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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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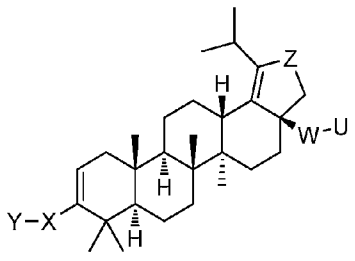
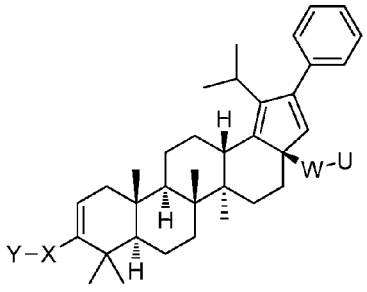
(54) Title: OXOLUPENE DERIVATIVES



Formula I



Formula II

(57) Abstract: Compounds having drug and bio-affecting properties, their pharmaceutical compositions and methods of use are set forth. In particular, betulinic acid derivatives that possess unique antiviral activity are provided as HIV maturation inhibitors, as represented by compounds of Formulas I and II. These compounds are useful for the treatment of HIV and AIDS.

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OXOLUPENE DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATION

This application claims the priority of U.S. Provisional Application Serial No. 62/079,977 filed November 14, 2014, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds useful against HIV and, more particularly, to compounds derived from betulinic acid and other structurally-related compounds which are useful as HIV maturation inhibitors, and to pharmaceutical compositions containing same, as well as to methods for their preparation.

BACKGROUND OF THE INVENTION

HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 45-50 million people infected worldwide at the end of 2010. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations: zidovudine (or AZT or RETROVIR®), didanosine (or VIDEX®), stavudine (or ZERIT®), lamivudine (or 3TC or EPIVIR®), zalcitabine (or DDC or HIVID®), abacavir succinate (or ZIAGEN®), Tenofovir disoproxil fumarate salt (or VIREAD®), emtricitabine (or FTC- EMTRIVA®), COMBIVIR® (contains -3TC plus AZT), TRIZIVIR® (contains abacavir, lamivudine, and zidovudine), EPZICOM® (contains abacavir and lamivudine), TRUVADA® (contains VIREAD® and EMTRIVA®); non-nucleoside reverse transcriptase inhibitors: nevirapine (or VIRAMUNE®), delavirdine (or RESCRIPTOR®) and efavirenz (or SUSTIVA®), ATRIPLA® (TRUVADA® + SUSTIVA®), and etravirine, and peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir,

ritonavir, nelfinavir, amprenavir, lopinavir, KALETRA®(lopinavir and Ritonavir), darunavir, atazanavir (REYATAZ®) and tipranavir (APTIVUS®) and cobicistat, and integrase inhibitors such as raltegravir (ISENTRESS®), and entry inhibitors such as enfuvirtide (T-20) (FUZEON®) and maraviroc (SELZENTRY®).

Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients may ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options. Improved HIV fusion inhibitors and HIV entry coreceptor antagonists are two examples of new classes of anti-HIV agents further being studied by a number of investigators.

HIV attachment inhibitors are a further subclass of antiviral compounds that bind to the HIV surface glycoprotein gp120, and interfere with the interaction between the surface protein gp120 and the host cell receptor CD4. Thus, they prevent HIV from attaching to the human CD4 T-cell, and block HIV replication in the first stage of the HIV life cycle. The properties of HIV attachment inhibitors have been improved in an effort to obtain compounds with maximized utility and efficacy as antiviral agents. In particular, U.S. Patent Nos. 7,354,924 and US 7,745,625 are illustrative of HIV attachment inhibitors.

Another emerging class of compounds for the treatment of HIV are called HIV maturation inhibitors. Maturation is the last of as many as 10 or more steps in HIV replication or the HIV life cycle, in which HIV becomes infectious as a consequence of several HIV protease-mediated cleavage events in the gag protein that ultimately results in release of the capsid (CA) protein. Maturation inhibitors prevent the HIV capsid from properly assembling and maturing, from forming a protective outer coat, or from emerging from human cells. Instead, non-infectious viruses are produced, preventing subsequent cycles of HIV infection.

Certain derivatives of betulinic acid have now been shown to exhibit potent anti-HIV activity as HIV maturation inhibitors. For example, US 7,365,221 discloses monoacylated betulin and dihydrobetuline derivatives, and their use as anti-HIV agents. As discussed in the '221 reference, esterification of betulinic acid (1) with certain substituted acyl groups, such as 3',3'-dimethylglutaryl and 3',3'-dimethylsuccinyl groups produced derivatives having enhanced activity (Kashiwada, Y., et al., J. Med. Chem. 39:1016-1017 (1996)). Acylated betulinic acid and dihydrobetulinic acid derivatives that are potent anti-HIV agents are also described in U.S. Pat. No. 5,679,828. Esterification of the hydroxyl in the 3 carbon of betulin with succinic acid also produced a compound capable of inhibiting HIV-1 activity (Pokrovskii, A. G., et al., "Synthesis of derivatives of plant triterpenes and study of their antiviral and immunostimulating activity," Khimiya y Interesakh Ustoichivogo Razvitiya, Vol. 9, No. 3, pp. 485-491 (2001) (English abstract).

Other references to the use of treating HIV infection with compounds derived from betulinic acid include US 2005/0239748 and US 2008/0207573, as well as WO2006/053255, WO2009/100532 and WO2011/007230.

One HIV maturation compound that has been in development has been identified as Bevirimat or PA-457, with the chemical formula of $C_{36}H_{56}O_6$ and the IUPAC name of 3β-(3-carboxy-3-methyl-butanoyloxy) lup-20(29)-en-28-oic acid.

Reference is also made herein to the applications by Bristol-Myers Squibb entitled "MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,706 filed on June 2, 2011 (now US 8,754,068) and "C-28

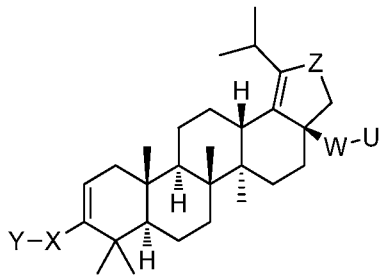
AMIDES OF MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,722, filed on June 2, 2011 (now US 8,802,661). Reference is also made to the application entitled "C-28 AMINES OF C-3 MODIFIED BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/359,680, filed on January 27, 2012 (now US 8,748,415). In addition, reference is made to the application entitled "C-17 AND C-3 MODIFIED TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY" USSN 13/359,727 filed on January 27, 2012 (now now US 8,846,647). Further reference is also made to the application "C-3 CYCLOALKENYL TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY" filed USSN 13/760,726 on February 6, 2013 (now US 2013-0210787), as well as to the application entitled "ALKYLHALO-SUBSTITUTED C-3 CYCLOALKENYL TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY" filed USSN 61/978,306 on April 11, 2014.

What is now needed in the art are new compounds which are useful as HIV maturation inhibitors, as well as new pharmaceutical compositions containing these compounds.

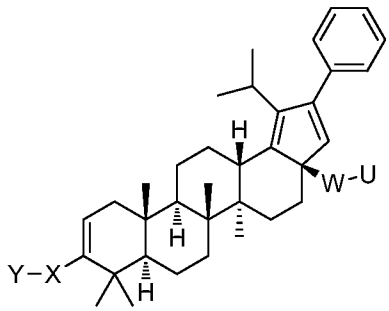
SUMMARY OF THE INVENTION

The present invention provides compounds of Formulas I and II below, including pharmaceutically acceptable salts thereof, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formulas I and II are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

One embodiment of the present invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from a compound of Formulas I and II:



Formula I ;



Formula II

wherein X is selected from the group of phenyl, heteroaryl, C_{4-8} cycloalkyl, C_{4-8} cycloalkenyl, C_{4-9} spirocycloalkyl, C_{4-9} spirocycloalkenyl, C_{4-8} oxacycloalkyl, C_{6-8} dioxacycloalkenyl, C_{6-9} oxaspirocycloalkyl, and C_{6-9} oxaspirocycloalkenyl ring;
and further wherein X is substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{1-6}haloalkyl, -CN, -NR_8R_9, -$COOR_2$, -$CONR_2R_2$ and -C_{1-6} alkyl-Q;

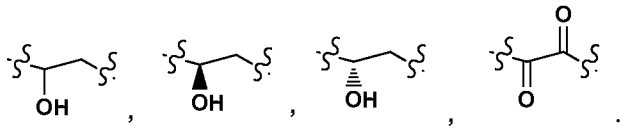
Q is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_3$, -NR_2R_2, -SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or -arylsubstituted C_{1-6} alkyl;

Y is selected from the group of -$COOR_2$, -$C(O)NR_2SO_2R_3$, - $C(O)NHSO_2NR_2R_2$, -$NR_2SO_2R_2$, -$SO_2NR_2R_2$, -C_{3-6} cycloalkyl-$COOR_2$, -C_{2-6} alkenyl-$COOR_2$, -C_{2-6} alkynyl-$COOR_2$, -C_{1-6} alkyl-$COOR_2$, -alkylsubstituted C_{1-6} alkyl, -$COOR_2$, CF_2-$COOR_2$, -$NHC(O)(CH_2)_n$-$COOR_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and -CONHOH,
wherein n=1-6;

R_3 is –H, -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

W is absent, or is -CO- or is selected from the group of
-C_{2-6} alkyl-, -C_{2-6} alkyl-CO-, -C_{2-6} alkenyl-,-C_{2-6} alkenyl-CO-, and -heteroaryl-; or is selected from the group of:



U is selected from -NR_4R_5 and OR_2,
with the proviso that U cannot be OR_2 when W is absent;

Z is selected from the group of –CO-, -CHOH, -C=N-OR_2, -C=N-R_{24}, and –CH-NHR_{24}

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-$C(OR_3)_2$-C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -$COCOR_6$, -SO_2R_7, and -$SO_2NR_2R_2$;

Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_{10}, -COR_6, -$COCOR_6$, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that R_4 or R_5 cannot be COR_6 or $COCOR_6$ when W is CO,
and with the further proviso that only one of R_4 or R_5 can be selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

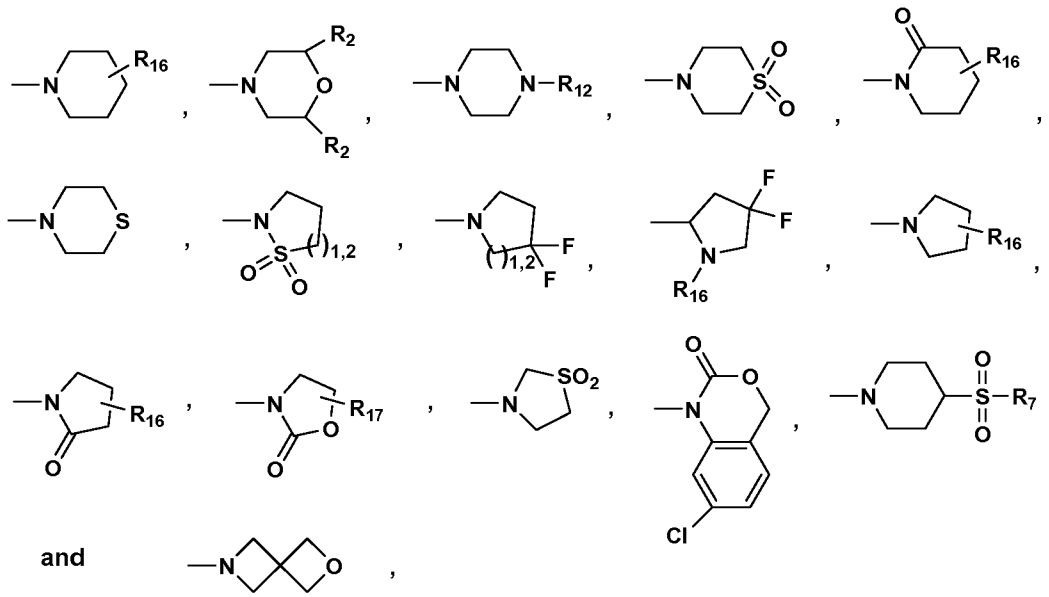
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, $-OR_2$, $-COOR_2$, $-NR_8R_9$, SO_2R_7, $-CONHSO_2R_3$, and $-CONHSO_2NR_2R_2$;

R_7 is selected from the group of –H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{3-6}$ cycloalkyl, $-CF_3$, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, $-C_{1-6}$ alkyl-Q_2, and $-COOR_3$,

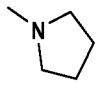
or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



with the proviso that only one of R_8 or R_9 can be $-COOR_3$;

R_{10} and R_{11} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl and $-C_{3-6}$ cycloalkyl,

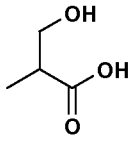
or R_{10} and R_{11} are taken together with the adjacent N to form the cycle



;

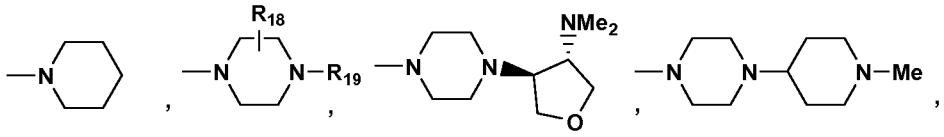
R_{12} is selected from the group of -C_{1-6} alkyl, -C_{1-6} alkyl-OH; -C_{1-6} alkyl, -C_{1-6} substituted alkyl,-C_{3-6} cycloalkyl, -COR_7, -$COONR_{22}R_{23}$, -SOR_7, and -$SONR_{24}R_{25}$;

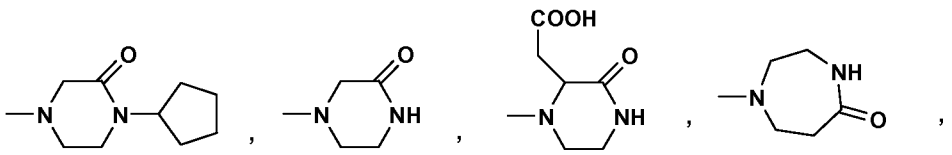
R_{13} and R_{14} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3, C_{1-6} substituted alkyl-Q_3 and

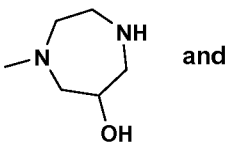


,

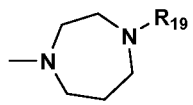
or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the group of:







and



;

Q_3 is selected from the group of heteroaryl, substituted heteroaryl, -$NR_{20}R_{21}$, -$CONR_2R_2$, -$COOR_2$, -OR_2, and -SO_2R_3;

R_{15} is selected from the group of –H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3 and -C_{1-6} substituted alkyl-Q_3;

R_{16} is selected from the group of -H, -C_{1-6} alkyl, -NR_2R_2, and -$COOR_3$;

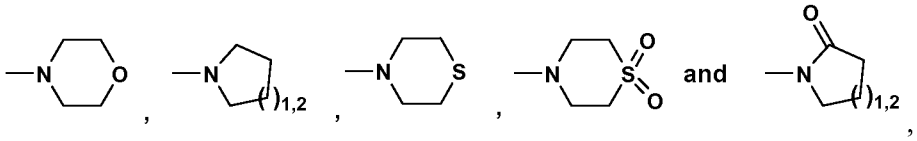
R_{17} is selected from the group of -H, -C_{1-6} alkyl, -$COOR_3$, and aryl;

R_{18} is selected from the group of –H, -$COOR_2$ and -C_{1-6} alkyl-$COOR_2$;

R_{19} is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-Q_4, -COR_3, and -$COOR_3$;

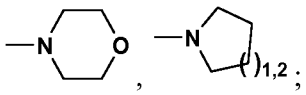
Q_4 is selected from the group of -NR_2R_2 and -OR_2;

R_{20} and R_{21} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} substituted alkyl-OR_2, and -COR_3,
or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R_{20} or R_{21} can be -COR_3;

R_{22} and R_{23} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, and -C_{1-6} cycloalkyl,
or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



R_{24} and R_{25} are independently from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_5, -C_{1-6} cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
Q_5 is selected from the group of halogen and SO_2R_3.

In a further embodiment, there is provided a method for treating mammals infected with a virus, especially wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound which is selected from the group of compounds of Formulas I and II, and one or more pharmaceutically acceptable carriers, excipients or diluents. Optionally, the compound of Formulas I and II can be

administered in combination with an antiviral effective amount of another AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

Another embodiment of the present invention is a pharmaceutical composition comprising one or more compounds of Formulas I and II, and one or more pharmaceutically acceptable carriers, excipients, and/or diluents; and optionally in combination with another AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

In another embodiment of the invention there is provided one or more methods for making the compounds of Formulas I and II herein.

Also provided herein are intermediate compounds useful in making the compounds of Formulas I and II herein.

The present invention is directed to these, as well as other important ends, hereinafter described.

DETAILED DESCRIPTION OF THE EMBODIMENTS

As used herein, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

Since the compounds of the present invention may possess asymmetric centers and therefore occur as mixtures of diastereomers, the present disclosure includes the individual diastereoisomeric forms of the compounds of Formulas I and II in addition to the mixtures thereof.

Definitions

Unless otherwise specifically set forth elsewhere in the application, one or more of the following terms may be used herein, and shall have the following meanings:

"H" refers to hydrogen, including its isotopes, such as deuterium.

The term "$C_{1\text{-}6}$ alkyl" as used herein and in the claims (unless specified otherwise) means straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl, and the like.

"C_1 –C_4 fluoroalkyl" refers to F-substituted C_1 –C_4 alkyl wherein at least one H atom is substituted with an F atom, and each H atom can be independently substituted by an F atom;

"Halogen" or "halo" refers to chlorine, bromine, iodine or fluorine.

An "aryl" or "Ar" group refers to all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted, the substituent group(s) are preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and -NR^xR^y, wherein R^x and R^y are independently selected from the group of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

A "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from

the group of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl. diazinyl, pyrazine, triazinyl, tetrazinyl, and tetrazolyl. When substituted, the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thioalkoxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $-NR^xR^y$, wherein R^x and R^y are as defined above.

A "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group of nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encompass systems which would not exist. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and its S oxides and tetrahydropyranyl. When substituted, the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$, wherein R^x and R^y are as defined above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane, cycloheptene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalo-methanesulfonamido, trihalomethanesulfonyl, silyl, amidino, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon double bond.

An “alkynyl” group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon triple bond.

A “hydroxy” group refers to an –OH group.

An “alkoxy” group refers to both an –O-alkyl and an –O-cycloalkyl group as defined herein.

An “aryloxy” group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

A “heteroaryloxy” group refers to a heteroaryl-O- group with heteroaryl as defined herein.

A “heteroalicycloxy” group refers to a heteroalicyclic-O- group with heteroalicyclic as defined herein.

A “thiohydroxy” group refers to an –SH group.

A “thioalkoxy” group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

A “thioaryloxy” group refers to both an –S-aryl and an –S-heteroaryl group, as defined herein.

A “thioheteroaryloxy” group refers to a heteroaryl-S- group with heteroaryl as defined herein.

A “thioheteroalicycloxy” group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

A “carbonyl” group refers to a –C(=O)-R” group, where R” is selected from the group of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An “aldehyde” group refers to a carbonyl group where R” is hydrogen.

A “thiocarbonyl” group refers to a –C(=S)-R” group, with R” as defined herein.

A “keto” group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroalicyclic group.

A “trihalomethanecarbonyl” group refers to a $Z_3CC(=O)$- group with said Z being a halogen.

A “C-carboxy” group refers to a –C(=O)O-R” groups, with R” as defined herein.

An “O-carboxy” group refers to a R”C(-O)O-group, with R” as defined herein.

A “carboxylic acid” group refers to a C-carboxy group in which R” is hydrogen.

A “trihalomethyl” group refers to a $–CZ_3$, group wherein Z is a halogen group as defined herein.

A “trihalomethanesulfonyl” group refers to an $Z_3CS(=O)_2$- groups with Z as defined above.

A “trihalomethanesulfonamido” group refers to a $Z_3CS(=O)_2NR^x$- group with Z as defined above and R^x being H or (C_{1-6})alkyl.

A “sulfinyl” group refers to a –S(=O)-R” group, with R” being (C_{1-6})alkyl.

A “sulfonyl” group refers to a $–S(=O)_2R$” group with R” being (C_{1-6})alkyl.

A "S-sulfonamido" group refers to a $-S(=O)_2NR^XR^Y$, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-sulfonamido" group refers to a $R"S(=O)_2NR_X-$ group, with R_x being H or (C_{1-6})alkyl.

A "O-carbamyl" group refers to a $-OC(=O)NR^xR^y$ group, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "O-thiocarbamyl" group refers to a $-OC(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y-$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "amino" group refers to an $-NH_2$ group.

A "C-amido" group refers to a $-C(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-amido" group refers to a $R^xC(=O)NR^y-$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "guanidino" group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "amidino" group refers to a $R^xR^yNC(=N)-$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

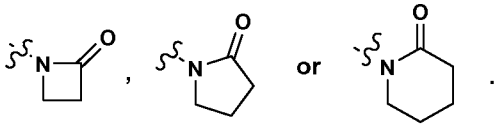
A "cyano" group refers to a –CN group.

A "silyl" group refers to a $-Si(R")_3$, with R" being (C_{1-6})alkyl or phenyl.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x being (C_{1-6})alkyl.

A "hydrazino" group refers to a $-NR^xNR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "4, 5, or 6 membered ring cyclic N-lactam" group refers to



A "spiro" group is a bicyclic organic group with rings connected through just one atom. The rings can be different in nature or identical. The connecting atom is also called the spiroatom, most often a quaternary carbon ("spiro carbon").

An "oxospiro" or "oxaspiro" group is a spiro group having an oxygen contained within the bicyclic ring structure. A "dioxospiro" or "dioxaspiro" group has two oxygens within the bicyclic ring structure.

Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

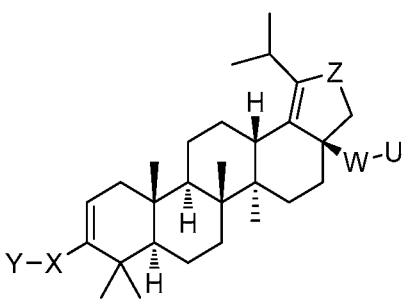
It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double

bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present disclosure are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

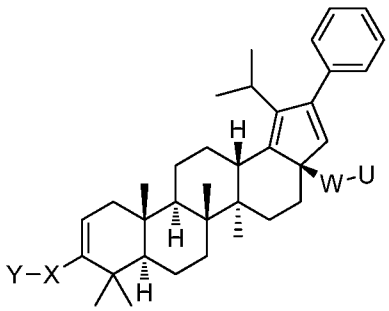
Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of the invention. The term “pharmaceutically acceptable salt” as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)- aminomethane), or with bases such as piperidine or morpholine.

As stated above, the compounds of the invention also include “prodrugs”. The term “prodrug” as used herein encompasses both the term “prodrug esters” and the term “prodrug ethers”.

As set forth above, the invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from a compound of Formulas I and II:



Formula I



Formula II ;

wherein X is selected from the group of phenyl, heteroaryl, C_{4-8} cycloalkyl, C_{4-8} cycloalkenyl, C_{4-9} spirocycloalkyl, C_{4-9} spirocycloalkenyl, C_{4-8} oxacycloalkyl, C_{6-8} dioxacycloalkenyl, C_{6-9} oxaspirocycloalkyl, and C_{6-9} oxaspirocycloalkenyl ring;

and further wherein X is substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{1-6}haloalkyl, -CN, -NR_8R_9, -$COOR_2$, -$CONR_2R_2$ and -C_{1-6} alkyl-Q;

Q is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_3$, -NR_2R_2, -SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

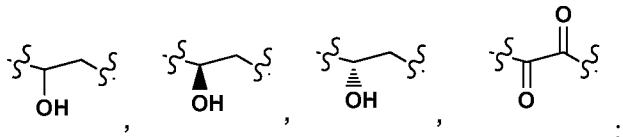
R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or -arylsubstituted C_{1-6} alkyl;

Y is selected from the group of –$COOR_2$, -$C(O)NR_2SO_2R_3$, - $C(O)NHSO_2NR_2R_2$, -$NR_2SO_2R_2$, -$SO_2NR_2R_2$, -C_{3-6} cycloalkyl-$COOR_2$, -C_{2-6} alkenyl-$COOR_2$, -C_{2-6} alkynyl-$COOR_2$, -C_{1-6} alkyl-$COOR_2$, -alkylsubstituted C_{1-6} alkyl, -$COOR_2$, CF_2-$COOR_2$, -$NHC(O)(CH_2)_n$-$COOR_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and -CONHOH,

wherein n=1-6;

R_3 is –H, -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

W is absent, or is -CO- or is selected from the group of -C_{2-6} alkyl-, -C_{2-6} alkyl-CO-, -C_{2-6} alkenyl-,-C_{2-6} alkenyl-CO-, and -heteroaryl-; or is selected from the group of:



U is selected from -NR_4R_5 and OR_2,
with the proviso that U cannot be OR_2 when W is absent;

Z is selected from the group of –CO-, -CHOH, -C=N-OR_2, -C=N-R_{24} and –CH-NHR_{24};

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-$C(OR_3)_2$-C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -$COCOR_6$, -SO_2R_7, and -$SO_2NR_2R_2$;

Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_{10}, -COR_6, -$COCOR_6$, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that R_4 or R_5 cannot be COR_6 or $COCOR_6$ when W is CO,
and with the further proviso that only one of R_4 or R_5 can be selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

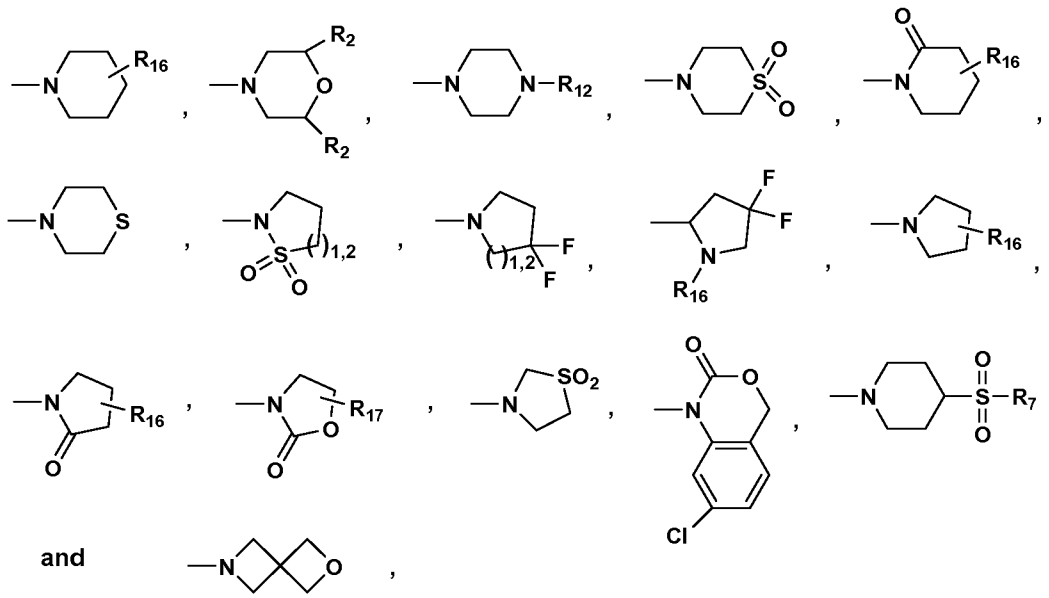
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2, -C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

R_7 is selected from the group of –H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{3-6} cycloalkyl, -CF_3, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C_{1-6} alkyl-Q_2, and -$COOR_3$,

or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



and

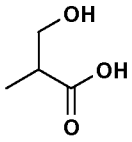
with the proviso that only one of R_8 or R_9 can be -$COOR_3$;

R_{10} and R_{11} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl and -C_{3-6} cycloalkyl,
or R_{10} and R_{11} are taken together with the adjacent N to form the cycle

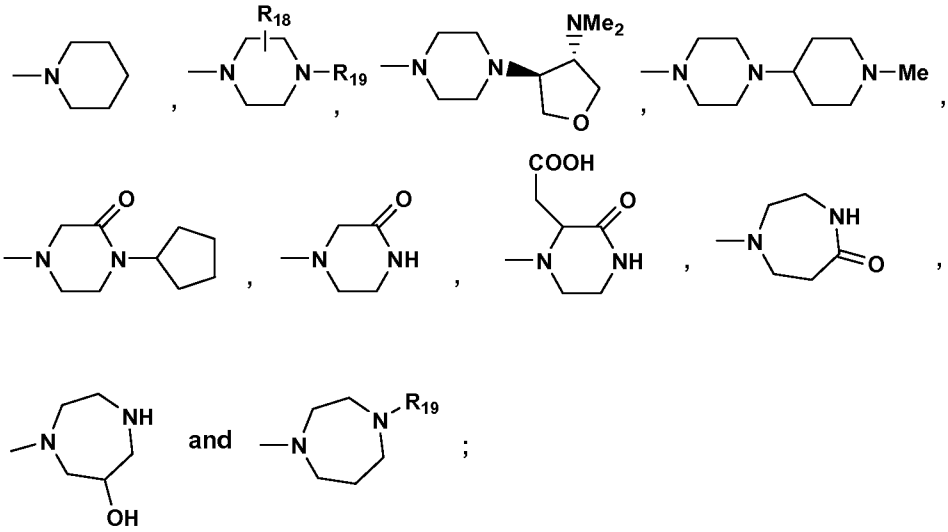

;

R_{12} is selected from the group of –H, -C_{1-6} alkyl, -C_{1-6} alkyl-OH; -C_{1-6} alkyl, -C_{1-6} substituted alkyl,-C_{3-6} cycloalkyl, -COR_7, -$COONR_{22}R_{23}$, -SOR_7, and -$SONR_{24}R_{25}$;

R_{13} and R_{14} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3, C_{1-6} substituted alkyl-Q_3 and



or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the group of:



Q_3 is selected from the group of heteroaryl, substituted heteroaryl, $-NR_{20}R_{21}$, $-CONR_2R_2$, $-COOR_2$, $-OR_2$, and $-SO_2R_3$;

R_{15} is selected from the group of –H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_3, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl-Q_3 and $-C_{1-6}$ substituted alkyl-Q_3;

R_{16} is selected from the group of -H, $-C_{1-6}$ alkyl, $-NR_2R_2$, and $-COOR_3$;

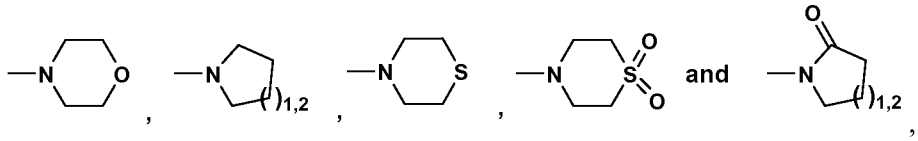
R_{17} is selected from the group of -H, $-C_{1-6}$ alkyl, $-COOR_3$, and aryl;

R_{18} is selected from the group of –H, $-COOR_2$ and $-C_{1-6}$ alkyl-$COOR_2$;

R_{19} is selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-Q_4, $-COR_3$, and $-COOR_3$;

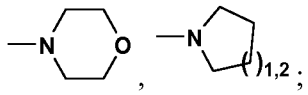
Q_4 is selected from the group of $-NR_2R_2$ and $-OR_2$;

R_{20} and R_{21} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} substituted alkyl-OR_2, and -COR_3,
or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R_{20} or R_{21} can be -COR_3;

R_{22} and R_{23} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, and -C_{1-6} cycloalkyl,
or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



R_{24} and R_{25} are independently from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_5, -C_{1-6} cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
Q_5 is selected from the group of halogen and SO_2R_3.

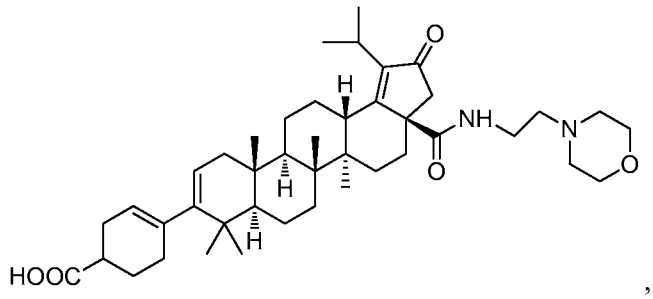
In a preferred embodiment of the invention, X is phenyl or is C_{4-8} cycloalkenyl. When X is C_{4-8} cycloalkenyl, it is preferred to be C_6 cycloalkenyl.

It is also preferred that Y is –COOH.

It is further preferred that A is -C_{1-6} haloalkyl. Halo is preferably –fluoro.

In a further embodiment, it is preferred that Z is –CO-.

Preferred compounds, including pharmaceutically acceptable salts thereof, as part of the invention include the following:



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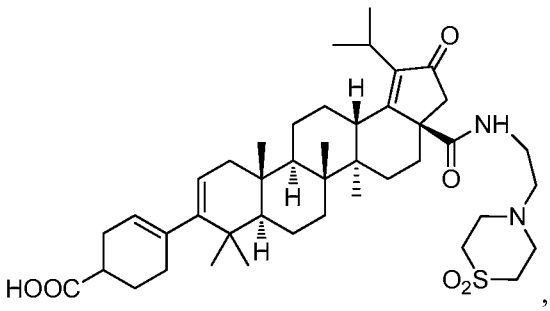

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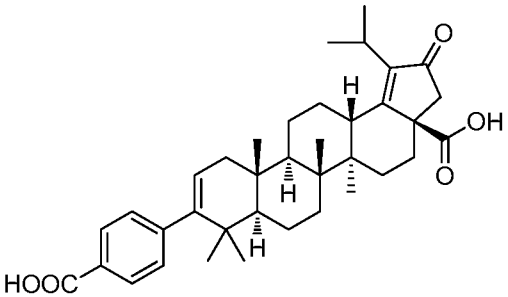

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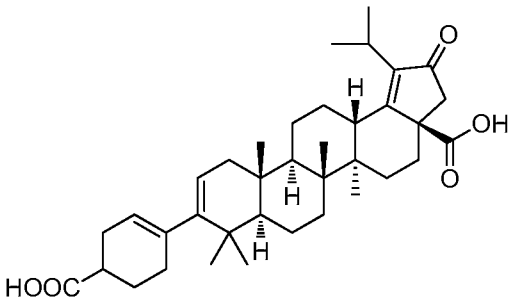

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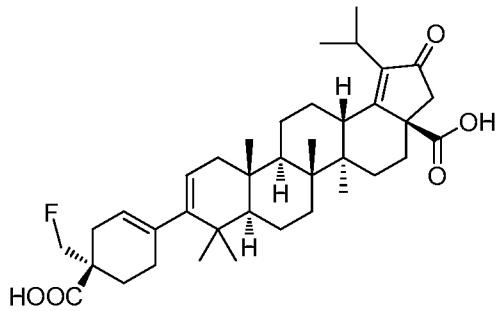

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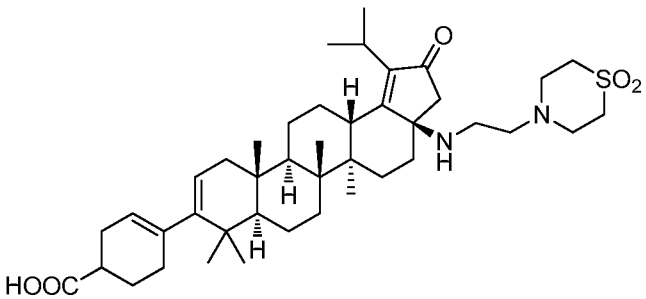

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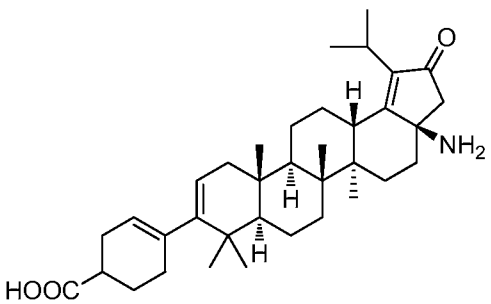

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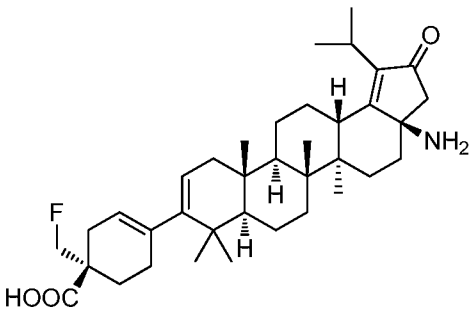

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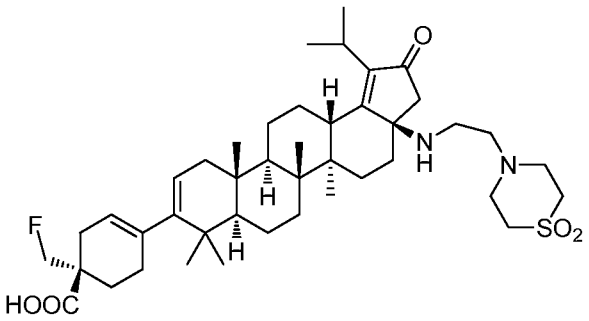

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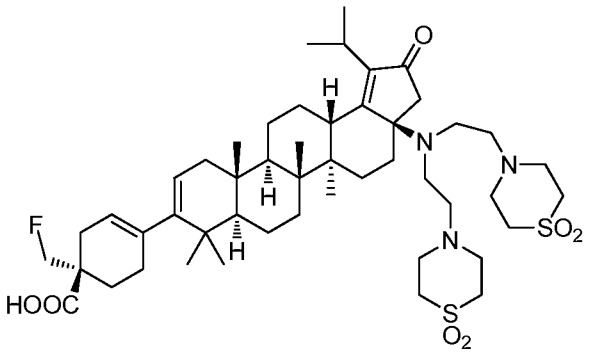

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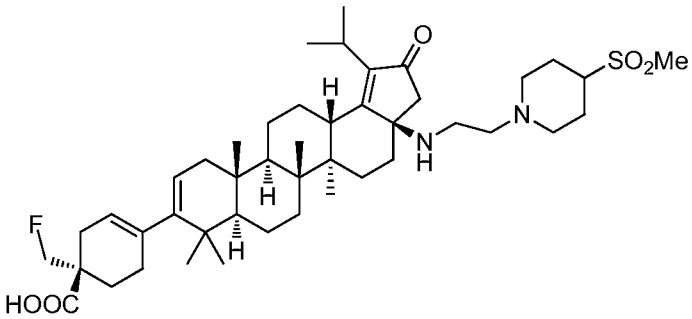

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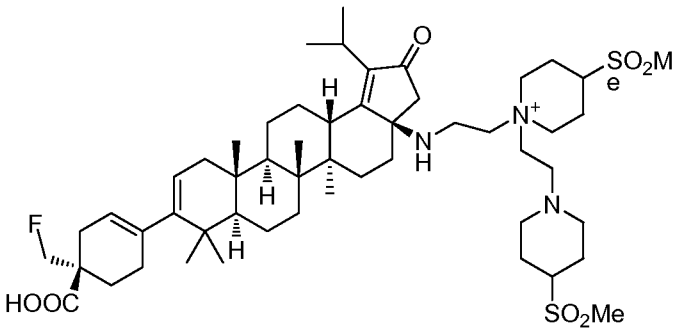

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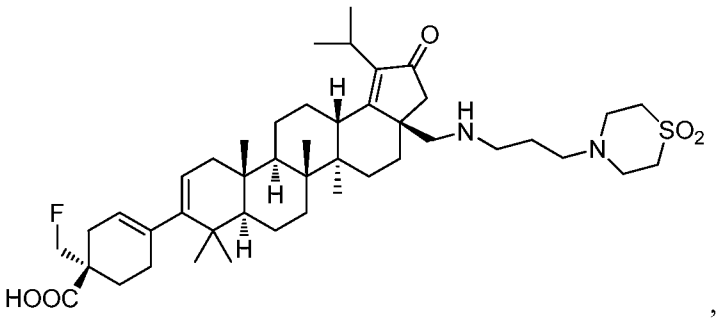

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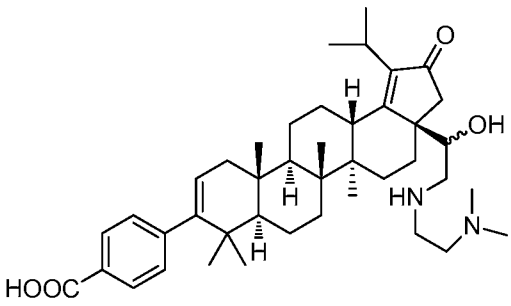

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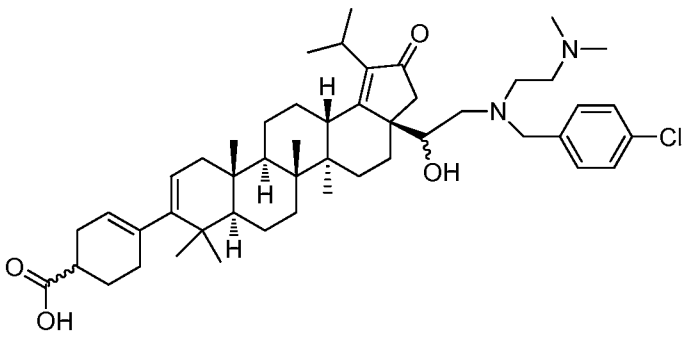

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The compounds above represent the mixture of diastereoisomers, and the two individual disastereomers. In certain embodiments, one of the specific diastereomers may be particularly preferred.

The compounds of the present invention, according to all the various embodiments described above, may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, and by other means, in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, excipients and diluents available to the skilled artisan. One or more adjuvants may also be included.

Thus, in accordance with the present invention, there is further provided a method of treatment, and a pharmaceutical composition, for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition which contains an antiviral effective amount of one or more of the compounds of Formulas I and II together with one or more pharmaceutically acceptable carriers, excipients or diluents. As used herein, the term "antiviral effective amount" means the total amount of each active component of the composition and method that is sufficient to show a meaningful patient benefit, i.e., inhibiting, ameliorating, or healing of acute conditions characterized by inhibition of HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing, inhibiting, ameliorating and/or healing diseases and conditions associated with HIV infection.

The pharmaceutical compositions of the invention may be in the form of orally administrable suspensions or tablets; as well as nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories. Pharmaceutically acceptable carriers, excipients or diluents may be utilized in the pharmaceutical compositions, and are those utilized in the art of pharmaceutical preparations.

When administered orally as a suspension, these compositions are prepared according to techniques typically known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds herein set forth can be administered orally to humans in a dosage range of about 1 to 100 mg/kg body weight in divided doses, usually over an extended period, such as days, weeks, months, or even years. One preferred dosage range is about 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is about 1 to 20 mg/kg body weight in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Also contemplated herein are combinations of the compounds of Formulas I and II herein set forth, together with one or more other agents useful in the treatment of AIDS. For example, the compounds of this disclosure may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following non-limiting table:

ANTIVIRALS

Drug Name	*Manufacturer*	*Indication*
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse trans-criptase (RT) inhibitor)
Amprenavir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen	HIV infection ARC, PGL

	(Los Angeles, CA)	HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus	MedImmune	CMV retinitis

Immune globin		
Cytovene	Syntex	Sight threatening
Ganciclovir		CMV peripheral CMV retinitis
Darunavir	Tibotec- J & J	HIV infection, AIDS, ARC (protease inhibitor)
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)

Efavirenz (DMP 266, SUSTIVA®) (-)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, STOCRINE	Bristol Myers Squibb	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Etravirine	Tibotec/ J & J	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC

Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)

Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-Thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Tipranavir	Boehringer Ingelheim	HIV infection, AIDS, ARC

		(protease inhibitor)
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (VIREAD®)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
EMTRIVA® (Emtricitabine) (FTC)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
COMBIVIR®	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)

Abacavir succinate (or ZIAGEN®)	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
REYATAZ® (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDs, protease inhibitor
FUZEON® (Enfuvirtide or T-20)	Roche / Trimeris	HIV infection AIDs, viral Fusion inhibitor
LEXIVA® (or Fosamprenavir calcium)	GSK/Vertex	HIV infection AIDs, viral protease inhibitor
SELZENTRY® Maraviroc; (UK 427857)	Pfizer	HIV infection AIDs, (CCR5 antagonist, in development)
TRIZIVIR®	GSK	HIV infection AIDs, (three drug combination)
Sch-417690 (vicriviroc)	Schering-Plough	HIV infection AIDs, (CCR5 antagonist, in development)
TAK-652	Takeda	HIV infection

		AIDs, (CCR5 antagonist, in development)
GSK 873140 (ONO-4128)	GSK/ONO	HIV infection AIDs, (CCR5 antagonist, in development)
Integrase Inhibitor MK-0518 Raltegravir	Merck	HIV infection AIDs
TRUVADA®	Gilead	Combination of Tenofovir disoproxil fumarate salt (VIREAD®) and EMTRIVA® (Emtricitabine)
Integrase Inhibitor GS917/JTK-303 Elvitegravir	Gilead/Japan Tobacco	HIV Infection AIDs in development
Triple drug combination ATRIPLA®	Gilead/Bristol-Myers Squibb	Combination of Tenofovir disoproxil fumarate salt (VIREAD®), EMTRIVA® (Emtricitabine), and SUSTIVA® (Efavirenz)
FESTINAVIR® 4'-ethynyl-d4T	Oncolys BioPharma BMS	HIV infection AIDs in development
CMX-157	Chimerix	HIV infection

Lipid conjugate of nucleotide tenofovir		AIDs
GSK1349572 Integrase inhibitor dolutegravir	GSK	HIV infection AIDs
S/GSK1265744 Integrase inhibitor	GSK	HIV infection AIDs

IMMUNOMODULATORS

Drug Name	*Manufacturer*	*Indication*
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	Wyeth Lederle Labs	AIDS, Kaposi's sarcoma
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony	Genetics Institute Sandoz	AIDS

Stimulating Factor		
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl	Merieux Institute	AIDS, ARC

Dithio Carbamate		
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT

SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	*Manufacturer*	*Indication*
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial

Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc diarrhea	Cryptosporidial
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

Additionally, the compounds of the disclosure herein set forth may be used in combination with HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194 and *Inhibitors of the entry of HIV into host cells*. Meanwell, Nicholas A.; Kadow, John F., Current Opinion in Drug Discovery & Development (2003), 6(4), 451-461. Specifically the compounds can be utilized in combination with attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor. HIV attachment inhibitors are also set forth in US 7,354,924 and US 7,745,625.

It will be understood that the scope of combinations of the compounds of this application with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table but includes, in principle, any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present disclosure and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is REYATAZ® (active ingredient Atazanavir). Typically a dose of 300 to 600 mg is administered once a day. This may be co-administered with a low dose of Ritonavir (50 to 500mgs). Another preferred inhibitor of HIV protease is KALETRA®. Another useful inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. These combinations

may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) tenofovir disoproxil fumarate salt and emtricitabine.

In such combinations the compound(s) of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

GENERAL CHEMISTRY (METHODS OF SYNTHESIS)

The present invention comprises compounds of Formulas I and II, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formulas I and II also include pharmaceutically acceptable salts thereof. Procedures to construct compounds of Formulas I and II and intermediates useful for their synthesis are described after the Abbreviations.

Abbreviations

One or more of the following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, may be used throughout the description of the disclosure and the examples:

RT = room temperature
BHT = 2,6-di-tert-butyl-4-hydroxytoluene
CSA = camphorsulfonic acid
LDA = lithium diisopropylamide
KHMDS = potassium bis(trimethylsilyl)amide
SFC = supercritical fluid chromatography
Quant = quantitative
TBDMS = tert-butyldimethylsilane
PTFE = polytetrafluoroethylene
NMO = 4-methylmorpholine-N-oxide

THF = tetrahydrofuran

TLC = thin layer chromatography

DCM = dichloromethane

DCE = dichloroethane

TFA = trifluoroacetic acid

LCMS = liquid chromatography mass spectroscopy

Prep = preparative

HPLC = high performance liquid chromatography

DAST = (diethylamino)sulfur trifluoride

TEA = triethylamine

DIPEA = N,N-diisopropylethylamine

HATU = [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]

DCC = N,N'-dicyclohexylcarbodiimide

DMAP = dimethylaminopyridine

TMS = trimethylsilyl

NMR = nuclear magnetic resonance

DPPA = diphenyl phosphoryl azide

AIBN = azobisisobutyronitrile

TBAF = tetrabutylammonium fluoride

DMF = dimethylformamide

TBTU = O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

Min(s) = minute(s)

h = hour(s)

sat. = saturated

TEA = triethylamine

EtOAc = ethyl acetate

TFA = trifluoroacetic acid

PCC = pyridinium chlorochromate

TLC = thin layer chromatography

Tf_2NPh = (trifluoromethylsulfonyl)methanesulfonamide

dioxane = 1,4-dioxane

PG = protective group

atm = atmosphere(s)

mol = mole(s)

mmol= milimole(s)

mg = milligram(s)

µg = microgram(s)

µl = microliter(s)

µm= micrometer(s)

mm= millimeter(s)

Rpm = revolutions per minute

SM = starting material

TLC = thin layer chromatography

AP = area percentage

Equiv. = equivalent(s)

DMP = Dess-Martin periodinane

TMSCl = trimethylsilyl chloride

TBSCl = tert-Butyldimethylsilyl chloride

TBSOTf = trimethylsilyl trifluoromethanesulfonate

PhMe = toluene

$PhNTf_2$ = N-Phenyl-bis(trifluoromethanesulfonimide)

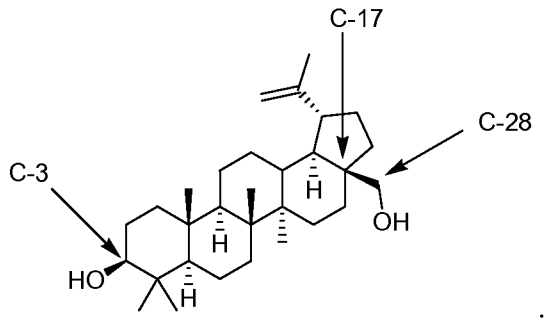
S-Phos = 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TFDO = methyl(trifluoromethyl)dioxirane

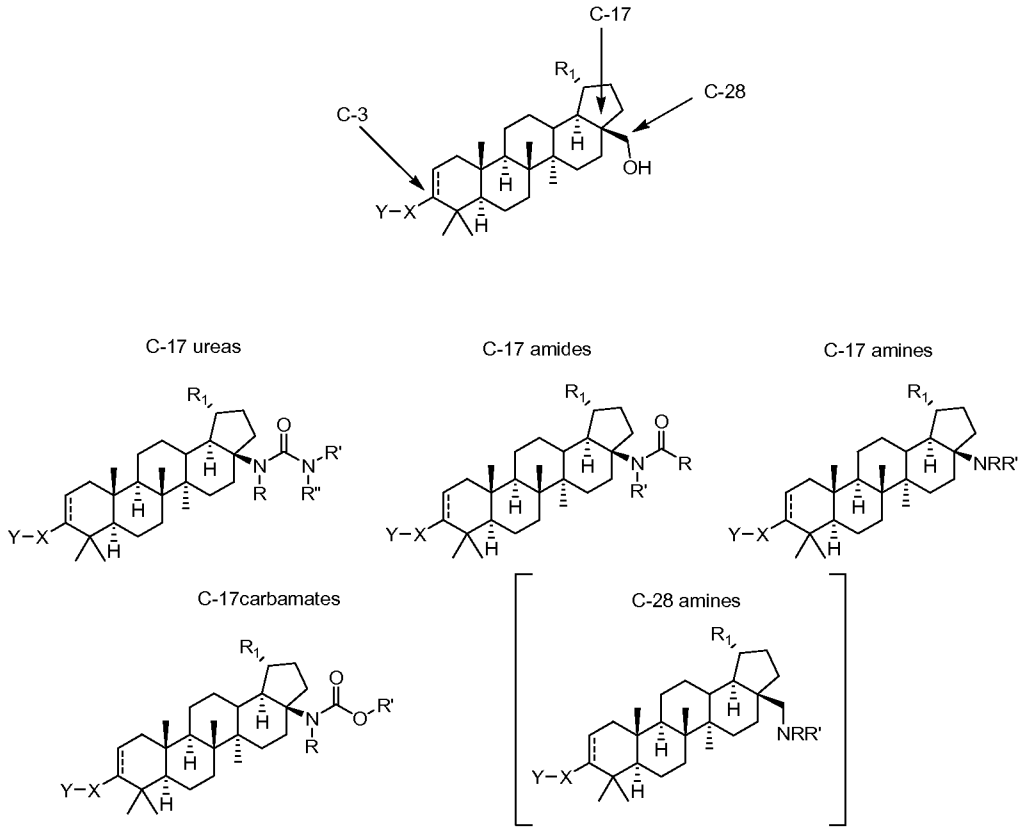
TEMPO = 2,2,6,6-tetramethylpiperidinyloxy

DI = deionized water

The terms "C-3" and "C-28" refer to certain positions of a triterpene core as numbered in accordance with IUPAC rules (positions depicted below with respect to an illustrative triterpene: betulin):



The same numbering is maintained when referring to the compound series in schemes and general descriptions of methods.



EXAMPLES

The following examples illustrate typical syntheses of the compounds of Formulas I and II as described generally above. These examples are illustrative only and are not intended to limit the disclosure in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Chemistry

Typical Procedures and Characterization of Selected Examples:

Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ^{1}H NMR spectra were recorded on Bruker DRX-500f at 500 MHz (or Bruker AV 400 MHz, Bruker DPX-300B, or Varian Gemini 300 at 300 MHz as stated). The

chemical shifts were reported in ppm on the δ scale relative to δTMS = 0. The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30), acetic-d4 (*Acetic Acid d4*) (δ_H 11.6, 2.07), DMSO mix or DMSO-D6-$CDCl_3$ (δ_H 2.50 and 8.25) (ratio 75%:25%), and DMSO-D6 (δ_H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (*J*) is in Hertz. All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

LC/MS methods:

Method 1

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 mL / min
Wavelength = 220 nm
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Phenomenex Luna C18, 3µm, 2.0 x 30 mm

Method 2

Start%B = 0, Final%B = 100 over 1 minute gradient, hold at 100%B
Flow Rate = 1 mL / min
Wavelength = 220 nm
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Phenomenex Luna C18, 3µm, 2.0 x 30 mm

Method 3

Start%B = 2, Final%B = 98 over 1.5 minute gradient, hold at 98%B
Flow Rate = 0.8 mL / min
Wavelength = 220 nm

Solvent A = 100% water, 0.05%TFA

Solvent B = 100% acetonitrile, 0.05% TFA

Column = Waters Aquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm

Method 4

Start%B = 20, Final%B = 100 over 2 minute gradient, hold at 100%B

Flow Rate = 0.8 mL/ min

Wavelength = 220 nm

Solvent A = 90% water, 10% methanol, 0.1% TFA

Solvent B = 10% water, 90% methanol, 0.1% TFA

Column = Waters Xbridge Phenyl, 2.5µm, 2.1 x 50 mm

Method 5

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B

Flow Rate = 1 mL/min

Wavelength = 220 nm

Solvent A = 90% water, 10% methanol, 0.1% TFA

Solvent B = 10% water, 90% methanol, 0.1% TFA

Column = Phenomenex Luna C18, 3µm, 2.0 x 30 mm

Prep HPLC methods:

Method 1

Start %B = 25 Final %B = 100 over 15 minute gradient, hold at 100% B

Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H_2O - 0.1% TFA

Solvent B = 90% ACN - 10% H_2O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5µm

Method 2

Start %B = 25 Final %B = 100 over 20 minute gradient, hold at 100% B

Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H_2O - 0.1% TFA

Solvent B = 90% ACN - 10% H_2O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5µm

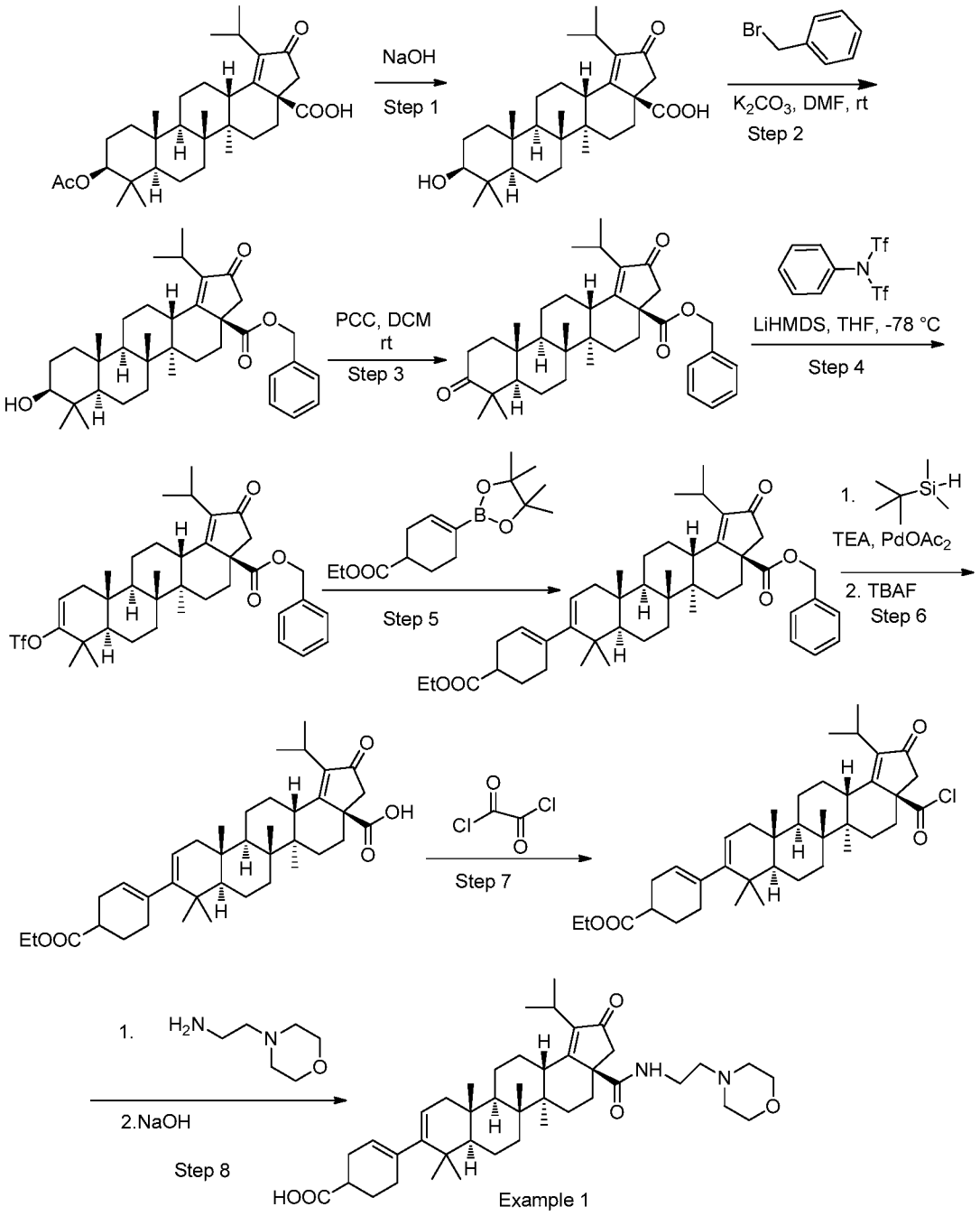
SFC method

First pass

Preparative Column:	Whelko-RR (5´50cm, 10µm, #786710)
BPR pressure:	100 bars
Temperature:	30 °C
Flow rate:	350 mL/min
Mobile Phase:	CO_2/ 2-propanol (85/15)
Detector Wavelength:	215 nm
Separation Program: :	stack injection
Injection:	1.46mL with cycle time: 1.9mins
Sample preparation :	180g / 1000mL IPA:DCM (1:1), 180mg/mL
Throughput:	7.88g/hr

Example 1

Preparation of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)carbamoyl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid



Step 1. Preparation of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid

A mixture of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-acetoxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-

octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid (2 g, 3.90 mmol) and sodium hydroxide (1.560 g, 39.0 mmol) in THF (20 mL), methanol (10 mL) and water (10 mL) was stirred at rt for 48 hours. The reaction mixture was neutralized with 5N HCl and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as a pale yellow solid. (1.92 g, 100%). LCMS: m/e 471.4 $(M+H)^+$, 1.90 min (method 1).

Step 2. Preparation of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-benzyl 9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate

A mixture of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid (1.92 g, 4.08 mmol), (bromomethyl)benzene (0.533 mL, 4.49 mmol) and potassium carbonate (1.240 g, 8.97 mmol) in DMF (10 mL) was stirred at rt for 14 hours. The reaction mixture was quenched with water (20 mL). The solid formed was collected and dried under reduced pressure to provide the title compound as a white solid (2.2 g, 96%). LCMS: m/e 561.4 $(M+H)^+$, 2.44 min (method 1).

Step 3. Preparation of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-benzyl 1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate

A mixture of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-benzyl 9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate (2.2 g, 3.92 mmol) and pyridinium chlorochromate (1.27 g, 5.88 mmol) in THF (10 mL) was stirred at rt for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography using 0-20% ethyl acetate/hexanes to provide the title compound as a white solid. (1.92 g, 88%). LCMS: m/e 559.35 $(M+H)^+$, 2.49 min (method 1).

Step 4. Preparation of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-benzyl 1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-9-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate

To a solution of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-benzyl 1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate (200 mg, 0.358 mmol) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (192 mg, 0.537 mmol) in THF (5 mL) at -78 °C was added lithium bis(trimethylsilyl)amide (0.859 mL, 0.859 mmol). The reaction mixture was stirred at -78 °C for 6 hours. The reaction mixture was quenched with distilled water (8 mL) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude obtained was purified by column chromatography using 0-21% ethyl acetate/hexanes to provide the title compound as a pale yellow solid. (200 mg, 81%). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.52 - 7.31 (m, 5H), 5.60 (dd, *J*=6.8, 1.9 Hz, 1H), 5.32 (d, *J*=12 Hz, 1H), 5.01 (d, *J*=12.1 Hz, 1H), 3.19 (dt, *J*=14.0, 7.0 Hz, 1H), 2.61 - 2.47 (m, 2H), 2.43 (dd, *J*=12.1, 3.8 Hz, 1H), 2.24 (dd, *J*=16.9, 6.9 Hz, 1H), 2.15 (d, *J*=18.6 Hz, 1H), 1.99 - 1.70 (m, 4H), 1.54 - 1.23 (m, 15H), 1.18-1.12 (m, 1H), 1.14 (s, 3H), 1.04 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.78 (s, 3H).

Step 5. Preparation of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-benzyl 9-(4-(ethoxycarbonyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate

A mixture of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-benzyl 1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-9-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate (200 mg, 0.289 mmol), ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (105 mg, 0.375 mmol), (prepared as described in WO 2013123019) sodium carbonate (153 mg, 1.447 mmol) and tetrakis(triphenylphosphine)palladium (16.73 mg, 0.014 mmol) in dioxane (3 mL) and water (1.5 mL) was heated at 80 °C for 2 hours. The reaction mixture was quenched with

distilled water (4 mL) and extracted with ethyl acetate (2 x 4 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude obtained was purified by column chromatography using 0-20% ethyl acetate/hexanes to provide the title compound as a pale yellow oil (156 mg, 78%). LCMS: m/e 695.4 $(M+H)^+$, 3.82 min (method 1). ^1H NMR (500MHz, CHLOROFORM-d) δ 7.42 - 7.31 (m, 5H), 5.42 - 5.35 (m, 1H), 5.31 (d, *J*=12.1 Hz, 1H), 5.24 - 5.17 (m, 1H), 5.01 (d, *J*=12.1 Hz, 1H), 4.16 (q, *J*=7.1 Hz, 2H), 3.20 (dt, *J*=14.0, 7.1 Hz, 1H), 2.58 - 2.47 (m, 3H), 2.44 (dd, *J*=12.1, 3.7 Hz, 1H), 2.37 - 2.29 (m, 2H), 2.25 - 2.12 (m, 3H), 2.09 - 1.98 (m, 2H), 1.91-1.27 (m, 20H), 1.23 (t, *J*=6.7 Hz, 3H), 1.13 - 1.03 (m, 1H), 1.01 - 0.87 (m, 12H), 0.78 (s, 3H).

Step 6. Preparation of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-(4-(ethoxycarbonyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid

A mixture of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-benzyl 9-(4-(ethoxycarbonyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate (150 mg, 0.216 mmol), tert-butyldimethylsilane (37.6 mg, 0.324 mmol), triethylamine (0.060 mL, 0.432 mmol) and palladium acetate (12.11 mg, 0.054 mmol) in dichloroethane (2 mL) was heated at 60 °C for 3 hours. To the mixture were added tert-butyldimethylsilane (37.6 mg, 0.324 mmol), triethylamine (0.060 mL, 0.432 mmol) and palladium acetate (12.11 mg, 0.054 mmol) again and the reaction mixture was heated at 60 °C for another 3 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in dichloromethane (2 mL) and filtered through a pad of celite. To the red filtrate was added tetra-N-butylammonium fluoride (527 mg, 1.511 mmol), the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography using 0-10% MeOH/ethyl acetate to provide the desired product as a pale red oil. (100 mg, 77%). LCMS: m/e 605.4 $(M+H)^+$, 2.74 min (method 1).

Step 7. Preparation of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(chlorocarbonyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-

3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

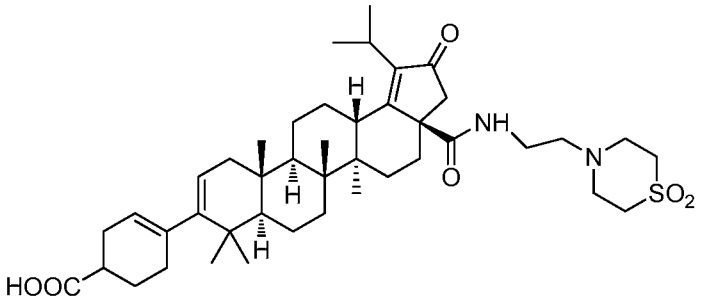
A mixture of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-(4-(ethoxycarbonyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid (70 mg, 0.116 mmol) and oxalyl dichloride (0.039 mL, 0.463 mmol) in dichloromethane (3 mL) was stirred at 20 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to provide the title compound as a pale yellow oil. (60 mg, 83%) which was used in the next step without further purification. LCMS: m/e 619.4 $(M\text{-}Cl+MeOH)^+$, 2.41 min (method 2). LCMS sample was quenched with methanol.

Step 8. To a solution of 2-morpholinoethanamine (9.40 mg, 0.072 mmol), Hunig's Base (0.025 mL, 0.144 mmol) and 4-di(methylamino)pyridine (5.88 mg, 0.048 mmol) in dichloromethane (1 mL) was added a solution of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(chlorocarbonyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (30 mg, 0.048 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was concentrated under reduced pressure and the crude material was purified by HPLC to provide methyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)carbamoyl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate. This ester intermediate was dissolved in dioxane (1 mL) and sodium hydroxide (0.481 mL, 0.481 mmol) was added. The reaction mixture was heated at 80 °C for 2 hours. The reaction mixture was filtered and purified by prep. HPLC to provide the title compound as colorless oil (5.8 mg, 17%). LCMS: m/e 689.4 $(M+H)^+$, 1.78 min (method 1). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.91 (t, *J*=5.6 Hz, 1H), 5.38 (br. s., 1H), 5.30 - 5.19 (m, 1H), 4.09 (br. s., 2H), 3.80 (br. s., 2H), 3.72 - 3.50 (m, 4H), 3.38 - 3.15 (m, 5H), 2.86 (dd, *J*=12.8, 3.0 Hz, 1H), 2.60 - 2.49 (m, 2H), 2.46 (d, *J*=18.9 Hz, 1H), 2.35 - 2.27 (m, 2H), 2.26 - 2.18 (m, 3H), 2.16 - 1.94 (m, 4H), 1.81 (td, *J*=13.8, 3.5 Hz, 1H), 1.76 - 1.63 (m, 3H), 1.62 - 1.43 (m, 6H), 1.41 - 1.30 (m, 2H), 1.27

(d, *J*=6.9 Hz, 3H), 1.22 (d, *J*=6.9 Hz, 3H), 1.19 - 1.14 (m, 1H), 1.12 - 1.08 (m, 3H), 1.05 - 0.93 (m, 12H).

Example 2

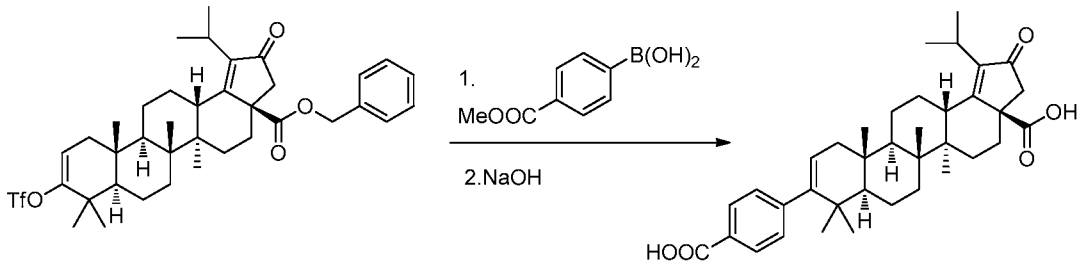
Preparation of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)carbamoyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid



The title compound was prepared following the procedure described above for the preparation of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)carbamoyl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, only 4-(2-aminoethyl)thiomorpholine 1, 1-dioxide was used instead of 4-di(methylamino)pyridine in step 8. The title compound was isolated as colorless oil (7 mg, 19 %). LCMS: m/e 737.4 $(M+H)^+$, 1.86 min (method 1). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.71 (t, *J*=5.5 Hz, 1H), 5.38 (br. s., 1H), 5.30 - 5.20 (m, 1H), 3.67 - 3.57 (m, 4H), 3.56 - 3.49 (m, 2H), 3.45 - 3.37 (m, 4H), 3.33 - 3.26 (m, 1H), 3.14 (t, *J*=6.3 Hz, 2H), 2.88 (dd, *J*=12.7, 3.1 Hz, 1H), 2.60 - 2.49 (m, 2H), 2.44 (d, *J*=18.9 Hz, 1H), 2.36 - 2.27 (m, 2H), 2.26 - 2.18 (m, 3H), 2.16 - 1.94 (m, 4H), 1.82 (td, *J*=13.7, 3.6 Hz, 1H), 1.77 - 1.63 (m, 3H), 1.62 - 1.54 (m, 2H), 1.53 - 1.42 (m, 4H), 1.41 - 1.31 (m, 2H), 1.27 (d, *J*=6.9 Hz, 3H), 1.22 (d, *J*=6.9 Hz, 3H), 1.20 - 1.14 (m, 1H), 1.11 (s, 3H), 1.06 - 0.93 (m, 12H).

Example 3

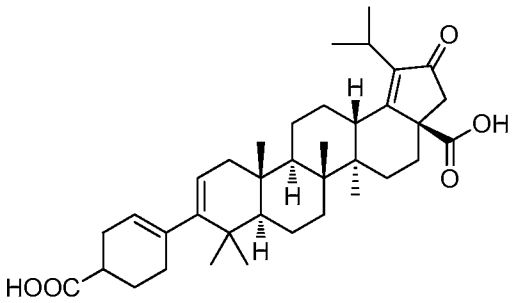
Preparation of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-(4-carboxyphenyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid



A mixture of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-benzyl 1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-9-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate (10 mg, 0.014 mmol), (4-(methoxycarbonyl)phenyl)boronic acid (3.39 mg, 0.019 mmol), tetrakis(triphenylphosphine)palladium (0.836 mg, 0.724 μmol) and sodium carbonate (1.534 mg, 0.014 mmol) in a mixture of dioxane (1 mL) and water (0.5 mL) was heated at 80 °C for 3 hours. The reaction mixture was quenched with distilled water (2 mL) and extracted with ethyl acetate (2 x 2 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to provide (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid. This ester intermediate was dissolved in dioxane (1 mL) and 1N sodium hydroxide (0.145 mL, 0.145 mmol) was added. The reaction mixture was heated at 80 °C for 2 hours. The reaction mixture was filtered and purified by prep. HPLC to provide the title compound as a white solid (1.7 mg, 19%). LCMS: m/e 573.5 $(M+H)^+$, 2.15 min (method 1). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 8.03 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.2 Hz, 5H), 5.36 (d, *J*=5.0 Hz, 1H), 3.39 - 3.14 (m, 1H), 2.96 - 2.44 (m, 3H), 2.32 - 2.18 (m, 1H), 2.10 (d, *J*=6.0 Hz, 1H), 2.04 - 1.87 (m, 2H), 1.80 (d, *J*=16.9 Hz, 1H), 1.71 - 1.34 (m, 9H), 1.33 - 1.26 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.98 (s, 3H).

Example 4

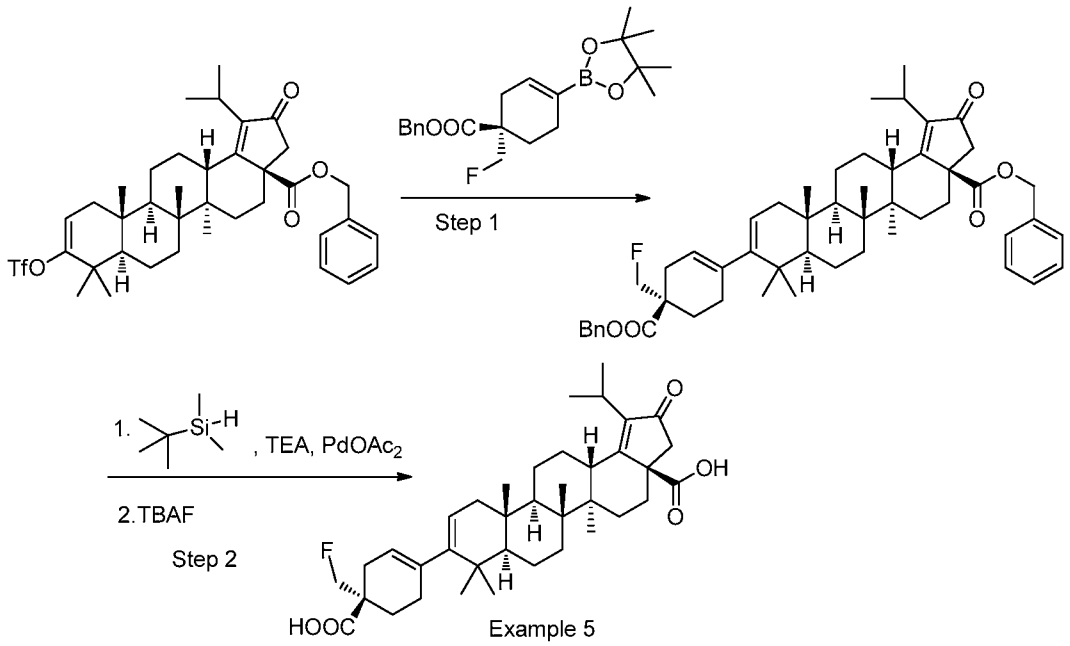
Preparation of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-(4-carboxycyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid



The title compound was prepared following the procedure described for the preparation of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-(4-carboxyphenyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid only 4-(ethoxycarbonyl)cyclohex-1-en-1-yl)boronic acid was used instead of (4-(methoxycarbonyl)phenyl)boronic acid. The product was isolated as colorless oil (2 mg, 29%). LCMS: m/e 577.4 $(M+H)^+$, 2.21 min (method 1). ^{1}H NMR (500MHz, METHANOL-d_4) δ 5.38 (s., 1H), 5.29 - 5.19 (m, 1H), 3.30 - 3.24 (m, 1H), 2.88 (dd, *J*=12.4, 3.5 Hz, 1H), 2.65 - 2.40 (m, 3H), 2.38 - 1.90 (m, 10H), 1.81 - 1.28 (m, 11H), 1.23 (s, 3H), 1.21 (s, 3H), 1.18 – 1.16 (m, 1H), 1.13 (s, 3H), 1.08 - 0.86 (m, 12H).

Example 5

Preparation of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-carboxy-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid



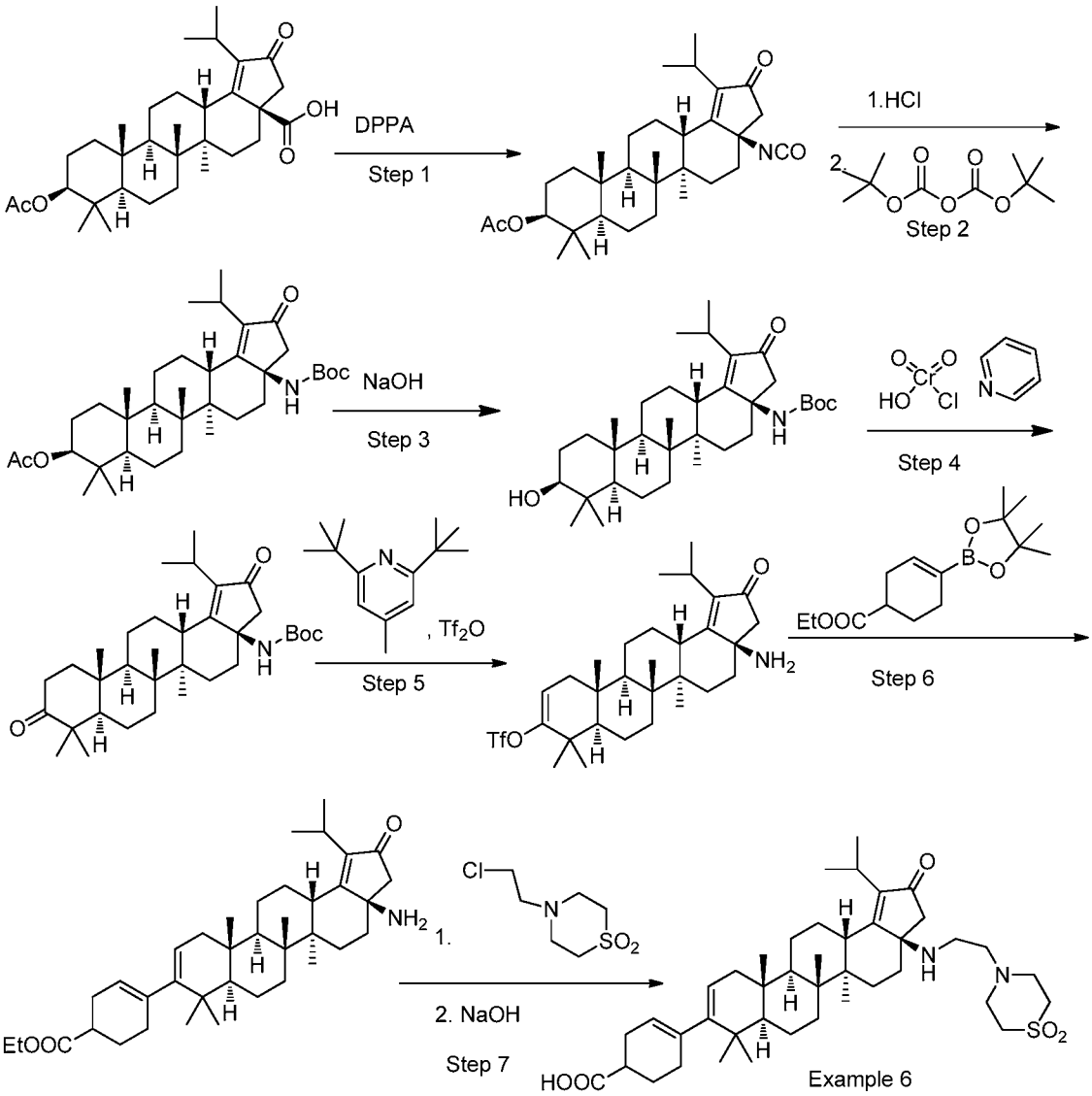
Step 1. Preparation of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-benzyl 9-((S)-4-((benzyloxy)carbonyl)-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate

A mixture of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-benzyl 1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-9-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate (320 mg, 0.463 mmol), (S)-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (191 mg, 0.510 mmol), tetrakis(triphenylphosphine)palladium (26.8 mg, 0.023 mmol) and sodium carbonate (245 mg, 2.316 mmol) in a mixture of dioxane (3 mL) and water (1.500 mL) was heated at 80 °C for 2 hours. The reaction mixture was quenched with distilled water (6 mL) and extracted with ethyl acetate (2 x 6 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography with 0-20% ethyl acetate/hexanes to provide the title compound as a pale yellow oil (180 mg, 49%). LCMS: m/e 789.5 $(M+H)^+$, 2.73 min (method 2).

Step 2. A mixture of (3aR,5aR,5bR,7aR,11aS,11bR,13aS)-benzyl 9-((S)-4-((benzyloxy)carbonyl)-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylate (180 mg, 0.228 mmol), tert-butyldimethylsilane (39.8 mg, 0.342 mmol), triethylamine (0.064 mL, 0.456 mmol) and palladium acetate (12.80 mg, 0.057 mmol) in dichloroethane (5 mL) was heated at 60 °C for 3 hours. The reaction mixture was filtered and the filtrates were concentrated under reduced pressure to provide corresponding silylester intermediate. The intermediate was dissolved in THF (5 mL) and tetra-N-butylammonium fluoride (557 mg, 1.597 mmol) was added. The reaction mixture was stirred for 2 hours and then concentrated under reduced pressure. The resulting crude was dissolved in methanol (5 mL) and purified by HPLC to provide the title compound as a white solid (62 mg, 42%). LCMS: m/e 609.3 $(M+H)^+$, 2.24 min (method 1). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 5.41 (s., 1H), 5.27 (d, *J*=4.9 Hz, 1H), 4.59 (s, 1H), 4.50 (s, 1H), 3.23 (dt, *J*=14.0, 7.0 Hz, 1H), 2.80 (dd, *J*=12.7, 2.8 Hz, 1H), 2.69 - 2.57 (m, 2H), 2.55 - 2.46 (m, 1H), 2.41 - 2.28 (m, 1H), 2.27 - 2.00 (m, 6H), 1.98 - 1.73 (m, 3H), 1.71 - 1.27 (m, 10H), 1.24 (s, 3H), 1.23 (s, 3H), 1.13 – 1.11 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.92 (s, 6H).

Example 6

Preparation of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid



Step 1. Preparation of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-3a-isocyanato-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-9-yl acetate

A mixture of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-acetoxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carboxylic acid (500 mg, 0.975 mmol), diphenyl phosphorazidate (0.317 mL, 1.463 mmol) and triethylamine (0.272 mL, 1.950 mmol) in toluene (10 mL) was refluxed at 110 °C for 3 hours. The reaction mixture was

concentrated under reduced pressure and the residue was purified by column chromatography using 0-16 % ethyl acetate/hexanes to provide the title compound as a white solid (410 mg, 82%). LCMS: m/e 510.35 $(M+H)^+$, 2.72 min (method 1).

Step 2. Preparation of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-3a-((tert-butoxycarbonyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-9-yl acetate

A mixture of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-3a-isocyanato-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-9-yl acetate (410 mg, 0.804 mmol) and HCl (0.244 mL, 8.04 mmol) in THF (10 mL) was stirred at 20 °C for 18 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in THF (10 mL), triethylamine (0.336 mL, 2.413 mmol) and di-tert-butyl dicarbonate (0.374 mL, 1.609 mmol) were added. The reaction mixture was stirred for 20 hours at room temperature. The reaction mixture was quenched with distilled water (20 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as a colorless oil (460 mg, 98%). LCMS: m/e 584.5 $(M+H)^+$, 2.59 min (method 1).

Step 3. Preparation of tert-butyl ((3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)carbamate

A mixture of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-3a-((tert-butoxycarbonyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-9-yl acetate (460 mg, 0.788 mmol) and sodium hydroxide (315 mg, 7.88 mmol) in THF (6 mL), methanol (2 mL) and water (5 mL) was stirred at rt for 18 hours. The reaction mixture was neutralized with 5N HCl and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and

concentrated under reduced pressure to provide the title compound as a pale yellow solid (400 mg, 94%). LCMS: m/e 542.6 $(M+H)^+$, 2.33 min (method 1).

Step 4. Preparation of tert-butyl ((3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)carbamate

A mixture of tert-butyl ((3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)carbamate (400 mg, 0.738 mmol) and pyridinium chlorochromate (239 mg, 1.107 mmol) in THF (5 mL) was stirred at rt for 15 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography using 0-50% ethyl acetate/hexanes to provide the desired product as a white solid (220 mg, 55%). LCMS: m/e 540.5 $(M+H)^+$, 2.44 min (method 1).

Step 5. Preparation of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate

To a solution of tert-butyl ((3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)carbamate (70 mg, 0.13 mmol) in 1,2-dichloroethane (2 mL) was added 2,6-di-tert-butyl-4-methylpyridine (53.22 mg, 0.26 mmol) followed by trifluoromethanesulfonic anhydride (0.033 mL, 0.194 mmol) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C, 2 hours at room temperature and 2 hours at 73 °C. The minute was cooled to room temperature and trifluoromethanesulfonic anhydride (0.016 mL, 0.093 mmol) was added. The reaction mixture was heated at 73 °C for another 4 hours and then cooled at room temperature. Trifluoromethanesulfonic anhydride (0.019 mL, 0.111 mmol) was added and the reaction mixture was heated at 73 °C for another 2 hours. The reaction mixture was quenched with sat. $NaHCO_3$ (3 mL) and extracted with dichloromethane (3 x 3 mL). The combined organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by column chromatography using 30-100% ethyl acetate/hexanes to provide the title

compound as a yellow oil (20 mg, 27%). LCMS: m/e 555.4 $(M-NH_2)^+$, 1.92 min (method 1).

Step 6. Preparation of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

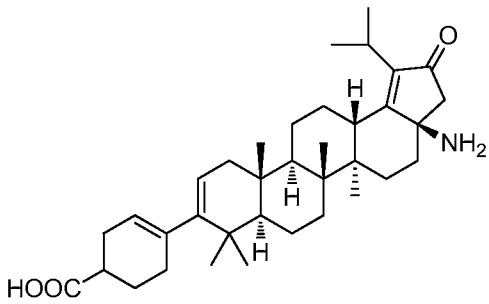
A mixture of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (20 mg, 0.035 mmol), ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (14.56 mg, 0.052 mmol) (prepared as describe in WO 2013123019), sodium carbonate (3.71 mg, 0.035 mmol) and tetrakis(triphenylphosphine)palladium (2.021 mg, 1.749 µmol) in dioxane (1 mL) and water (0.5 mL) was heated at 80 °C for 3 hours. The reaction mixture was quenched with distilled water (2 mL) and extracted with ethyl acetate (2 x 2 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced. The crude was dissolved in dioxane (1 mL), filtered and purified by prep. HPLC to provide the title compound as a white solid (9 mg, 45%). LCMS: m/e 559.4 $(M-NH_2)^+$, 1.78 min (method 1).

Step 7. A mixture of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (4 mg, 6.95 µmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide (2.334 mg, 0.012 mmol), potassium iodide (1.153 mg, 6.95 µmol) and potassium phosphate (4.42 mg, 0.021 mmol) in acetonitrile (0.5 mL) was heated at 100 °C for 12 hours. The reaction mixture was quenched with distilled water (1 mL) and extracted with ethyl acetate (2 x 1 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was dissolved in dioxane (0.5 mL), then sodium hydroxide (0.069 mL, 0.069 mmol) was added. The reaction mixture was heated at 80°C for 1 hour, filtered and purified by prep. HPLC to provide the title compound as a colorless oil (1.2 mg, 23%). LCMS: m/e 709.5 $(M+H)^+$, 1.70 min (method 1). ^1H NMR (500MHz, METHANOL-d_4) δ 5.39 (s., 1H), 5.31 - 5.20 (m, 1H), 3.39 - 3.13 (m, 9H), 3.10 - 3.02 (m, 1H), 3.00 - 2.83 (m, 3H), 2.78 (dd, *J*=12.1, 3.6 Hz, 1H), 2.70 - 2.60 (m, 1H), 2.58 -

2.47 (m, 2H), 2.40 - 1.92 (m, 11H), 1.80 - 1.37 (m, 10H), 1.31 - 1.23 (m, 9H), 1.22-1.20 (m, 1H), 1.10 - 0.95 (m, 12H).

Example 7

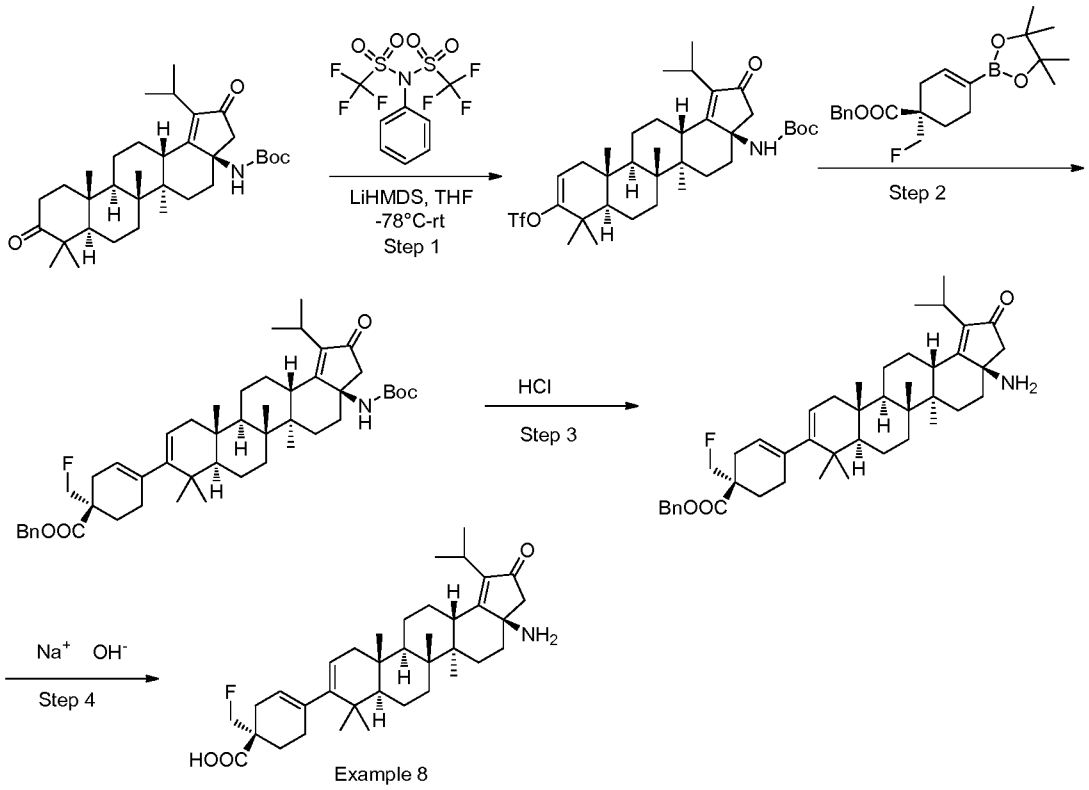
Preparation of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid



A mixture of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (5 mg, 8.68 μmol) and sodium hydroxide (0.087 mL, 0.087 mmol) in dioxane (1 mL) was heated at 80 °C for 2 hours. The reaction was filtered and purified by prep. HPLC to provide the title compound as a colorless oil (2.3 mg, 45%). LCMS: m/e 548.4 $(M+H)^+$, 1.56 min (method 1). ^{1}H NMR (500MHz, METHANOL-d_4) δ 5.39 (br. s., 1H), 5.26 (dt, *J*=6.2, 2.2 Hz, 1H), 3.37-3.33 (m, 1H), 2.89 (dd, *J*=12.5, 3.3 Hz, 1H), 2.66 - 2.46 (m, 3H), 2.38 - 2.06 (m, 7H), 2.05 - 1.83 (m, 4H), 1.80 - 1.66 (m, 3H), 1.62-1.61 (m, 2H), 1.57 - 1.37 (m, 5H), 1.31 - 1.22 (m, 9H), 1.20 (d, *J*=10.7 Hz, 1H), 1.10 - 0.94 (m, 12H).

Example 8

Preparation of (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid



Step 1. Preparation of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-3a-((tert-butoxycarbonyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate

To a solution of tert-butyl ((3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)carbamate (280 mg, 0.519 mmol) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (241 mg, 0.674 mmol) in THF (5 mL) at -78 °C was added lithium bis(trimethylsilyl)amide (0.778 mL, 0.778 mmol). The reaction mixture was stirred at -78 °C for 18 hours. The reaction mixture was quenched with distilled water (20 mL), extracted with ethyl acetate(3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude was purified using silica gel with 0-30% ethyl acetate/hexanes to provide the title compound as a colorless oil (250 mg, 58%). LCMS: m/e 672.4 $(M+H)^+$, 2.78 min (method 1).

Step 2. Preparation of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((tert-butoxycarbonyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate

A mixture of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-3a-((tert-butoxycarbonyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (250 mg, 0.372 mmol), (S)-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (153 mg, 0.409 mmol), tetrakis(triphenylphosphine)palladium (21.50 mg, 0.019 mmol) and sodium bicarbonate (197 mg, 1.861 mmol) in dioxane (3 mL) and water (1.5 mL) was heated up at 80 °C for 4 hours. The reaction mixture was quenched with distilled water (6 mL) and extracted with ethyl acetate (2 x 6 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude obtained was purified using silica gel with 0-25% ethyl acetate/hexanes to provide the title compound as a pale yellow oil (253 mg, 88%). LCMS: m/e 770.6 $(M+H)^+$, 3.09 min (method 1).

Step 3. Preparation of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate

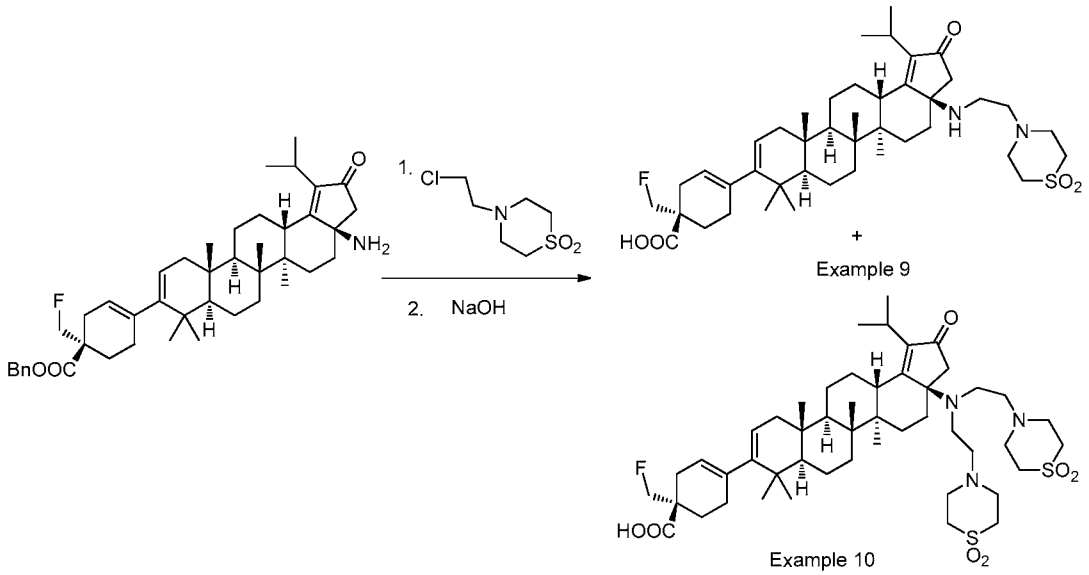
A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((tert-butoxycarbonyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (250 mg, 0.325 mmol) and conc. HCl (0.141 mL, 1.623 mmol) in dioxane (3 mL) was stirred at 20 °C for 15 hours. The reaction mixture was concentrated under reduced pressure to provide the title compound as a pale yellow oil (160 mg, 74%). This material was used in the next step without further purification. LCMS: m/e 653.5 $(M+H-17)^+$, 2.14 min (method 1).

Step 4. A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-

enecarboxylate (9 mg, 0.013 mmol) and 1N sodium hydroxide (0.134 mL, 0.134 mmol) in dioxane (1 mL) was heated up at 80 °C for 2 hours. The reaction mixture was filtered and purified by prep HPLC with 0-70 HCN/water/TFA to provide (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid as a colorless oil (4.2 mg, 51%). LCMS: m/e 563.5 $(M+H-17)^+$, 1.77 min (method 1). ^{1}H NMR (500MHz, ACETONITRILE-d_3) δ 5.36 (br. s., 1H), 5.24 (dd, *J*=6.3, 1.9 Hz, 1H), 4.65 - 4.53 (m, 1H), 4.53 - 4.43 (m, 1H), 3.29 (dt, *J*=14.0, 7.0 Hz, 1H), 2.84 (dd, *J*=12.1, 3.6 Hz, 1H), 2.62 (d, *J*=18.9 Hz, 1H), 2.54 (d, *J*=17.3 Hz, 1H), 2.44 (d, *J*=18.9 Hz, 1H), 2.32 - 1.29 (m, 20H), 1.23 (s, 3H), 1.20 (d, *J*=3.5 Hz, 3H), 1.19 (d, *J*=3.5 Hz, 3H), 1.16 (d, *J*=1.9 Hz, 1H), 0.99 (s, 6H), 0.97 (s, 3H), 0.96 (s, 3H).

Example 9 and Example 10

Preparation of (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid
and (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(bis(2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid



A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (40 mg, 0.060 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide (47.2 mg, 0.239 mmol), potassium iodide (14.87 mg, 0.090 mmol) and potassium phosphate (50.7 mg, 0.239 mmol) in acetonitrile (1 mL) was heated up at 100 °C for 3 days. The reaction mixture was quenched with distilled water (1 mL) and extracted with ethyl acetate (2 x1 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude was dissolved in methanol (1 mL) and purified by prep. HPLC to provide two intermediates: (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate as a colorless oil (8 mg, 16%). LCMS: m/e 831.6 $(M+H)^+$, 2.13 min (method 1) and (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(bis(2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate as colorless oil (15 mg, 25%) . LCMS:

m/e 992.6 $(M+H)^+$, 2.22 min (method 1). These two intermediates were treated with sodium hydroxide independently as follows:

A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (8 mg, 9.62 μmol) and 1N sodium hydroxide (0.151 ml, 0.151 mmol) in acetonitrile (0.5 mL) and dioxane (0.5 mL) was heated up at 80 °C for 2 hours. The reaction mixture was filtered and purified by prep. HPLC to provide (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid as a colorless oil (3 mg, 25%). LCMS: m/e 741.6 $(M+H)^+$, 1.73 min (method 1). ^{1}H NMR (500MHz, ACETONITRILE-d_3) δ 5.36 (br. s., 1H), 5.24 (dd, *J*=6.2, 1.7 Hz, 1H), 4.63 - 4.53 (m, 1H), 4.53 - 4.42 (m, 1H), 3.31 (quin, *J*=6.9 Hz, 1H), 3.17 (d, *J*=3.6 Hz, 4H), 3.09 (d, *J*=3.9 Hz, 4H), 3.03 (ddd, *J*=12.4, 6.5, 3.5 Hz, 1H), 2.99 - 2.85 (m, 2H), 2.85 - 2.78 (m, 1H), 2.77 - 2.72 (m, 1H), 2.69 (d, *J*=19.2 Hz, 1H), 2.54 (d, *J*=17.3 Hz, 1H), 2.41 - 2.32 (m, 2H), 2.29 - 1.42 (m, 19H), 1.24 (s, 3H), 1.22 (dd, *J*=6.9, 3.8 Hz, 6H), 1.19 - 1.15 (m, 1H), 1.00 (s, 3H), 0.99 (s, 6H), 0.97 (s, 3H).

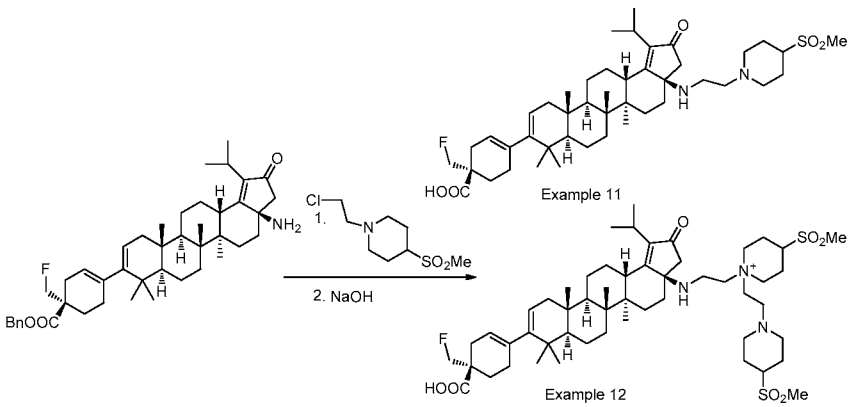
(S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(bis(2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate was treated with NaOH in the same manner described above to afford (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(bis(2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid as a colorless oil (8.1 mg, 56%). LCMS: m/e 902.7 $(M+H)^+$, 1.82 min (method 10). ^{1}H NMR (500MHz, ACETONITRILE-d_3) δ 5.36 (br. s., 1H), 5.24 (dd, *J*=6.1, 1.7 Hz, 1H), 4.73 - 4.27 (m, 2H), 3.89 - 3.58 (m, 8H), 3.56 - 3.40 (m, 8H), 3.38 - 3.05 (m, 6H), 2.98 (dd, *J*=13.2, 3.1

Hz, 2H), 2.79 - 2.61 (m, 2H), 2.54 (d, *J*=17.0 Hz, 1H), 2.33 - 1.85 (m, 11H), 1.80 - 1.65 (m, 2H), 1.62 - 1.36 (m, 8H), 1.27 - 1.05 (m, 11H), 1.03 - 0.85 (m, 12H).

Example 11 and example 12

Preparation of (S)-1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

and 1-(2-(((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-carboxy-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)-4-(methylsulfonyl)-1-(2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)piperidin-1-ium



A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (40 mg, 0.060 mmol), 1-(2-chloroethyl)-4-(methylsulfonyl)piperidine (53.9 mg, 0.239 mmol), potassium iodide (14.87 mg, 0.090 mmol) and potassium phosphate (50.7 mg, 0.239 mmol) in acetonitrile (1 mL) was heated up at 90 °C for 25 hours. The reaction mixture was quenched with distilled water (2 mL) and extracted with ethyl acetate (2 x 2 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude was dissolved in methanol (2 mL) and purified by prep. HPLC to provide two intermediates: (S)-benzyl 1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-

pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as a colorless oil. (12 mg, 24%). LCMS: m/e 859.6 $(M+H)^+$, 2.13 min (method 1) and 1-(2-(((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-((benzyloxy)carbonyl)-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)-4-(methylsulfonyl)-1-(2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)piperidin-1-ium as colorless oil (13 mg, 21%). LCMS: m/e 1048.7 $(M)^+$, 1.49 min (method 3). These two intermediates were treated with sodium hydroxide independently as follows:

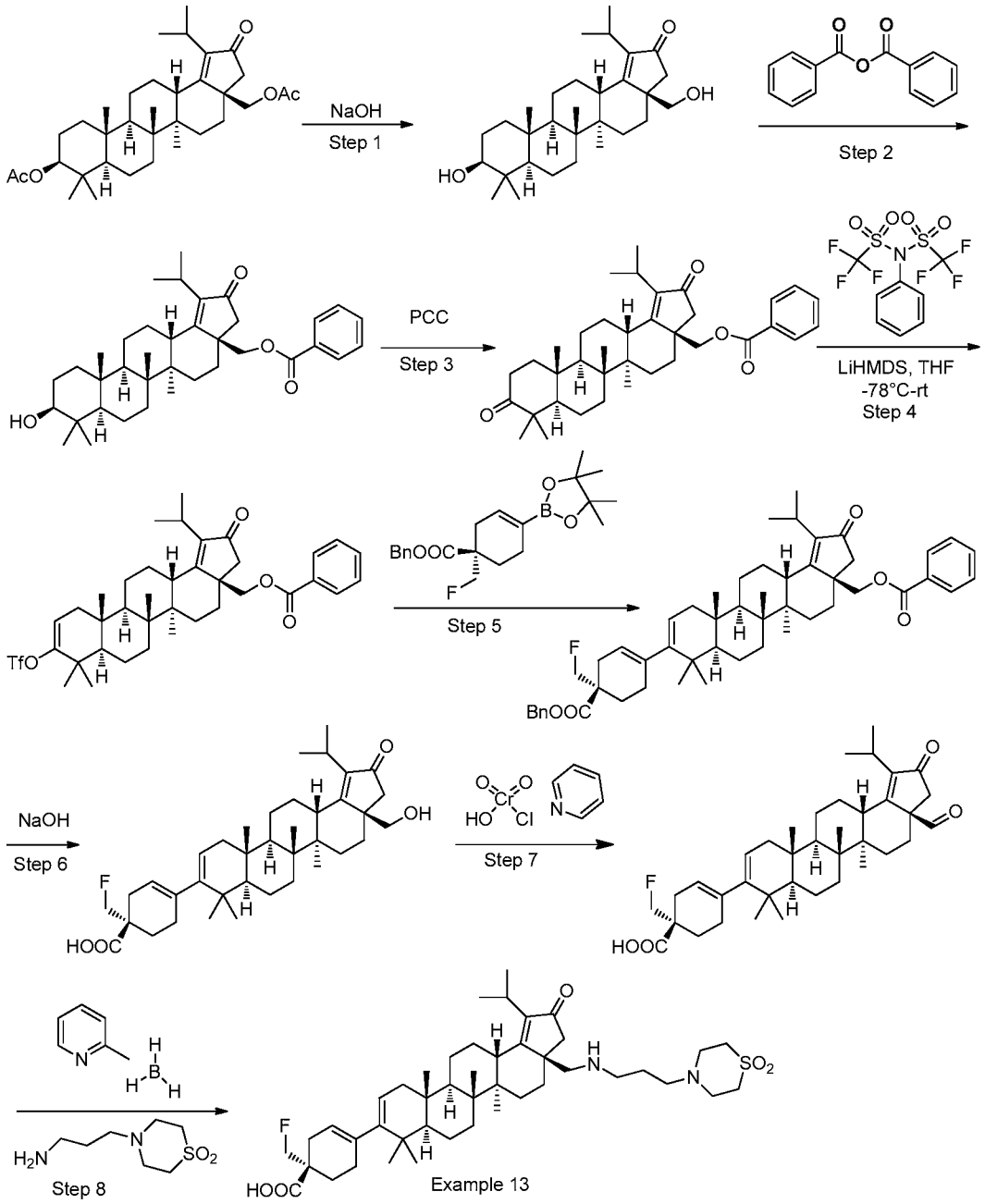
A mixture of (S)-benzyl 1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (12 mg, 0.014 mmol) and 1N sodium hydroxide (0.140 mL, 0.140 mmol) in acetonitrile (0.5 mL) and dioxane (0.5 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and purified by prep. HPLC to provide (S)-1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid as a colorless oil (5 mg, 44%). LCMS: m/e 769.5 $(M+H)^+$, 1.67 min (method 1). ^{1}H NMR (500MHz, ACETONITRILE-d_3) δ 5.36 (br. s., 1H), 5.24 (dd, *J*=6.1, 1.9 Hz, 1H), 4.66 - 4.42 (m, 2H), 3.74 - 3.58 (m, 2H), 3.57 - 3.47 (m, 1H), 3.46 - 3.38 (m, 1H), 3.33 (quin, *J*=6.9 Hz, 1H), 3.24 (tt, *J*=11.6, 3.9 Hz, 1H), 3.17 - 3.10 (m, 1H), 3.08 - 2.92 (m, 3H), 2.91 (s, 3H), 2.81 (dd, *J*=12.4, 3.4 Hz, 1H), 2.68 (d, *J*=19.2 Hz, 1H), 2.54 (d, *J*=16.9 Hz, 1H), 2.40 - 1.90 (m, 14H), 1.89 - 1.79 (m, 1H), 1.78 - 1.66 (m, 2H), 1.65 - 1.52 (m, 3H), 1.51 - 1.35 (m, 5H), 1.24 (s, 3H), 1.22 (dd, *J*=8.4, 7.0 Hz, 6H), 1.19 - 1.14 (m, 1H), 0.98 (s, 3H), 0.98 (s, 3H), 0.97 (s, 6H).

1-(2-(((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-((benzyloxy)carbonyl)-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-

3a-yl)amino)ethyl)-4-(methylsulfonyl)-1-(2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)piperidin-1-ium was treated with NaOH in the same manner described above to afford as a 1-(2-(((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-carboxy-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)-4-(methylsulfonyl)-1-(2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)piperidin-1-ium colorless oil (5.3 mg, 38%). LCMS: m/e 958.6 $(M)^+$, 1.68 min (method 1). ^{1}H NMR (500MHz, ACETONITRILE-d_3) δ 5.36 (br. s., 1H), 5.28 - 5.16 (m, 1H), 4.67 - 4.39 (m, 2H), 3.79 (d, *J*=13.4 Hz, 2H), 3.63 (br. s., 2H), 3.51 (t, *J*=6.6 Hz, 2H), 3.43 - 3.17 (m, 6H), 3.15 - 2.99 (m, 4H), 2.97 (s, 3H), 2.93 - 2.90 (m, 1H), 2.88 (s, 3H), 2.73 - 1.29 (m, 34H), 1.25 - 1.15 (m, 10H), 0.99 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Example 13

Preparation of (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid



Step 1. Preparation of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-2-one

A mixture of ((3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-acetoxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-

octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl acetate (1.5 g, 2.77 mmol) and sodium hydroxide (1.109 g, 27.7 mmol) in THF (40 mL), water (10 mL) and MeOH (10 mL) was stirred at 20 °C for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate (3 x 50 mL). The extracts were combined, washed with brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure to provide the title compound as a white solid (1.28 g, 100%). LCMS: m/e 457.4 $(M+H)^+$, 1.94 min (method 1).

Step 2. Preparation of ((3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate

A mixture of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-2-one (1.28 g, 2.80 mmol), benzoic anhydride (1.268 g, 5.61 mmol) and N,N-dimethylpyridin-4-amine (0.342 g, 2.80 mmol) in pyridine (20 mL) was stirred at 20 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified using silica gel with 0-20% ethyl acetate/hexanes to provide the title compound as a white solid (1.3 g, 83%). LCMS: m/e 561.4 $(M+H)^+$, 2.46 min (method 1).

Step 3. Preparation of ((3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate

A mixture of ((3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate (1.3 g, 2.318 mmol) and pyridinium chlorochromate (1.0 g, 4.64 mmol) in THF (40 mL) was stirred at 20 °C for 15 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified using silica gel with 0-40% ethyl acetate/hexanes to provide the title compound as a white solid. (1.1 g, 85%). LCMS: m/e 559.4 $(M+H)^+$, 2.55 min (method 1).

Step 4. Preparation of ((3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-9-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate

To a solution of ((3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate (210 mg, 0.376 mmol) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (161 mg, 0.451 mmol) in THF (5 mL) at -78 °C was added lithium bis(trimethylsilyl)amide (0.752 mL, 0.752 mmol). The reaction mixture was stirred at -78 °C for 18 hours. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 x 6 mL), the combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude was purified using silica gel with 0-21% ethyl acetate/hexanes to provide the title compound as a white solid (150 mg, 58%). LCMS: m/e 691.4 $(M+H)^+$, 3.05 min (method 1).

Step 5. Preparation of ((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-((benzyloxy)carbonyl)-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate

A mixture of (S)-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (89 mg, 0.239 mmol), ((3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-9-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate (150 mg, 0.217 mmol), tetrakis(triphenylphosphine)palladium (12.54 mg, 10.86 μmol) and sodium carbonate (69.0 mg, 0.651 mmol) in dioxane (3 mL) and water (1 mL) under nitrogen atmosphere was heated up at 80 °C for 4 hours. The reaction mixture was quenched with water (8 ml) and extracted with ethyl acetate (3x 6 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to provide a crude. The crude was purified using silica gel with 0-27% ethyl acetate/hexanes to provide the title compound as a colorless oil (120 mg, 70%). LCMS: m/e 789.6 $(M+H)^+$, 3.65 min (method 1).

Step 6. Preparation of (S)-1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

A mixture of ((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-((benzyloxy)carbonyl)-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate (90 mg, 0.114 mmol) and 1N sodium hydroxide (0.684 mL, 0.684 mmol) in THF (2 mL) was stirred at 20 °C for 3 hours. The reaction mixture was quenched with distilled water (4 mL) and extracted with ethyl acetate (3x4 mL). The extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as a white solid (60 mg, 88%). LCMS: m/e 595.6 $(M+H)^+$, 2.25 min (method 1).

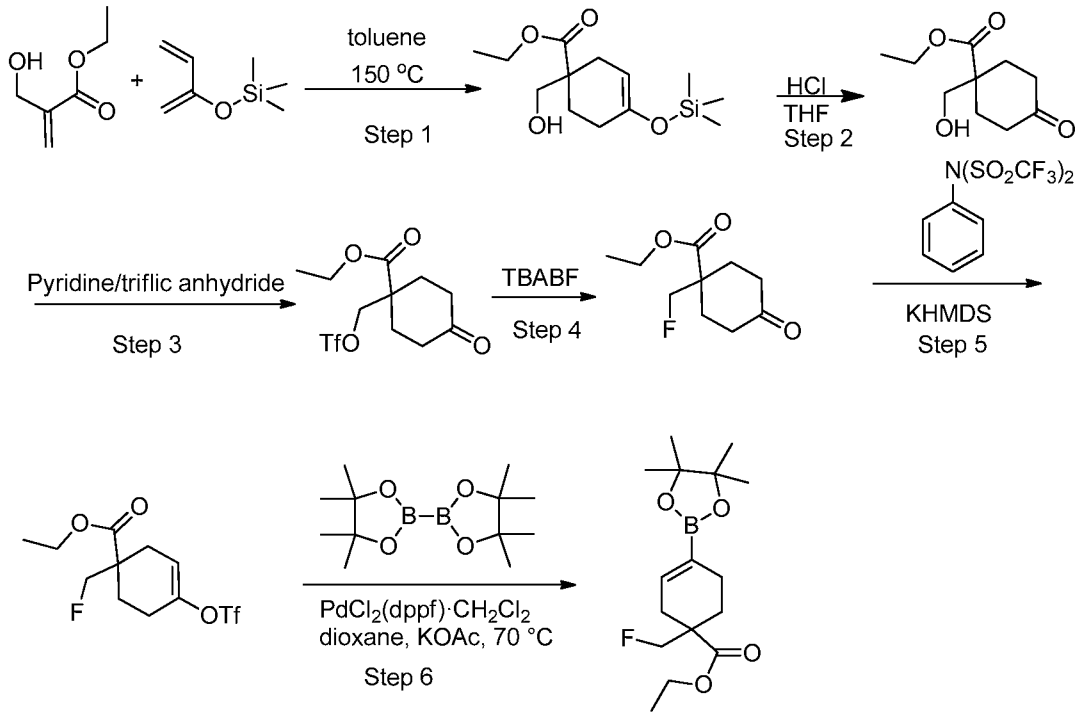
Step 7. Preparation of (S)-1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-formyl-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

A mixture of (S)-1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid (35 mg, 0.059 mmol) and pyridinium chlorochromate (19.02 mg, 0.088 mmol) in dioxane (1 mL) was stirred at 20 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and purified using silica gel with 0-40% ethyl acetate/hexanes to provide the title compound as a pale yellow oil (15 mg, 43%). LCMS: m/e 593.45 $(M+H)^+$, 2.48 min (method 1).

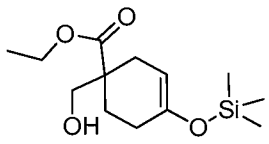
Step 8. A mixture of (S)-1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-formyl-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid (15 mg, 0.025 mmol),borane-2-methylpyridine complex (5.41 mg, 0.051 mmol) and 4-(3-aminopropyl)thiomorpholine 1,1-dioxide (7.30

mg, 0.038 mmol) in methanol (1 mL) was stirred at 20 °C for 3 hours. The reaction mixture was filtered and purified by HPLC with 0-70 actonitrile/water/TFA to provide (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid as a colorless oil (4 mg, 20%). LCMS: m/e 769.7 $(M+H)^+$, 1.74 min (method 1). ^{1}H NMR (500MHz, ACETONITRILE-d_3) δ 5.36 (br. s., 1H), 5.24 (dd, *J*=6.1, 1.7 Hz, 1H), 4.70 - 4.39 (m, 2H), 3.61 - 3.47 (m, 4H), 3.38 (d, *J*=4.9 Hz, 4H), 3.32 - 3.12 (m, 5H), 3.08 (t, *J*=6.8 Hz, 2H), 2.85 (dd, *J*=12.4, 2.9 Hz, 1H), 2.54 (d, *J*=17.2 Hz, 1H), 2.43 (d, *J*=19.2 Hz, 1H), 2.31 - 1.25 (m, 23H), 1.24 - 1.14 (m, 10H), 0.98 (s, 3H), 0.97 (s, 3H), 0.97 (s, 6H).

Preparation of ethyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate

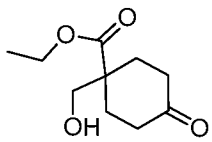


Step 1. Preparation of ethyl 1-(hydroxymethyl)-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate



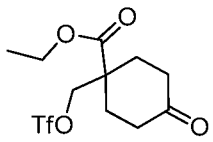
A solution of ethyl 2-(hydroxymethyl)acrylate (5.21 g, 40 mmol) and (buta-1,3-dien-2-yloxy)trimethylsilane (8.54 g, 60.0 mmol) in toluene (100 mL) was flushed with nitrogen, sealed and heated in a pressure flask at 150 °C for 48 h. The resulting light yellow reaction mixture was cooled to room temperature and concentrated in vacuum to give the crude product as an oil which was used for the next step without purification. MS: m/e 201.05 $(M+H\text{-silyl})^+$, 0.839 min (method 4).

Step 2. Preparation of ethyl 1-(hydroxymethyl)-4-oxocyclohexanecarboxylate



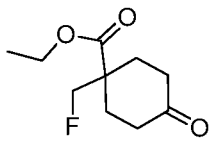
To a solution of ethyl 1-(hydroxymethyl)-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate (10.9 g, 40.0 mmol) in THF (5 mL) was added HCl (0.005N) (1 mL, 5.00 μmol). The resulting solution was stirred at room temperature for 18 h. The reaction mixture was extracted with EtOAc (2 x 10 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) followed by brine (10 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by silica gel chromatography using ethyl acetate/hexanes to give the title compound as a colorless oil (3 g, 37.4%). MS: m/e 200.95 $(M+H)^+$, 0.853 min (method 4). ^1H NMR (400MHz, CHLOROFORM-d) δ 4.28 (q, *J*=7.3 Hz, 2H), 3.75 (s, 2H), 2.57 - 2.45 (m, 2H), 2.45 - 2.33 (m, 4H), 1.86 - 1.71 (m, 2H), 1.39 - 1.30 (m, 3H).

Step 3. Preparation of ethyl 4-oxo-1-((((trifluoromethyl)sulfonyl)oxy)methyl)cyclohexanecarboxylate



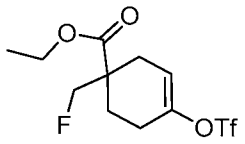
To a stirred mixture of ethyl 1-(hydroxymethyl)-4-oxocyclohexanecarboxylate (1,170 mg, 5.84 mmol) and pyridine (0.614 mL, 7.60 mmol) in DCM (10 mL) at -10 °C was added trifluoromethanesulfonic anhydride (7.60 mL, 7.60 mmol) dropwise. The resulting mixture was stirred at -10 °C for 30 min and washed with ice cold 1N HCl solution and brine. The separated organic layer was dried over sodium sulfate. The solvent was removed and the residue was used as it without purification. MS: m/e 333.05 $(M+H)^+$, 1.969 min (method 4).

Step 4. Preparation of ethyl 1-(fluoromethyl)-4-oxocyclohexanecarboxylate



To a stirred mixture of ethyl 4-oxo-1-((((trifluoromethyl)sulfonyl)oxy)methyl)cyclohexanecarboxylate (1.941 g, 5.84 mmol) in DCM (10 mL) at 25 °C was added tetrabutylammonium bifluoride (3.63 mL, 7.01 mmol) dropwise. The resulting mixture was stirred at 25 °C for 18 hours. The reaction mixture was concentrated under vacuum. Two layers were formed upon stirring the residue obtained in 50 mL of hexanes. The top layer was decanted to a flask and dried under vacuum to yield a colorless oil. This residue was purified by flash chromatography using a 12 g silica gel column and a 0-35% EtOAc in hexanes gradient to yield the title compound as a colorless oil (0.20g, 9.0%). MS: m/e 203.15 $(M+H)^+$, 1.470 min (method 4). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.49 - 4.30 (m, 2H), 4.25 - 4.11 (m, 2H), 2.50 - 2.35 (m, 4H), 2.33 - 2.20 (m, 2H), 1.80 - 1.64 (m, 2H), 1.30 - 1.20 (m, 3H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -223.02 - -225.00 (m, 1F).

Step 5. Preparation of ethyl 1-(fluoromethyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate

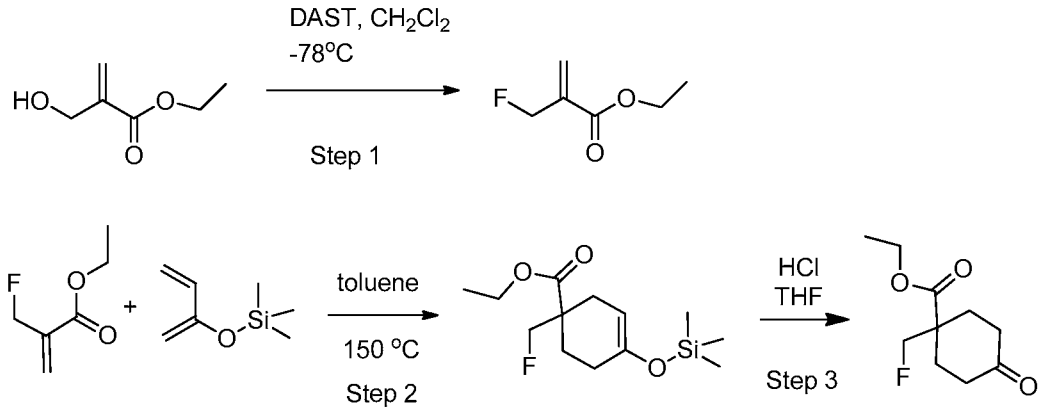


KHMDS (1.27 mL, 1.27 mmol) was added to a pale yellow solution of ethyl 1-(fluoromethyl)-4-oxocyclohexanecarboxylate (0.20 g, 0.98 mmol) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (0.38 g, 1.07 mmol) in THF (20 mL) at -78 °C. The resulting yellow solution was stirred at -78 °C for 2 hr. The reaction mixture was quenched with aqueous saturated ammonium chloride and extracted once with 10 mL of EtOAc. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 12g silica gel column and a 0-10% EtOAc in hexanes gradient to give the title compound as a colorless oil (179 mg, 54.7%). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 5.84 - 5.69 (m, 1H), 4.60 - 4.37 (m, 2H), 4.30 - 4.15 (m, 2H), 2.89 - 2.70 (m, 1H), 2.56 - 2.33 (m, 2H), 2.32 - 2.14 (m, 2H), 2.07 - 1.81 (m, 1H), 1.34 - 1.22 (m, 3H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -225.18 - -225.70 (m, 1F)

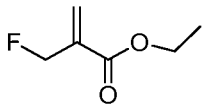
Step 6. To a flask containing ethyl 1-(fluoromethyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (0.179 g, 0.53 mmol) was added bis(pinacolato)diboron (0.143 g, 0.56 mmol), potassium acetate (0.156 g, 1.59 mmol), and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (0.013 g, 0.016 mmol). The mixture was diluted with dioxane (8 mL), flushed with nitrogen, and heated to 70 °C for 5 h. Upon cooling to rt, the mixture was diluted with water (25 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography using a 12 g Isco silica gel column and a 0-10% EtOAc in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give the title compound as a clear, colorless oil (91 mg, 54%). MS: m/e 313.20 $(M+H)^+$, 2.299 min (method 4). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 6.50 (td, *J*=3.9, 2.0 Hz, 1H), 4.59 - 4.32 (m, 2H), 4.23 - 4.13 (m, 2H), 2.74 - 2.52 (m,

1H), 2.30 - 2.08 (m, 3H), 1.98 - 1.69 (m, 2H), 1.32 - 1.20 (m, 15H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -225.59 - -226.36 (m, 1F) .

Alternative method of preparation for the preparation of ethyl 1-(fluoromethyl)-4-oxocyclohexanecarboxylate

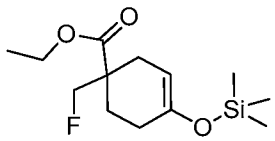


Step 1. Preparation of ethyl 2-(fluoromethyl)acrylate



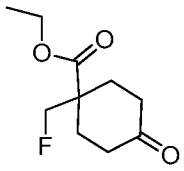
To the solution of ethyl 2-(hydroxymethyl)acrylate (5 g, 38.4 mmol) in DCM (50 mL) was added DAST (6.60 mL, 49.9 mmol) at -78 °C. The reaction mixture was stirred at -78°C for 1 hour. The mixture was warmed to 25°C and continuously stirred for another 3 hours. The reaction mixture was quenched by the addition of CH_2Cl_2 (20 mL) and $NaHCO_3$ saturated aqueous solution (20 mL). The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to give a residual oil which was used in the next step without purification. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 6.49 - 6.33 (m, 1H), 6.03 - 5.87 (m, 1H), 6.45 - 5.84 (m, 2H), 4.27 (q, *J*=7.1 Hz, 2H), 1.33 (t, *J*=7.1 Hz, 3H). ^{19}F NMR (470MHz, CHLOROFORM-d) δ -220.33 - -221.86 (m, 1F).

Step 2. Preparation of ethyl 1-(fluoromethyl)-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate



A solution of ethyl 2-(fluoromethyl)acrylate (4.7 g, 35.6 mmol)) and (buta-1,3-dien-2-yloxy)trimethylsilane (10.12 g, 71.1 mmol) in toluene (100 mL)) was flushed with nitrogen, sealed and heated at 150 °C in a pressure vessel for 48 h. The resulting pale yellow solution was cooled to room temperature and concentrated in vacuum to give the title compound as an oil which was used in the next step without further purification. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.83 (t, *J*=3.3 Hz, 1H), 4.64 - 4.38 (m, 2H), 4.25 - 4.12 (m, 2H), 2.62 - 2.48 (m, 1H), 2.19 - 1.99 (m, 4H), 1.93 - 1.78 (m, 1H), 1.34 - 1.22 (m, 3H), 0.24 - 0.15 (m, 9H). ^{19}F NMR (470MHz, CHLOROFORM-d) δ -224.80 - -225.37 (m, 1F).

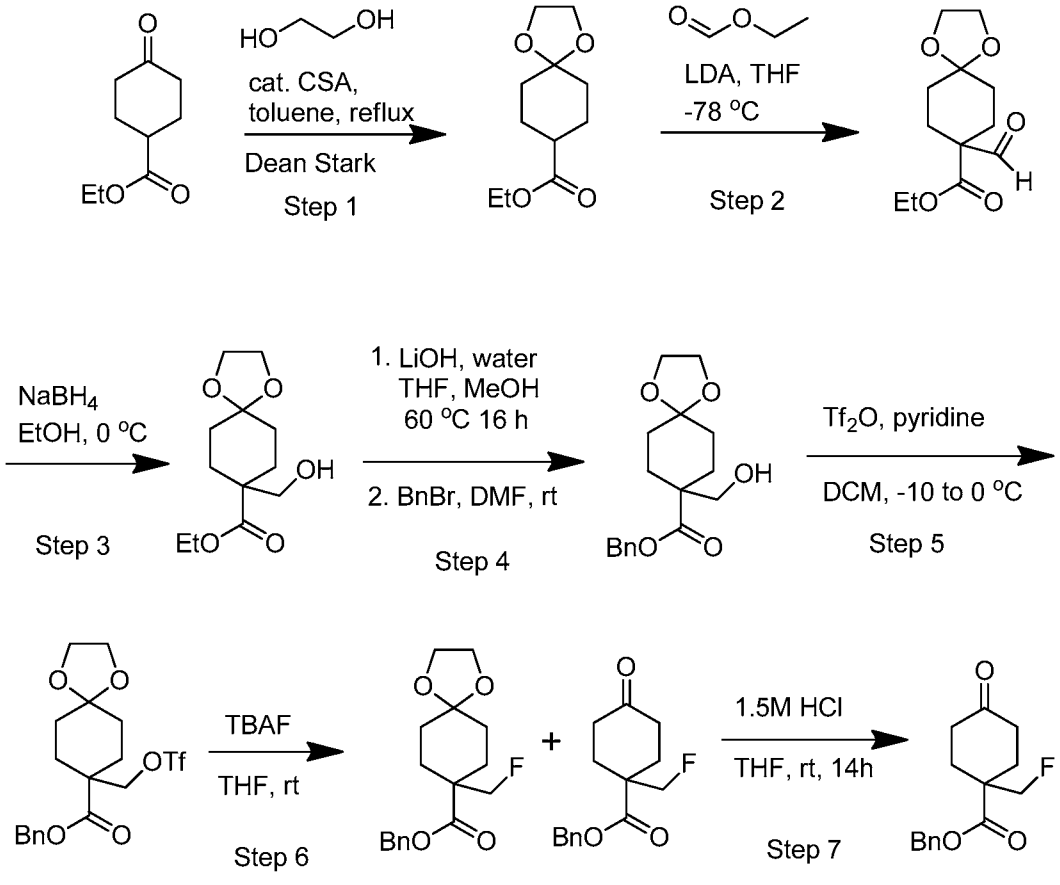
Step 3. Preparation of ethyl 1-(fluoromethyl)-4-oxocyclohexanecarboxylate



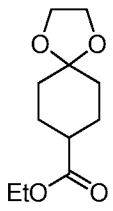
To a solution of ethyl 1-(fluoromethyl)-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate (9.76 g, 35.6 mmol) in THF (5 mL) was added HCl (0.005N) (1 mL, 5.00 µmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (2 x 10 mL), washed with aqueous saturated $NaHCO_3$ (5 mL) followed by brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in* vacuum. The crude product was purified by flash chromatography using a 80 g silica gel column and a 0-25% EtOAc in hexanes gradient. The fraction containing the expected product was collected and concentrated in vacuum to give the title compound as a colorless oil (6.5g, 90.2%). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.59 - 4.42 (m, 2H), 4.30 (q, *J*=7.0 Hz, 2H), 2.58 - 2.34 (m, 6H), 1.88 - 1.73 (m, 2H), 1.33 (t, *J*=7.2 Hz, 3H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -223.54 - -223.99 (m, 1F).

Preparation of benzyl 1-(fluoromethyl)-4-oxocyclohexanecarboxylate

Method A.



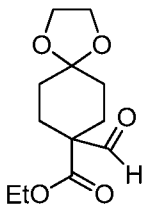
Step 1. Preparation of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate.



Into a 3L, 3 neck round bottom flask was placed ethyl 4-oxocyclohexanecarboxylate (100 g, 570 mmol), ethane-1,2-diol (0.159 L, 2849 mmol), ((1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid (1.324 g, 5.70 mmol) and dry toluene

(1.2 L). A Dean-Stark water trap and a condenser were installed and the mixture heated to reflux with stirring. Immiscible distillate was collected in the Dean-Stark trap and was periodically removed. After 28h of total reflux time, a total of 82 mL of immiscible distillate had been removed from the Dean-Stark trap. After the mixture had cooled to approximately 40 °C, sat. $NaHCO_3$ (400 mL) was added to the reaction mixture with rapid stirring. The mixture was transferred to a separatory funnel, shaken and the phases separated. The organic layer was washed with water (4 x 500 mL), then with 5% $NaHCO_3$ (200 mL) and then with brine (100 mL). The organic material was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum to give a slightly yellow viscous oil (118.50 g, 97% yield). ^1H NMR (400MHz, CHLOROFORM-d) δ 4.15 (q, *J*=7.3 Hz, 2H), 3.96 (s, 4H), 2.41 - 2.27 (m, 1H), 1.96 (dt, *J*=8.7, 4.3 Hz, 2H), 1.89 - 1.74 (m, 4H), 1.68 - 1.49 (m, 2H), 1.27 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (101MHz, CHLOROFORM-d) δ 175.2, 108.1, 64.3, 60.3, 41.6, 33.8, 26.3, 14.3.

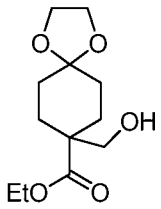
Step 2: Preparation of ethyl 8-formyl-1,4-dioxaspiro[4.5]decane-8-carboxylate.



To a -78 °C solution of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (32.31 g, 151 mmol) in THF (250 mL) was added a solution of 2M lithium diisopropylamide (98 mL, 196 mmol) in THF via a cannula over 5 mins. The resulting brown solution was stirred at -78 °C. After 1h, the cold bath was replaced with an ice bath and the reaction mixture was stirred at 0 °C for 1h. The reaction mixture was again chilled to -78 °C and treated with a solution of ethyl formate (18.65 mL, 226 mmol) in THF (40 mL) added dropwise over 45 min. The resulting light brown reaction mixture was stirred at -78 °C for 1h. The cold bath was removed and to the mixture was added dropwise saturated aqueous NH_4Cl (250 mL) and the mixture stirred at ambient temperature for 30 min. The resulting yellow mixture was extracted with EtOAc (3 x 300 mL). The combined organic phase was washed with 0.5N HCl (300 mL), then with brine, dried over $MgSO_4$, filtered and

concentrated to a brown viscous oil. The crude material was purified by flash column chromatography over silica gel (750 g silica, step elution 9:1 hexanes/EtOAc and 5:1 hexanes/EtOAc) to provide recovered starting material, ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (8.6 g, 40.1 mmol, 26.6 % yield) and the desired product, ethyl 8-formyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (20.1 g, 83 mmol, 55.0 % yield), both as viscous yellow oils. ^{1}H NMR (400MHz, *CHLOROFORM-d*) δ 9.50 (s, 1H), 4.17 (q, *J*=7.2 Hz, 2H), 3.94 - 3.86 (m, 4H), 2.24 - 2.09 (m, 2H), 2.01 (ddd, *J*=13.5, 8.3, 5.1 Hz, 2H), 1.75 - 1.48 (m, 4H), 1.23 (t, *J*=7.2 Hz, 3H).

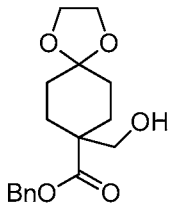
Step 3: Preparation of ethyl 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate.



To a 0 °C solution of ethyl 8-formyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (28.9 g, 119 mmol) in ethanol (300 mL) was added sodium borohydride (5.30 g, 137 mmol) and the resulting mixture was stirred at 0 °C. After 3h, the reaction mixture was quenched with saturated aqueous NH_4Cl (200 mL) added dropwise via a dropping funnel. The ice bath was removed and the resulting slurry was treated slowly with H_2O (150 mL). The resulting mixture was filtered to remove a small amount of white solid. The liquid filtrate was concentrated to remove most of the organic solvent, and the remainder was extracted with EtOAc (4 x 250 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, concentrated and dried in vacuum to give ethyl 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (27.7 g, 113 mmol, 95 % yield) as a clear viscous oil. The material from this experiment was used directly in the next step without further purification. In a separate experiment the crude material was purified by flash column chromatography (SiO_2, elution 3:1 hexanes:EtOAc) to give ethyl 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate in 91% yield. ^{1}H NMR (400MHz, *CHLOROFORM-d*) δ 4.18 (q, *J*=7.1 Hz, 2H), 3.98 - 3.87 (m, 4H), 3.61 (d,

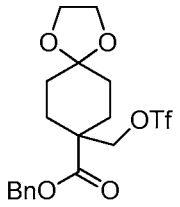
J=6.1 Hz, 2H), 2.23 (br. s., 1H), 2.17 - 2.07 (m, 2H), 1.72 - 1.51 (m, 6H), 1.32 - 1.20 (m, 3H).

Step 4. Preparation of benzyl 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate.



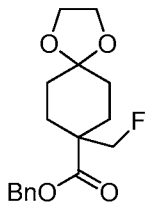
To a solution of ethyl 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (27.6 g, 113 mmol) in THF (150 mL) and MeOH (50 mL) was added a solution of 3N aqueous lithium hydroxide (45.2 mL, 136 mmol) and the mixture was heated to 60 °C with stirring for 17 h. Additional 3N aqueous lithium hydroxide (30.1 mL, 90 mmol) was then added and the mixture was heated to 60 °C for an additional 14h. The reaction mixture was concentrated and dried in vacuum to give a residue containing the corresponding carboxylate (24.5 g, 107 mmol) which was used without further purification.
To this residue in DMF (200 mL) was added benzyl bromide (12.98 mL, 107 mmol) and the resulting mixture was stirred at rt for 17h. The reaction mixture was concentrated to about half of the original volume, diluted with EtOAc (250 mL) and washed with 1N HCl (200 mL). The aqueous phase was extracted with 3 x 250 mL EtOAc. The combined organic phase was washed with H_2O (100 mL), brine, dried over $MgSO_4$, filtered and concentrated to a light yellow viscous oil. The crude material was purified by flash column chromatography (SiO_2, elution step gradient 70:30 hex:EtOAc then 1:1 hex:EtOAc) and dried in vacuum to give benzyl 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (23.1 g, 71.6 mmol, 63% yield over 3 steps). ^{1}H NMR (400MHz, *CHLOROFORM-d*) δ 7.40 - 7.28 (m, 5H), 5.16 (s, 2H), 3.91 (s, 4H), 3.64 (s, 2H), 2.34 (br. s., 1H), 2.22 - 2.12 (m, 2H), 1.70 - 1.63 (m, 4H), 1.62 - 1.54 (m, 2H). ^{13}C NMR (101MHz, *CHLOROFORM-d*) δ 175.3, 135.8, 128.5 (s, 2C), 128.1, 127.8, 108.3, 68.5, 66.4, 64.2, 64.1, 48.1, 31.3, 27.9.

Step 5. Preparation of benzyl 8-((((trifluoromethyl)sulfonyl)oxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate.



In a 500 mL round bottom flask were combined benzyl 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (14.9 g, 48.6 mmol) with dry DCM (250 mL). The solution was chilled in an ice/acetone bath to approx. -10 °C and to it was added pyridine (5.31 mL, 65.7 mmol) followed by the dropwise addition of Tf_2O (11.09 mL, 65.7 mmol) over 30 min. The slightly yellow suspension was stirred at 0 °C (ice water bath) for 1.5 h. The resulting deep orange mixture with significant suspended solids was concentrated in vacuum to leave a residue that was put under vacuum to remove excess triflic anhydride, then the residue was redissolved in DCM (150 mL). The mixture was filtered to remove a significant quantity of white solid which was rinsed with DCM. The deep reddish/orange filtrate was concentrated and purified by flash silica gel column chromatography (330 g silica, elution 100% DCM). Product fractions were combined and concentrated to a thick orange oil which was placed under high vacuum with stirring overnight. The color turned to blue/green. Thus was obtained the desired product (20.94 g, 98% yield) as a blue/green viscous oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.48 - 7.30 (m, 5H), 5.21 (s, 2H), 4.53 (s, 2H), 4.04 - 3.87 (m, 4H), 2.30 - 2.14 (m, 2H), 1.76 - 1.56 (m, 6H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -74.39 (s, 1F).

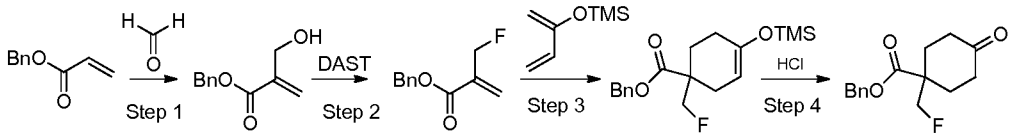
Step 6. Preparation of benzyl 8-(fluoromethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate.



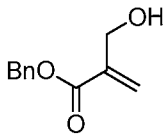
In a 500 mL round bottom flask under nitrogen atmosphere were combined benzyl 8-((((trifluoromethyl)sulfonyl)oxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (20.76 g, 47.4 mmol) with anhydrous THF (150 mL) which was introduced *via* cannula. To the blue solution was added dropwise *via* addition funnel TBAF, 1.0M in THF (71.0 mL, 71.0 mmol) dropwise over 15 min. The mixture immediately turned canary yellow when TBAF was added. The mixture was stirred at rt for 1h. The crude mixture was concentrated to leave a thick oil which was diluted with ethyl acetate (700 mL) and washed with water (2 x 250 mL) and with brine (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to a thick yellow residue. Purification by flash silica gel column chromatography (330 g silica, elution gradient 100% hexanes to 2:1 hexanes:EtOAc) gave the desired product as a yellow oil (13.73 g, 94% yield). LCMS: m/e 309.2 $(M+H)^+$, 1.27 min (method 3). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.44 - 7.31 (m, 5H), 5.21 (s, 2H), 4.45 (d, *J*=47.2 Hz, 2H), 4.01 - 3.89 (m, 4H), 2.28 - 2.16 (m, 2H), 1.75 - 1.55 (m, 6H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -223.25 (t, *J*=46.8 Hz, 1F).

Step 7. In a 2 L round bottom flask cooled in an ice bath were combined benzyl 8-(fluoromethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (13.72 g, 44.5 mmol) with THF (500 mL) and then hydrochloric acid, 1.5M aqueous (534 mL, 801 mmol) was added slowly over 2 min. The ice bath was removed and the mixture was stirred at rt for 15 h. The mixture was concentrated in vacuum to remove the organic and the remnant was extracted with ethyl acetate (300 mL). The ethyl acetate phase was washed with water (2 x 200 mL) and with brine (50 mL). Concentration in vacuum provided the desired product (12.13 g, quantitative) as a yellow oil. LCMS: m/e 265.3 $(M+H)^+$, 1.19 min (method 3). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.47 - 7.32 (m, 5H), 5.27 (s, 2H), 4.52 (d, *J*=47.2 Hz, 2H), 2.57 - 2.42 (m, 4H), 2.42 - 2.31 (m, 2H), 1.87 - 1.76 (m, 2H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -223.41 (t, *J*=46.8 Hz, 1F).

Method B

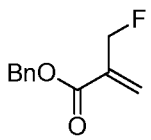


Step 1. Preparation of benzyl 2-(hydroxymethyl)acrylate



In a 1-L flask was placed benzyl acrylate (44.6 mL, 292 mmol), dioxane (290 mL), 1,4-diazabicyclo[2.2.2]octane (32.7 g, 292 mmol) and water (270 mL). The mixture was vigorously stirred at RT forming an emulsion. To the stirring mixture was added an aqueous solution of formaldehyde (37%, 23.9 mL, 321 mmol) and the stirring was continued for 14 hours at RT. The crude reaction mixture was extracted with methylene chloride (3 x 150 mL). The organic layers were separated, combined and washed with a 50:50 mixture of saturated aqueous ammonium chloride and HCl (0.2 N). Evaporation and concentration in vacuum (2 cm Hg) at 45 °C gave 49.1 g of a free flowing syrup. The crude product was purified on a silica gel column eluted with a gradient mixture of EtOAc/Hexanes to give the title compound as a clear colorless syrup (27 g, 141 mmol, 48%). LCMS: m/e 193.05 $(M+H)^+$, 1.78 min (Method 5). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.50 - 7.30 (m, 5H), 6.34 (s, 1H), 5.89 (s, 1H), 5.25 (s, 2H), 4.38 (d, *J*=6.4 Hz, 2H), 2.20 (t, *J*=6.6 Hz, 1H); ^{13}C NMR (126MHz, CHLOROFORM-d) δ 166.1, 139.3, 135.7, 128.7, 128.4, 128.2, 126.2, 66.6, 62.7.

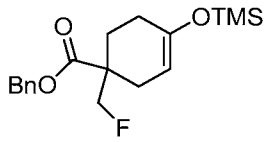
Step 2. Preparation of benzyl 2-(fluoromethyl)acrylate



Benzyl 2-(hydroxymethyl)acrylate (13.7 g, 71.3 mmol) was dissolved in dry methylene chloride (100 mL) under nitrogen and the mixture was cooled at -78 °C. To this stirring solution and using a polyethylene pipette, was added diethylaminosulfur trifluoride (DAST, 13.0 mL, 98 mmol) in 4 portions over a period of 5 minutes. A pale orange

solution was formed. Once addition was complete, the dry-ice bath was removed and the reaction temperature was allowed to rise to RT. Stirring continued at RT for a total of 4 hours. The reaction mixture was transferred dropwise, into a chilled (~4 °C) 50:50 mixture of saturated aqueous sodium bicarbonate and water. Once all of the crude reaction mixture was transferred, it was extracted with BHT-stabilized ether (3 x 150 mL). The organic layers were combined, and washed once with water (50 mL). The solvent from the organic phase was removed in vacuum at sub-ambient temperature (~15 °C) to constant weight (14.2 g, quant.). The crude material was used immediately in the next step. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.44 - 7.34 (m, 5H), 6.49 - 6.43 (m, 1H), 5.99 (dt, *J*=2.8, 1.5 Hz, 1H), 5.26 (s, 2H), 5.13 (d, *J*=46.5 Hz, 2H); ^{19}F NMR (470MHz, CHLOROFORM-d) δ -220.91 (t, *J*=46.2 Hz).

Step 3 - Preparation of benzyl 1-(fluoromethyl)-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate

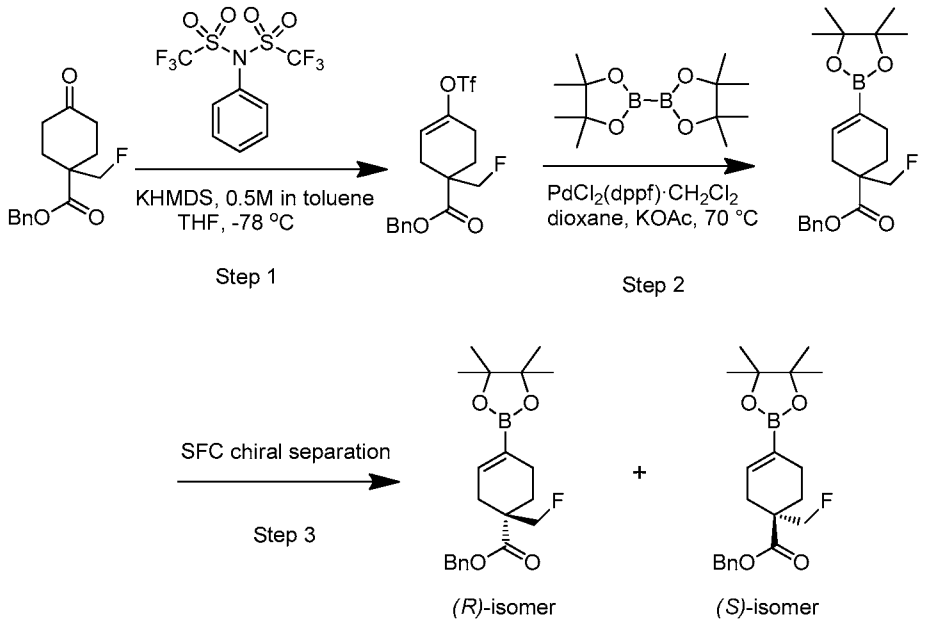


To a 500 mL resealable pressure vessel was added the crude starting material benzyl 2-(fluoromethyl)acrylate (14.2 g, 73.1 mmol) and (buta-1,3-dien-2-yloxy)trimethylsilane (Sigma Aldrich material used as supplied, 18.73 g, 132 mmol) in toluene (200 mL). The vessel was evacuated to 80 micron Hg at -78 °C, followed by purging with nitrogen. The process was repeated twice. The flask was sealed, and warmed to RT before it was immersed into an oil bath at 125 °C for 22 hours. The mixture was allowed to cool to RT. A small aliquot (25 µL) was removed from the crude reaction, vacuum-dried at RT for NMR analyses in ^{1}H and ^{19}F. The NMR results were consistent with the formation of the title compound and small amount of the corresponding Diels-Alder regioisomer. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.43 - 7.29 (m, 5H), 5.18 (s, 2H), 4.80 (d, *J*=3.0 Hz, 1H), 4.52 (dq, *J*=46.9, 8.4 Hz, 2H), 2.65 - 2.49 (m, 1H), 2.21 - 2.00 (m, 4H), 1.92 - 1.78 (m, 1H), 0.24 - 0.12 (m, 9H); ^{19}F NMR (376MHz, CHLOROFORM-d) δ -224.76 (t, *J*=47.7 Hz, 1F) and a minor ^{19}F NMR (376MHz, CHLOROFORM-d) δ -225.20 (t, *J*=46.8 Hz, 0.06F). The crude material was evaporated and dried under vacuum (20 micron Hg)

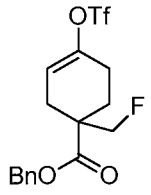
at ~35 °C until constant weight (24.6 g, quant.). This crude material was used in the next step as is without further purification.

Step 4. The crude material from the previous step (24.6 gm, 73 mmol) was dissolved in THF (200 mL) at RT to form a clear solution. Aqueous 1N HCl (2 mL, 2 mmol) and water 4 mL were added. The clear solution was stirred at RT for a total of 16 hours. The crude reaction mixture was quenched with 150 mL of a 50:50 mixture of saturated aqueous ammonium sodium bicarbonate and water. The organic layer was extracted with EtOAc (3 x 75 mL). The organic layers were combined, and evaporated to dryness to give 18.8 g of a thick syrup. The crude residue was purified using a 330 g silica gel column eluted with a gradient mixture of 0 to 25 % v/v of ethyl acetate in hexanes, in ~25 column volumes to render the title compound (15.6 g, 81.0 %). LCMS: m/e 265.15 $(M+H)^+$, 1.60 min (Method 1). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.50 - 7.30 (m, 5H), 5.26 (s, 2H), 4.43 (d, *J*=46.9 Hz, 2H), 2.54 - 2.29 (m, 6H), 1.90 - 1.71 (m, 2H); ^{19}F NMR (376MHz, CHLOROFORM-d) δ -223.47 (t, *J*=46.8 Hz, 1F).

Preparation of *(R)*-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate and *(S)*-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate.

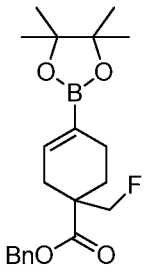


Step 1. Preparation of benzyl 1-(fluoromethyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate.



In a 500 mL round bottom flask were combined benzyl 1-(fluoromethyl)-4-oxocyclohexanecarboxylate (12.65 g, 47.9 mmol) and N,N-bis(trifluoromethylsulfonyl)aniline (18.81 g, 52.7 mmol) in anhydrous tetrahydrofuran (250 mL). The solution was cooled to -78 °C in a dry ice/acetone bath. To the cold solution was added dropwise potassium hexamethyldisilazide, 0.5M in toluene (105 mL, 52.7 mmol) over 30 min. The mixture was stirred at -78 °C for a total of 2.5 h and was then lifted out of the cold bath and stirred for an additional 20 min at rt. The mixture was placed back in the -78 °C bath and to it was added with stirring 125 mL of saturated aqueous ammonium chloride. The resulting suspension was removed from the cold bath and allowed to come to rt while stirring. The mixture was concentrated in vacuum to remove the organic solvent, then to the mixture was added ethyl acetate (600 mL) and water (300 mL) and the mixture was shaken and the phases were separated. The organic layer was washed with water (2 x 200 mL) and with brine (50mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuum to leave a yellow/orange oil. The crude residue was purified by flash silica gel column chromatography (800 g silica, elution isocratic 3:2 hexanes:DCM). Product fractions were combined and concentrated in vacuum to give the desired product (17.43 g, 92% yield) as a very slightly yellow oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.43 - 7.31 (m, 5H), 5.78 (br. s., 1H), 5.26 - 5.15 (m, 2H), 4.52 (dm, *J*=46.7 Hz, 2H), 2.78 (d, *J*=16.9 Hz, 1H), 2.52 - 2.33 (m, 2H), 2.33 - 2.17 (m, 2H), 1.94 (dt, *J*=13.8, 6.9 Hz, 1H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -73.88 (s, 1F), -225.02 (t, *J*=46.8 Hz, 1F).

Step 2. Preparation of benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate.



In a 500 mL round bottom flask were combined benzyl 1-(fluoromethyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (17.42 g, 44.0 mmol), potassium acetate (0.030 g, 0.307 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (11.72 g, 46.1 mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (3.03 mg, 3.69 μmol) and anhydrous dioxane (200 mL). The flask was placed under a nitrogen atmosphere and heated to 70 °C. After 5 h, the mixture was allowed to cool to rt and stood overnight. The reaction mixture was concentrated in vacuum and the crude deep red residue was diluted with ethyl acetate (600 mL) and water (300 mL). The mixture was shaken and phases were separated. The organic was washed with water (250 mL) and then with brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum to a deep red viscous oil. Purification of the crude mixture by flash silica gel column chromatography (800 g silica; step elution 1:3 hexanes:DCM for 4 L, then 100% DCM for 5 L. 2 g of material from the mixed fractions from the first purification were repurified over 80 g of silica gel, elution gradient 100% hexanes to 100% DC,) to give the desired product as a colorless thick oil (13.06 g, 79.4% yield). LCMS: m/e 375.3 $(M+H)^+$, 1.52 min (method 3). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.44 - 7.30 (m, 5H), 6.54 (br. s., 1H), 5.25 - 5.11 (m, 2H), 4.51 (dm, *J*=47.4 Hz, 2H), 2.67 (d, *J*=19.3 Hz, 1H), 2.29 - 2.10 (m, 3H), 2.02 - 1.89 (m, 1H), 1.86 - 1.74 (m, 1H), 1.28 (s, 12H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -225.62 (t, *J*=45.1 Hz, 1F).

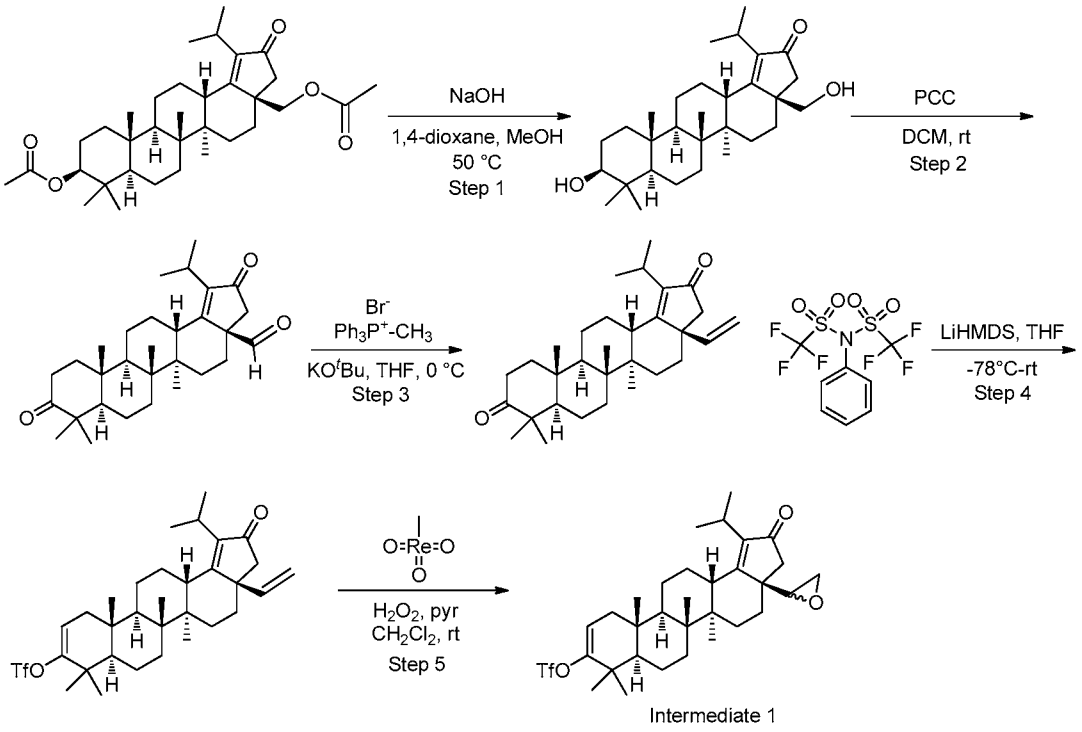
Step 3. Racemic benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (11.15 g, 0.0298 mmol) was purified by supercritical fluid chromatography (SFC Method) to provide the separated single isomer title compounds:

(R)-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate. This was the first isomer to elute from the SFC chiral separation. The product was isolated as a yellow oil (5.45 g, 98% SFC recovery, 99.2% chiral purity). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.42 - 7.30 (m, 5H), 6.54 (br. s., 1H), 5.24 - 5.12 (m, 2H), 4.51 (dm, *J*=47.2 Hz, 2H), 2.67 (d, *J*=19.3 Hz, 1H), 2.27 - 2.10 (m, 3H), 2.00 - 1.90 (m, 1H), 1.85 - 1.75 (m, 1H), 1.28 (s, 12H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -225.62 (t, *J*=46.8 Hz, 1F).

(S)-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate. This was the second isomer to elute from the SFC chiral separation. The product was isolated as a yellow oil (4.94 g, 89% SFC recovery, 99.3% chiral purity). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.43 - 7.31 (m, 5H), 6.54 (br. s., 1H), 5.24 - 5.13 (m, 2H), 4.52 (dm, *J*=47.2 Hz, 2H), 2.68 (d, *J*=19.3 Hz, 1H), 2.27 - 2.10 (m, 3H), 2.01 - 1.90 (m, 1H), 1.85 - 1.75 (m, 1H), 1.28 (s, 12H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -225.61 (t, *J*=48.6 Hz, 1F).

Intermediate 1

Preparation of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate



Step 1. Preparation of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-2-one

To a solution of ((3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-acetoxy-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl acetate (2.00 g, 3.70 mmol) in 1,4-dioxane (30 mL) and methanol (10 mL) was added sodium hydroxide (1N) (18.49 mL, 18.49 mmol). The suspension was warmed to 50 °C for six hours, then cooled to rt and stirred for 18 h. The mixture was partially concentrated under reduced pressure then was acidified with 1N HCl. The solids were collected by filtration and washed with water to give the title compound (1.7 g, 3.7 mmol, 100 % yield) as an off-white solid. LC/MS: m/e 457.4 $(M+H)^+$, 1.86 minutes (method 1). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 3.77 - 3.65 (m, 2H), 3.25 - 3.16 (m, 2H), 2.79 (dd, *J*=12.7, 3.4 Hz, 1H), 2.44 (d, *J*=18.6 Hz, 1H), 2.04 - 1.73 (m, 6H), 1.22 (d, *J*=6.9 Hz, 3H), 1.21 (d, *J*=6.8 Hz, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 1.72 - 0.85 (m, 14H), 0.78 (s, 3H), 0.74 - 0.71 (m, 1H).

Step 2. Preparation of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carbaldehyde

To a suspension of (3aR,5aR,5bR,7aR,9S,11aR,11bR,13aS)-9-hydroxy-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysen-2-one (1.69 g, 3.7 mmol) in dichloromethane (40 mL) was added PCC (1.994 g, 9.25 mmol) in two portions over 15 minutes. The mixture was stirred at rt. After 5 h an additional 0.5 g of PCC was added and the mixture was stirred at rt. After 6.5 h of stirring (total), the mixture was passed through a plug of silica gel and celite (washed with dichloromethane, then 1:1 ethyl acetate:hexanes). The filtrate was concentrated under reduced pressure to give the title product (1.52 g, 3.36 mmol, 91 % yield) as an off-white foam. LC/MS: m/e 453.4 $(M+H)^+$, 3.06 minutes (method 1). ^1H NMR (500MHz, CHLOROFORM-d) δ 9.33 (d, *J*=1.4 Hz, 1H), 3.25 (spt, *J*=6.9 Hz, 1H), 2.59 (dd, *J*=12.8, 3.2 Hz, 1H), 2.56 - 2.36 (m, 4H), 2.11 - 2.03 (m, 2H), 2.02 - 1.84 (m, 3H), 1.24 (d, *J*=6.9 Hz, 3H), 1.24 (d, *J*=6.9 Hz, 3H), 1.09 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 1.64 - 0.90 (m, 11H).

Step 3. (3aS,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-vinyl-3a,4,5,5a,5b,6,7,7a,8,10,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-2,9(3H)-dione

A suspension of methyltriphenylphosphonium bromide (1.559 g, 4.37 mmol) in THF (15 mL) was cooled to 0 °C and potassium *tert*-butoxide (1M in THF) (4.70 mL, 4.70 mmol) was added. The mixture was removed from the ice bath and stirred for 30 minutes at rt. The mixture was again cooled to 0 °C and a solution of (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,9-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13,13a-octadecahydro-2H-cyclopenta[a]chrysene-3a-carbaldehyde (1.52 g, 3.36 mmol) in THF (15 mL) was added to the cooled solution and the mixture was stirred for 30 minutes 0 °C. The mixture was diluted with water (50 mL) and partially concentrated under reduced pressure. The mixture was extracted with ethyl acetate (3 x 50 mL), washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was

purified by flash chromatography using a 0-20% ethyl acetate in hexanes gradient and an 80 g silica gel column to give the title compound (1.15 g, 2.55 mmol, 76 % yield) as an off-white solid. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 5.86 (dd, *J*=17.7, 10.7 Hz, 1H), 5.15 (dd, *J*=10.7, 0.9 Hz, 1H), 4.98 (dd, *J*=17.7, 0.8 Hz, 1H), 3.19 (spt, *J*=7.0 Hz, 1H), 2.92 (dd, *J*=12.8, 3.6 Hz, 1H), 2.56 - 2.43 (m, 2H), 2.27 (d, *J*=18.4 Hz, 1H), 2.13 (d, *J*=18.4 Hz, 1H), 2.10 - 2.05 (m, 1H), 2.01 - 1.82 (m, 4H), 1.23 (d, *J*=6.9 Hz, 3H), 1.22 (d, *J*=6.9 Hz, 3H), 1.10 (s, 3H), 1.09 (s, 3H), 1.64 - 1.07 (m, 11H), 1.04 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H).

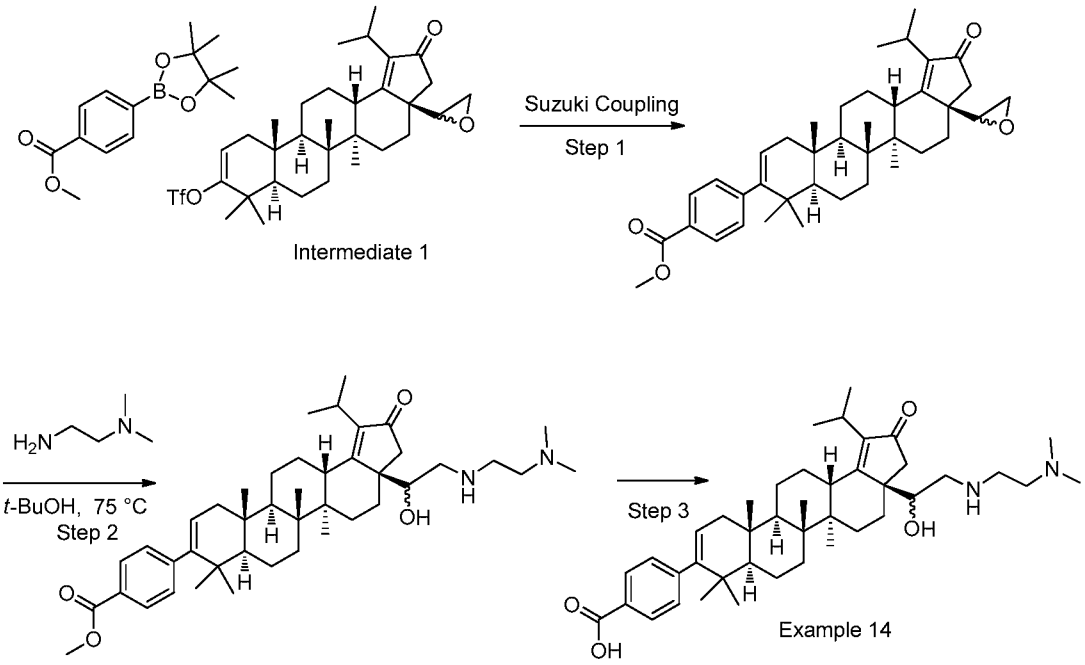
Step 4. Preparation of (3aS,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3a-vinyl-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate

A flask containing a solution of (3aS,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-vinyl-3a,4,5,5a,5b,6,7,7a,8,10,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysene-2,9(3H)-dione (1.15 g, 2.55 mmol) and N,N-bis(trifluoromethylsulfonyl)aniline (1.094 g, 3.06 mmol) in THF (20 mL) was cooled to -78 °C. To the cooled solution was added LiHMDS (1M in THF) (5.61 mL, 5.61 mmol). The mixture was stirred for 1h at -78 °C, then was removed from the ice bath and warmed to rt and monitored by TLC. After 45 minutes, TLC showed only a trace of starting material remaining. The mixture was diluted with sat. aq. ammonium chloride solution (40 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-8% acetone in hexanes gradient and an 80 g silica gel column. The residue was purified again by flash chromatography using a 0-7% acetone in hexanes gradient to give the title compound (1.02 g, 1.750 mmol, 69 % yield) as a white foam. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 5.86 (dd, *J*=17.7, 10.6 Hz, 1H), 5.60 (dd, *J*=6.8, 2.0 Hz, 1H), 5.16 (dd, *J*=10.6, 0.8 Hz, 1H), 4.98 (dd, *J*=17.7, 0.8 Hz, 1H), 3.19 (spt, *J*=6.9 Hz, 1H), 2.92 (dd, *J*=12.8, 3.4 Hz, 1H), 2.31 - 2.21 (m, 2H), 2.13 (d, *J*=18.6 Hz, 1H), 2.10 - 2.05 (m, 1H), 2.01 - 1.81 (m, 4H), 1.23 (d, *J*=6.9 Hz, 3H), 1.22 (d, *J*=6.9 Hz, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.61 - 1.07 (m, 10H), 1.04 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H). ^{19}F NMR (471MHz, CHLOROFORM-d) δ -74.79 (s, 1F).

Step 5. To a flask containing (3aS,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3a-vinyl-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.1 g, 0.172 mmol) and methyltrioxorhenium(VII) (2.138 mg, 8.58 μmol) was added dichloromethane (2 mL), pyridine (1.665 μl, 0.021 mmol), and

Example 14

Preparation of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)benzoate

To a sealable vial containing (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.03 g, 0.050 mmol) was added (4-(methoxycarbonyl)phenyl)boronic acid (0.018 g, 0.100 mmol), phosphoric acid,

potassium salt (0.032 g, 0.150 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-phos) (1.543 mg, 3.76 μmol), and palladium (II) acetate (0.562 mg, 2.505 μmol). The mixture was diluted with 1,4-dioxane (1 mL) and water (0.2 mL), then was flushed with nitrogen and the vial was sealed and heated to 70 °C. After 3 h of heating, the mixture was cooled to rt. The mixture was diluted with water (3 mL) and extracted with dichloromethane (3 x 4 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-20% ethyl acetate in hexanes gradient and a 24 g silica gel column to give the title compound along with minor impurities that were carried to the next step with no additional purification (18 mg total). LC/MS: m/e 585.3 $(M+H)^+$, 2.95 minutes (method 1).

Step 2. Preparation of methyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)benzoate

To a solution of methyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)benzoate (0.018 g, 0.031 mmol) in *t*-BuOH (0.5 mL) was added N,N-dimethylethylenediamine (0.034 mL, 0.308 mmol). The mixture was heated to 75 °C for 9 h and then cooled to rt. The crude reaction mixture was diluted with methanol and purified by prep HPLC (method 1) to give the TFA salt of the title compound (0.008 g, 10.17 μmol, 33% yield) as a clear film. LC/MS: m/e 673.5 $(M+H)^+$, 1.82 minutes (method 1). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.96 (d, *J*=8.4 Hz, 2H), 7.23 (d, *J*=8.4 Hz, 2H), 5.34 (d, *J*=4.7 Hz, 1H), 4.67 - 4.60 (m, 1H), 3.94 (s, 3H), 3.63 - 3.46 (m, 4H), 3.34 - 3.23 (m, 2H), 3.19 - 3.10 (m, 1H), 3.02 - 2.96 (m, 1H), 2.93 (s, 6H), 2.52 - 2.42 (m, 1H), 2.22 (dd, *J*=17.1, 6.2 Hz, 1H), 2.12 - 2.04 (m, 1H), 1.94 - 1.71 (m, 5H), 1.07 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 1.67 - 0.82 (m, 21H).

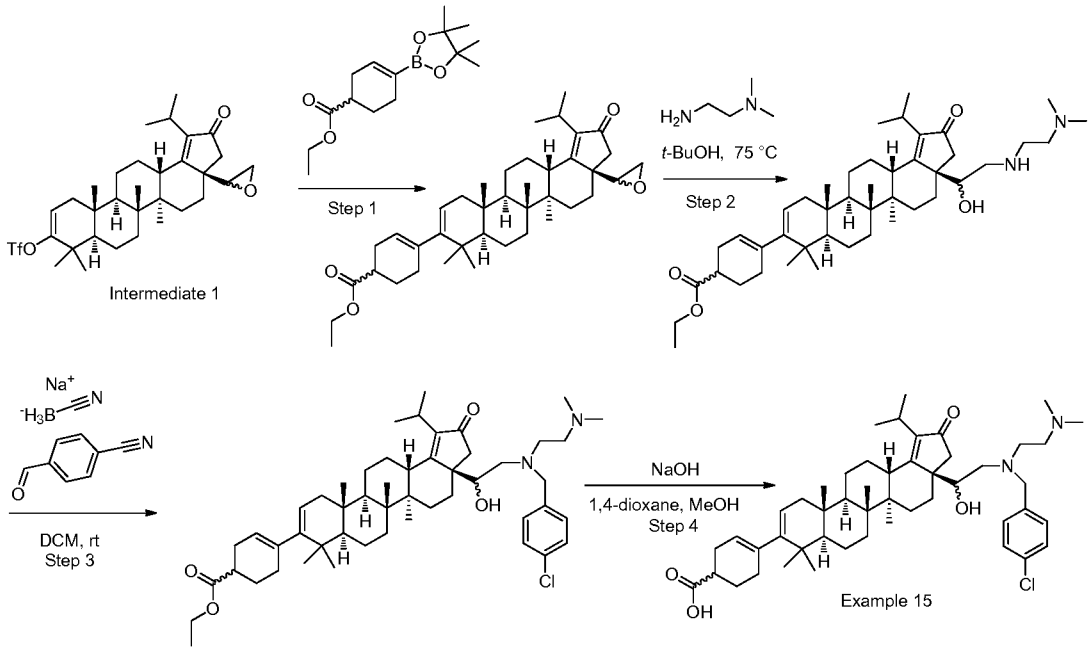
Step 3. To a solution of methyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-

cyclopenta[a]chrysen-9-yl)benzoate, TFA (0.008 g, 10.17 μmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.051 mL, 0.051 mmol) and the mixture was heated to 70 °C. After 4 h of heating, the mixture was cooled to rt and stirred overnight.

The mixture was again heated to 70 °C for 23.5 h and then, it was cooled to rt. An additional 0.051 mL of 1N NaOH was added and the mixture was heated to 70 °C for 4 h. The mixture was cooled to rt and purified by prep HPLC (method 2) to give the bis TFA salt of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)benzoic acid (0.0043 g, 0.0048 mmol, 47% yield) as a white solid. LC/MS: m/e 659.4 $(M+H)^+$, 1.54 minutes (method 1). ^{1}H NMR (500MHz, Acetic Acid-d_4) δ 8.04 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 5.40 (d, *J*=4.6 Hz, 1H), 4.77 (d, *J*=8.5 Hz, 1H), 3.86 - 3.67 (m, 4H), 3.67 - 3.58 (m, 1H), 3.35 - 3.25 (m, 1H), 3.17 (t, *J*=11.7 Hz, 1H), 3.09 (dd, *J*=11.6, 3.5 Hz, 1H), 3.03 (s, 6H), 2.58 (d, *J*=18.8 Hz, 1H), 1.15 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 2.33 - 0.75 (m, 26H).

Example 15

Preparation of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((4-chlorobenzyl)(2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid



Step 1. Preparation of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To vial containing (3aR,5aR,5bR,7aR,11aR,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.07 g, 0.117 mmol) was added ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.033 g, 0.117 mmol), (prepared as described in WO 20131230822), phosphoric acid, potassium salt (0.074 g, 0.351 mmol), palladium (II) acetate (1.312 mg, 5.85 µmol), and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-phos) (3.60 mg, 8.77 µmol). The mixture was flushed with nitrogen, then the vial was sealed and heated to 65-70 °C. After 10 h of heating, the mixture was cooled to rt. The mixture was diluted with water (7 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-25% EtOAc in hexanes gradient and a 12 g silica gel column to give 0.057g of the title compound as a mixture of isomers. LC/MS: m/e 603.5 $(M+H)^+$, 3.28 minutes (method 1).

Step 2: Preparation of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To a solution of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.057 g, 0.095 mmol) in *t*-BuOH (1 mL) was added N,N-dimethylethylenediamine (0.104 mL, 0.945 mmol) and the mixture was heated to 75 °C. After 23 h of heating, the mixture was cooled to rt, diluted with methanol, and purified by prep HPLC (method 2). The fractions containing the product were combined and concentrated under reduced pressure. The residue was dissolved with dichloromethane (15 mL) and washed with sat. aq. $NaHCO_3$. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the diastereomeric mixture of the title compound (0.029 g, 0.042 mmol, 44 % yield) as a clear, colorless film. LC/MS: m/e 691.6 $(M+H)^+$, 1.90 minutes (method 1).

Step 3. Preparation of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((4-chlorobenzyl)(2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

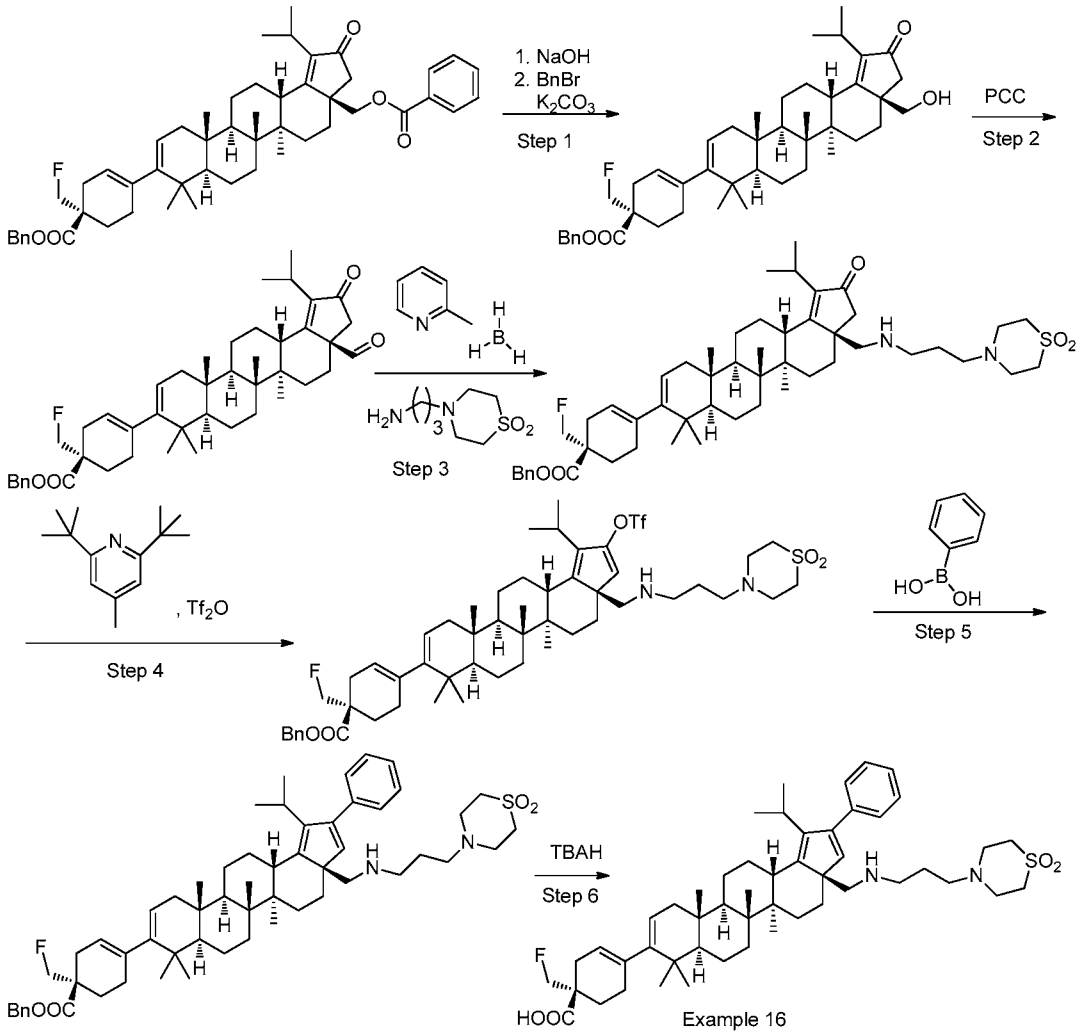
To a solution of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.029 g, 0.042 mmol) in dichloromethane (1 mL) was added 4-cyanobenzaldehyde (8.25 mg, 0.063 mmol) followed by sodium cyanoborohydride (5.27 mg, 0.084 mmol). The mixture was stirred at rt t for 16 h, then an additional 4 mg of 4-cyanobenzaldehyde followed by 5 mg of sodium cyanoborohydride were added to the mixture. The mixture was stirred at rt for 5 h and then diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method 1) to give the bis

TFA salt of the diasteromeric mixture of the title compound (0.015 g, 0.014 mmol, 34 % yield) as a clear, colorless film. LC/MS: m/e 815.6 $(M+H)^+$, 2.30 minutes (method 1).

Step 4. To a solution of ethyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((4-chlorobenzyl)(2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate, 2 TFA (0.015 g, 0.014 mmol) in 1,4-dioxane (1 mL) and methanol (0.5 mL) was added sodium hydroxide (1N) (0.092 mL, 0.092 mmol). The mixture was heated to 75 °C for 16 h then was cooled to rt and was purified by prep HPLC (method 1) to give the bis TFA salt of 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(2-((4-chlorobenzyl)(2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid (0.007 g, 6.89 μmol, 49 % yield) as a white film. LC/MS: m/e 787.6 $(M+H)^+$, 1.90 minutes (method 1). Some of the characteristic chemical shifts of the diasteromeric mixture are as follows: ^{1}H NMR (500MHz, Acetic Acid-d_4) δ 7.66 - 7.61 (m, 1.25 H), 7.59 - 7.55 (m, 0.75H), 7.52 - 7.47 (m, 2H), 5.40 (br. s., 1H), 5.25 (d, *J*=6.0 Hz, 1H), 4.58 - 4.52 (m, 1H), 4.44 - 4.20 (m, 2H), 2.99 (s, 2.25H), 2.94 (s, 3.75H).

Example 16

Preparation of (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-phenyl-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid



Step 1. Preparation of (S)-benzyl 1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

A mixture of ((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-9-((S)-4-((benzyloxy)carbonyl)-4-(fluoromethyl)cyclohex-1-en-1-yl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-3a-yl)methyl benzoate (350 mg, 0.444 mmol) and sodium hydroxide (2.218 mL, 2.218 mmol) in THF (6 mL), water (3 mL) and MeOH (3 mL) was stirred at 20 °C for 15 h. The reaction mixture was quenched with distilled water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic phases were dried over sodium

sulfate, filtered and concentrated under reduced pressure to provide the crude intermediate.

To this crude in DMF (8 mL) was added potassium carbonate (184 mg, 1.331 mmol) and benzyl bromide (0.079 mL, 0.665 mmol). The reaction mixture were stirred for 36 h. The reaction mixture was quenched with 10 mL distilled water and extracted with ethyl acetate (3 x 10 mL). The organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified in silica gel with 0-47% ethyl acetate/hexanes to provide the desired product as a white solid (200 mg, 66%). LCMS: m/e 685.7 $(M+H)^+$, 3.03 min (method 1).

Step 2. Preparation of (S)-benzyl 1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-formyl-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

(S)-benzyl 1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (200 mg, 0.292 mmol) was dissolved in dichloromethane (8 mL) and pyridinium chlorochromate (126 mg, 0.584 mmol) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified in silica gel with 0-45% ethyl acetate/hexanes to provide the desired product as a white solid (180 mg, 90%). LCMS: m/e 683.7 $(M+H)^+$, 3.50 min (method 1).

Step 3. Preparation of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate

A mixture of(S)-benzyl 1-(fluoromethyl)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-formyl-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (180 mg, 0.264 mmol) , 4-(3-aminopropyl)thiomorpholine 1,1-dioxide (65.9 mg, 0.343 mmol) and borane-2-methylpyridine complex (56.4 mg,

0.527 mmol) in methanol (4 mL) and acetic acid (1 mL) was stirred at 20 °C for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was purified in silica gel with 0-90% acetone/dichloromethane to provide the desired product as a pale yellow solid (190 mg, 84%). LCMS: m/e 859.9 $(M+H)^+$, 2.20 min (method 1).

Step 4. Preparation of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-(((trifluoromethyl)sulfonyl)oxy)-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate

To a solution of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (190 mg, 0.221 mmol) in 1,2-dichloroethane (6 mL) was added 2,6-di-tert-butyl-4-methylpyridine (114 mg, 0.553 mmol) followed by trifluoromethanesulfonic anhydride (0.112 mL, 0.663 mmol) at 0°C. The reaction mixture was stirred for 15 hours at room temperature, then quenched with sat. sodium bicarbonate (5 mL) and extracted with dichloromethane (3 x 4 mL). The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified in silica gel with 0-80% ethyl acetate/hexanes to provide the product as colorless oil (100 mg, 46%). LCMS: m/e 991.9 $(M+H)^+$, 2.54 min (method 1).

Step 5. Preparation of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-phenyl-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate

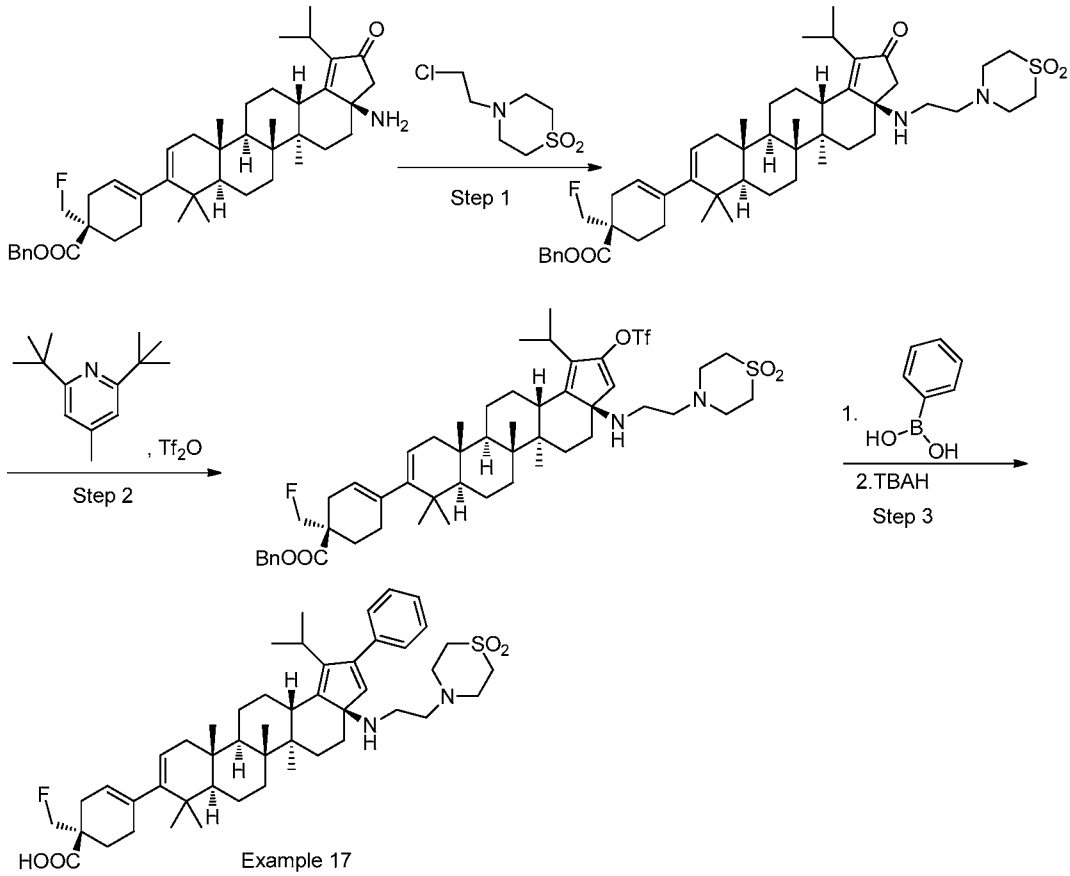
A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-(((trifluoromethyl)sulfonyl)oxy)-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (80 mg, 0.081 mmol), phenylboronic acid (11.81 mg, 0.097 mmol), tetrakis(triphenylphosphine)palladium (4.66 mg, 4.04 μmol) and sodium bicarbonate (33.9 mg, 0.404 mmol) in toluene (4 mL) and water (2 mL) was heated up at 80 °C for 3

hours. The reaction mixture was quenched with water (6 mL) and extracted with ethyl acetate (3 x 8 mL). The combined organic phases were washed with brine and dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified in silica gel with 0-20% ethyl acetate/hexanes to provide the title compound as a colorless oil (40 mg, 52%). LCMS: m/e 919.9 $(M+H)^+$, 2.52 min (method 1).

Step 6. A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-phenyl-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (15 mg, 0.016 mmol) and tetrabutylammonium hydroxide (30.8 mg, 0.065 mmol) in tetrahydrofuran (1 mL) and water (0.3 mL) was stirred at 20 °C for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep. HPLC with 0-80 acetonitrile/water/TFA in Phenomenex Luna C18 30x100 S10 to provide (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-phenyl-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid as a white solid (2.5 mg, 18%). LCMS: m/e 829.60 $(M+H)^+$, 2.78 min (method 1). ^{1}H NMR (Acetone) δ: 7.24-7.48 (m, 5H), 6.24 (s, 1H), 5.38 (br. s., 1H), 5.21-5.32 (m, 1H), 4.58-4.69 (m, 1H), 4.45-4.56 (m, 1H), 3.42-3.56 (m, 2H), 3.22-3.37 (m, 2H), 3.01-3.18 (m, 8H), 2.94 (dd, J=12.6, 3.0 Hz, 1H), 2.72-2.84 (m, 2H), 2.60 (d, J=16.4 Hz, 1H), 1.07-2.42 (m, 24H), 1.29 (s, 3H), 0.95-1.06 (m, 12H), 0.84-0.94 (m, 6H).

Example 17

Preparation of (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-phenyl-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid



Step 1. Preparation of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate

A mixture of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (320 mg, 0.478 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide (189 mg, 0.955 mmol), potassium iodide (119 mg, 0.716 mmol) and potassium phosphate (406 mg, 1.911 mmol) in acetonitrile (10 mL) was heated up at 100 °C for 18 h. The reaction mixture was quenched with distilled water (10 mL) and extracted with ethyl acetate (2 x15 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified silica gel with 0-40% acetone/dichloromethane to provide the title compound (240 mg, 61%). LCMS: m/e 831.6 $(M+H)^+$, 2.22 min (method 1).

Step 2. Preparation of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-(((trifluoromethyl)sulfonyl)oxy)-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate

To a solution of (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-oxo-3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-hexadecahydro-2H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate (240 mg, 0.289 mmol) in 1,2-dichloroethane (6 mL) was added 2,6-di-tert-butyl-4-methylpyridine (148 mg, 0.722 mmol) followed by trifluoromethanesulfonic anhydride (0.098 mL, 0.577 mmol) at 0°C. The reaction mixture was warmed up to room temperature and then heated up at 70°C for 1 h. The reaction mixture was quenched with sat. sodium bicarbonate (5 mL) and extracted with dichloromethane (3 x 4 mL). The combined organic phases were washed with brine and dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified in silica gel with 0-100% ethyl acetate/hexanes to provide the title compound as colorless oil (110 mg, 40%). LCMS: m/e 963.5 $(M+H)^+$, 2.42 min (method 1).

Step 3. A mixture of benzyl (S)-4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-(((trifluoromethyl)sulfonyl)oxy)-3a,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-4H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-ene-1-carboxylate (24 mg, 0.025 mmol), phenylboronic acid (3.59 mg, 0.029 mmol), tetrakis(triphenylphosphine)palladium (1.419 mg, 1.228 μmol) and sodium bicarbonate (10.32 mg, 0.123 mmol) in toluene (1 mL) and water (0.5 mL) was heated up at 80 °C for 3. The reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (3 x 2 mL). The combined organic phases were washed with brine and dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was filtered through a pad of silica gel using 50% ethyl acetate/hexanes to provide the intermediate silyl ester as a yellow oil.

The silyl ester intermediate was dissolved in tetrahydrofuran (1 mL) and water (0.3 mL) and treated with tetrabutylammonium hydroxide (25.4 mg, 0.054 mmol). The

reaction mixture was stirred at 20°C for 3 h and then purified by prep. HPLC with 0-80% acetonitrile/water/TFA in Phenomenex Luna C18 30x100 S10 to provide (S)-benzyl 4-((3aR,5aR,5bR,7aR,11aS,11bR,13aS)-3a-(((2-(1,1-dioxidothiomorpholino)ethyl)amino)methyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2-phenyl-4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a-tetradecahydro-3aH-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylate as a white solid (1.5 mg, 7%). LCMS: m/e 801.8 $(M+H)^+$, 2.15 min (method 1). ^{1}H NMR (METHANOL-d_4) δ: 7.38-7.47 (m, 3H), 7.28-7.36 (m, 2H), 6.08 (s, 1H), 5.58 (s., 1H), 4.90-4.94 (m, 1H), 4.50-4.63 (m, 1H), 4.38-4.48 (m, 1H), 3.42-3.53 (m, 1H), 3.35-3.39 (m, 1H), 3.07-3.23 (m, 8H), 2.77-2.98 (m, 4H), 2.54-2.66 (m, 2H), 2.44-2.51 (m, 1H), 2.31-2.41 (m, 1H), 1.46-2.21 (m, 18H), 1.45 (s, 3H), 1.43 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.05 (d, J=7.1 Hz, 3H), 0.89-0.97 (m, 6H).

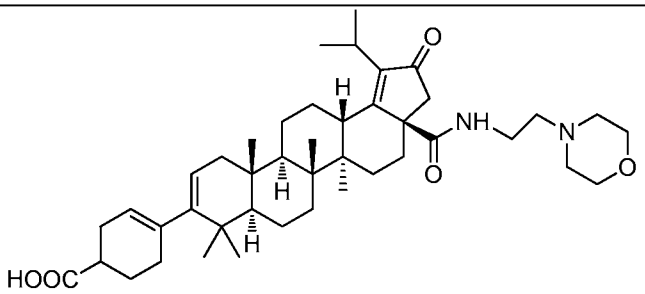
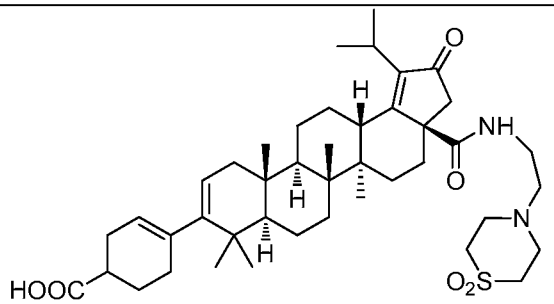
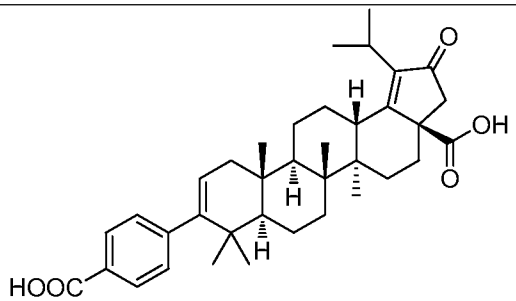
HIV cell culture assay - MT-2 cells and 293T cells were obtained from the NIH AIDS Research and Reference Reagent Program. MT-2 cells were propagated in RPMI 1640 media supplemented with 10% heat inactivated fetal bovine serum, 100 µg/mL penicillin G and up to 100 units/mL streptomycin. The 293T cells were propagated in DMEM media supplemented with 10% heat inactivated fetal bovine serum (FBS), 100 units/mL penicillin G and 100 µg/mL streptomycin. The proviral DNA clone of NL_{4-3} was obtained from the NIH AIDS Research and Reference Reagent Program. A recombinant NL_{4-3} virus, in which a section of the nef gene from NL4-3 was replaced with the *Renilla* luciferase gene, was used as a reference virus. In addition, residue Gag P373 was converted to P373S. Briefly, the recombinant virus was prepared by transfection of the altered proviral clone of NL_{4-3}. Transfections were performed in 293T cells using LipofectAMINE PLUS from Invitrogen (Carlsbad, CA), according to manufacturer's instruction. The virus was titered in MT-2 cells using luciferase enzyme activity as a marker. Luciferase was quantitated using the Dual Luciferase kit from Promega (Madison, WI), with modifications to the manufacturer's protocol. The diluted Passive Lysis solution was pre-mixed with the re-suspended Luciferase Assay Reagent and the re-suspended Stop & Glo Substrate (2:1:1 ratio). Fifty (50) µL of the mixture was added to each aspirated well on assay plates and luciferase activity was measured immediately on a Wallac TriLux (Perkin-Elmer). Antiviral activities of inhibitors toward the

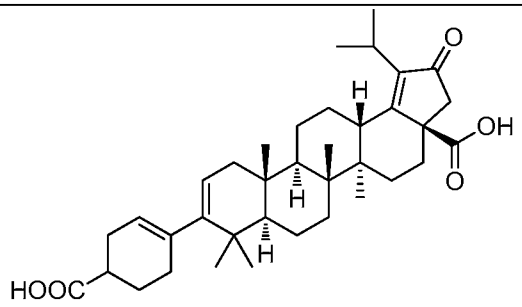
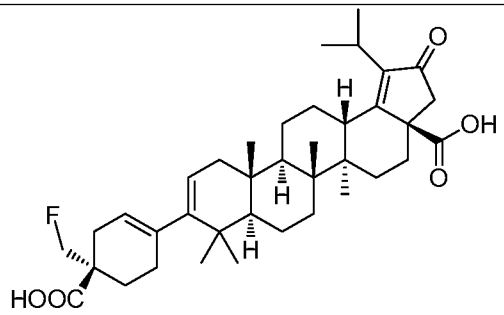
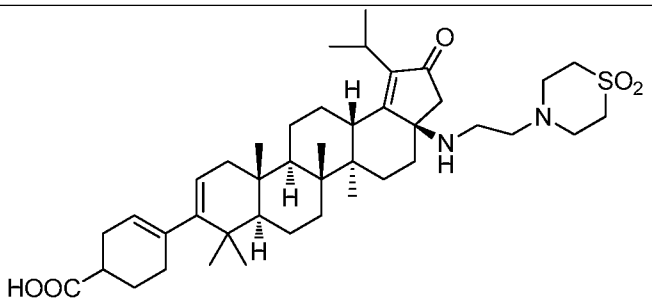
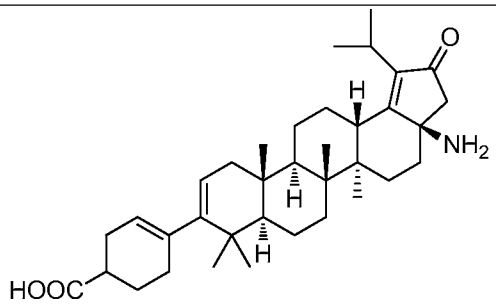
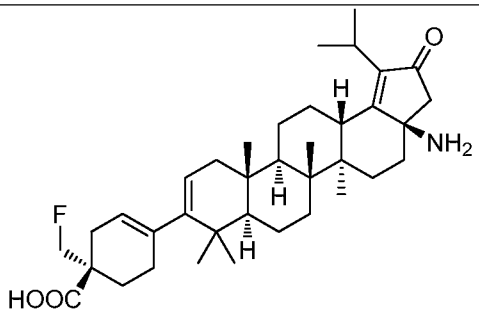
recombinant virus were quantified by measuring luciferase activity in cells infected for 4-5 days with NLRluc recombinants in the presence serial dilutions of the inhibitor. The EC_{50} data for the compounds is shown in Table 1.

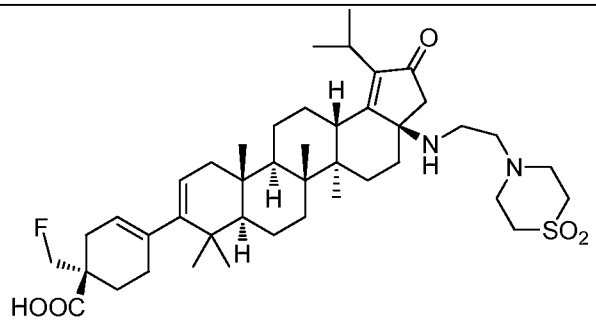
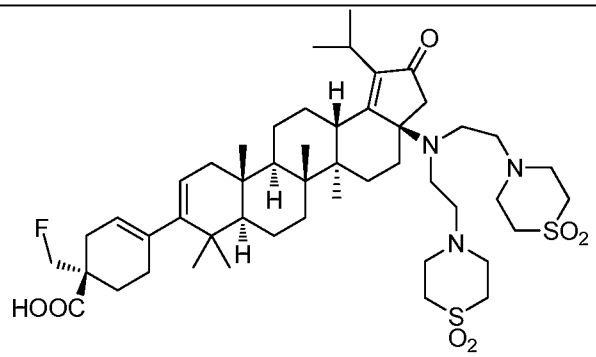
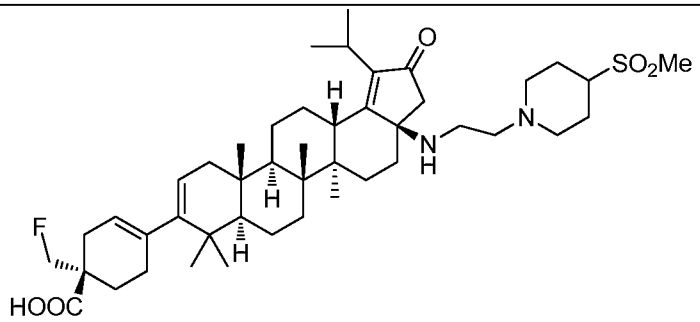
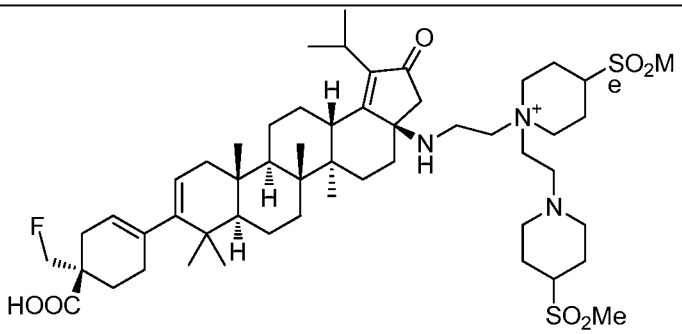
Biological Data Key for EC_{50}

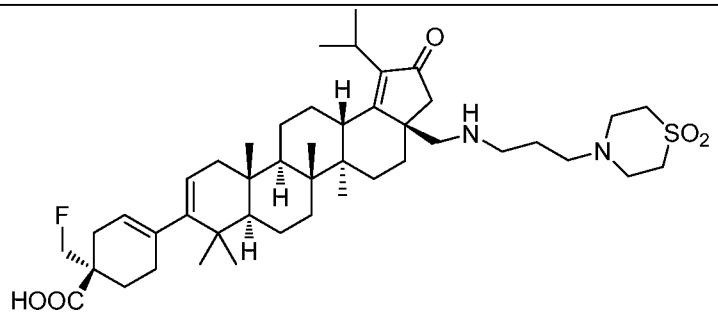
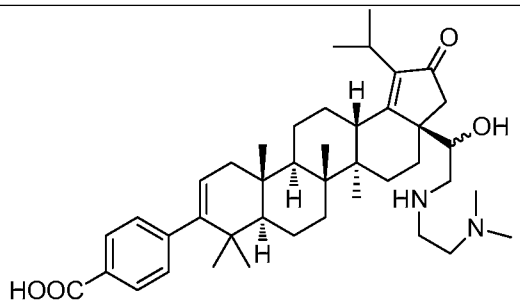
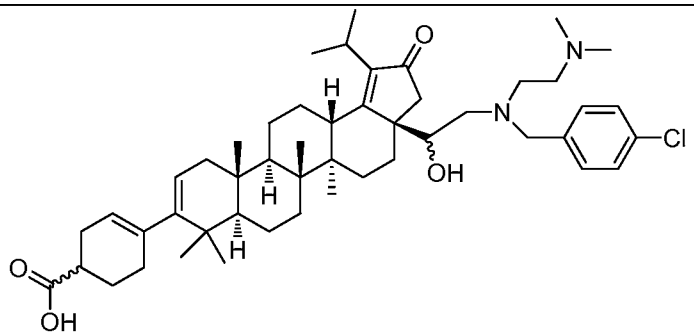
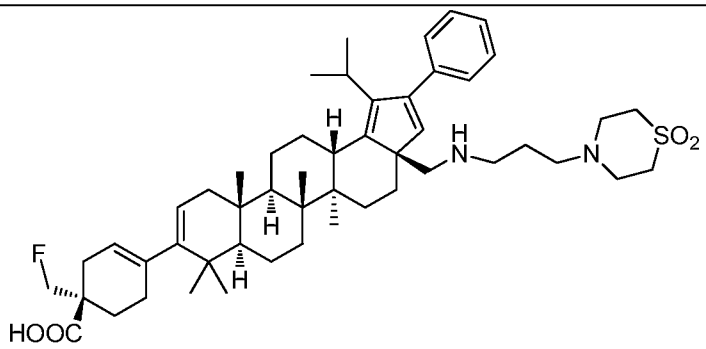
Compounds with EC_{50} >0.1 μM	Compounds with $EC_{50} \leq 0.1$ μM
Group "B"	Group "A"

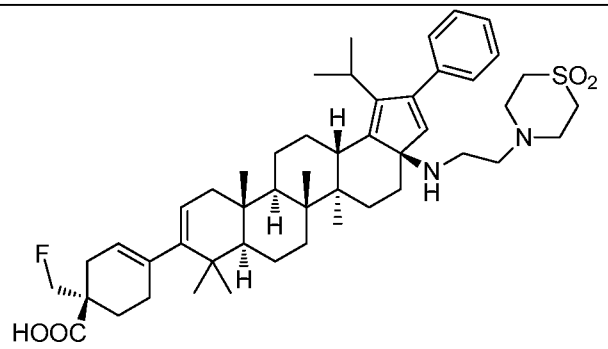
TABLE 1

Example #	Structure	EC50 (μM)
1		1.93E-03
2		A
3		A

4		A
5		A
6		A
7		9.73E-04
8		A

9		A
10		A
11		A
12		A

13		A
14		5.36E-03
15		A
16		2.64E-03

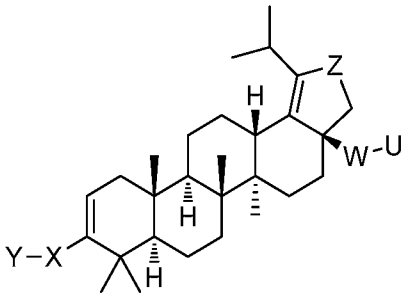
17		10.9E-02

The foregoing description is merely illustrative and should not be understood to limit the scope or underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

CLAIMS

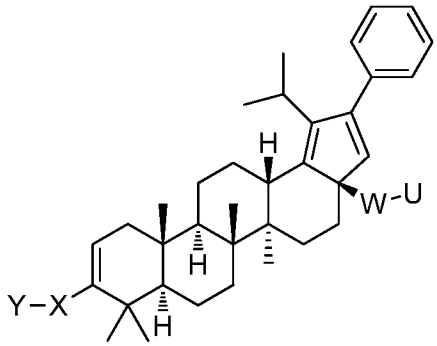
What is claimed is:

1. A compound, including pharmaceutically acceptable salts thereof, which is selected from a compound of Formulas I and II:



Formula I

and



Formula II ;

wherein X is selected from the group of phenyl, heteroaryl, C_{4-8} cycloalkyl, C_{4-8} cycloalkenyl, C_{4-9} spirocycloalkyl, C_{4-9} spirocycloalkenyl, C_{4-8} oxacycloalkyl, C_{6-8} dioxacycloalkenyl, C_{6-9} oxaspirocycloalkyl, and C_{6-9} oxaspirocycloalkenyl ring; and further wherein X is substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{1-6} haloalkyl, -CN, -NR_8R_9, -$COOR_2$, -$CONR_2R_2$ and -C_{1-6} alkyl-Q;

Q is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_3$, -NR_2R_2, -SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

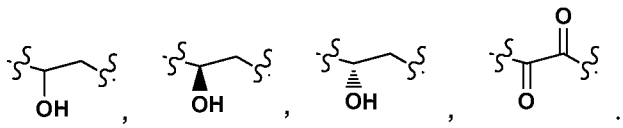
R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or -arylsubstituted C_{1-6} alkyl;

Y is selected from the group of –$COOR_2$, -$C(O)NR_2SO_2R_3$, -$C(O)NHSO_2NR_2R_2$, -$NR_2SO_2R_2$, -$SO_2NR_2R_2$, -C_{3-6} cycloalkyl-$COOR_2$, -C_{2-6} alkenyl-$COOR_2$, -C_{2-6} alkynyl-$COOR_2$, -C_{1-6} alkyl-$COOR_2$, -alkylsubstituted C_{1-6} alkyl, -$COOR_2$, CF_2-$COOR_2$, -$NHC(O)(CH_2)_n$-$COOR_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and -CONHOH,

wherein n=1-6;

R_3 is –H, -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

W is absent, or is -CO- or is selected from the group of
-C_{2-6} alkyl-, -C_{2-6} alkyl-CO-, -C_{2-6} alkenyl-,-C_{2-6} alkenyl-CO-, and -heteroaryl-; or is selected from the group of:



;

U is selected from -NR_4R_5 and OR_2,
with the proviso that U cannot be OR_2 when W is absent;

Z is selected from the group of –CO-, -CHOH, -C=N-OR_2, -C=N-R_{24} and –CH-NHR_{24};

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-$C(OR_3)_2$-C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -$COCOR_6$, -SO_2R_7, and -$SO_2NR_2R_2$;

Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_{10}, -COR_6, -$COCOR_6$, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that R_4 or R_5 cannot be COR_6 or $COCOR_6$ when W is CO,
and with the further proviso that only one of R_4 or R_5 can be selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

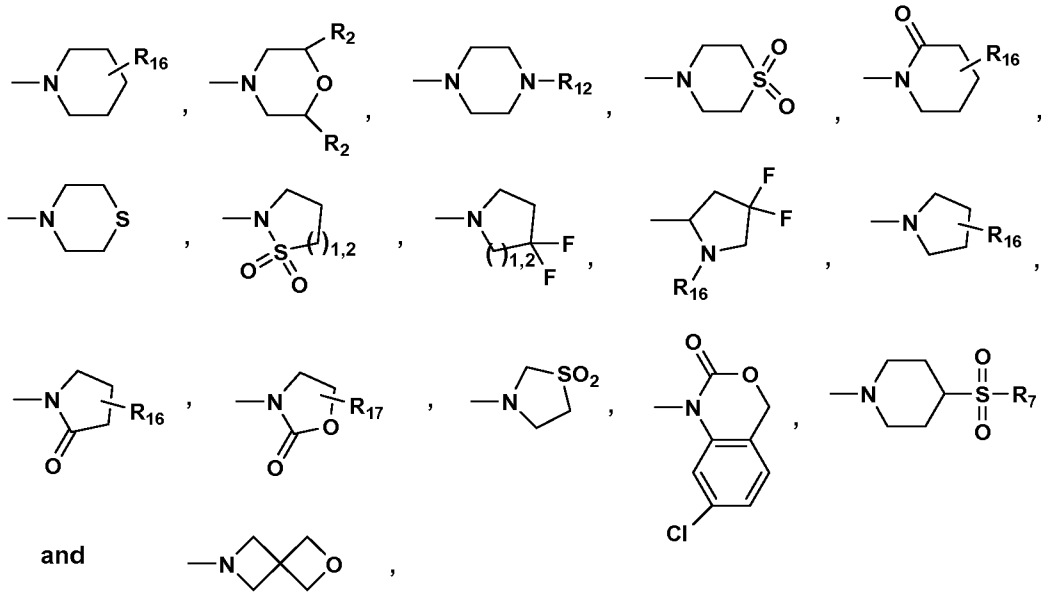
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, $-OR_2$, $-COOR_2$, $-NR_8R_9$, SO_2R_7, $-CONHSO_2R_3$, and $-CONHSO_2NR_2R_2$;

R_7 is selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{3-6}$ cycloalkyl, $-CF_3$, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, $-C_{1-6}$ alkyl-Q_2, and $-COOR_3$,

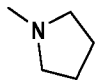
or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



with the proviso that only one of R_8 or R_9 can be $-COOR_3$;

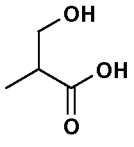
R_{10} and R_{11} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl and $-C_{3-6}$ cycloalkyl,

or R_{10} and R_{11} are taken together with the adjacent N to form the cycle


;

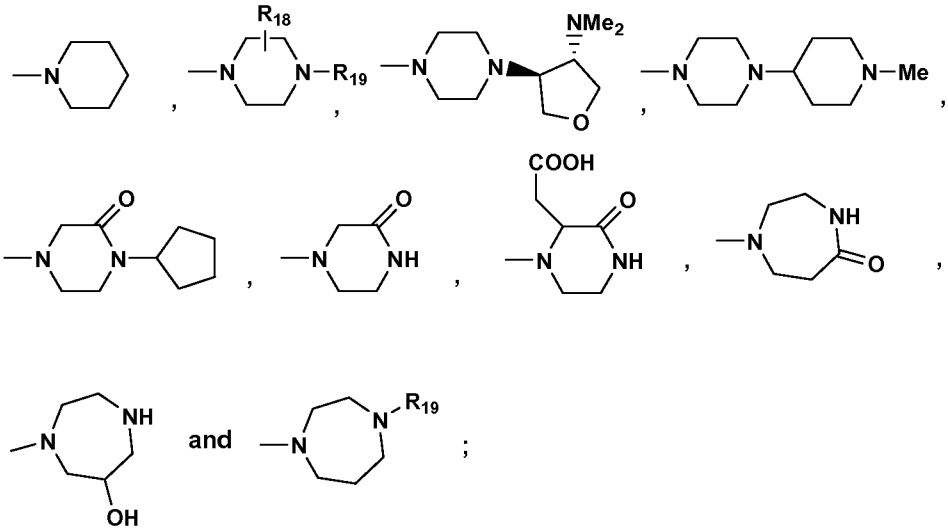
R_{12} is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-OH; -C_{1-6} alkyl, -C_{1-6} substituted alkyl,-C_{3-6} cycloalkyl, -COR_7, -$COONR_{22}R_{23}$, -SOR_7, and -$SONR_{24}R_{25}$;

R_{13} and R_{14} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3, C_{1-6} substituted alkyl-Q_3 and



,

or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the group of:



and

;

Q_3 is selected from the group of heteroaryl, substituted heteroaryl, -$NR_{20}R_{21}$, -$CONR_2R_2$, -$COOR_2$, -OR_2, and -SO_2R_3;

R_{15} is selected from the group of -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3 and -C_{1-6} substituted alkyl-Q_3;

R_{16} is selected from the group of -H, -C_{1-6} alkyl, -NR_2R_2, and -$COOR_3$;

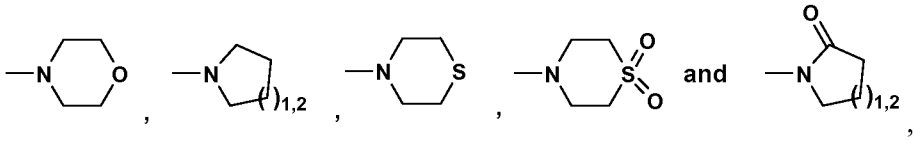
R_{17} is selected from the group of -H, -C_{1-6} alkyl, -$COOR_3$, and aryl;

R_{18} is selected from the group of –H, -$COOR_2$ and -C_{1-6} alkyl-$COOR_2$;

R_{19} is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-Q_4, -COR_3, and -$COOR_3$;

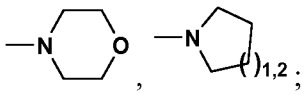
Q_4 is selected from the group of -NR_2R_2 and -OR_2;

R_{20} and R_{21} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} substituted alkyl-OR_2, and -COR_3,
or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R_{20} or R_{21} can be -COR_3;

R_{22} and R_{23} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, and -C_{1-6} cycloalkyl,
or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



R_{24} and R_{25} are independently from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_5, -C_{1-6} cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
Q_5 is selected from the group of halogen and SO_2R_3.

2. The compound as claimed in claim 1, wherein X is phenyl or C_{4-8} cycloalkenyl.

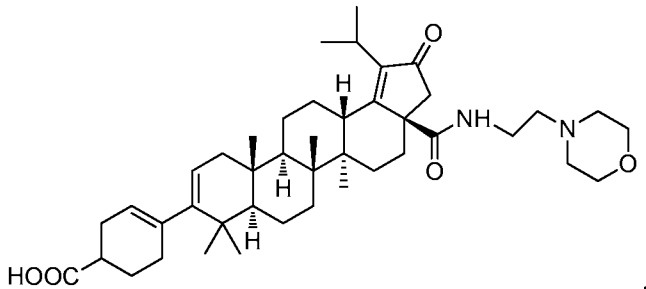
3. The compound as claimed in claim 2, wherein X is C_{4-8} cycloalkenyl.

4. The compound as claimed in claim 2, wherein Y is –COOH.

5. The compound as claimed in claim 2, wherein A is -C1-6 alkylhalo.

6. The compound as claimed in claim 1, wherein Z is –CO-.

7. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:



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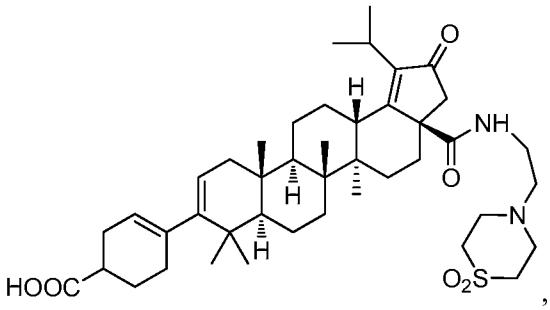

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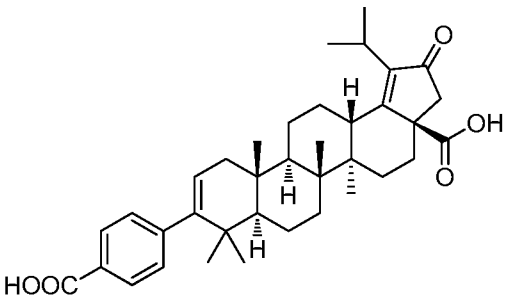

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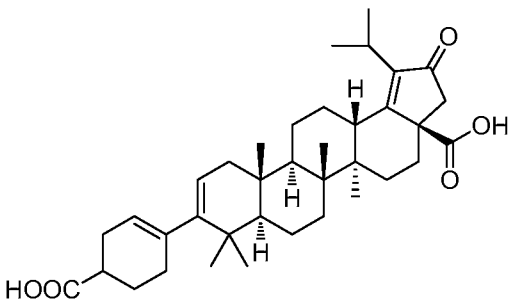

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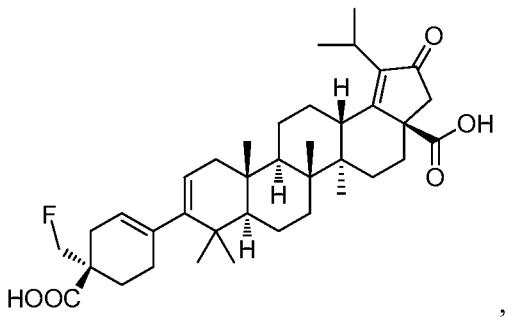

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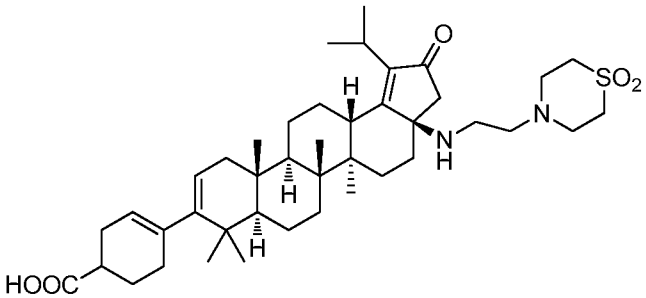

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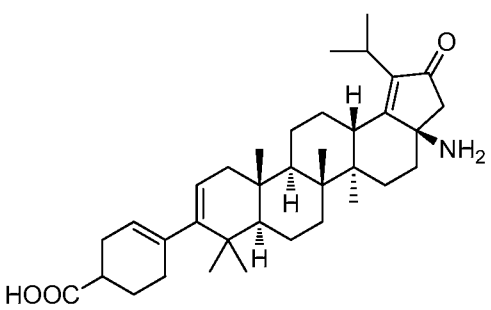
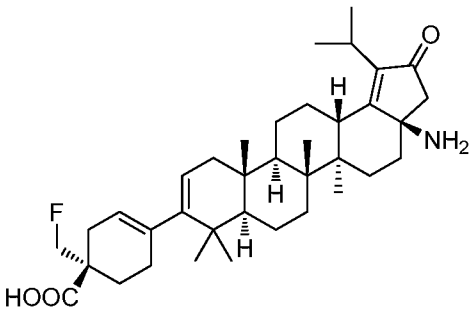
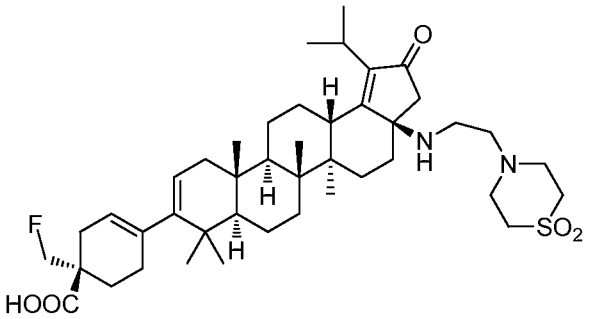

O
H
NH2
H
H
HOOC

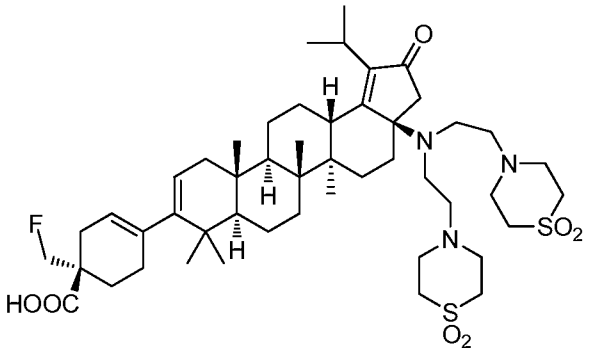
,


O
H
NH2
H
F
H
HOOC

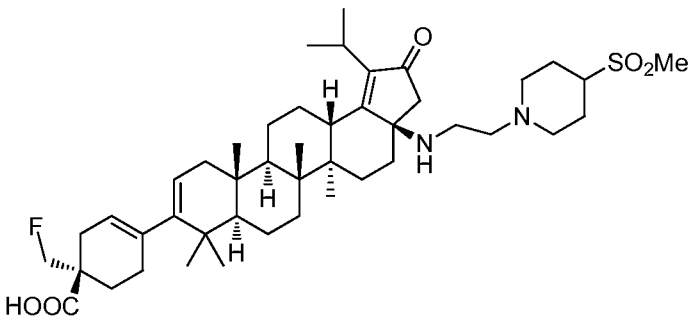
,


O
H
N
H
N
SO2
F
H
H
HOOC

,


O
H
N
N
SO2
F
H
H
N
S
O2
HOOC

,


O
SO2Me
H
N
N
H
F
H
H
HOOC

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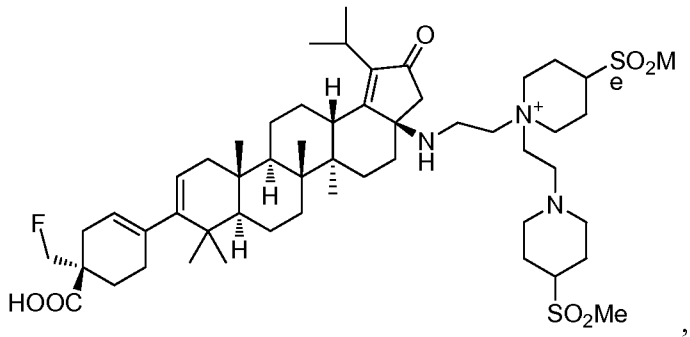

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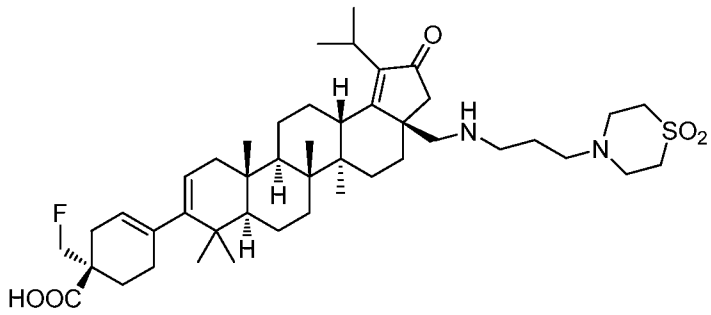

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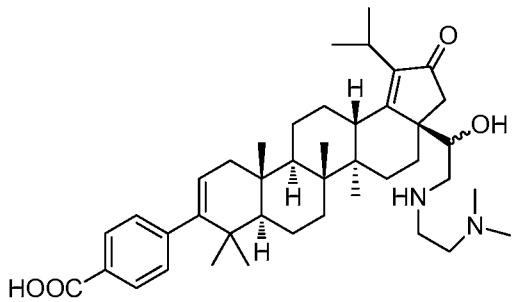
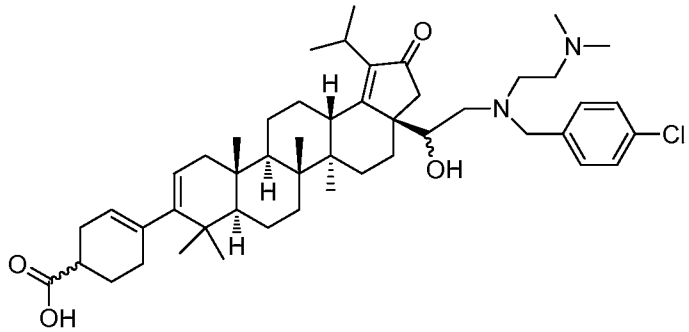


and



.

8. A composition which comprises an HIV ameliorating amount of one or more compounds as claimed in claim 1, together with one or more pharmaceutically acceptable carriers, excipients, and/or diluents.

9. A composition which comprises an HIV ameliorating amount of one or more compounds as claimed in claim 7, together with one or more pharmaceutically acceptable carriers, excipients, and/or diluents.

10. A method for treating a mammal infected with the HIV virus comprising administering to said mammal an HIV ameliorating amount of a compound as claimed in claim 1, together with one or more pharmaceutically acceptable carriers, excipients, and/or diluents.

11. A method for treating a mammal infected with the HIV virus comprising administering to said mammal an HIV ameliorating amount of a compound as claimed in claim 7, together with one or more pharmaceutically acceptable carriers, excipients, and/or diluents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/060344

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J63/00 A61K31/56 A61K31/575 A61P31/18
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/210787 A1 (SWIDORSKI JACOB [US] ET AL) 15 August 2013 (2013-08-15) page 143; example 4 page 144; example 8 page 147; example 17 page 153; example A13 -----	1-11
Y	WO 2011/153315 A1 (SQUIBB BRISTOL MYERS CO [US]; REGUEIRO-REN ALICIA [US]; SWIDORSKI JACO) 8 December 2011 (2011-12-08) page 123; example 2b -----	1-11

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[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 application or patent but published on or after the international filing date

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2016	27/01/2016

Name and mailing address of the ISA/	Authorized officer
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/153319 A1 (SQUIBB BRISTOL MYERS CO [US]; REGUEIRO-REN ALICIA [US]; LIU ZHENG [US]) 8 December 2011 (2011-12-08) page 261; example 12 page 283; example 106 page 286; examples 116, 120 page 287; example 121	1-11
Y	WO 2012/106188 A1 (SQUIBB BRISTOL MYERS CO [US]; REGUEIRO-REN ALICIA [US]; SWIDORSKI JACO) 9 August 2012 (2012-08-09) page 247; example 14 page 252; example 37 page 266; examples 92, 93 page 284; examples 171, 172	7
Y	WO 2013/117137 A1 (JIANGXI QINGFENG PHARMACEUTICAL INC [CN]; LU FENG [CN]; FENG QIAODI [C) 15 August 2013 (2013-08-15) pages 76-77; table 1 claims 9, 11	1-11
Y	US 2011/077227 A1 (MOINET CHRISTOPHE [FR] ET AL) 31 March 2011 (2011-03-31) page 57; compounds 15-1, 15-2 page 58; compounds 15-3	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/060344

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2013210787 A1	15-08-2013	AR 089996 A1	01-10-2014
		AU 2013221725 A1	02-10-2014
		CA 2864656 A1	22-08-2013
		CL 2014002141 A1	03-10-2014
		CN 104220451 A	17-12-2014
		CO 7061077 A2	19-09-2014
		EA 201491531 A1	28-11-2014
		EP 2814834 A1	24-12-2014
		HK 1204608 A1	27-11-2015
		JP 2015510515 A	09-04-2015
		KR 20140123584 A	22-10-2014
		NZ 631408 A	26-06-2015
		PE 23152014 A1	16-01-2015
		PH 12014501816 A1	17-11-2014
		SG 11201404748X A	26-09-2014
		TW 201336863 A	16-09-2013
		US 2013210787 A1	15-08-2013
		UY 34627 A	02-09-2013
		WO 2013123019 A1	22-08-2013
WO 2011153315 A1	08-12-2011	AR 081637 A1	10-10-2012
		CA 2801487 A1	08-12-2011
		CN 103038245 A	10-04-2013
		EA 201270780 A1	30-04-2013
		EP 2576585 A1	10-04-2013
		JP 5752789 B2	22-07-2015
		JP 2013527242 A	27-06-2013
		TW 201201793 A	16-01-2012
		US 2012142707 A1	07-06-2012
		WO 2011153315 A1	08-12-2011
WO 2011153319 A1	08-12-2011	AR 081638 A1	10-10-2012
		CA 2801491 A1	08-12-2011
		CN 102985438 A	20-03-2013
		DK 2576586 T3	23-11-2015
		EA 201270800 A1	30-04-2013
		EP 2576586 A1	10-04-2013
		ES 2548905 T3	21-10-2015
		HR P20150977 T1	09-10-2015
		JP 5755731 B2	29-07-2015
		JP 2013527243 A	27-06-2013
		PT 2576586 E	23-10-2015
		SI 2576586 T1	30-11-2015
		SM T201500272 B	08-01-2016
		TW 201201792 A	16-01-2012
		US 2012142653 A1	07-06-2012
		WO 2011153319 A1	08-12-2011
WO 2012106188 A1	09-08-2012	CA 2826257 A1	09-08-2012
		CN 103339141 A	02-10-2013
		DK 2670764 T3	07-12-2015
		EA 201391098 A1	30-12-2013
		EP 2670764 A1	11-12-2013
		ES 2552512 T3	30-11-2015
		HR P20151212 T1	04-12-2015
		JP 2014507422 A	27-03-2014
		PT 2670764 E	20-11-2015
		SM T201500303 B	08-01-2016

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/060344

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2013029954 A1	31-01-2013
		WO 2012106188 A1	09-08-2012
WO 2013117137 A1	15-08-2013	AU 2013218441 A1	24-07-2014
		CA 2860581 A1	15-08-2013
		CN 103242413 A	14-08-2013
		EA 201491479 A1	28-11-2014
		EP 2812343 A1	17-12-2014
		HK 1202553 A1	02-10-2015
		JP 2015505545 A	23-02-2015
		KR 20140126739 A	31-10-2014
		US 2015011517 A1	08-01-2015
		WO 2013117137 A1	15-08-2013
US 2011077227 A1	31-03-2011	US 2011077227 A1	31-03-2011
		US 2011077228 A1	31-03-2011