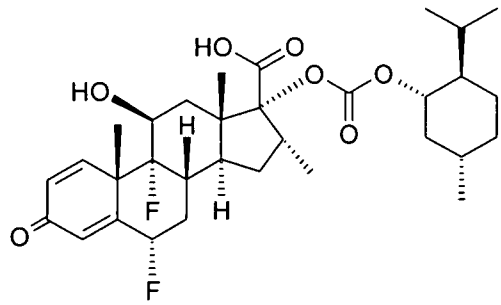
Prepared from (1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (P. Veeraraghavan Ramachandran et al., (1996) Journal of Organic Chemistry, **61**, Issue 1, 95-99) using a method similar to that described for Intermediate 4. LCMS retention time 3.84 min.

Intermediate 31: (6α,11β,16α,17α)-17-{[(Cyclopentyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



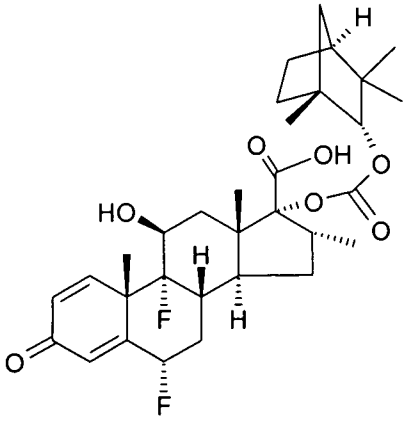
Cyclopentyl chloroformate (211mg, 1.44mmol) was added to a stirred solution of (6α,11β,16α,17α)-6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (500mg, 1.26mmol) in pyridine (5ml) and the mixture was stirred at room temperature under nitrogen for 12 hours. The reaction was poured into 6M hydrochloric acid (40ml) and the resulting precipitate extracted into ethyl acetate (2 x 40ml). The organic phase was separated, washed with 2M hydrochloric acid (2 x 50ml), dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the title compound (720mg): LCMS retention time 3.50 min.

Intermediate 32: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid



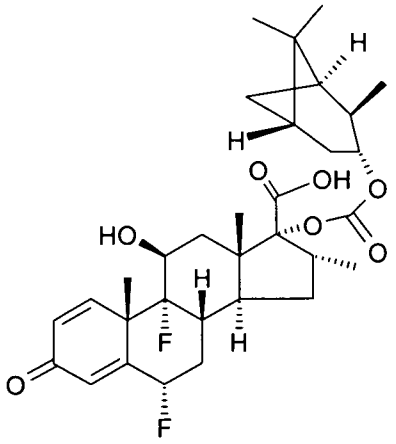
Prepared from (1*S*)-(+)-Menthyl chloroformate using a method similar to that described for Intermediate 3. LCMS retention time 3.89 min

Intermediate 33: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid



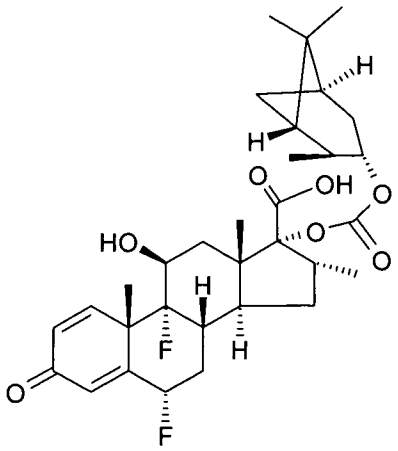
Prepared from (1*R*)-endo-(+)-fenchyl alcohol using a method similar to that described for Intermediate 4. LCMS retention time 3.87 min.

Intermediate 34: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid



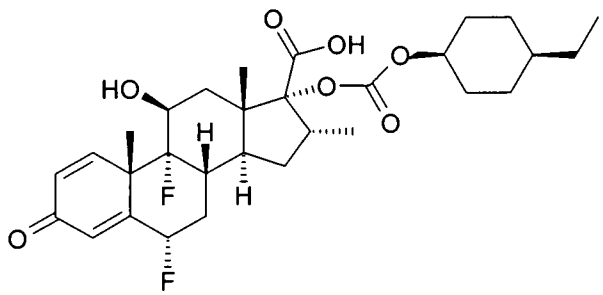
Prepared from (-)-isopinocampheol using a method similar to that described for Intermediate 4. LCMS retention time 3.87 min.

Intermediate 35: (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid



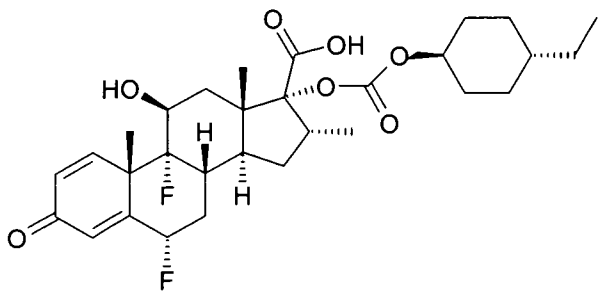
Prepared from (+)-isopinocampheol using a method similar to that described for Intermediate 4. LCMS retention time 3.86 min.

Intermediate 36: (6α,11β,16α,17α)-17-({[(*cis*-4-Ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



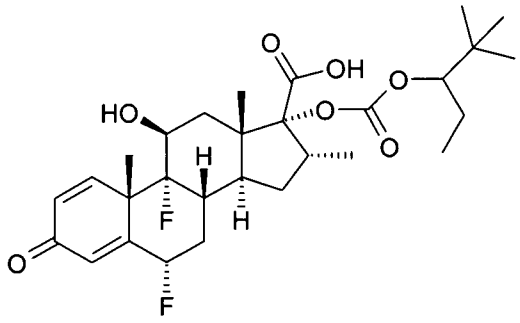
Prepared from *cis*-4-ethylcyclohexanol using a method similar to that described for Intermediate 4. LCMS retention time 3.76 min.

Intermediate 37: (6α,11β,16α,17α)-17-({[(*trans*-4-Ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



Prepared from *trans*-4-ethylcyclohexanol using a method similar to that described for Intermediate 4. LCMS retention time 3.78 min.

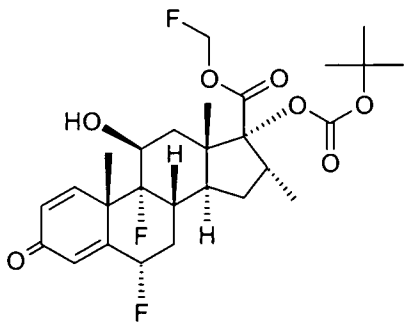
Intermediate 38: (6α,11β,16α,17α)-17-({[(1-Ethyl-2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid



Prepared from 2,2-dimethyl-3-pentanol using a method similar to that described for Intermediate 4. LCMS retention time 3.61 min.

Examples

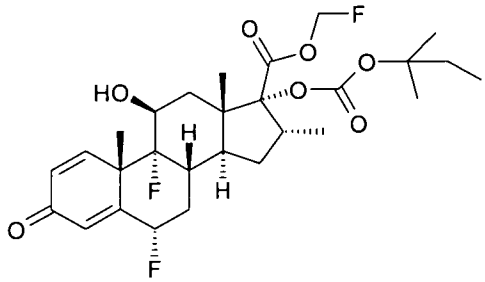
Example 1: Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Sodium carbonate (668mg, 6.3mmol) was added to a solution of (6α,11β,16α,17α)-17-({[(1,1-dimethylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 1) (250mg, 0.5mmol) in anhydrous N,N-dimethylformamide (5ml) and the mixture cooled to -20°C. Bromofluoromethane (96μl, 1.7mmol) was added and the reaction stirred at -30°C to -20°C for 2 hours before being allowed to warm to room temperature overnight. The

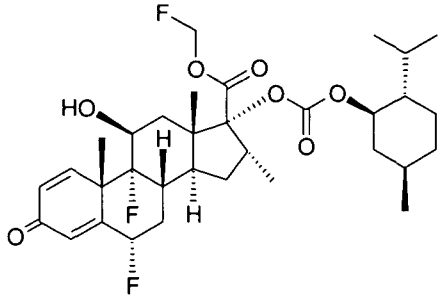
reaction was then treated with diethylamine (500µl, 7.56mmol) and added dropwise to 6M hydrochloric acid (30ml). The resulting precipitate was collected by filtration, washed with 2M hydrochloric acid (10ml) followed by water (3 x 10ml) and dried *in vacuo* at 50°C. The crude product was purified on a 10g silica Bond Elut cartridge using a 11-50% ethyl acetate in cyclohexane gradient to give the title compound (174mg): LCMS retention time 3.55 min, *m/z* 529 MH^+

Example 2: Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



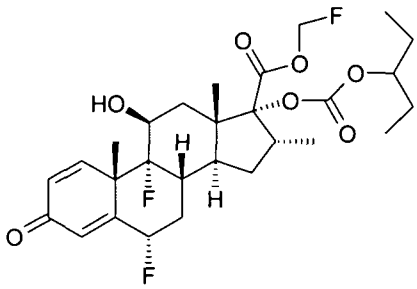
Sodium carbonate (208mg, 1.96mmol) was added to a stirred solution of (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 2) (100mg, 0.2mmol) in anhydrous N,N-dimethylformamide (3ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (30µl, 0.53mmol) was added and the reaction allowed to warm to room temperature overnight. The reaction was then treated with diethylamine (26µl, 0.34mmol) and added dropwise to 2M hydrochloric acid (20ml). The resulting precipitate was extracted into ethyl acetate which was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The crude product was purified on a 5g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient over 40 minutes to give the title compound (146mg): LCMS retention time 3.67 min, *m/z* 543 MH^+

Example 3: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate



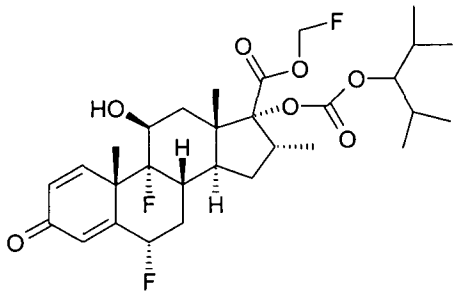
Example 3 was prepared from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 3) using a method similar to that described for Example 1. LCMS retention time 4.07 min, *m/z* 611 MH^+

Example 4: Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



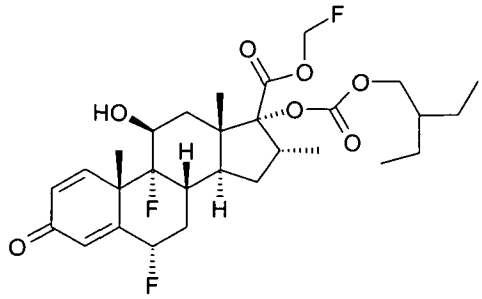
Sodium carbonate (311mg, 2.93mmol) was added to a stirred solution of (6α,11β,16α,17α)-17-({[(1-ethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 4) (150mg, 0.29mmol) in anhydrous N,N-dimethylformamide (3ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (45μl, 0.79mmol) was added and the reaction stirred at -25 to -35°C for 2 hours. Further bromofluoromethane (45μl, 0.79mmol) was added and the reaction allowed to warm to room temperature overnight. The reaction was then treated with diethylamine (87μl, 1.29mmol) and added dropwise to 2M hydrochloric acid. The resulting precipitate was extracted into ethyl acetate which was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The crude product was purified on a 5g silica Bond Elut cartridge eluted using 1:1 diethylether : cyclohexane to give the title compound (111mg): LCMS retention time 3.60 min, *m/z* 543 MH^+

Example 5: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[2-methyl-1-(1-methylethyl)propyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate



Example 5 was prepared from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[2-methyl-1-(1-methylethyl)propyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 5) using a method similar to that described for Example 4. The crude product was purified on a 5g silica Bond Elut cartridge using 1:1 diethylether : cyclohexane to give the title compound: LCMS retention time 3.76 min, *m/z* 571 MH^+

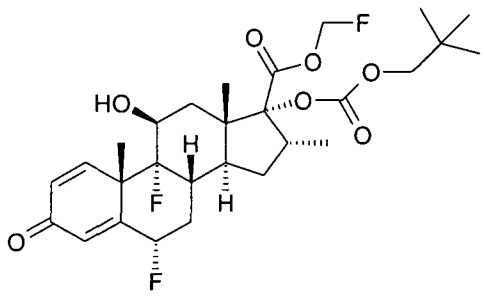
Example 6: Fluoromethyl (6α,11β,16α,17α)-17-({[(2-ethylbutyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Sodium carbonate (304mg, 2.86mmol) was added to a stirred solution of (6α,11β,16α,17α)-17-({[(2-ethylbutyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 6) (150mg, 0.29mmol) in anhydrous N,N-dimethylformamide (3ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (44μl, 0.77mmol) was added and the reaction stirred at -25 to -35°C for 2 hours followed by overnight at room temperature. Further

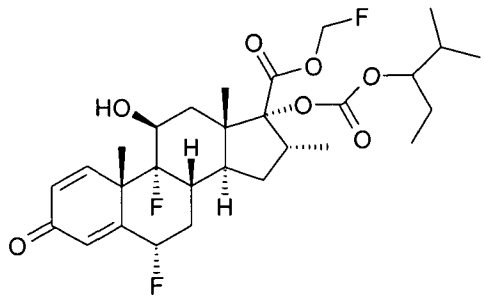
bromofluoromethane (22μl, 0.39mmol) was then added and the reaction stirred at room temperature for 2 hours. Again, further bromofluoromethane (22μl, 0.39mmol) was added and the reaction stirred at room temperature overnight. The reaction was then treated with diethylamine (85μl, 1.26mmol) and added dropwise to 2M hydrochloric acid (20ml). The resulting precipitate was extracted into ethyl acetate which was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The crude product was purified on a 10g silica Bond Elut cartridge eluted using a 0-100% diethylether in cyclohexane gradient over 40 minutes to give the title compound (70mg): LCMS retention time 3.78 min, *m/z* 557 MH^+

Example 7: Fluoromethyl (6α,11β,16α,17α)-17-({[(2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



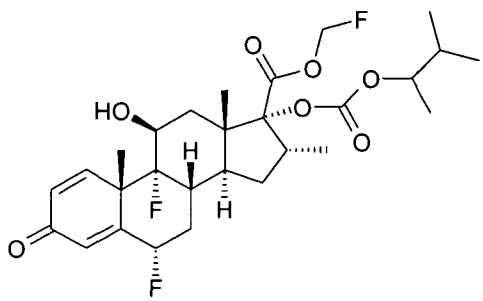
Example 7 was prepared from (6α,11β,16α,17α)-17-({[(2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 7) using a method similar to that described for Example 4. The crude product was purified on a 10g silica Bond Elut cartridge eluted using 0-100% diethylether in cyclohexane gradient over 40 minutes to give the title compound: LCMS retention time 3.61 min, *m/z* 543 MH^+

Example 8: Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



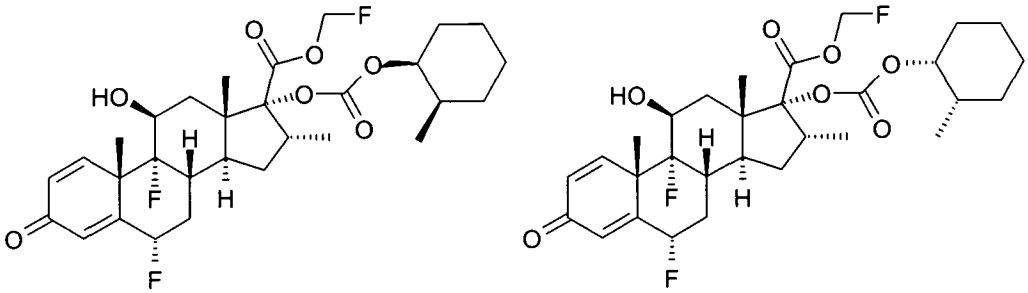
Sodium carbonate (304mg, 2.86mmol) was added to a stirred solution of (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 8) (150mg, 0.29mmol) in anhydrous N,N-dimethylformamide (3ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (44μl, 0.77mmol) was added and the reaction stirred at -25 to -35°C for 2 hours followed by overnight at room temperature. Further bromofluoromethane (22μl, 0.39mmol) was then added and the reaction stirred at room temperature overnight. The reaction was then treated with diethylamine (85μl, 1.26mmol) and added dropwise to 2M hydrochloric acid (20ml). The resulting precipitate was extracted into ethyl acetate which was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The crude product was purified on a 10g silica Bond Elut cartridge eluted using a 0-100% diethylether in cyclohexane gradient over 40 minutes to give the title compound as a mixture of diastereomers (86mg): LCMS retention time 3.67 min, *m/z* 557 MH^+

Example 9: Fluoromethyl (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 9 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 9) using a method similar to that described for Example 2. The crude product was purified on a 10g silica Bond Elut cartridge eluted using a 0-100% diethylether in cyclohexane gradient over 40 minutes to give the title compound: LCMS retention time 3.58 min, *m/z* 543 MH^+

Example 10: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*SR*,2*RS*)-2-methylcyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate



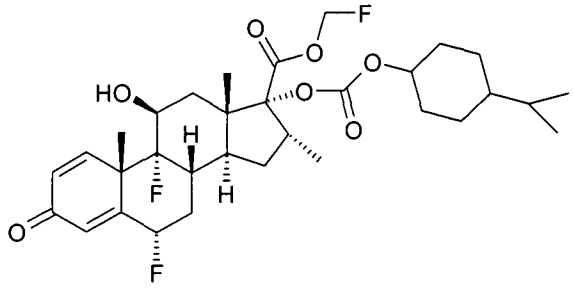
Sodium carbonate (297mg, 2.8mmol) was added to a stirred solution of (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*SR*,2*RS*)-2-methylcyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 10) (150mg, 0.28mmol) in anhydrous N,N-dimethylformamide (3ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (43μl, 0.76mmol) was added and the reaction stirred at -25 to -35°C for 2 hours. Further bromofluoromethane (43μl, 0.76mmol) was then added and the reaction stirred at room temperature overnight. The reaction was then treated with diethylamine (82μl, 1.23mmol) and added dropwise to 2M hydrochloric acid. The resulting precipitate was filtered and dried *in vacuo* to give the title compound as a mixture of diastereomers (94mg).

The diastereomers were then separated using normal phase HPLC to give:

Example 10A: LCMS retention time 3.80 min, *m/z* 569 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.85 (dd, 50.5, 2Hz) and δ 5.70 (dd, 50.5, 2Hz)

Example 10B: LCMS retention time 3.80 min, *m/z* 569 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.85 (dd, 50.5, 2Hz) and δ 5.74 (dd, 50.5, 2Hz)

Example 11: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[4-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate



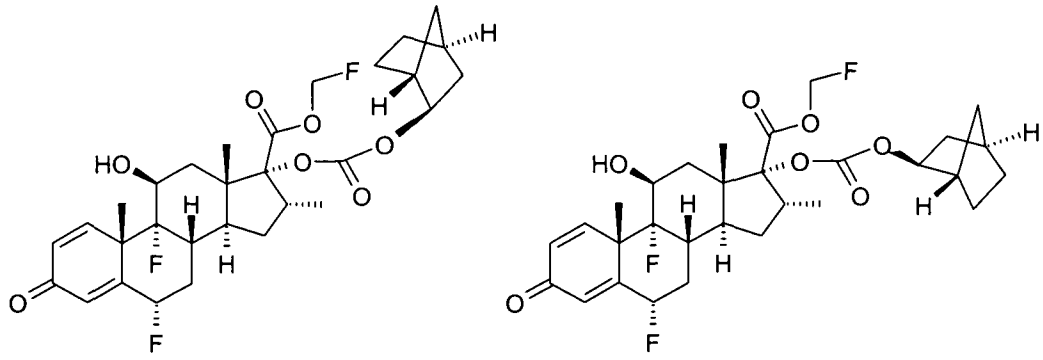
Sodium carbonate (188mg, 1.77mmol) was added to a stirred solution of (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[4-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 11) (100mg, 0.18mmol) in anhydrous N,N-dimethylformamide (3ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (27μl, 0.48mmol) was added and the reaction stirred at -25 to -35°C for 2.5 hours followed by overnight at room temperature. The reaction was then treated with diethylamine (20μl, 0.3mmol) and added dropwise to 2M hydrochloric acid. The resulting precipitate was filtered and dried *in vacuo* to give the title compound as a ca 4:1 mixture of diastereomers (39mg).

The diastereomers were then separated by reverse phase HPLC – isocratic conditions - eluting with 55% mobile phase B, run time 45min, flow rate 20ml/min.

Mobile phase A – water / 0.1% formic acid v/v
Mobile phase B - 95% aq Acetonitrile / 0.05% formic acid v/v

Example 11A: (minor isomer) LCMS retention time 3.90 min, *m/z* 597 MH^+
Example 11B: (major isomer) LCMS retention time 3.97 min, *m/z* 597 MH^+

Example 12: Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



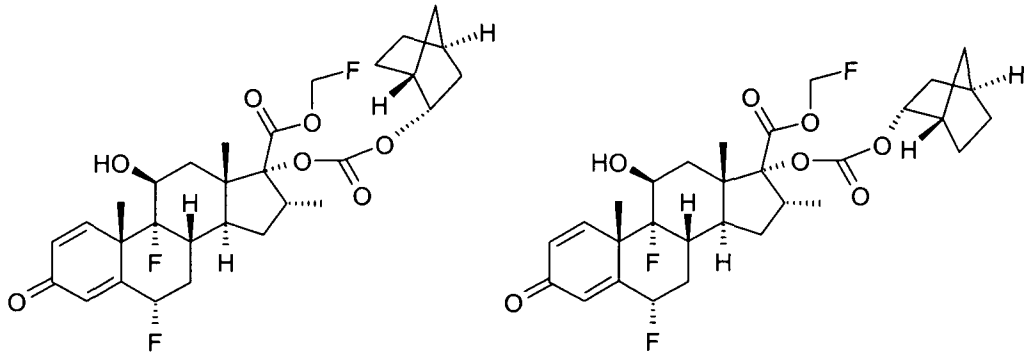
Example 12 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-17-({[(1*RS*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 12) using a method similar to that described for Example 10.

The diastereomers were then separated using a 2 x 25cm Chiralpak AD column eluting with 10% isopropyl alcohol in heptane with a flow rate of 20ml/min.

Example 12A: On analytical chiral HPLC (25 x 0.46cm Chiralpak AD column, 10% isopropyl alcohol in heptane with a flow rate of 1ml/min) showed a retention time 17.2min. LCMS retention time 3.74 min, *m/z* 567 MH^+

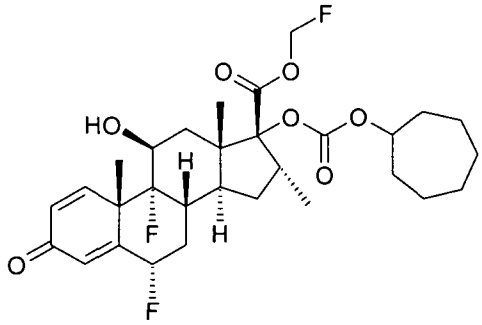
Example 12B: On analytical chiral HPLC (25 x 0.46cm Chiralpak AD column, 10% isopropyl alcohol in heptane with a flow rate of 1ml/min) showed a retention time 21.8min. LCMS retention time 3.73 min, *m/z* 567 MH^+

Example 13: Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 13 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 13) using a method similar to that described for Example 10. LCMS retention time 3.77 min, *m/z* 567 MH^+

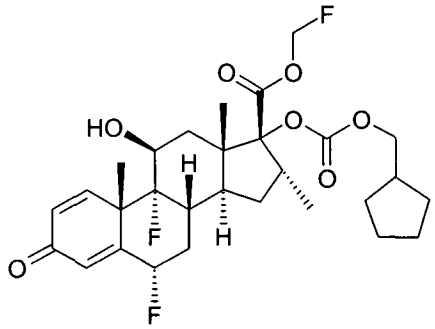
Example 14: Fluoromethyl (6α,11β,16α,17α)-17-{[(cycloheptyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Sodium carbonate (680mg, 6.4mmol) was added to a stirred solution of (6α,11β,16α,17α)-17-{[(cycloheptyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 14) (341mg, 0.64mmol) in anhydrous N,N-dimethylformamide (5ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (98μl, 1.73mmol) was added and the reaction stirred at -25 to -35°C for 1 hour. Further bromofluoromethane (98μl, 1.73mmol) was then added and the reaction stirred at -25 to -35°C for 5 hours. Again, further bromofluoromethane (98μl, 1.73mmol) was added to the reaction mixture which was stirred at room temperature for 72 hours. The reaction was then treated with diethylamine (470μl, 7.1mmol) and added dropwise to 5M hydrochloric acid. The resulting precipitate was

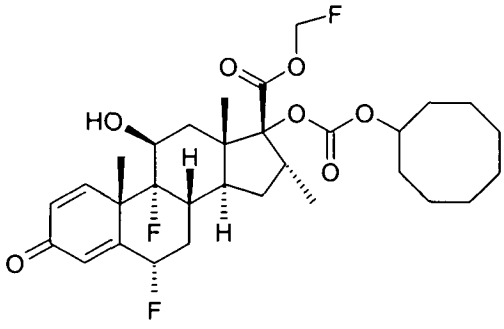
filtered and dried *in vacuo* to give the title compound (287mg): LCMS retention time 3.79 min, *m/z* 569 MH^+

Example 15: Fluoromethyl (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 15 was prepared from (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 15) using a method similar to that described for Example 10. The crude product was purified on a 2g silica Bond Elut cartridge eluted using a 0-100% diethylether in cyclohexane gradient over 9 minutes to give the title compound: LCMS retention time 3.71 min, *m/z* 555 MH^+

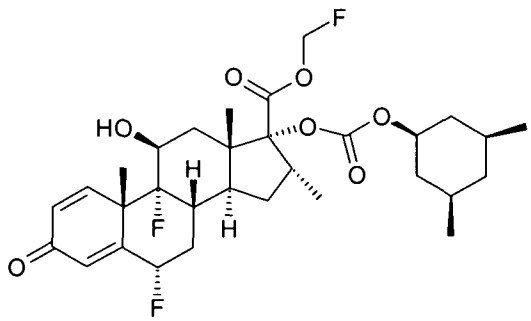
Example 16: Fluoromethyl (6α,11β,16α,17α)-17-{[(cyclooctyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 16 was prepared from (6α,11β,16α,17α)-17-{[(cyclooctyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 16) using a method similar to that described for Example 10. The crude

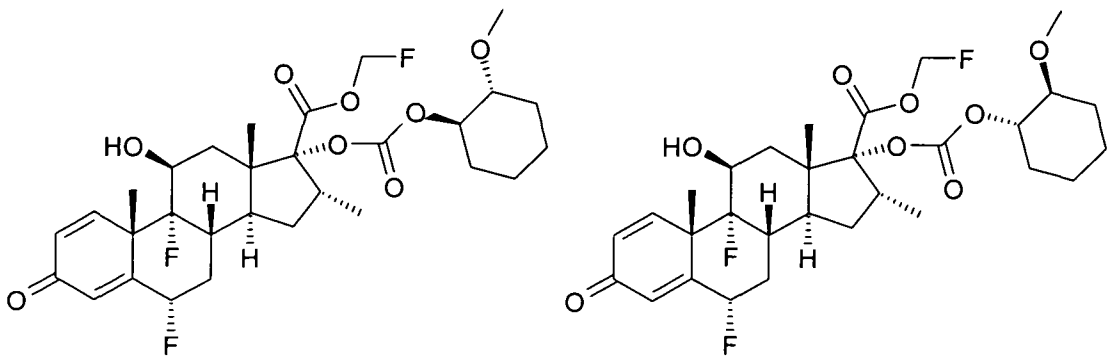
product was purified on a 2g silica Bond Elut cartridge eluted using a 0-100% diethylether in cyclohexane gradient over 9 minutes to give the title compound: LCMS retention time 3.87 min, *m/z* 583 MH^+

Example 17: Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*S*,3*R*,5*S*)-3,5-dimethylcyclohexyl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 17 was prepared from (6α,11β,16α,17α)-17-[({[(1*S*,3*R*,5*S*)-3,5-Dimethylcyclohexyl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 17) using a method similar to that described for Example 11. The crude product was purified on a silica biotage cartridge eluted using 25% ethyl acetate in cyclohexane to give the title compound: LCMS retention time 3.90 min, *m/z* 583 MH^+

Example 18: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*RS*,2*RS*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate



Example 18 was prepared as a ca 1:1 mixture of diastereomers from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*RS*,2*RS*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 18) using a method similar to that described for Example 11.

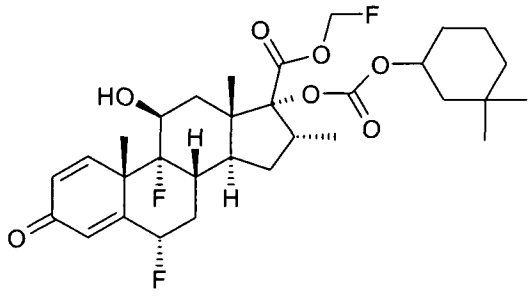
The diastereomers were then separated by reverse phase HPLC – isocratic conditions - eluting with 45% mobile phase B, run time 30min, flow rate 20ml/min.

Mobile phase A – water / 0.1% formic acid v/v
Mobile phase B - 95% aq Acetonitrile / 0.05% formic acid v/v

Example 18A: LCMS retention time 3.51 min, *m/z* 585 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.86 (d, 50Hz) and δ 5.73 (d, 50Hz)

Example 18B: LCMS retention time 3.56 min, *m/z* 585 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.88 (d, 50.5Hz) and δ 5.70 (d, 50.5Hz)

Example 19: Fluoromethyl (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Sodium carbonate (289mg, 2.72mmol) was added to a stirred solution of (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 19) (150mg, 0.27mmol) in anhydrous N,N-dimethylformamide (3ml) and after stirring at room temperature for 15 minutes the mixture was cooled to -30°C under nitrogen. Bromofluoromethane (41μl, 0.73mmol) was added and the reaction stirred at -25 to -35°C for 2 hours. Further bromofluoromethane (41μl, 0.73mmol) was then added and the reaction stirred at -20 to -30°C for 2.5 hours. The reaction was allowed to warm to room temperature, treated with diethylamine (79μl, 1.2mmol) and added dropwise to

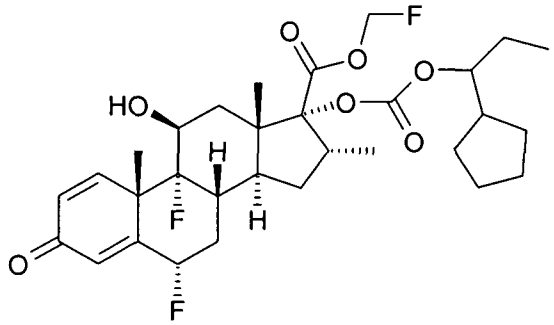
5M hydrochloric acid. The resulting precipitate was filtered and dried *in vacuo* to give the title compound as a mixture of diastereomers:

The diastereomers were then separated using normal phase HPLC to give:

Example 19A: LCMS retention time 3.88 min, *m/z* 583 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.87 (dd, 50.5, 2Hz) and δ 5.76 (dd, 50.5, 2Hz)

Example 19B: LCMS retention time 3.89 min, *m/z* 583 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.86 (dd, 50, 2Hz) and δ 5.74 (dd, 50, 2Hz)

Example 20: Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



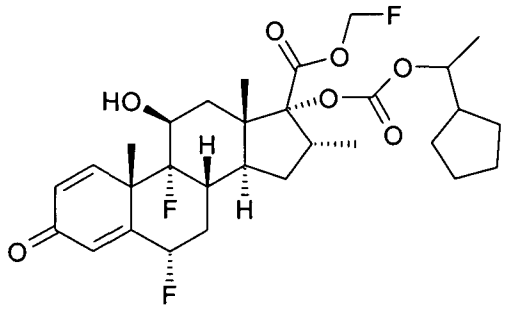
Example 20 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-17-({[(1-cyclopentylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 20) using a method similar to that described for Example 4. The crude product was purified on a 5g silica Bond Elut cartridge eluted using 0-100% diethylether in cyclohexane gradient over 30 minutes to give the title compound:

The diastereomers were then separated using normal phase HPLC to give:

Example 20A: LCMS retention time 3.82 min, *m/z* 583 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.84 (d, 51Hz) and δ 5.67 (d, 51Hz)

Example 20B: LCMS retention time 3.84 min, *m/z* 583 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.83 (d, 50.5Hz) and δ 5.68 (d, 50.5Hz)

Example 21: Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



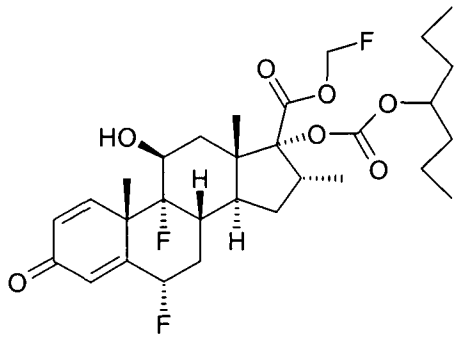
Example 21 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-17-({[(1-Cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 21) using a method similar to that described for Example 4. The crude product was purified on a 5g silica Bond Elut cartridge eluted using 0-100% diethylether in cyclohexane gradient over 30 minutes to give the title compound:

The diastereomers were then separated using normal phase HPLC to give:

Example 21A: LCMS retention time 3.72 min, *m/z* 570 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.85 (d, 50.5Hz) and δ 5.70 (d, 50.5Hz)

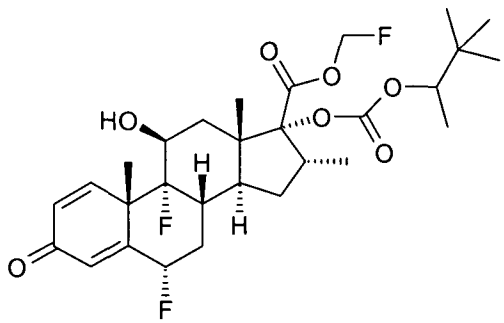
Example 21B: LCMS retention time 3.75 min, *m/z* 570 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.85 (dd, 51, 1.5Hz) and δ 5.75 (dd, 51, 1.5Hz)

Example 22: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1-propylbutyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate



Example 22 was prepared from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1-propylbutyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid (Intermediate 22) using a method similar to that described for Example 4. The crude product was purified on a 5g silica Bond Elut cartridge using 1:1 diethylether : cyclohexane to give the title compound: LCMS retention time 3.82 min, *m/z* 571 MH^+

Example 23: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate



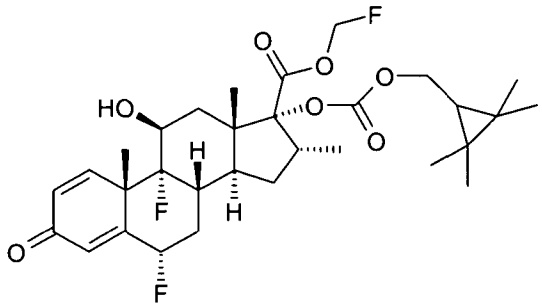
Example 23 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid (Intermediate 23) using a method similar to that described for Example 2. The crude product was purified on a 5g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient over 60 minutes to give the title compound:

The diastereomers were then separated using normal phase HPLC to give:

Example 23A: LCMS retention time 3.77 min, *m/z* 557 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.84 (dd, 50.5, 2Hz) and δ 5.67 (dd, 50.5, 2Hz)

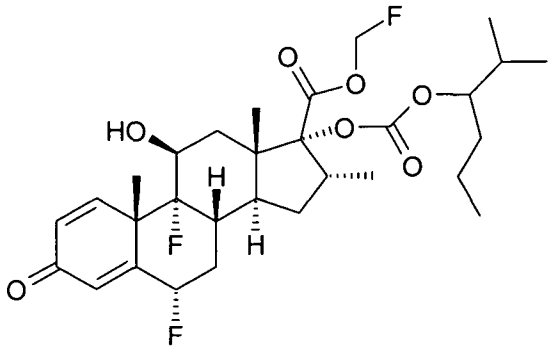
Example 23B: LCMS retention time 3.78 min, *m/z* 557 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.85 (dd, 50.5, 2Hz) and δ 5.76 (dd, 50.5, 2Hz)

Example 24: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(2,2,3,3-tetramethylcyclopropyl)methyl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate



Example 24 was prepared from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(2,2,3,3-tetramethylcyclopropyl)methyl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid (Intermediate 24) using a method similar to that described for Example 2. The crude product was purified on a 2g silica Bond Elut cartridge using a 0-20% ethyl acetate in cyclohexane gradient to give the title compound: LCMS retention time 3.89 min, *m/z* 583 MH^+

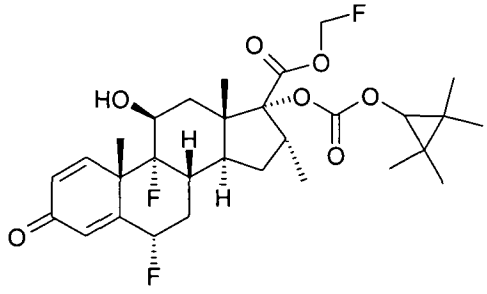
Example 25: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[1-(1-methylethyl)butyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate



Example 25 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[1-(1-methylethyl)butyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 25) using a method similar to

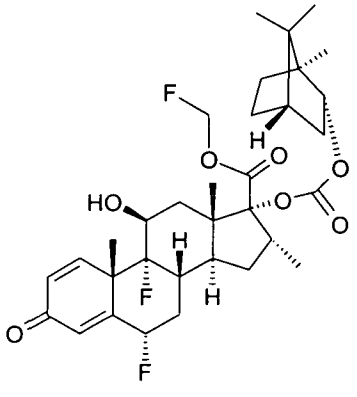
that described for Example 2. The crude product was purified on a 10g silica Bond Elut cartridge using a 0-100% diethylether in cyclohexane gradient over 40 minutes to give the title compound: LCMS retention time 3.84 min, *m/z* 571 MH^+

Example 26: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(2,2,3,3-tetramethylcyclopropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate



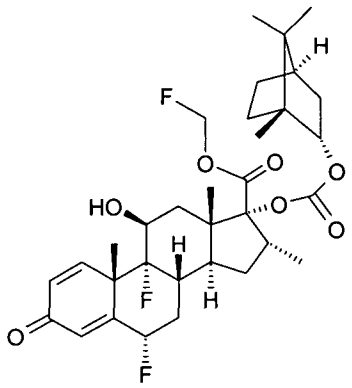
Example 26 was prepared from (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(2,2,3,3-tetramethylcyclopropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid (Intermediate 26) using a method similar to that described for Example 8. The crude reaction mixture was applied to silica Bond Elut cartridges but this failed to give pure material. The crude reaction mixture was therefore purified by mass-directed autopreparation to give the title compound: LCMS retention time 3.82 min, *m/z* 569 MH^+

Example 27: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate



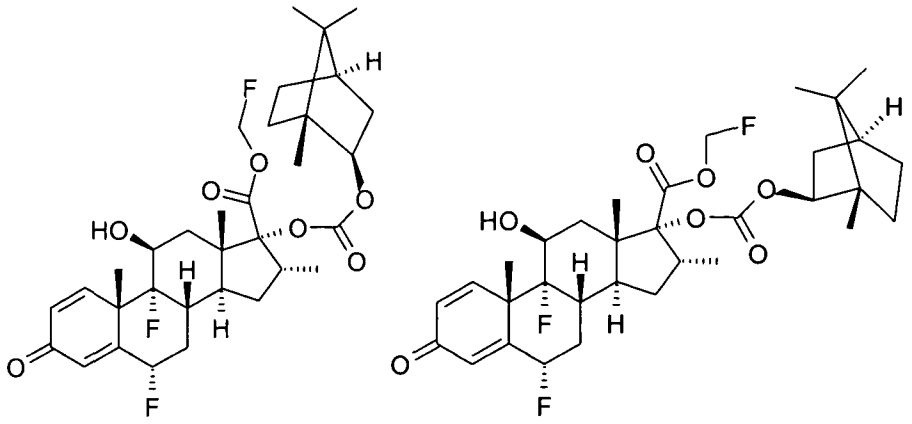
Example 27 was prepared from (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid (Intermediate 27) using a method similar to that described for Example 10. The crude product was purified on a 10g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient over 20 minutes to give the title compound: LCMS retention time 3.95 min, *m/z* 609 MH^+

Example 28: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate



Example 28 was prepared from (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid (Intermediate 28) using a method similar to that described for Example 10. The crude product was purified on a 10g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient over 20 minutes to give the title compound: LCMS retention time 3.95 min, *m/z* 609 MH^+

Example 29: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate



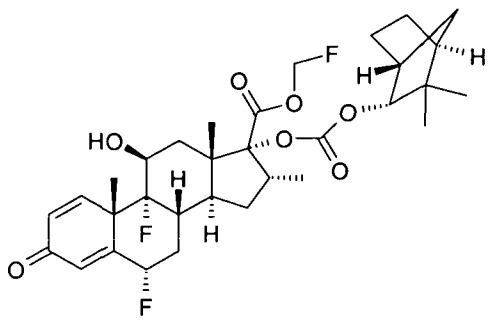
Example 29 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*RS*,2*RS*,4*RS*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid (Intermediate 29) using a method similar to that described for Example 10.

The diastereomers were then separated using normal phase HPLC to give:

Example 29A: LCMS retention time 4.00 min, *m/z* 609 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.86 (dd, 50.5, 2Hz) and δ 5.68 (dd, 50.5, 2Hz)

Example 29B: LCMS retention time 4.00 min, *m/z* 609 MH^+. ^{1}H-NMR: (DMSO-d_6, 400 MHz) 17β fluoromethylene protons δ 5.84 (dd, 50.5, 2Hz) and δ 5.74 (dd, 50.5, 2Hz)

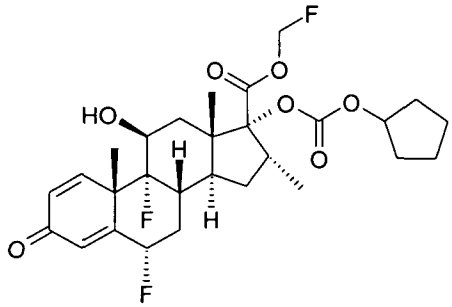
Example 30: Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 30 was prepared from (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-

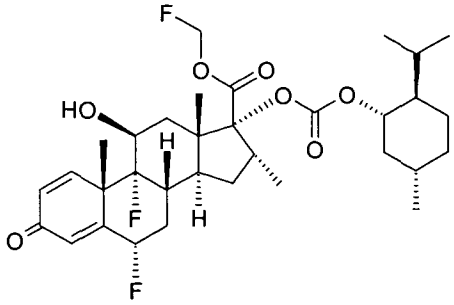
3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 30) using a method similar to that described for Example 4. The crude product was purified on a 10g silica Bond Elut cartridge using a 0-100% diethylether in cyclohexane gradient over 40 minutes to give the title compound: LCMS retention time 3.88 min, *m/z* 595 MH^+

Example 31: Fluoromethyl (6α,11β,16α,17α)-17-{[(cyclopentyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



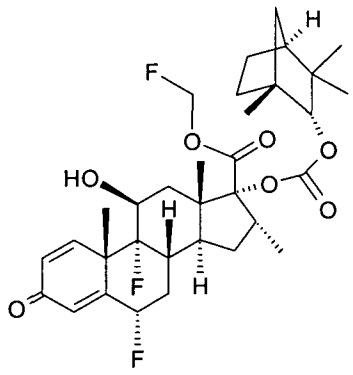
Sodium carbonate (313mg, 2.95mmol) was added to a stirred solution of (6α,11β,16α,17α)-17-{[(cyclopentyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 31) (150mg, 0.29mmol) in anhydrous N,N-dimethylformamide (5ml) and after stirring at room temperature for 30 minutes the mixture was cooled to -20°C. Bromofluoromethane (45µl, 0.80mmol) was added and the reaction stirred at -20°C for 3 hours followed by overnight at room temperature. The reaction was then treated with diethylamine (39µl, 0.38mmol), 2M hydrochloric acid (10ml) and water (10ml). The product was extracted into dichloromethane (10ml) which was separated, washed with saturated aqueous sodium hydrogen carbonate solution (10ml) followed by brine / water and evaporated *in vacuo*. The crude product was purified on a 10g silica Bond Elut cartridge eluted using a 10-40% ethyl acetate in cyclohexane gradient to give the title compound (125mg): LCMS retention time 3.63 min, *m/z* 541 MH^+

Example 32: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate



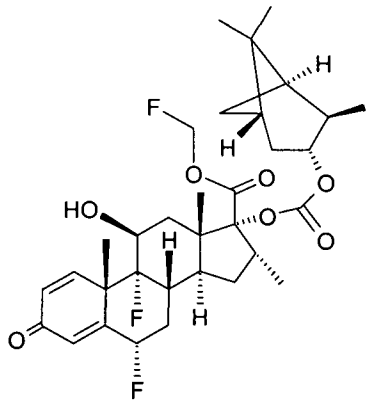
Example 32 was prepared from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 32) using a method similar to that described for Example 1. LCMS retention time 4.08 min, *m/z* 611 MH^+

Example 33: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate



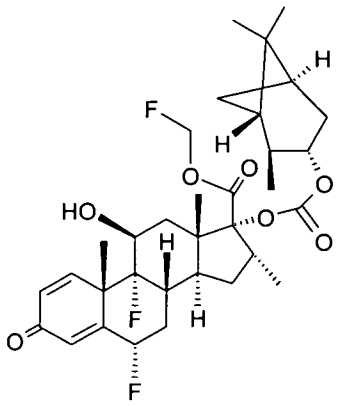
Example 33 was prepared from (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid (Intermediate 33) using a method similar to that described for Example 10. The crude product was purified on a 10g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient over 20 minutes to give the title compound: LCMS retention time 4.00 min, *m/z* 609 MH^+

Example 34: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate



Example 34 was prepared from (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid (Intermediate 34) using a method similar to that described for Example 10. The crude product was purified on a 10g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient over 20 minutes to give the title compound: LCMS retention time 4.00 min, *m/z* 609 MH^+

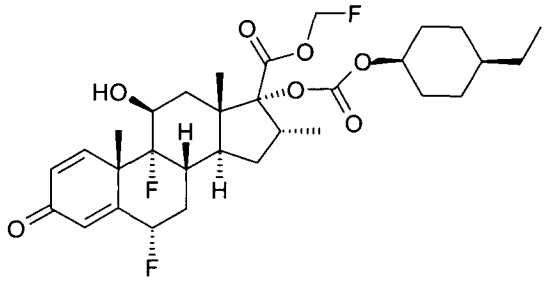
Example 35: Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate



Example 35 was prepared from (6α,11β,16α,17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid (Intermediate 35) using a method similar to that described for Example 10. The crude product was purified on a 10g silica Bond Elut cartridge using a 0-100% ethyl acetate in cyclohexane gradient

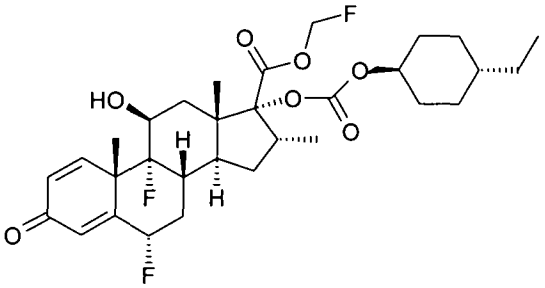
over 20 minutes to give the title compound: LCMS retention time 4.00 min, *m/z* 609 MH^+

Example 36: Fluoromethyl (6α,11β,16α,17α)-17-({[(*cis*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 36 was prepared from (6α,11β,16α,17α)-17-({[(*cis*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 36) using a method similar to that described for Example 19. The crude product was purified on a 1g silica Bond Elut cartridge eluting with 1:1 diethylether:cyclohexane to give the title compound: LCMS retention time 3.92 min, *m/z* 583 MH^+

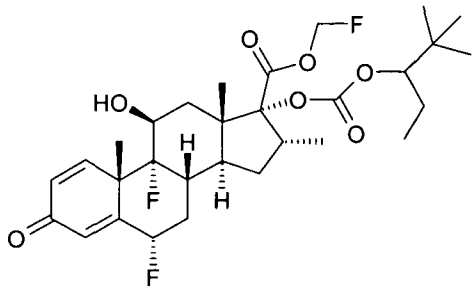
Example 37: Fluoromethyl (6α,11β,16α,17α)-17-({[(*trans*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 37 was prepared from (6α,11β,16α,17α)-17-({[(*trans*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 37) using a method similar to that described for Example 19. The crude product was purified on a 1g silica Bond Elut

cartridge eluting with 1:1 diethylether:cyclohexane to give the title compound: LCMS retention time 3.97 min, *m/z* 583 MH^+

Example 38: Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate



Example 38 was prepared as a mixture of diastereomers from (6α,11β,16α,17α)-17-({[(1-Ethyl-2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid (Intermediate 38) using a method similar to that described for Example 2. The crude product was purified on a 10g silica Bond Elut cartridge eluted using a 0-100% diethylether in cyclohexane gradient over 40 minutes to give the title compound: LCMS retention time 3.82 min, *m/z* 571 MH^+

Pharmacological Activity

Pharmacological activity may be assessed in functional *in vitro* assays of glucocorticoid agonist activity.

Assay for Transrepression Activity of the Glucocorticoid Agonists

The functional assay based on that described by K.P.Ray *et al.*, Biochem J. (1997), **328**, 707-715 provides a measure of transrepressive activity of a glucocorticoid agonist. A549 cells stably transfected with a reporter gene containing the NF-κB responsive elements from the ELAM gene promoter coupled to sPAP (secreted alkaline phosphatase) are treated with test compounds at appropriate doses for 1 hour at 37°C. The cells are then stimulated with tumour necrosis factor (TNF, 10ng/ml) for 16 hours, at which time the amount of alkaline phosphatase produced is measured by a standard colourimetric assay. Dose response curves were constructed from which EC_{50} values were estimated.

The pIC_{50} values for compounds of Examples 1 to 38 were > 8.0 in this assay.

The pIC_{50} values for compounds of Examples 1 to 11A, 12A to 20A, 21A to 23A, 24 to 31 and 33 to 38 were > 9.0 in this assay.

The pIC_{50} values of Examples 1, 2, 6, 8, 9, 12B, 13, 15, 18A, 18B 19A, 21A, 23A and 30 were >10 in this assay.

Assay for Transactivation Activity of the Glucocorticoid Agonists

The functional assay based on that described by R.J.H. Austin et al., Eur Resp J. (2002), **20**,1386-1392 measures the ability of compounds to directly transactivate gene expression. A549 cells stably transfected with a reporter gene containing the glucocorticoid responsive region of the mouse mammary tumour virus long terminal repeat (MMTV-LTR) coupled to renilla luciferase were treated with test compounds at appropriate doses for 6 hour at 37°C. The amount of luciferase activity present within the cells is then determined by measuring the light emitted following incubation with a suitable substrate. Dose response curves were constructed from which EC_{50} values were estimated and from which maximal responses are calculated relative to Dexamethasone (100%).

Compounds of Examples 1 to 38 showed maximal responses of <25% in this assay.

Compounds of Examples 2, 3, 5, 7 to 13, 19A to 25, 27 to 30 and 32 to 38 showed maximal responses of <10% in this assay.

Assay for Progesterone Receptor Activity

A T225 flask of CV-1 cells at a density of 80% confluency was washed with PBS, detached from the flask using 0.25% trypsin and counted using a Sysmex KX-21N. Cells were diluted in DMEM containing 10% Hyclone, 2mM L-Glutamate and 1% Pen/Strep at 140 cells/ µl and transduced with 10% PRb-BacMam and 10% MMTV-BacMam. 70 ml of suspension cells were dispensed to each well of white Nunc 384-well plates, containing compounds at the required concentration. After 24h 10 µl of Steady Glo were added to each well of the plates. Plates were incubated in the dark

for 10 min before reading them on a Viewlux reader. Dose response curves were constructed from which pEC_{50} values were estimated.

The pEC_{50} values for compounds of Examples 2, 4 to 6, 8, 10A to 11B, 14, 18A, 18B, 20A to 23B, 25 to 28, 29B, 30, 32, 34 and 38 were <8 in this assay.

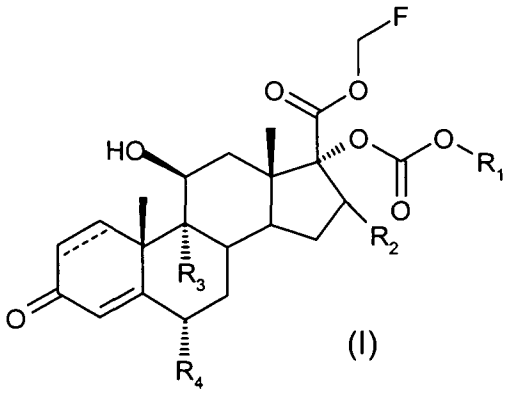
Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims.

The patents and patent applications described in this application are herein incorporated by reference.

CLAIMS

1. A compound of formula (I):



(I)

wherein

R_1 represents C_4-C_7 branched chain alkyl,

C_3-C_8 cycloalkyl optionally substituted by one or more groups independently selected from C_1-C_3 alkyl and methoxy,

C_4-C_6 cycloalkylmethyl wherein the methyl group is optionally substituted by a group selected from methyl or ethyl,

or a bicycloalkyl group optionally substituted by one or more methyl groups;

R_2 represents hydrogen, a methyl group, which may be in either the α or β configuration, or a methylene group;

R_3 and R_4 are the same or a different group and each independently represents hydrogen, halogen or a methyl group;

and ⎓ represents a single or a double bond;

or a physiologically acceptable solvate thereof.

2. A compound as claimed in claim 1 wherein R_1 represents C_4-C_6 branched chain alkyl.

3. A compound as claimed in claim 2 wherein R_1 represents 1,1-dimethylethyl, 1,1-dimethylpropyl, 2-ethylbutyl, 1-ethyl-2-methylpropyl, 1, 2-dimethylpropyl or a 1,2,2-trimethylpropyl Isomer A group.

4. A compound as claimed in claim 1 wherein R_1 represents cyclohexyl optionally substituted by one or more groups independently selected from C_1-C_3 alkyl and methoxy.

5. A compound as claimed in claim 4 wherein R_1 represents cyclohexyl optionally substituted by one or more groups independently selected from methyl and methoxy.

6. A compound as claimed in claim 4 or claim 5 wherein R_1 represents (1*R*, 2*R*)-2-(methyloxy)cyclohexyl, (1*S*, 2*S*)-2-(methyloxy)cyclohexyl or a 3, 3-dimethylcyclohexyl Isomer A group.

7. A compound as claimed in claim 1 wherein R_1 represents cyclopentylmethyl wherein the methyl group is optionally substituted by a group selected from methyl or ethyl.

8. A compound as claimed in claim 7 wherein R_1 represents cyclopentylmethyl or a 1-cyclopentylethyl Isomer A group.

9. A compound as claimed in claim 1 wherein R_1 represents a bicycloalkyl group optionally substituted by one or more methyl groups.

10. A compound as claimed in claim 9 wherein R_1 represents 1*RS*,2*RS*,4*SR* – bicyclo[2.2.1]hept-2-yl Isomer B, 1*RS*,2*SR*,4*SR* bicyclo [2.2.1]hept-2-yl or a (1*R*, 2*R*, 4*S*)-3, 3-dimethylbicyclo{2.2.1]hept-2-yl group.

11. A compound as claimed in any one of claims 1 to 10 wherein R_2 represents a methyl group in the α-configuration.

12. A compound as claimed in any one of claims 1 to 11 wherein R_3 and R_4 are both fluorine.

13. A compound as claimed in any one of claims 1 to 12 wherein ⁼⁼⁼⁼ represents a double bond.

14. A compound which is
Fluoromethyl(6α,11β,16α,17α)-17-({[(1,1-dimethylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[2-methyl-1-(1-methylethyl)propyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(2-ethylbutyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*)-2-methylcyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*)-2-methylcyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[4-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*S*,2*S*,4*R*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*R*,2*R*,4*S*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-{[(cycloheptyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-{[(cyclooctyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*S*,3*R*,5*S*)-3,5-dimethylcyclohexyl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*R*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*S*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1-propylbutyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(2,2,3,3-tetramethylcyclopropyl)methyl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[1-(1-methylethyl)butyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(2,2,3,3-tetramethylcyclopropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-{[(cyclopentyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(*cis*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(*trans*-4-ethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate; or

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate.

15. A compound as claimed in claim 14 which is

Fluoromethyl(6α,11β,16α,17α)-17-({[(1,1-dimethylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(2-ethylbutyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer B;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*R*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*S*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;
Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate Isomer A; or
Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate.

16. A compound as claimed in claim 15 which is
Fluoromethyl (6α,11β,16α,17α)-17-({[(1,1-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1-ethyl-2-methylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;
Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer B;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1*RS*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-2-yloxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*R*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*S*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylate;

Fluoromethyl (6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;

Fluoromethyl (6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate Isomer A;

Fluoromethyl (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(1,2,2-trimethylpropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylate Isomer A; or

Fluoromethyl (6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylate.

17. A compound of formula (I) as defined in any one of claims 1 to 16 or a physiologically acceptable solvate thereof for use in veterinary or human medicine.

18. Use of a compound of formula (I) as defined in any one of claims 1 to 16 or a physiologically acceptable solvate thereof for the manufacture of a medicament for the treatment of inflammatory and/or allergic conditions.

19. A pharmaceutical composition comprising a compound of formula (I), or a physiologically acceptable solvate thereof, as defined in any one of claims 1 to 16 together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.

20. A pharmaceutical composition as claimed in claim 19 which is an aerosol formulation further comprising a fluorocarbon or hydrogen-containing chlorofluoro carbon as propellant, optionally in combination with a surfactant and/or a cosolvent.

21. A pharmaceutical composition according to claim 19 or claim 20 which further comprises another therapeutically active agent.

22. A pharmaceutical composition according to claim 21 in which said another therapeutically active agent is a β_2-adrenoreceptor agonist.

23. A method for the treatment of a human or animal subject with an anti-inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) as defined in any one of claims 1 to 16 or a physiologically acceptable solvate thereof.

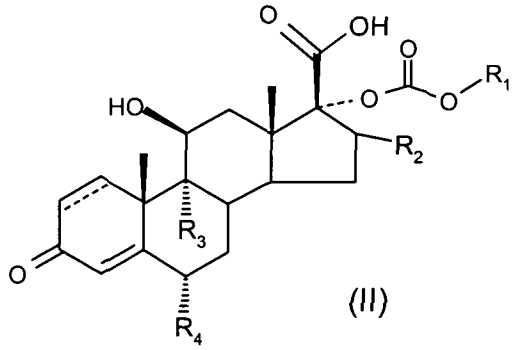
24. A compound which is:
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-{[(cycloheptyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-({[(cyclopentylmethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-{[(cyclooctyloxy)carbonyl]oxy}-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-[({[(1*S*,3*R*,5*S*)-3,5-dimethylcyclohexyl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*RS*,2*RS*)-2-(methyloxy)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-({[(3,3-dimethylcyclohexyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-({[(1-cyclopentylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-17-({[(1-cyclopentylethyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-[({[(2,2,3,3-tetramethylcyclopropyl)methyl]oxy}carbonyl)oxy]androsta-1,4-diene-17-carboxylic acid;
(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-({[(2,2,3,3-tetramethylcyclopropyl)oxy]carbonyl}oxy)androsta-1,4-diene-17-carboxylic acid;

(6α,11β,16α,17α)-17-[({[(1*R*,2*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]oxy}carbonyl)oxy]-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid;

(6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-17-[({[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}carbonyl)oxy]-3-oxoandrosta-1,4-diene-17-carboxylic acid; or

(6α,11β,16α,17α)-17-({[(1-ethyl-2,2-dimethylpropyl)oxy]carbonyl}oxy)-6,9-difluoro-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid.

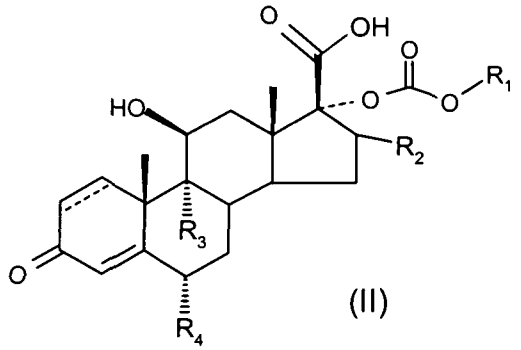
25. A process for preparing a compound of formula (I) which comprises reaction of a carboxylic acid of formula (II);



(II)

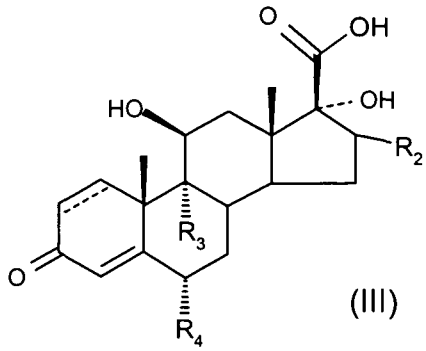
wherein R_1, R_2, R_3, R_4 and ⎓ are as defined above,
with a compound of formula L-CH_2-F wherein L represents a leaving group.

26. A process for preparing a compound of formula (II)



(II)

wherein R_1, R_2, R_3, R_4 and ⎓ are as defined above; which process comprises the reaction of a hydroxyacid (III)



(III)

with a chloroformate R_1OCOCl or anhydride $(R_1OCO)_2O$ in pyridine solution;

wherein R_2, R_3, R_4 and ⎓ are as defined above.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/010894

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J3/00 A61K31/56 A61P5/44

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/000317 A (BODOR NICHOLAS S [US]) 6 January 2005 (2005-01-06) claim 5; compounds G,I page 1, paragraph 1	1-26
X	US 4 996 335 A1 (BODOR NICHOLAS S [US]) 26 February 1991 (1991-02-26) cited in the application columns 51-52; compounds 7A-9, 7A-10, 7A-15 columns 53-54; example 28; compounds 7A-22 columns 57-58; compounds 7B-6 column 1, paragraph 2	1-26

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2007	16/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Watchorn, Peter

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/010894

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BUCHWALD, P. ET AL: "Soft glucocorticoid design: structural elements and physicochemical parameters determining receptor-binding affinity" PHARMAZIE , 59(5), 396-404 CODEN: PHARAT; ISSN: 0031-7144, 2004, XP002426503 page 400; compound LE5671 page 401; compound LE5712	1-26
Y	EP 0 470 617 A (HOECHST AG [DE]) 12 February 1992 (1992-02-12) example 2 page 25; table 5b page 26; table 5c page 5, paragraph 4	1-26
Y	EP 0 137 212 A (OTSUKA PHARMA CO LTD [JP]) 17 April 1985 (1985-04-17) page 25; example 13; compound LAST page 26; example 13; compound THIRD page 13, lines 17-25	1-26
P,Y	WO 2006/072599 A (GLAXO GROUP LTD [GB]; BIGGADIKE KEITH [GB]; NEEDHAM DEBORAH [GB]) 13 July 2006 (2006-07-13) page 3, line 32 - page 8, line 32 page 1, paragraphs 1,2	1-26
P,Y	WO 2006/072600 A (GLAXO GROUP LTD [GB]; BIGGADIKE KEITH [GB]; NEEDHAM DEBORAH [GB]) 13 July 2006 (2006-07-13) page 2, lines 1-6 page 1, paragraphs 1,2	1-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/010894

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/010894

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005000317 A	06-01-2005	CA 2558944 A1	06-01-2005
		CN 1838960 A	27-09-2006
		EP 1653974 A1	10-05-2006
		KR 20060032596 A	17-04-2006
		MX PA05013898 A	25-05-2006
US 4996335 A1		NONE	
EP 0470617 A	12-02-1992	AU 646066 B2	03-02-1994
		AU 8256091 A	13-02-1992
		CA 2048841 A1	11-02-1992
		CS 9102461 A3	18-03-1992
		DE 4025342 A1	13-02-1992
		EG 19928 A	31-07-1996
		FI 913775 A	11-02-1992
		HU 59155 A2	28-04-1992
		IE 912827 A1	12-02-1992
		IL 99135 A	08-12-1995
		JP 6041187 A	15-02-1994
		LT 709 A	31-01-1995
		LV 10459 A	20-02-1995
		MX 9100613 A1	01-04-1992
		NO 913115 A	11-02-1992
		PT 98605 A	30-06-1992
		RU 2060997 C1	27-05-1996
		ZA 9106291 A	29-04-1992
EP 0137212 A	17-04-1985	JP 1815833 C	18-01-1994
		JP 5024131 B	06-04-1993
		JP 60041607 A	05-03-1985
WO 2006072599 A	13-07-2006	NONE	
WO 2006072600 A	13-07-2006	NONE	