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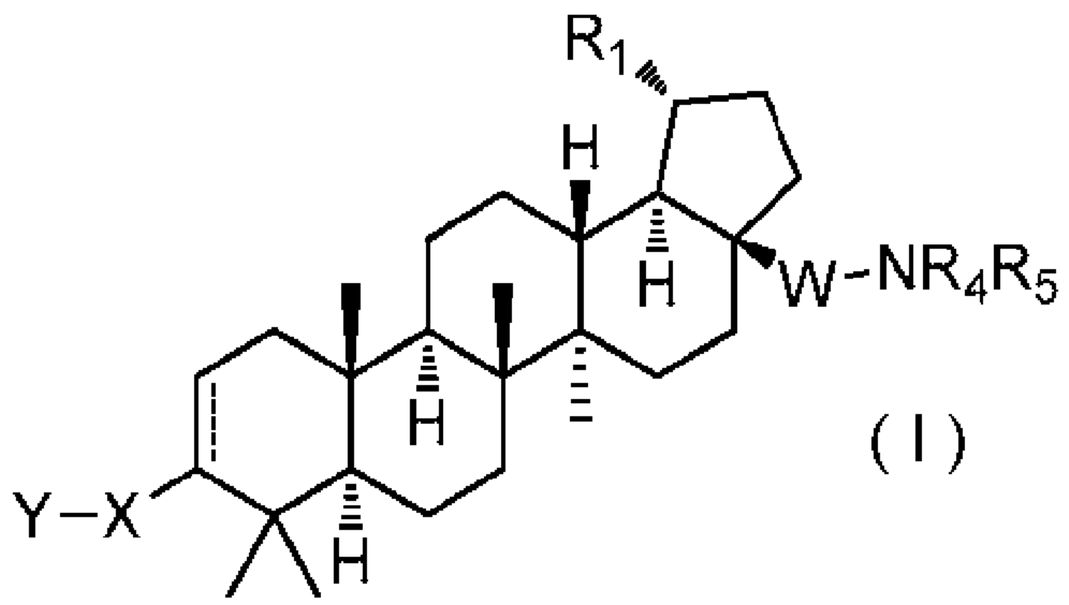
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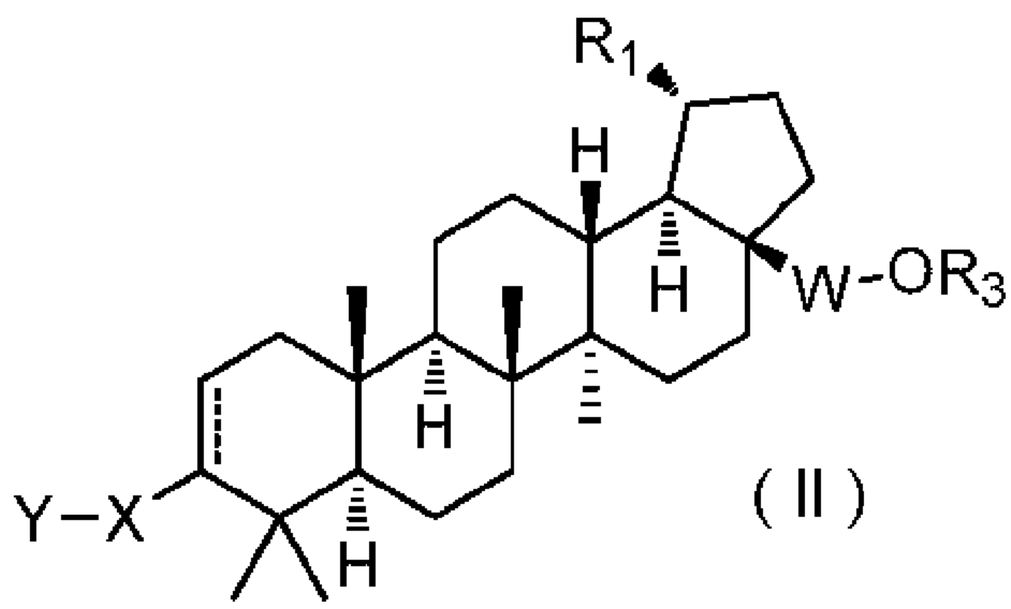
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(54) Titre : ANALOGUES DE L'ACIDE BETULINIQUE ADMINISTRES SUR UNE PERIODE PROLONGEE
(54) Title: EXTENDED BETULINIC ACID ANALOGS



(I)



(II)

(57) Abrégé/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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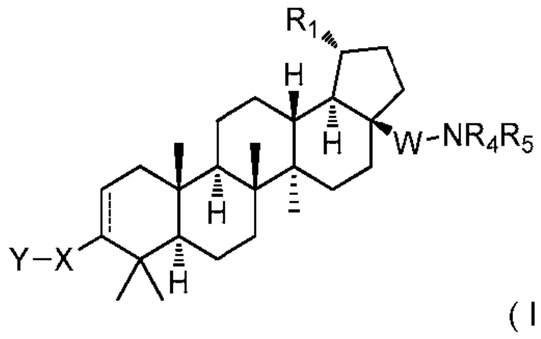
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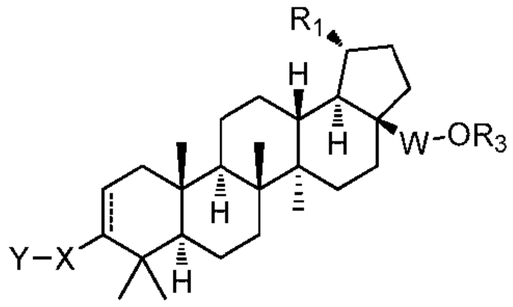
[Continued on next page]

(54) **Title**: EXTENDED BETULINIC ACID ANALOGS

(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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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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EXTENDED BETULINIC ACID ANALOGS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the priority of U.S. Provisional Application Serial No. 62/079,957 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 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 8,906,889), as well as to the application entitled "TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY" USSN 14/682,179 filed on April 9, 2015.

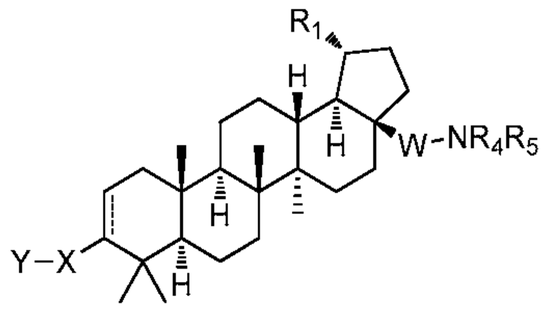
What is now needed in the art are new compounds which are useful as HIV maturation inhibitors, as well as new pharmaceutical compositions containing these compounds.

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 – II are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

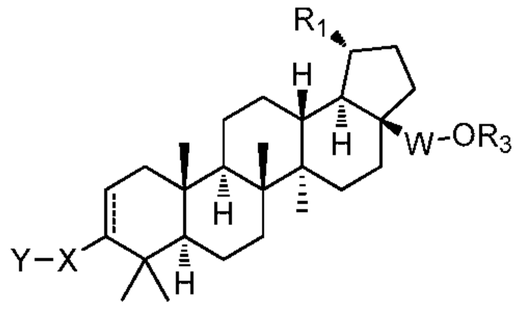
One embodiment of the present invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

a compound of formula I



Formula I ;

and a compound of formula II



Formula II ;

wherein R_1 is isopropenyl or isopropyl;

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;

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;

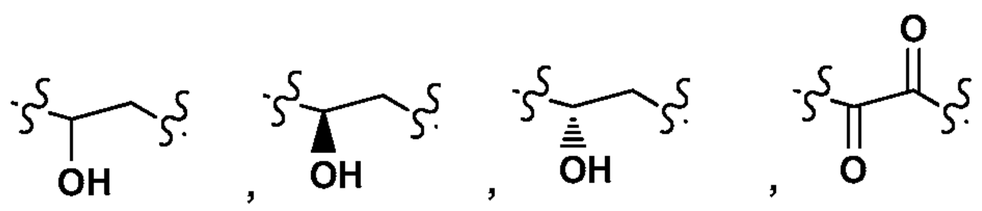
Q is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_3$, -NR_2R_2, -SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

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

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;

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



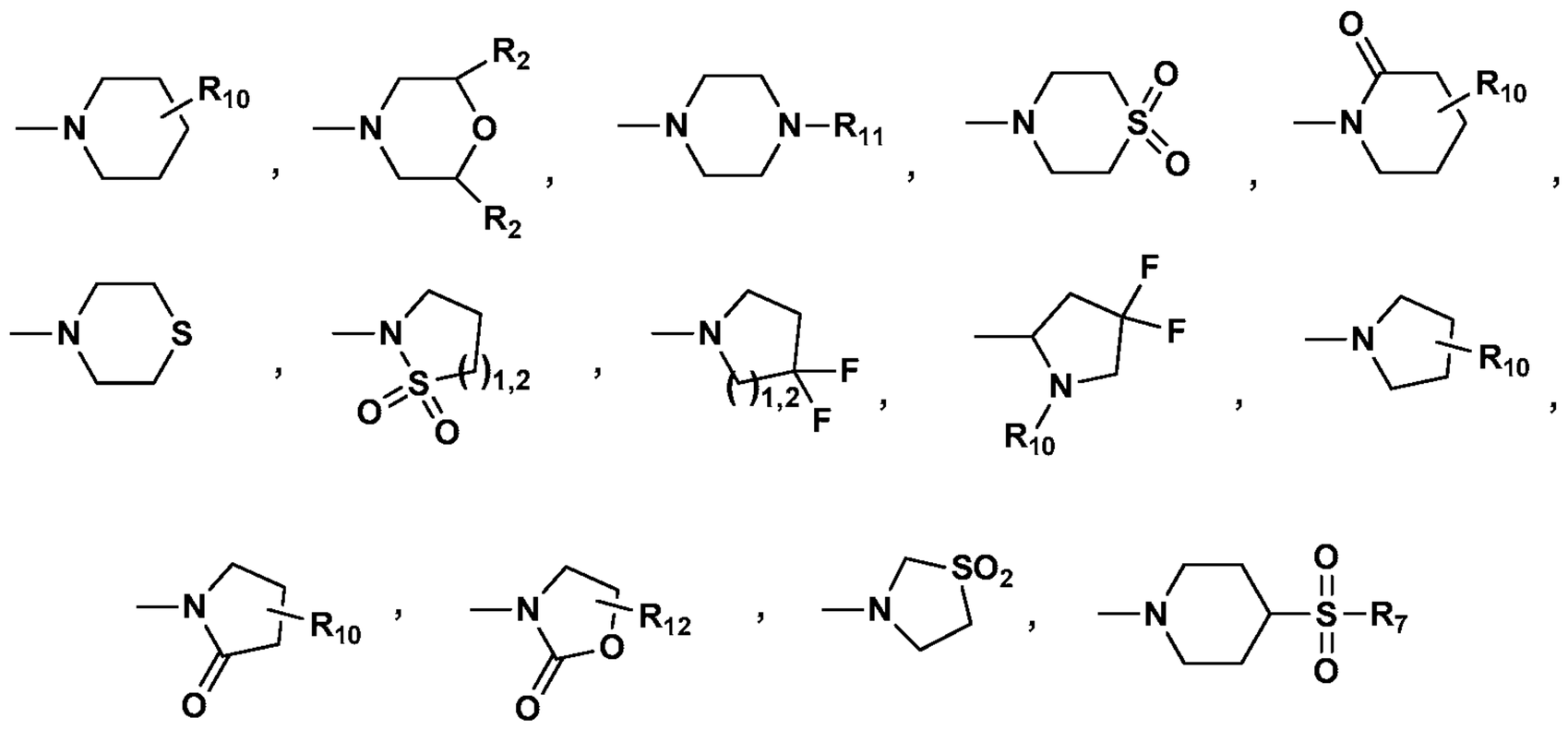
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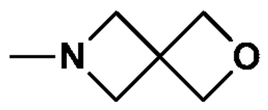
R_3 is –H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or benzyl;

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 -$SO_2NR_2R_2$;

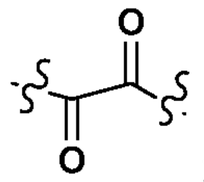
Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

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 -$SO_2NR_2R_2$;
or R_4 and R_5 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_4 or R_5 can be selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$, and with the further proviso that R_4 or R_5 cannot be -COR_6 or -$COCOR_6$ when W is -C_{2-6} alkyl-CO-, -C_{2-6} alkenyl-CO-, or



;

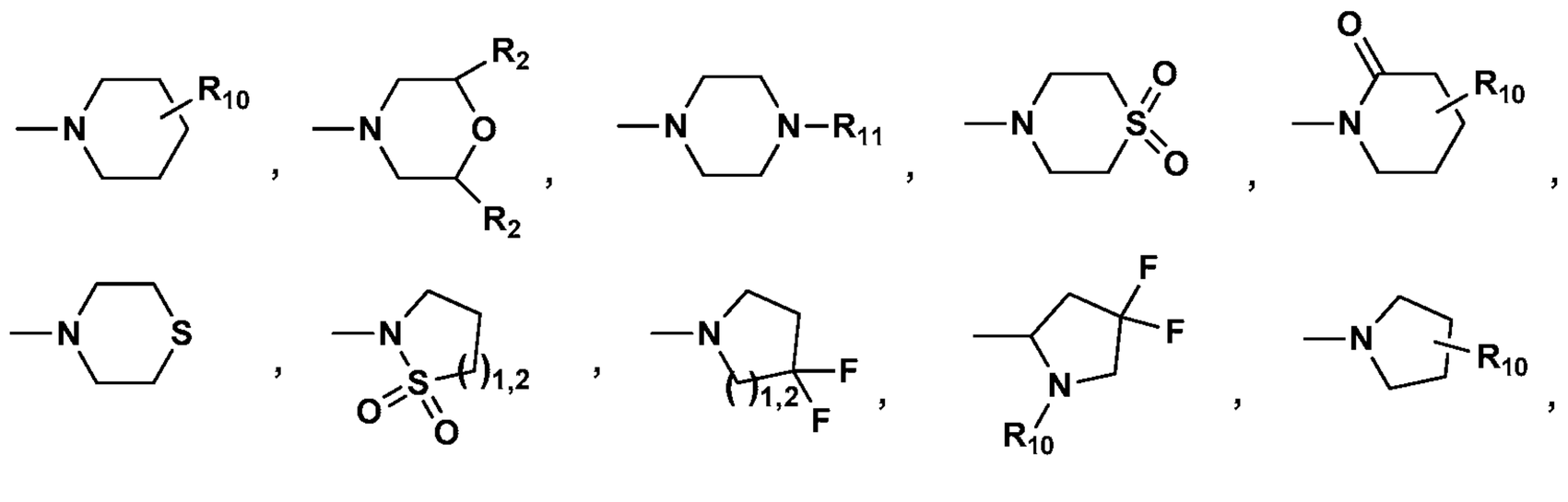
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -NR_2R_2, and –OR_2;

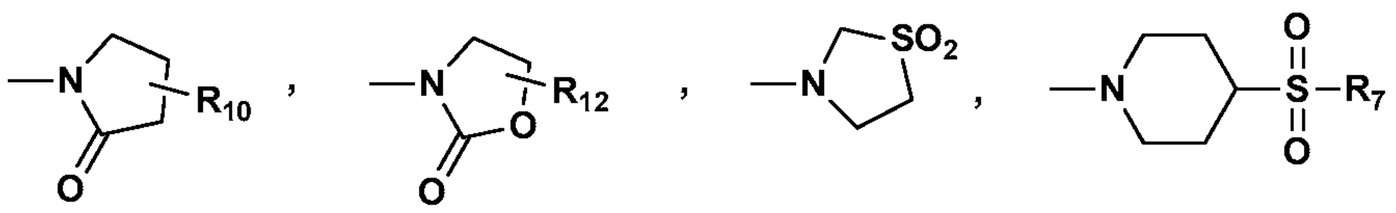
Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

R_7 is selected from the group of -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} is selected from the group of -H, -$C_{1\text{-}6}$ alkyl, -NR_2R_2, and -$COOR_3$;

R_{11} is selected from the group of -$C_{1\text{-}6}$ alkyl, -$C_{1\text{-}6}$ alkyl-OH; -$C_{1\text{-}6}$ alkyl, -$C_{1\text{-}6}$ substituted alkyl,-$C_{3\text{-}6}$ cycloalkyl, -COR_7, -$COONR_2R_2$, -SOR_7, and -$SONR_2R_2$; and

R_{12} is selected from the group of -H, -$C_{1\text{-}6}$ alkyl, -$COOR_3$, and aryl.

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) other 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) other 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) mean 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 F atom, and each H atom can be independently substituted by F atom;

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

An "aryl" or "Ar" group refers to an 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 consisting 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 consisting 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 consisting 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 consisting 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.

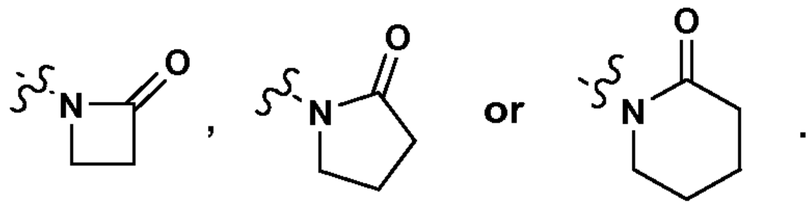
A "cyano" group refers to a –CN group.

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.

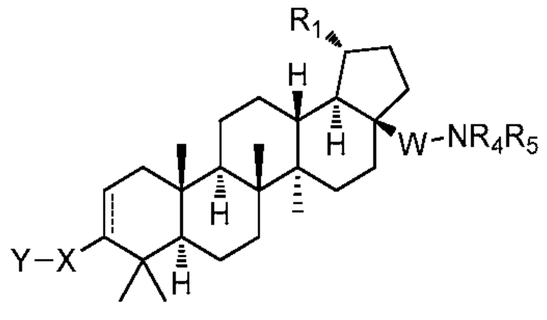
Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of the invention. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic 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”.

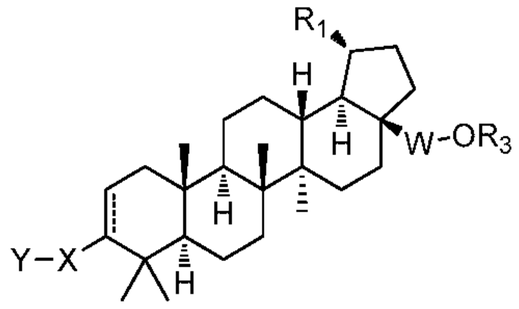
As set forth above, the invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

a compound of formula I



Formula I ;

and a compound of formula II



Formula II ;

wherein R_1 is isopropenyl or isopropyl;

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;

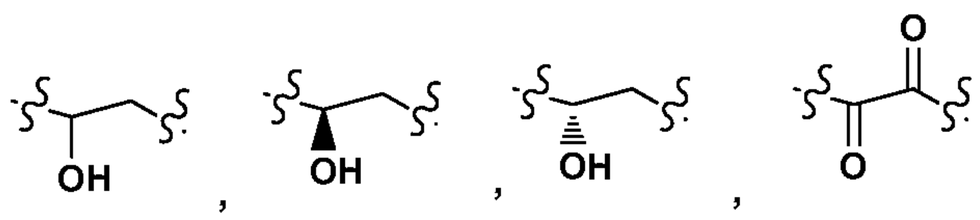
wherein X is substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{1-6}haloalkyl, -CN, -NR_8R_9, -$COOR_2$, -$CONR_2R_2$ and -C_{1-6} alkyl-Q;

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 benzyl;

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;

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



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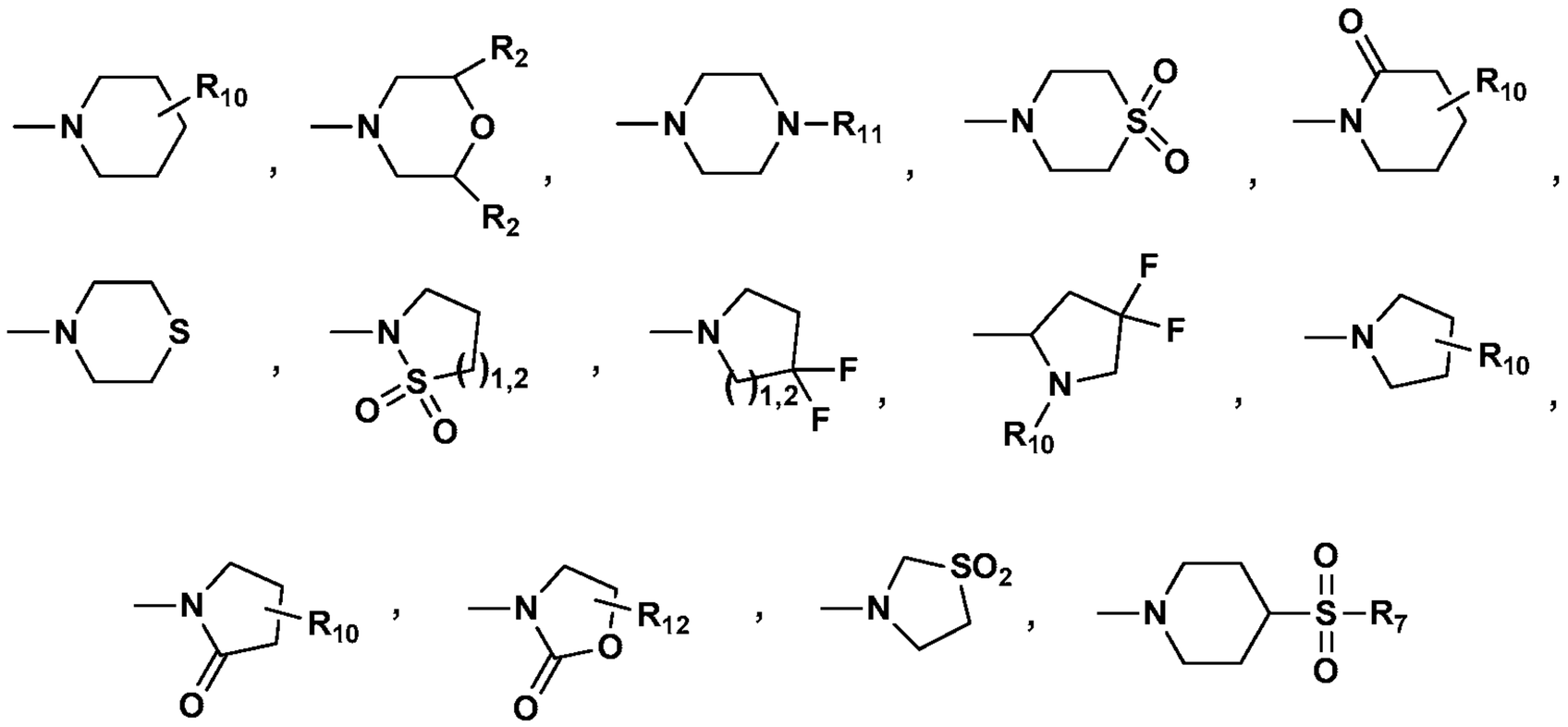
R_3 is –H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or benzyl;

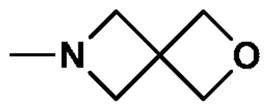
R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-$C(OR_3)_2$-C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -$COCOR_6$, -SO_2R_7, and -$SO_2NR_2R_2$;

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 $-SO_2R_7$;

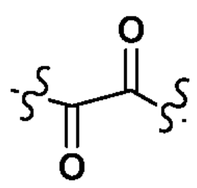
R_5 is selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ alkylsubstituted alkyl, $-C_{1-6}$ alkyl-NR_8R_9, $-COR_{10}$, $-COR_6$, $-COCOR_6$, $-SO_2R_7$ and $-SO_2NR_2R_2$;

or R_4 and R_5 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_4 or R_5 can be selected from the group of $-COR_6$, $-COCOR_6$,$-SO_2R_7$ and $-SO_2NR_2R_2$, and with the further proviso that R_4 or R_5 cannot be $-COR_6$ or $-COCOR_6$ when W is $-C_{2-6}$ alkyl-CO-, $-C_{2-6}$ alkenyl-CO-, or

;

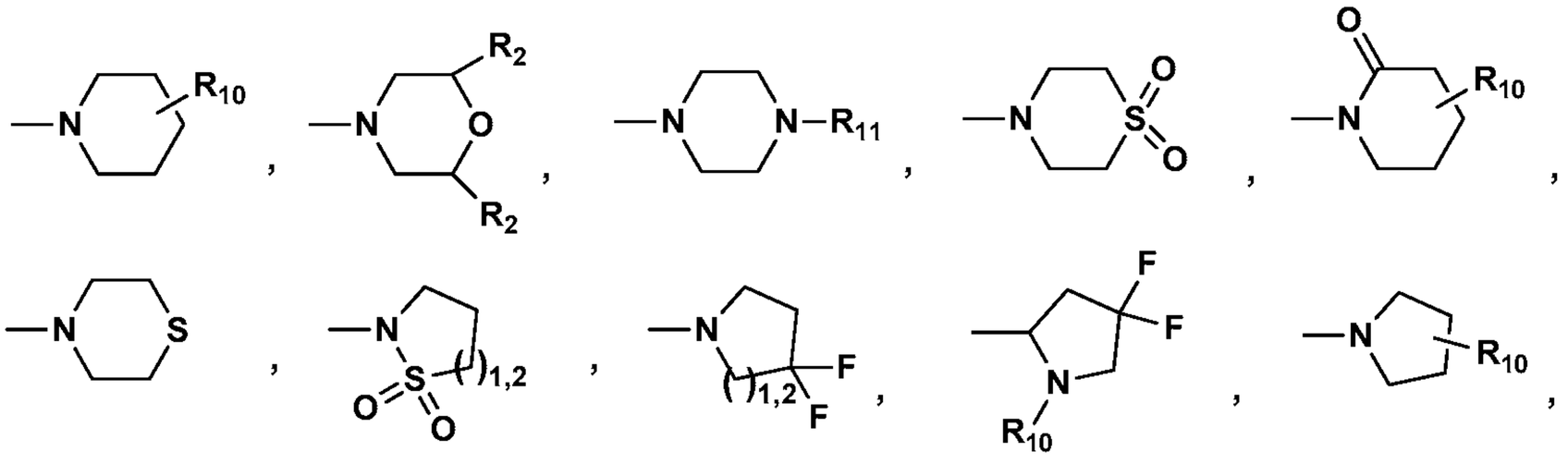
R_6 is selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-substitutedalkyl, $-C_{3-6}$ cycloalkyl, $-C_{3-6}$ substitutedcycloalkyl-Q_2, $-C_{1-6}$ alkyl-Q_2, $-C_{1-6}$ alkyl-substitutedalkyl-Q_2,$-C_{3-6}$ cycloalkyl-Q_2, aryl-Q_2, $-NR_2R_2$, and $-OR_2$;

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

R_{11} 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, -$COONR_2R_2$, -SOR_7, and -$SONR_2R_2$; and

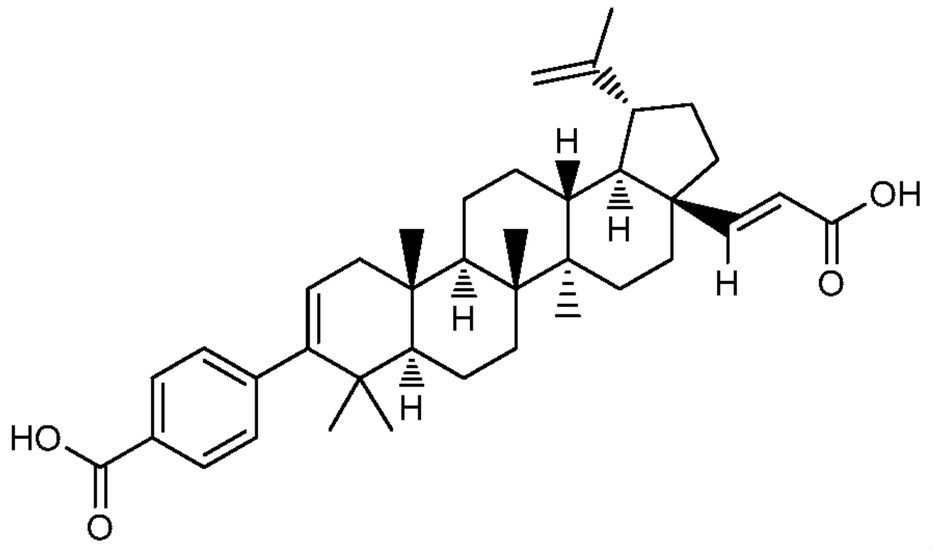
R_{12} is selected from the group of -H, -C_{1-6} alkyl, -$COOR_3$, and aryl.

In a preferred embodiment of the invention, X is selected from the group of phenyl and C_{4-8} cycloalkenyl.

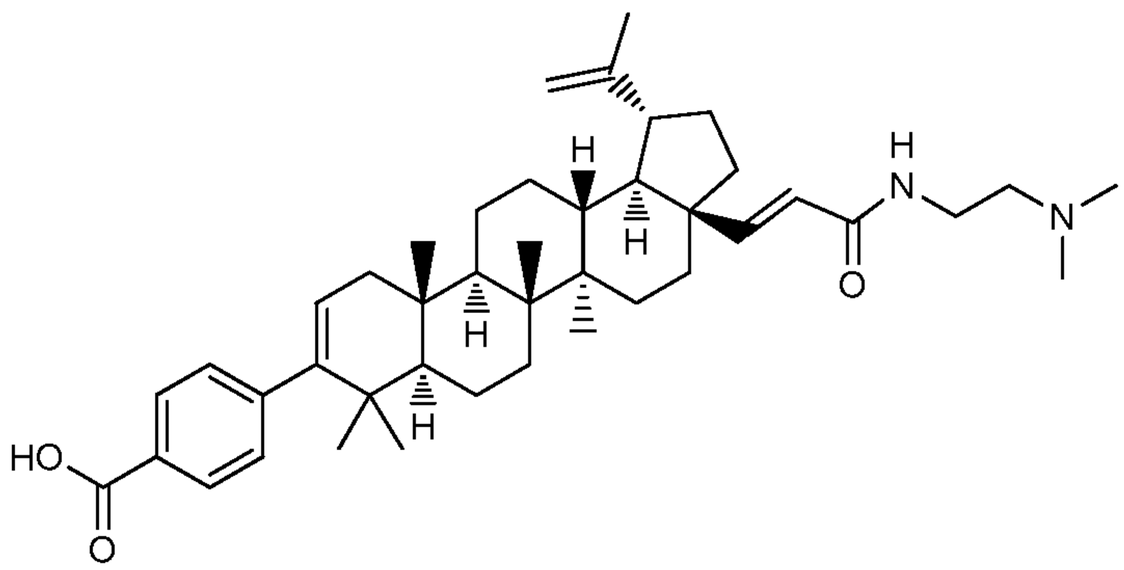
It is also preferred that Y is –COOH.

In another embodiment of the invention, it is preferred that the compounds have the Formula I.

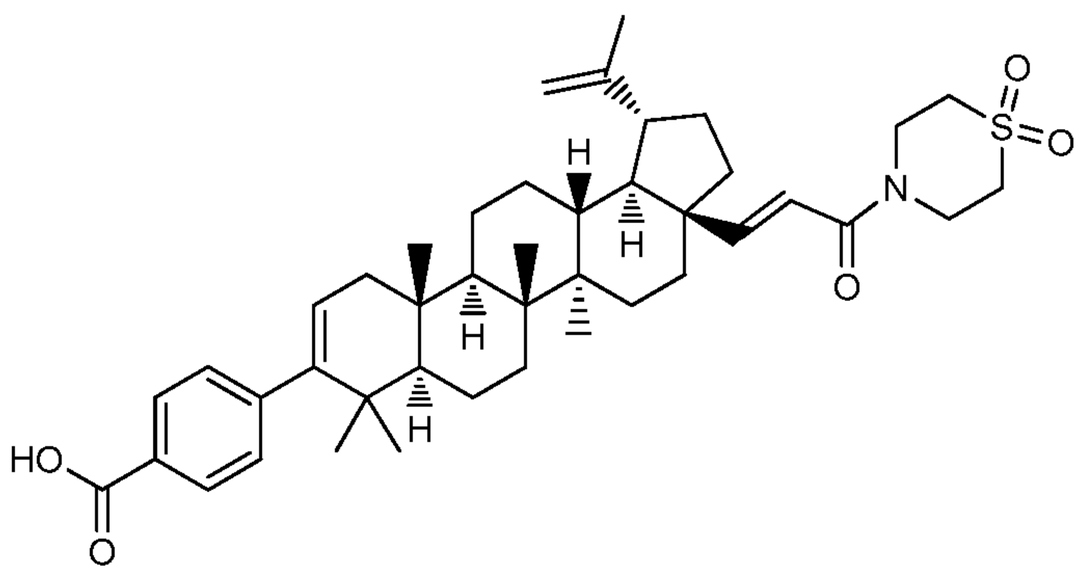
Preferred compounds, including pharmaceutically acceptable salts thereof, as part of the invention include the following:



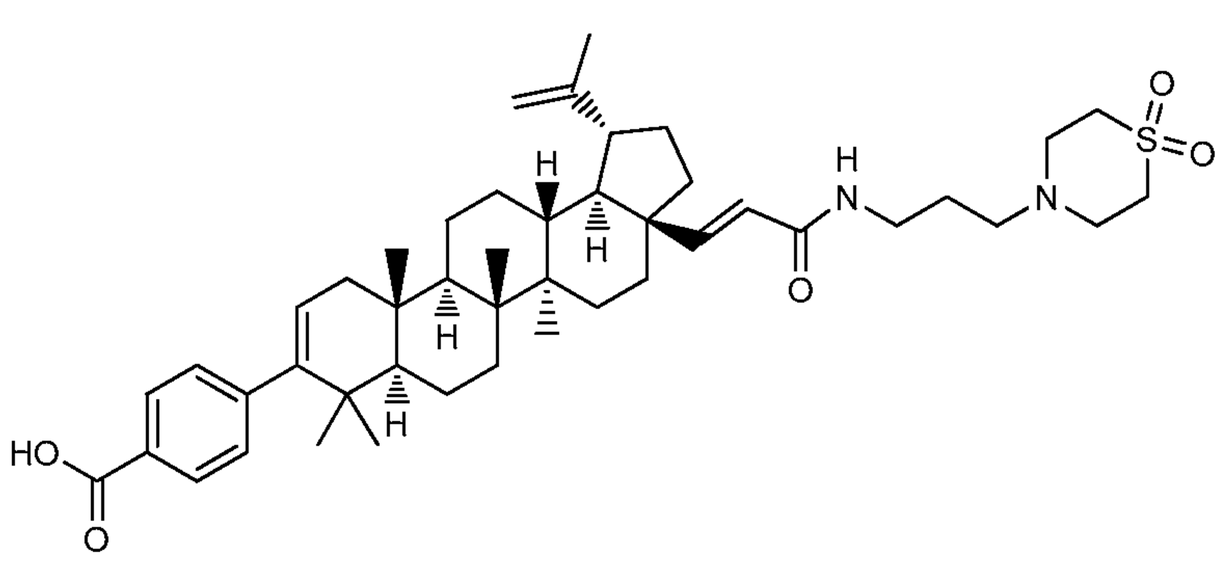
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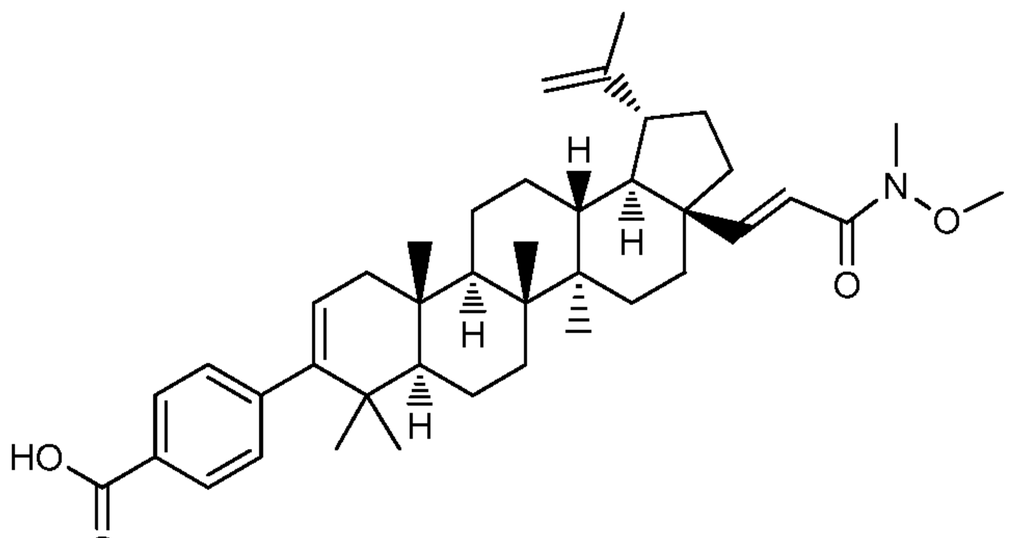
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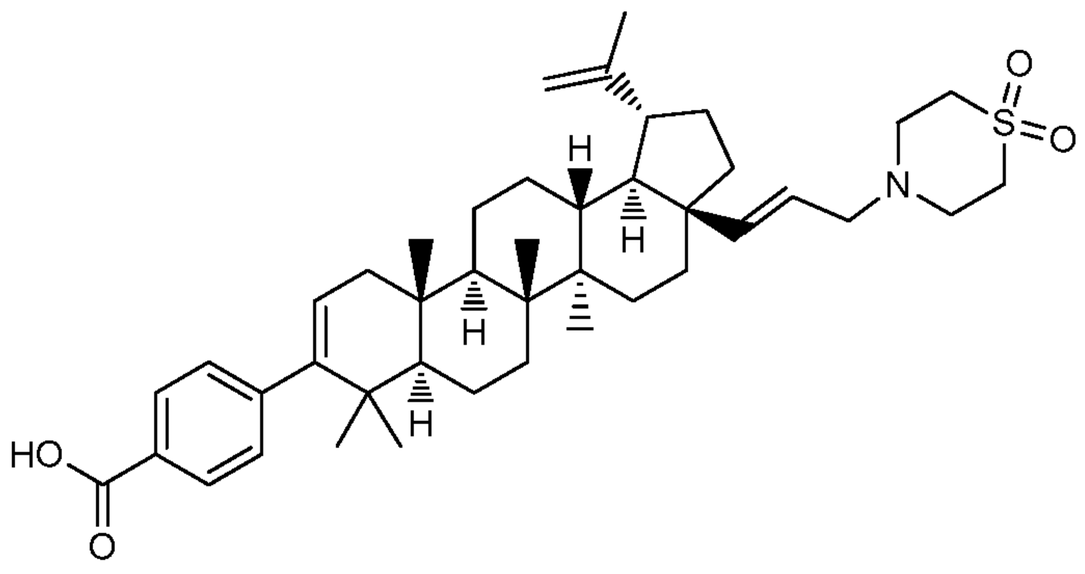
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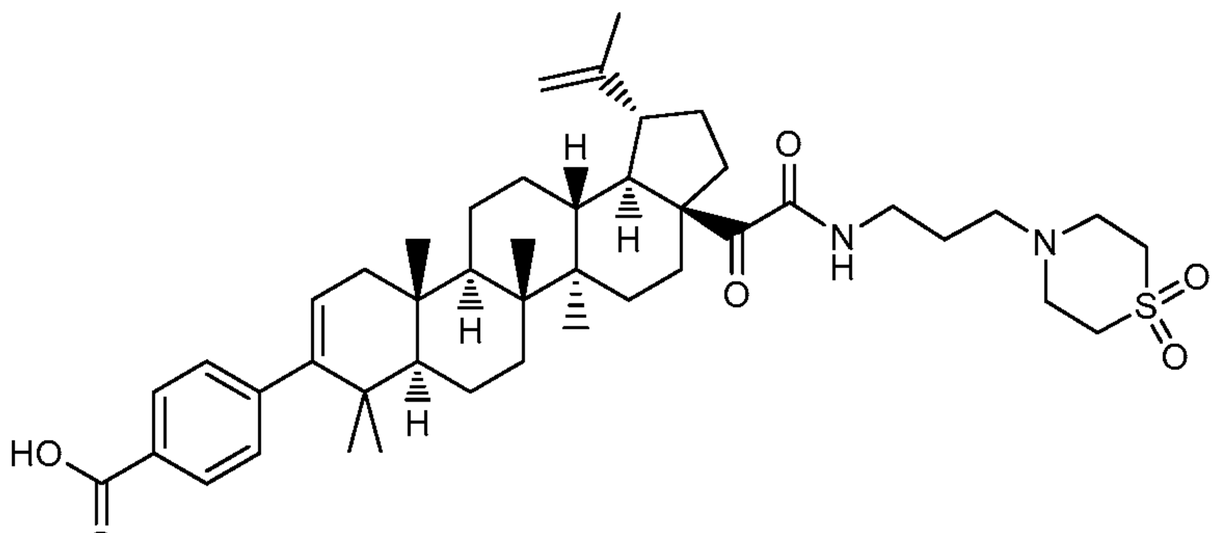


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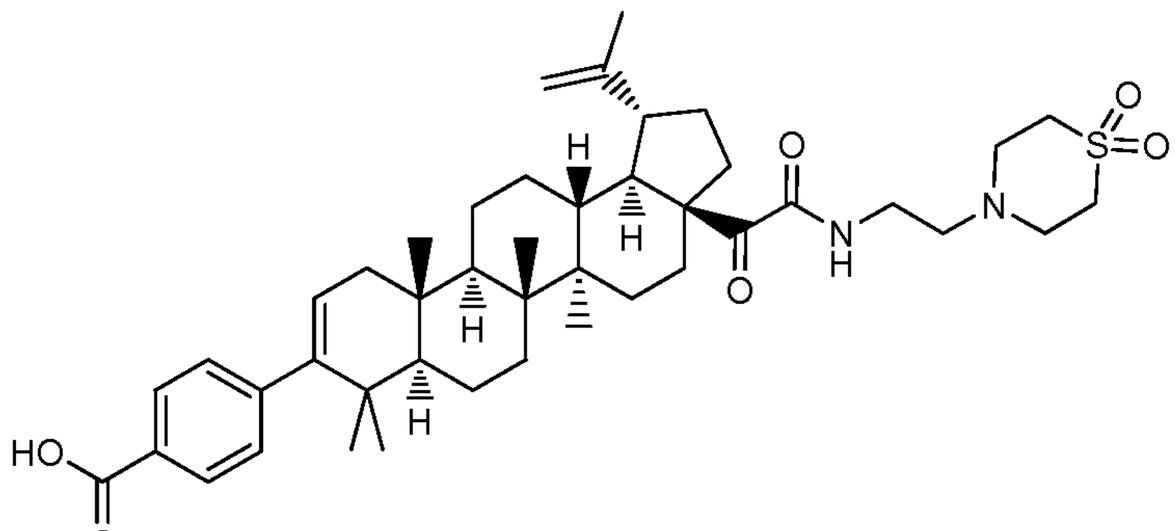


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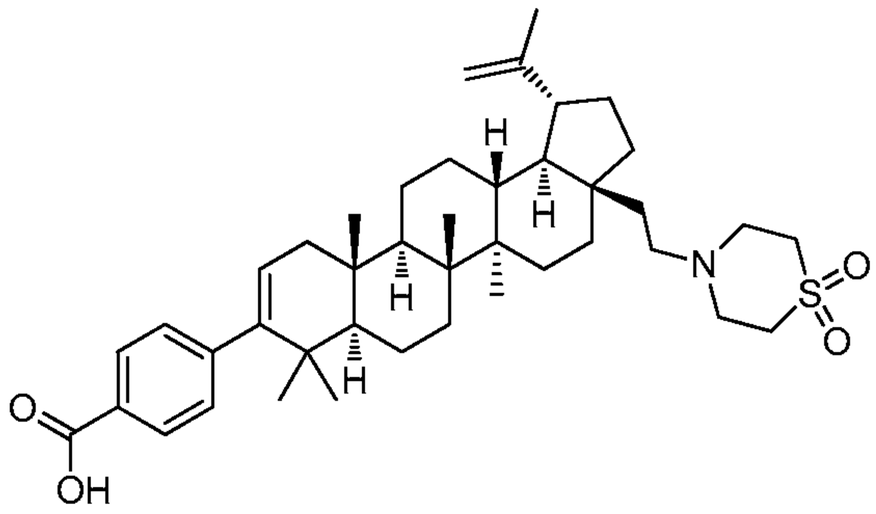
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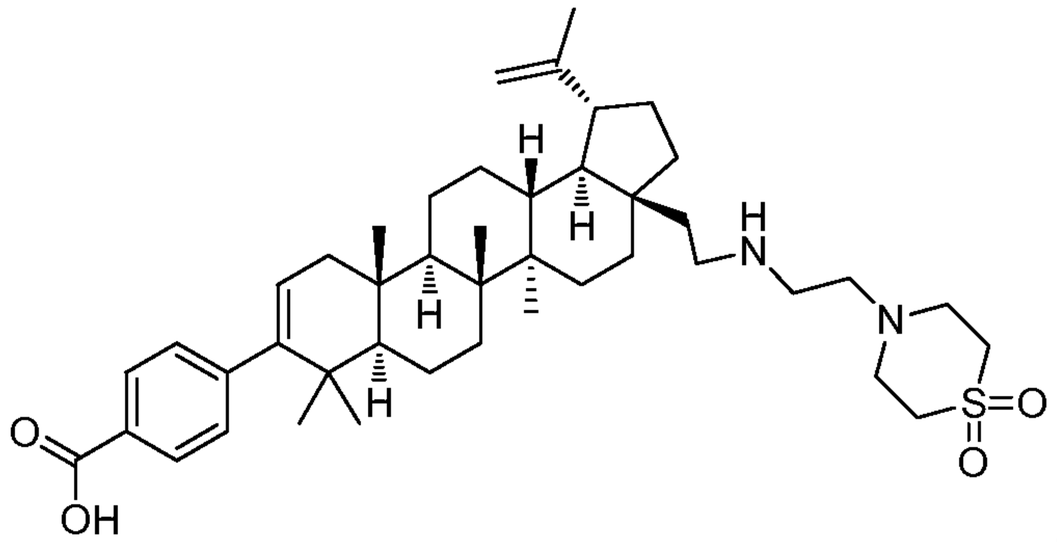
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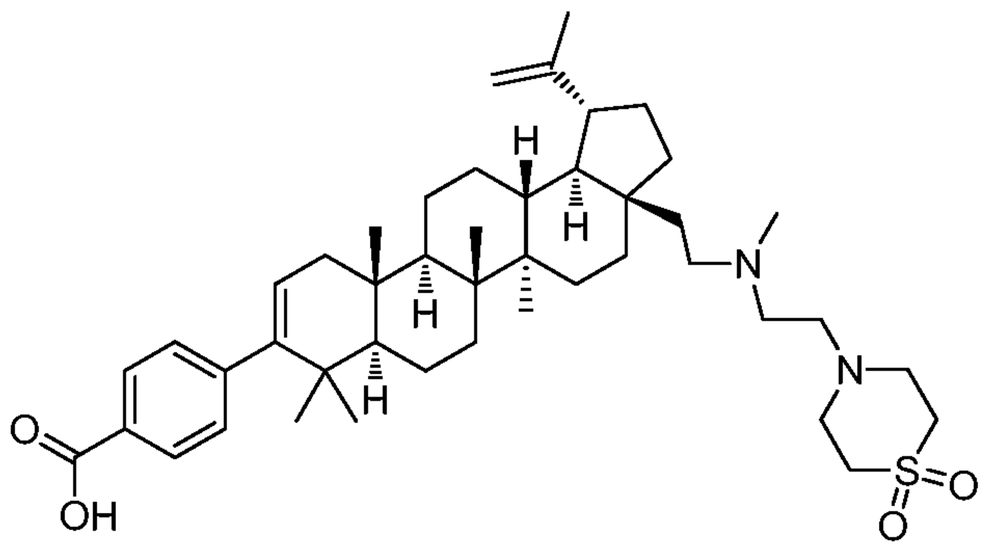
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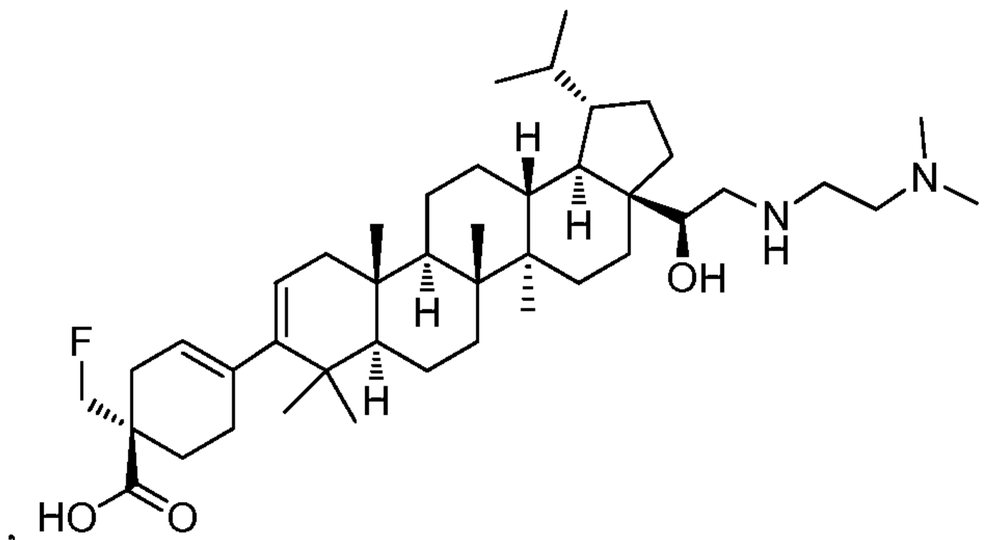
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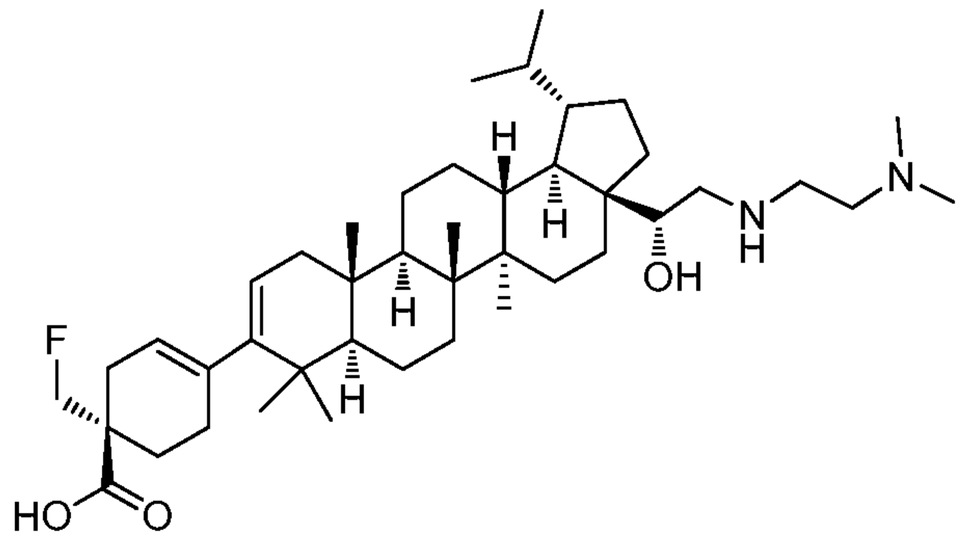


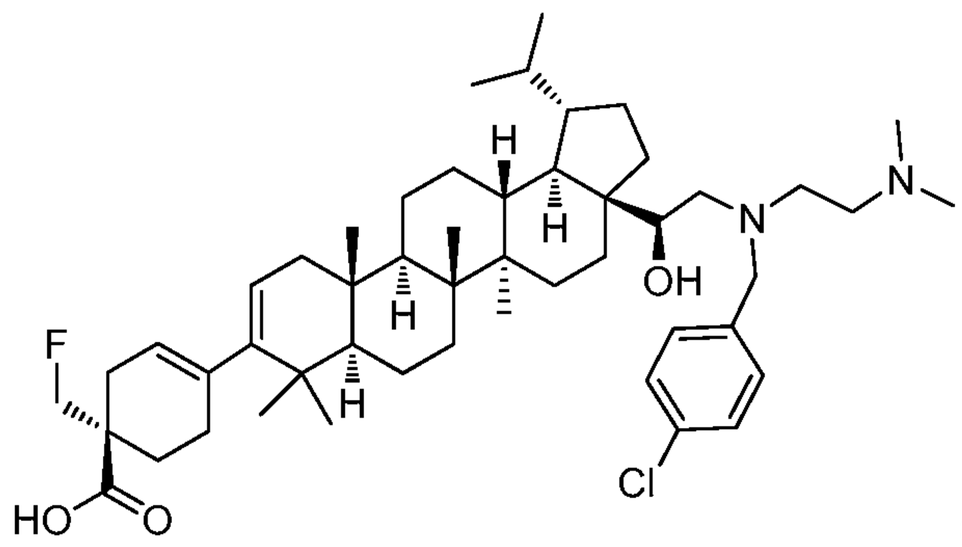
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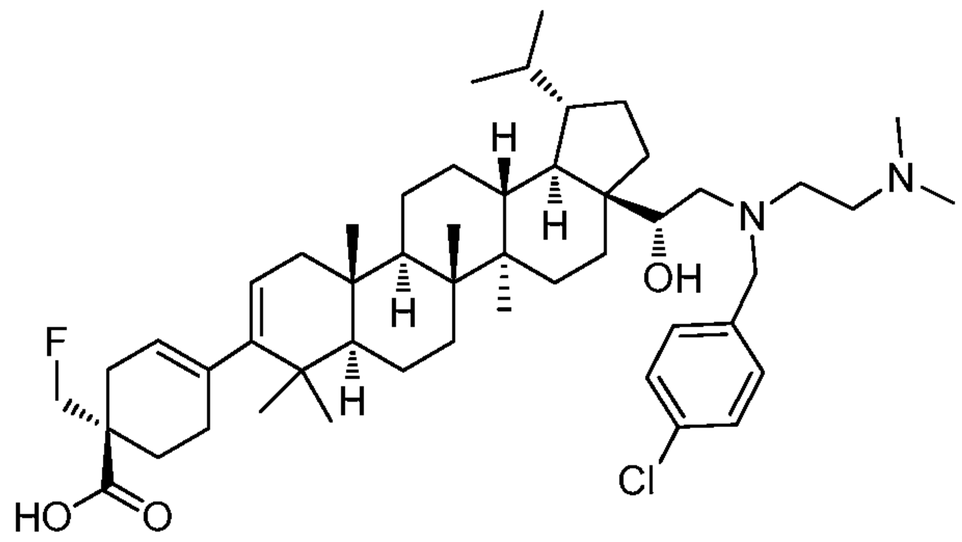


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The compounds above represent the mixture of diastereoisomers, and the two individual disastereomers. In certain embodiments, one of the specific diastereomers may be particularly preferred.

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 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®	Oncolys BioPharma	HIV infection
4'-ethynyl-d4T	BMS	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)

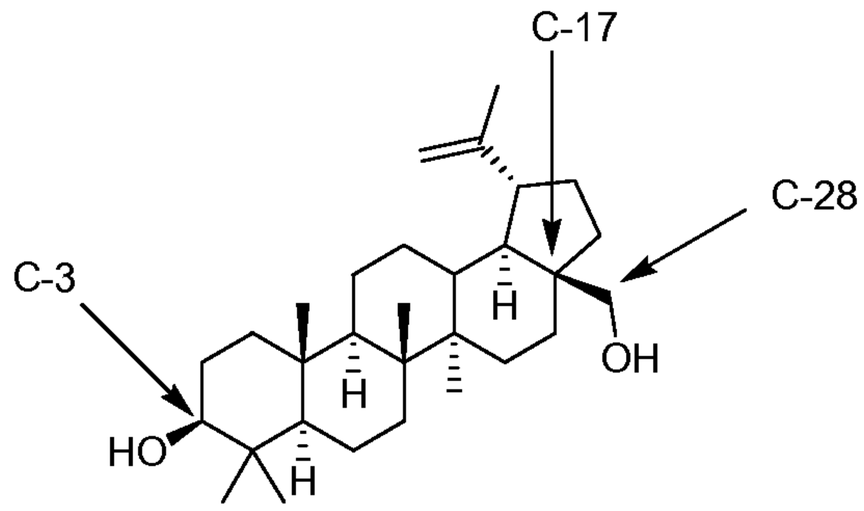
S-Phos = 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TFDO = methyl(trifluoromethyl)dioxirane

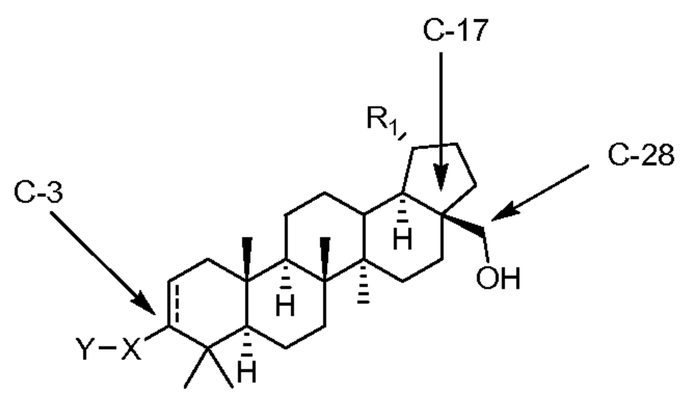
TEMPO = 2,2,6,6-tetramethylpiperidinyloxy

DI = deionized water

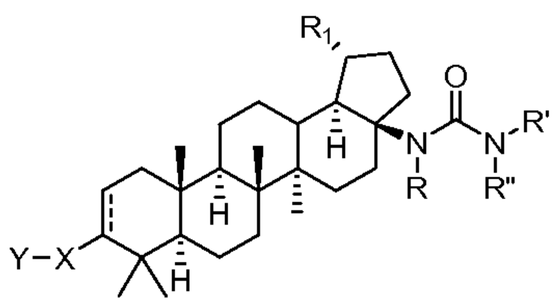
The terms “C-3” and “C-28” refer to certain positions of a triterpene core as numbered in accordance with IUPAC rules (positions depicted below with respect to an illustrative triterpene: betulin):



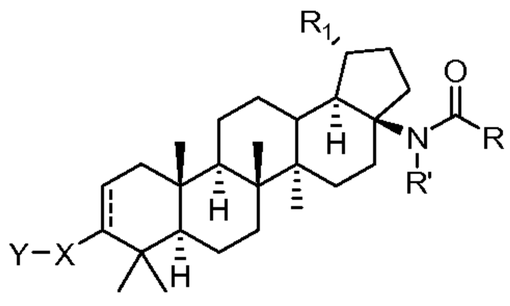
The same numbering is maintained when referring to the compound series in schemes and general descriptions of methods.



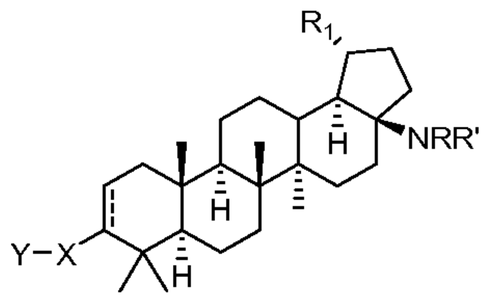
C-17 ureas



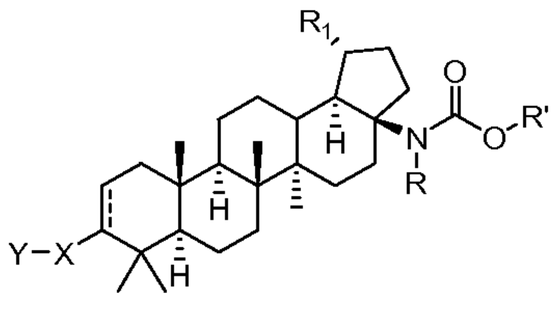
C-17 amides



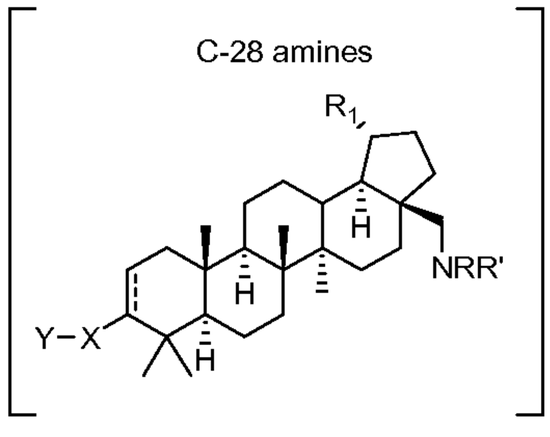
C-17 amines



C-17carbamates



C-28 amines



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.

Section 1

LC/MS Methods:

Method 1

Start % B = 30, Final % B = 100, gradient time = 2 min

Flow Rate = 0.8 mL/min

Wavelength = 220

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

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

Column = Xbridge Phenyl 2.1 x 50 mm 2.5µm

Method 2

Start % B = 40, Final % B = 100, gradient time = 2 min

Flow Rate = 1 mL/min

Wavelength = 220

Solvent A = 5% MeOH - 95% H_2O - 10mM NH_4OAc

Solvent B = 95% MeOH - 5% H_2O - 10mM NH_4OAc

Column = Phenomenex LUNA C18 30 x 2 mm 3µm

Method 3

Start % B = 30, Final % B = 100, gradient time = 1 min

Flow Rate = 0.8 mL/min

Wavelength = 220

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

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

Column = Xbridge Phenyl 2.1 x 50 mm 2.5µm

Method 4

Start % B = 30, Final % B = 100, gradient Time = 2 min

Flow Rate = 1 mL/min

Wavelength = 220

Solvent A = 5% MeOH - 95% H_2O - 10mM NH_4OAc

Solvent B = 95% MeOH - 5% H_2O - 10mM NH_4OAc

Column = Phenomenex LUNA C18 30x2 mm 3µm

Method 5

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

Flow Rate = 1 mL / min

Wavelength = 220 nm

Solvent A = 95% water, 5% methanol, 10mM Ammonium Actetate

Solvent B = 5% water, 95% methanol, 10mM Ammonium Actetate

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

Method 6

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 = Xbridge Phenyl, 2.5µm, 2.1 x 50 mm

Prep-HPLC Methods:

Method 1

Start %B = 10, Final %B = 100 over 10 minute gradient, hold at 100% B

Flow Rate = 40 mL/min

Wavelength = 220 nm

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

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

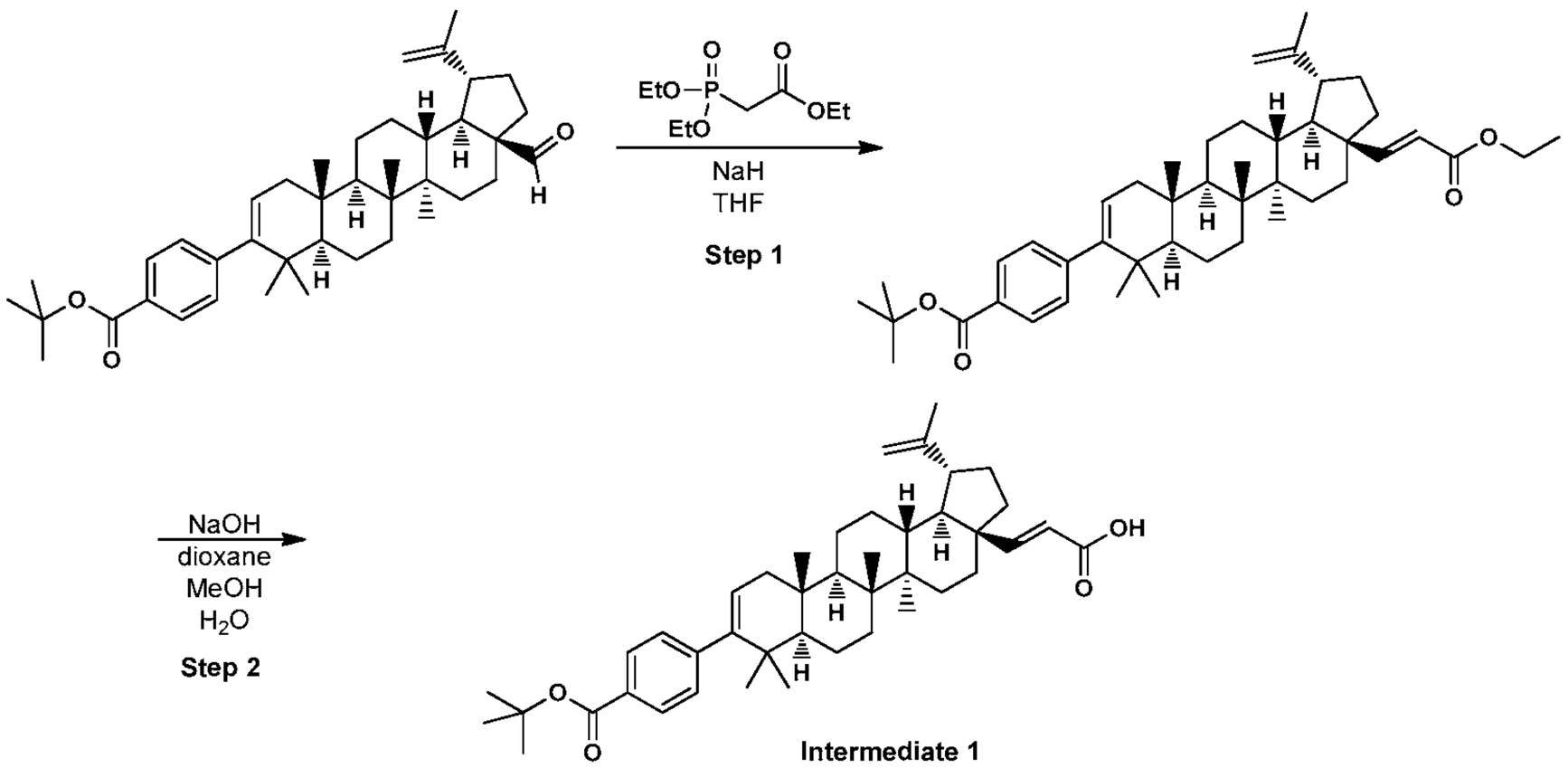
Column = YMC COMBIPREP ODS 30 x 50 mm S5

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

Intermediate 1

Preparation of (E)-3-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)acrylic acid



Intermediate 1

Step 1: Preparation of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a suspension of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-formyl-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (2.0 g, 3.34 mmol) (prepared as described in WO 2012106188) in THF (20 mL) at 0 °C was added triethyl phosphonoacetate (1.34 mL, 6.68 mmol) followed by NaH (60% in mineral oil) (0.22 g, 5.6 mmol). The mixture was stirred at 0 °C for 30 min then warmed to RT and stirred for 3 days. The reaction was quenched with saturated NH_4Cl (20 mL), followed by 0.5N HCl (20 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by a silica gel column eluted with a mixture of ethyl acetate and hexanes to give the title compound (2.06 g, 88%) as a solid. MS: m/e 611.6 $(M\text{-}t\text{-}Bu\text{-}H)^-$, 2.70 min (method 2). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.89 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=15.3 Hz, 1H), 7.17 (d, *J*=8.3 Hz, 2H), 5.92 (d, *J*=16.1 Hz, 1H), 5.28 (dd, *J*=6.3, 1.8 Hz, 1H), 4.75 (d, *J*=1.8 Hz, 1H), 4.62 (s, 1H), 4.24 (q, *J*=7.1 Hz, 2H), 2.58 - 2.50 (m, 1H), 2.14 - 2.07 (m, 1H), 1.95 - 0.85 (m, 21H), 1.72 (s, 3H), 1.60 (s, 9H), 1.33 (t, *J*=7.0 Hz,

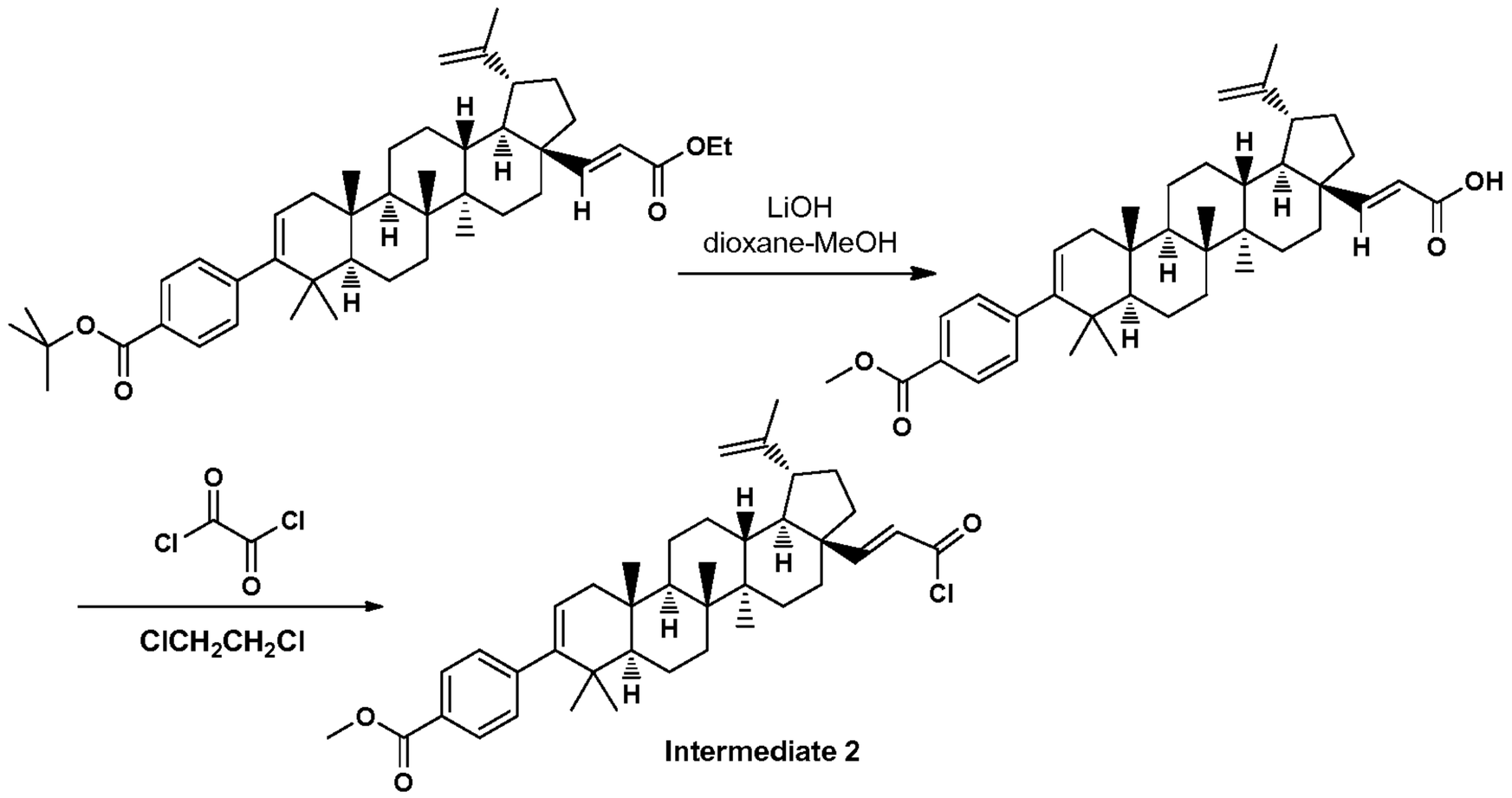
3H), 1.02 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.92 (s, 6H).

Step 2: Preparation of (E)-3-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)acrylic acid

To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (1.0 g, 1.50 mmol) in 1,4-dioxane (100 mL) and MeOH (10 mL) was added 10 N NaOH (3 mL, 30 mmol). The resulted mixture was stirred at RT overnight. The reaction mixture was neutralized with 1N HCl and concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 50 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified in silica gel to give the product (527 mg, 55%) as a solid. MS: m/e 639.7 $(M-H)^-$, 2.89 min (method 2). ^1H NMR (400MHz, METHANOL-d_4) δ 7.84 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=16.1 Hz, 1H), 7.19 (d, *J*=8.5 Hz, 2H), 5.91 (d, *J*=16.1 Hz, 1H), 5.28 (dd, *J*=6.1, 1.6 Hz, 1H), 4.76 (d, *J*=1.8 Hz, 1H), 4.62 (s, 1H), 2.54 (td, *J*=11.0, 5.1 Hz, 1H), 2.14 (dd, *J*=17.1, 6.3 Hz, 1H), 1.95 - 0.86 (m, 21H), 1.72 (s, 3H), 1.58 (s, 9H), 1.06 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H).

Intermediate 2

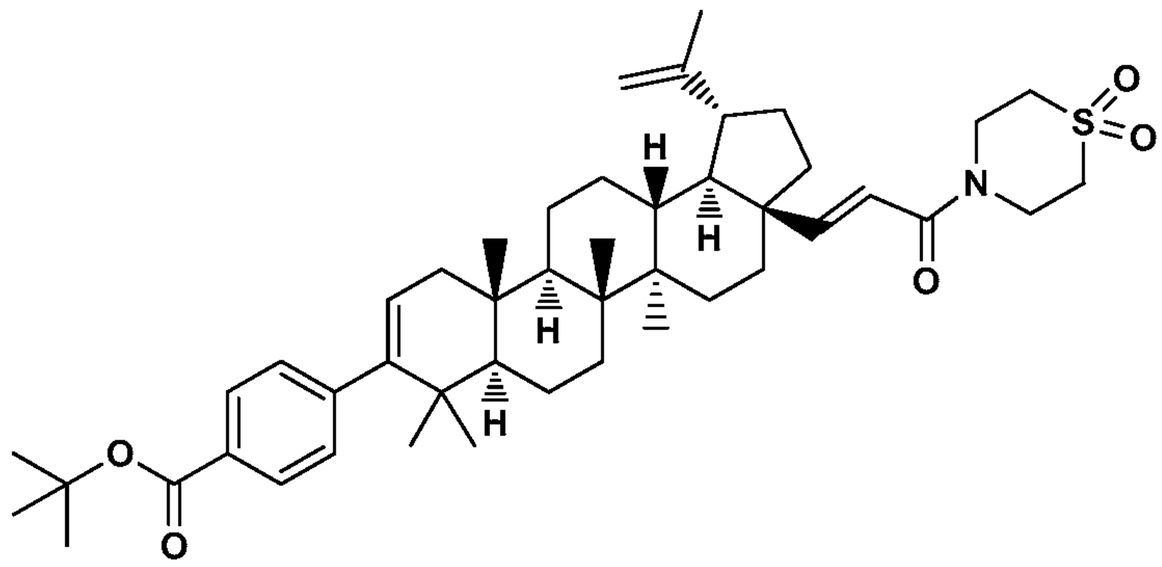
Preparation of (E)-3-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)acrylic acid



tert-Butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-ethoxy-3-oxoprop-1-enyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (161 mg, 0.241 mmol) was dissolved in a mixture of methanol (5 mL) and dioxane (15 mL). To this solution was added lithium hydroxide (1N, 0.72 mL, 0.72 mmol) and the suspension was stirred for 40 hours at RT. A small aliquot was removed from the crude reaction, quenched with excess of 1N HCl, and evaporated into a dry film. This film was taken into 1,2-dichloroethane (4 mL), and a 2 M stock solution of oxalyl chloride in DCM (1.362 mL) in a resealable pressure tube, and heated to 60 °C for 24 hours. The reaction solution was dried in vacuo to afford the crude acyl chloride which was used immediately without further purification. Selected diagnostic signals from ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.56 (d, *J*=15.9 Hz, 1H), 6.18 (d, *J*=15.9 Hz, 1H).

Intermediate 3

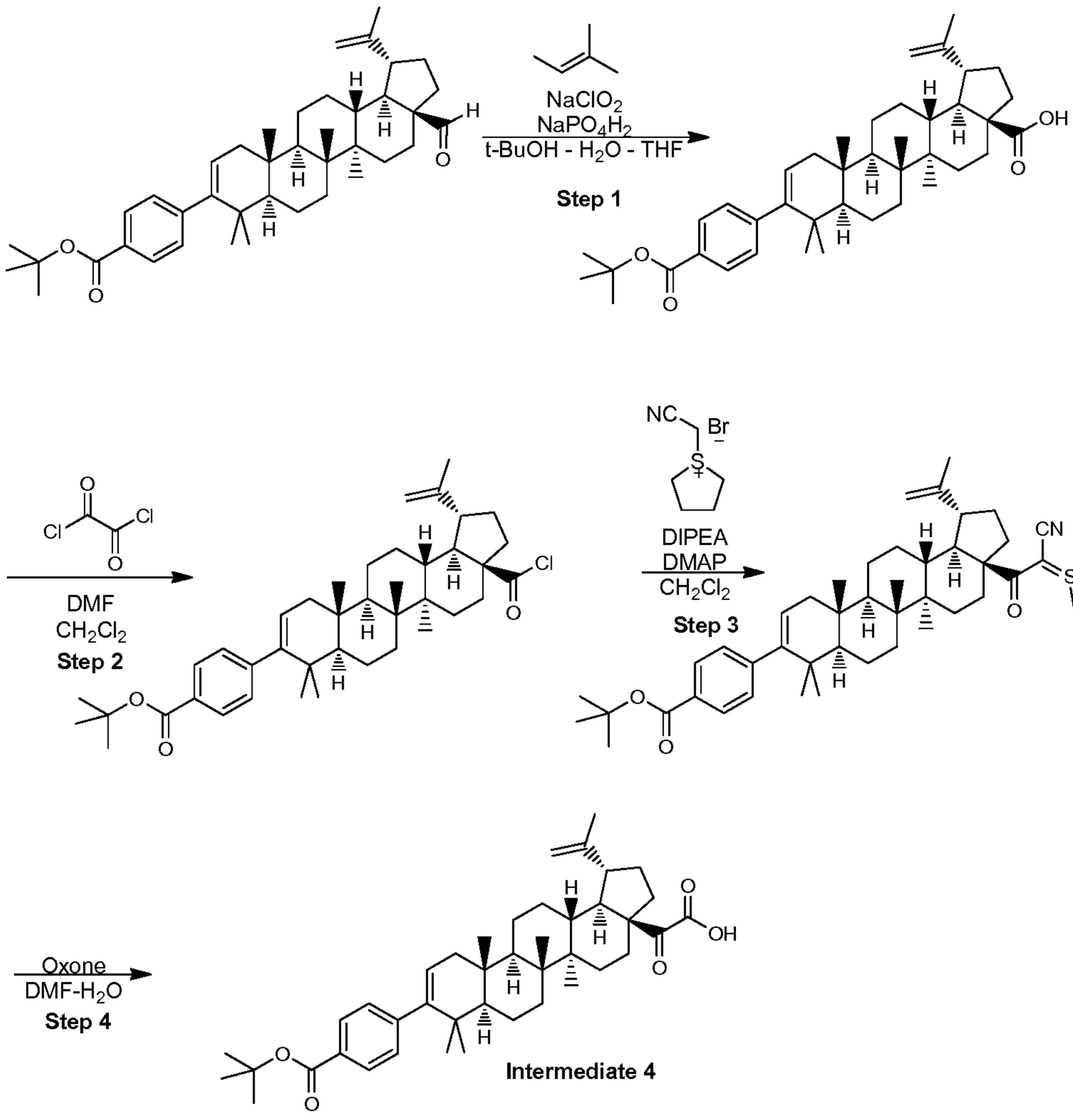
Preparation of *tert*-Butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate



To a solution of (E)-3-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)acrylic acid (100 mg, 0.16 mmol) and thiomorpholine 1,1-dioxide (25 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was added DIPEA (0.14 mL, 0.78 mmol) followed by HATU (89 mg, 0.23 mmol). The solution was stirred at RT for 1 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified on silica gel to give the title compound (115 mg, 97%) as a solid. MS: m/e 758.6 $(M+H)^+$, 2.80 min (method 1). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.89 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=14.3 Hz, 1H), 7.17 (d, *J*=8.3 Hz, 2H), 6.31 (d, *J*=15.6 Hz, 1H), 5.28 (d, *J*=4.5 Hz, 1H), 4.74 (s, 1H), 4.64 (s, 1H), 4.20 - 4.04 (m, 4H), 3.17 - 3.01 (m, 4H), 2.57 (dt, *J*=11.1, 5.9 Hz, 1H), 2.10 (dd, *J*=17.2, 6.4 Hz, 1H), 1.96 - 0.85 (m, 21H), 1.72 (s, 3H), 1.60 (s, 9H), 1.03 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.92 (s, 6H).

Intermediate 4

Preparation of 2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)-2-oxoacetic acid



Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid

To a solution of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-formyl-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (150 mg, 0.25 mmol) in *tert*-BuOH (2 mL) and THF (2 mL) was added 2-methylbut-2-ene (2 mL, 24 mmol). A solution of sodium chlorite (227 mg, 2.5 mmol) and sodium phosphate monobasic monohydrate (450 mg, 3.3 mmol) in H_2O (4 mL) was added dropwise over 10 min. The reaction mixture was stirred at RT for 4 h. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 10 mL).

The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude mixture was purified on silica gel to give the product (121 mg, 79%) as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.89 (d, *J*=8.5 Hz, 2H), 7.17 (d, *J*=8.3 Hz, 2H), 5.28 (dd, *J*=6.0, 1.8 Hz, 1H), 4.76 (d, *J*=1.8 Hz, 1H), 4.63 (s, 1H), 3.03 (td, *J*=10.9, 4.4 Hz, 1H), 2.32 - 2.23 (m, 1H), 2.11 (dd, *J*=17.4, 6.7 Hz, 1H), 2.06 - 0.89 (m, 20H), 1.71 (s, 3H), 1.60 (s, 9H), 1.02 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.92 (s, 6H).

Step 2: Preparation of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(chlorocarbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

To a solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid from step 1(60 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) was added oxalyl dichloride (2 M in CH_2Cl_2) (0.075 mL, 0.15 mmol) followed by DMF (0.76 µL, 0.01 mmol). The reaction mixture was stirred for 2 h and then concentrated under reduce pressure to give the crude product as a solid.

Step 3: Preparation of the α-keto-cyanosulfur ylide

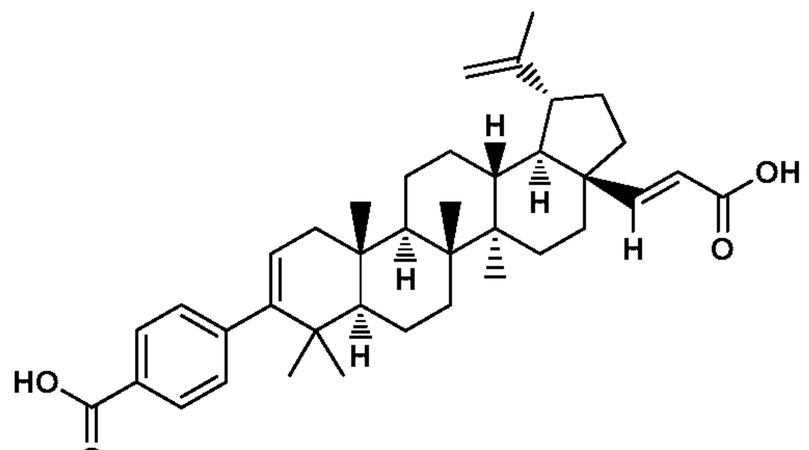
To a solution of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(chlorocarbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate from step 2 (62 mg, 0.098 mmol), 1-(cyanomethyl)tetrahydro-1H-thiophen-1-ium bromide [Ju, L.; Lippert, A. R.; Bode, J. W. *J. Am. Chem. Soc.* 2008, *130*, 4253 - 4255 (31 mg, 0.15 mmol) and DMAP (0.6 mg, 4.9 µmol) in CH_2Cl_2 (5 mL) was added DIPEA (0.05 mL, 0.29 mmol). The reaction mixture was stirred at RT overnight. Additional 1-(cyanomethyl)tetrahydro-1H-thiophen-1-ium bromide (31 mg, 0.15 mmol) was added and the stirring was continued overnight. The reaction was quenched with NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrate under reduced pressure. The crude mixture was purified by flash

chromatography to give the product (14 mg, 20%) as a solid. MS: m/e 724.5 $(M+H)^+$, 3.71 min (method 1). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.89 (d, *J*=8.0 Hz, 2H), 7.18 (d, *J*=8.0 Hz, 2H), 5.28 (d, *J*=5.0 Hz, 1H), 4.76 (s, 1H), 4.64 (s, 1H), 3.10 - 3.00 (m, 1H), 2.38 - 2.28 (m, 1H), 2.24 (d, *J*=12.0 Hz, 1H), 2.12 (dd, *J*=17.1, 6.3 Hz, 1H), 2.07 - 1.95 (m, 2H), 1.80 - 1.07 (m, 25H), 1.72 (s, 3H), 1.60 (s, 9H), 1.05 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.93 (s, 6H).

Step 4: To a suspension of product from step 3 (14 mg, 0.02 mmol) in DMF (2 mL) and H_2O (1 mL) was added oxone (48 mg, 0.08 mmol). The reaction mixture was stirred at RT overnight. The reaction mixture was concentrated *in vacuo*. The residue was washed with H_2O, the solid was collected by filtration, washed with H_2O, and dried under vacuum to give a crude containing 2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)-2-oxoacetic acid, which was used in the next step without further purification. MS: m/e 643.6 $(M+H)^+$, 2.71 min (method 4).

Example 1

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-2-carboxyvinyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

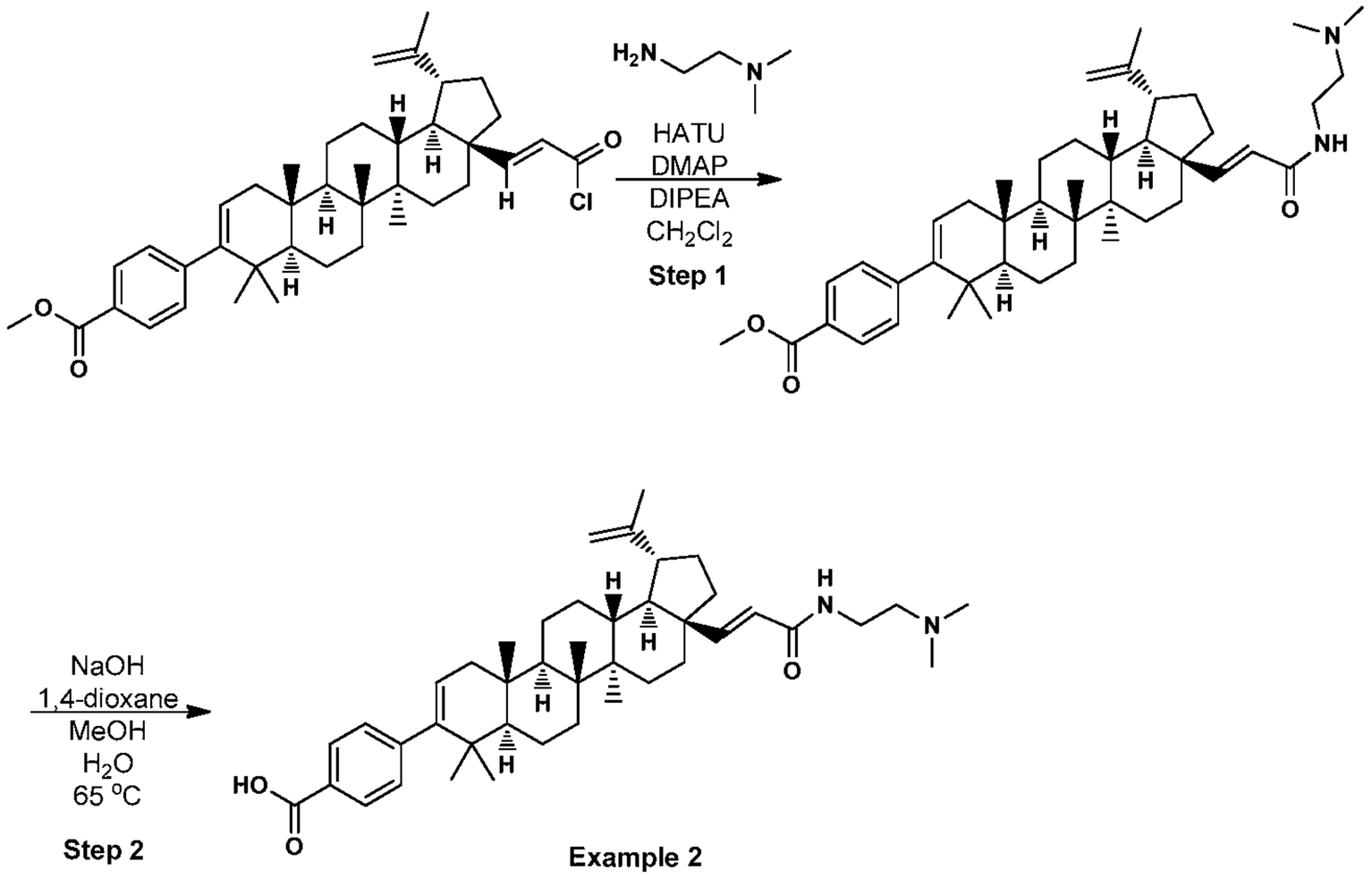


tert-Butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-ethoxy-3-oxoprop-1-enyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoate (163 mg, 0.244 mmol) in a mixture of methanol (5 mL) and dioxane (4 mL) was treated with LiOH (1N, 1.0 mL, 1.0 mmol). The mixture was heated at 80 °C for 16 hr. After cooling to room temperature the reaction was neutralized with excess of HCl (0.5N). The organic material was extracted with ethyl acetate. Removal of the solvent in vacuo afforded a glassy material that was purified using prep HPLC to afford the title compound as a white solid (85 mg, 60%). MS: m/e 585.4 $(M+H)^+$, 6.02 min (method 5). ^1H NMR (400MHz, METHANOL-d_4) δ 7.94 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=16.1 Hz, 1H), 7.24 (d, *J*=8.5 Hz, 2H), 5.94 (d, *J*=16.3 Hz, 1H), 5.32 (dd, *J*=6.1, 1.6 Hz, 1H), 4.79 (d, *J*=2.0 Hz, 1H), 4.67 - 4.63 (m, 1H), 2.58 (td, *J*=11.1, 5.1 Hz, 1H), 2.17 (dd, *J*=17.2, 6.4 Hz, 1H), 1.98 - 1.78 (m, 5H), 1.75 (s, 3H), 1.73 - 1.64 (m, 4H), 1.63 - 1.55 (m, 4H), 1.49 (dd, *J*=12.5, 3.5 Hz, 5H), 1.40 - 1.28 (m, 3H), 1.22 - 1.11 (m, 2H), 1.09 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Example 2

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((2-(dimethylamino)ethyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1: Preparation of methyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((2-(dimethylamino)ethyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

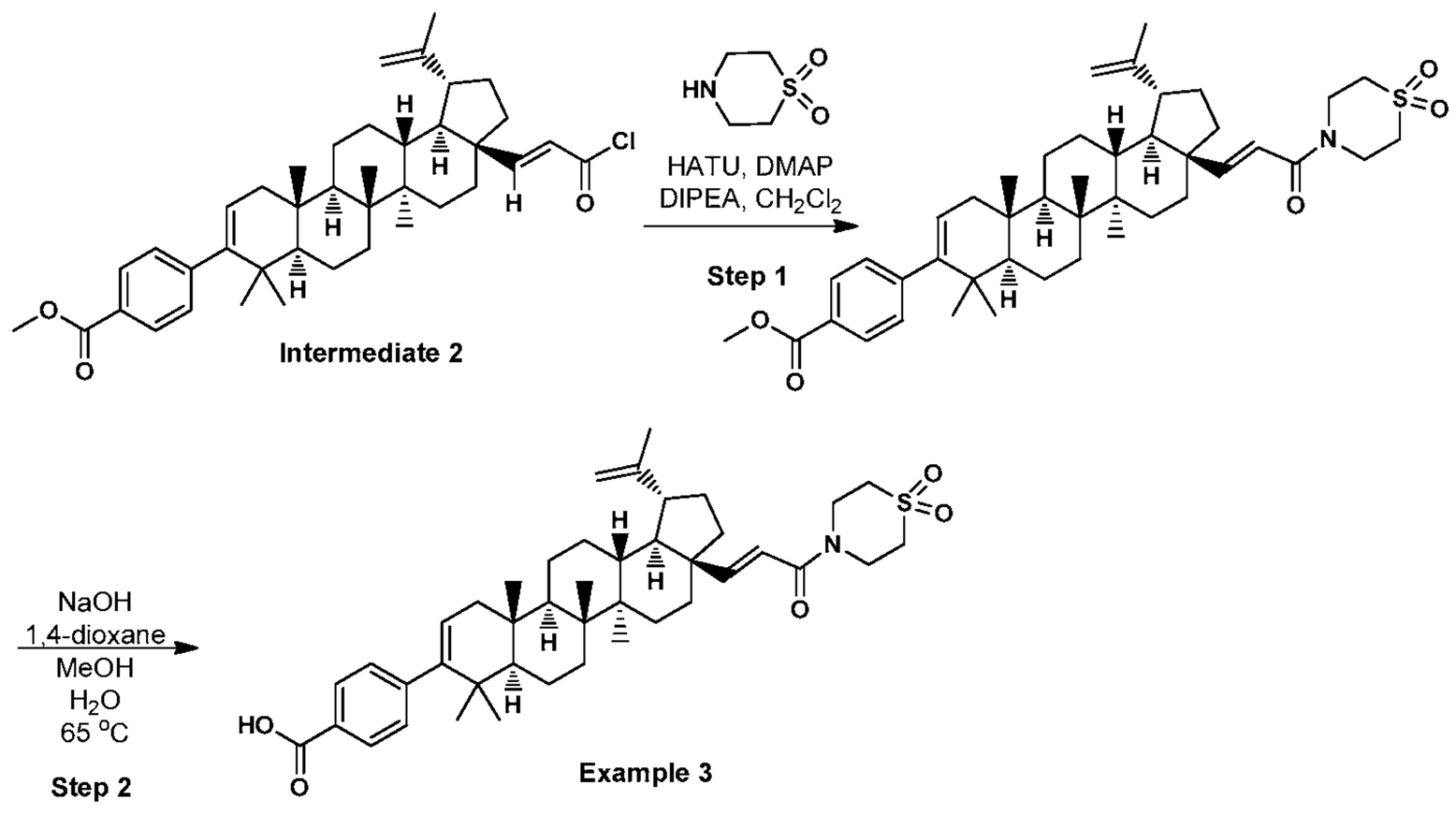
To a solution of crude methyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-chloro-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.061 mmol) in CH_2Cl_2 (2 mL) was added 2-(dimethylamino)ethaniminium (8 mg, 0.09 mmol), HATU (35 mg, 0.09 mmol), DIPEA (0.05 mL, 0.3 mmol) and DMAP (0.4 mg, 0.003 mmol). The mixture was stirred at RT for 3 h. The crude mixture was purified by Prep HPLC to give the title compound (6 mg, 15%) as a solid. MS: m/e 669.6 $(M+H)^+$, 1.87 min (method 3). ^1H NMR (400MHz, CHLOROFORM-d) δ 8.23 (br. s, 1H), 7.77 (d, *J*=8.0 Hz, 2H), 7.28(d, *J*=16.0 Hz, 1H), 7.19 (d, *J*=7.8 Hz, 2H), 5.93 (d, *J*=16.1 Hz, 1H), 5.27 (d, *J*=4.3 Hz, 1H), 4.75 (s, 1H), 4.63 (s, 1H), 3.94 - 3.85 (m, 2H), 3.78 (s, 3H), 3.40 - 3.29 (m, 2H), 2.92 (s, 6H), 2.59 - 2.50(m, 1H), 2.10 (dd, *J*=16.1, 5.3 Hz, 1H), 1.95 - 0.85 (m, 21H), 1.72 (s, 3H), 1.02 (s, 6H), 0.97 (s, 3H), 0.91 (s, 6H).

Step 2: To a solution of methyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((2-(dimethylamino)ethyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (6 mg, 0.009 mmol) in 1,4-dioxane (1 mL) and MeOH (1 mL) was added 1 N NaOH (0.5 mL, 0.500 mmol). The solution was heated at 65 °C for 2 h. The crude mixture was neutralized with 1N HCl, concentrated under reduced pressure, and the residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The organic layer was washed with H_2O (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by Prep HPLC to give the product (4.3 mg, 73%) as a solid. MS: m/e 655.7 $(M+H)^+$, 1.77 min (method 3). ^1H NMR (400MHz, METHANOL-d_4) δ 7.77 (d, *J*=8.5 Hz, 2H), 7.30 (d, *J*=16.1 Hz, 1H), 7.23 (d, *J*=8.3 Hz, 2H), 5.91 (d, *J*=16.1 Hz, 1H), 5.29 (dd, *J*=6.1, 1.6 Hz, 1H), 4.76 (d, *J*=2.0 Hz, 1H), 4.62 (s, 1H), 3.75 (t, *J*=5.8 Hz, 2H), 3.37 (t, *J*=5.8 Hz, 2H), 2.98 (s, 6H), 2.54 (td, *J*=11.0, 5.3 Hz, 1H), 2.14 (dd, *J*=17.2, 6.4 Hz, 1H),

1.96 - 0.88 (m, 21H), 1.72 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H).

Example 3

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1: Preparation of methyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

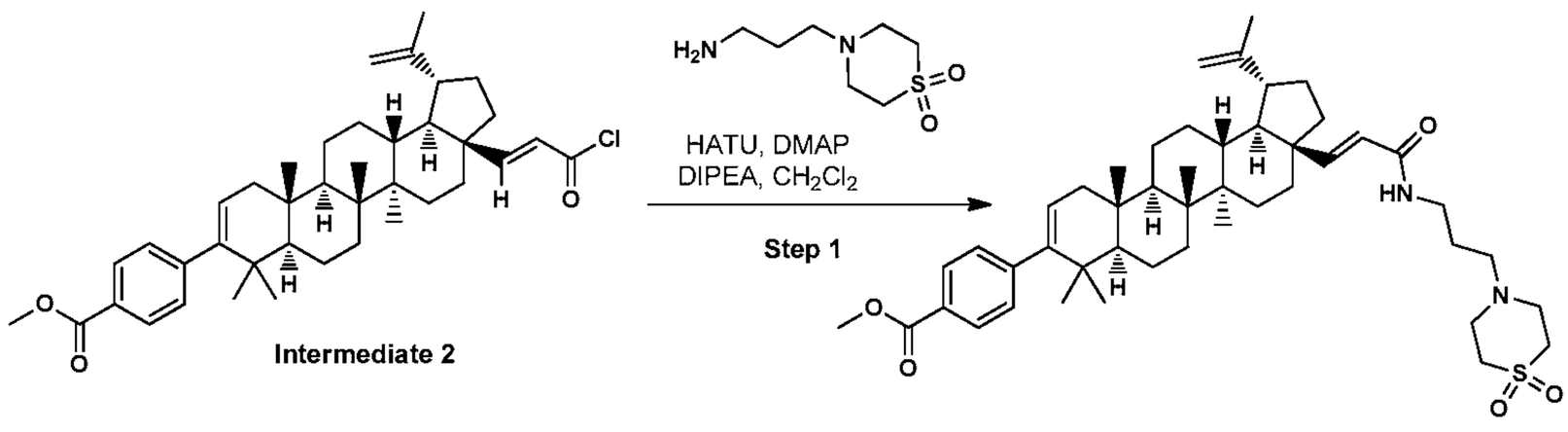
The title compound (solid, 12% yield) was prepared from intermediate 2 following the procedure described in step 1 for the preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((2-(dimethylamino)ethyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, using thiomorpholine 1,1-dioxide as the reactant. MS: m/e 716.6 $(M+H)^+$, 2.42 min (method 3). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.33 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=16.0 Hz, 1H), 7.22 (d, *J*=8.3 Hz, 2H), 5.93 (d, *J*=16.3

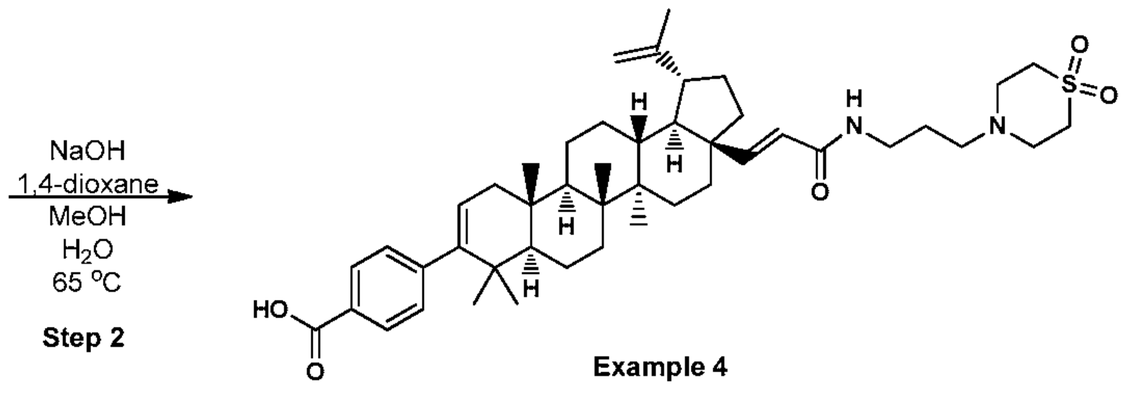
Hz, 1H), 5.29 (dd, *J*=6.1, 1.6 Hz, 1H), 4.75 (d, *J*=2.0 Hz, 1H), 4.63 (s, 1H), 4.25 - 4.03 (m, *J*=17.6 Hz, 4H), 3.78 (s, 3H), 3.21 - 2.99 (m, *J*=16.3 Hz, 4H), 2.55 (dt, *J*=11.0, 5.5 Hz, 1H), 2.11 (dd, *J*=17.1, 6.3 Hz, 1H), 1.95 - 0.86 (m, 21H), 1.71 (s, 3H), 1.02 (s, 6H), 0.97 (s, 3H), 0.93 (s, 6H).

Step 2: The title compound (solid, 31% yield) was prepared following the procedure described in step 2 for the preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((2-(dimethylamino)ethyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. MS: m/e 702.6 $(M+H)^+$, 2.12 min (method 3). ^1H NMR (400MHz, METHANOL-d_4) δ 7.91 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=16.1 Hz, 1H), 7.21 (d, *J*=8.5 Hz, 2H), 5.91 (d, *J*=16.3 Hz, 1H), 5.29 (dd, *J*=6.1, 1.9 Hz, 1H), 4.76 (d, *J*=1.8 Hz, 1H), 4.62 (s, 1H), 4.23 - 3.88 (m, 2H), 3.30 - 3.15 (m, 6H), 2.55 (dt, *J*=10.9, 5.6 Hz, 1H), 2.15 (dd, *J*=17.2, 6.4 Hz, 1H), 1.96 - 0.84 (m, 21H). 1.73 (s, 3H), 1.06 (s, 3H), 1.06 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H).

Example 4

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((3-(1,1-dioxidothiomorpholino)propyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid





Step 1: Preparation of methyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((3-(1,1-dioxidothiomorpholino)propyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

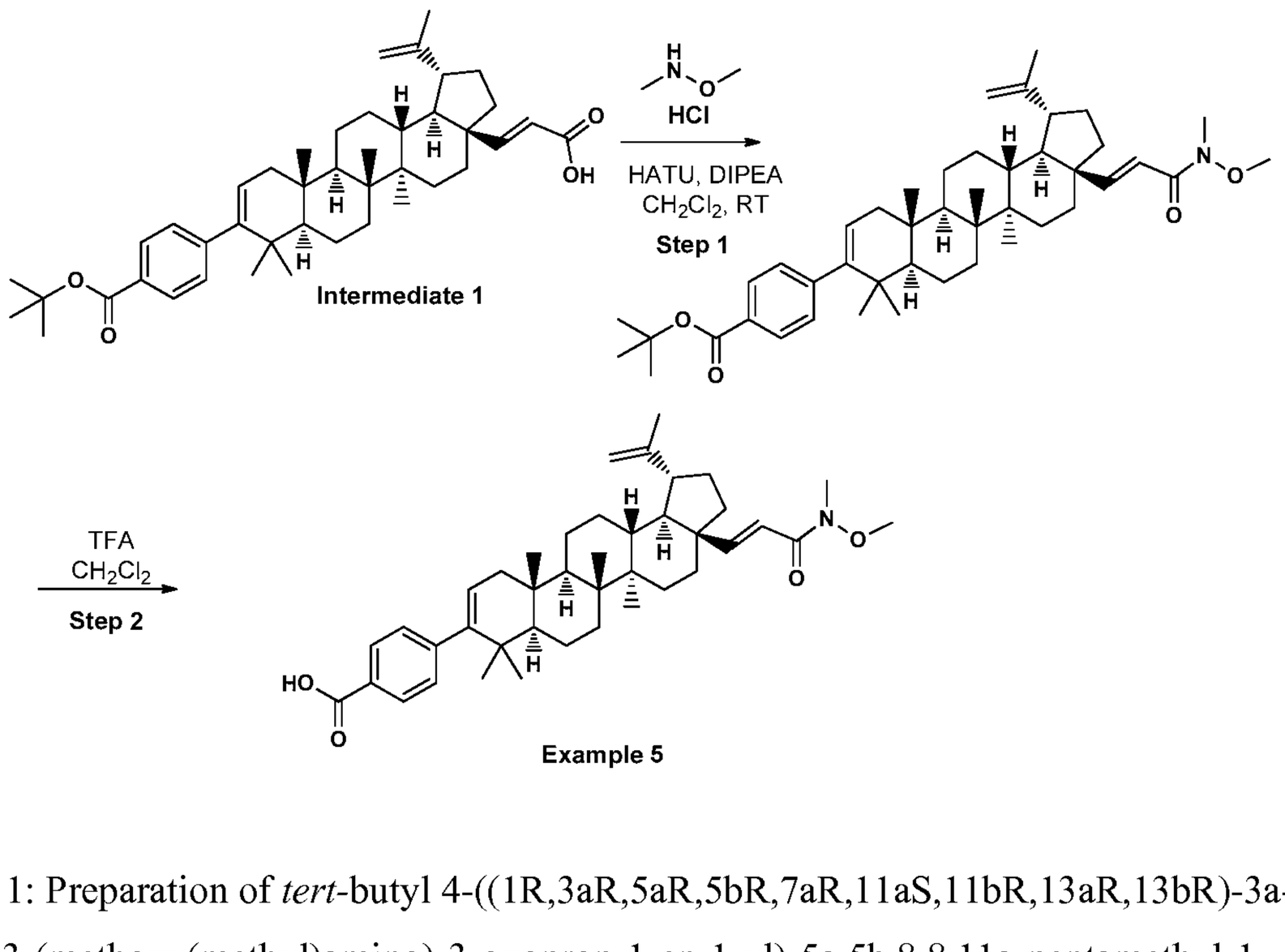
The title compound (solid, 12% yield) was prepared from intermediate 2 following the procedure described in step 1 for the preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((2-(dimethylamino)ethyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, using 4-(3-aminopropyl)thiomorpholine 1,1-dioxide as reactant. MS: m/e 773.5 $(M+H)^+$, 1.94 min (method 3). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.72 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=16.0 Hz, 1H), 7.22 (d, *J*=8.0 Hz, 2H), 5.93 (d, *J*=16.1 Hz, 1H), 5.28 (d, *J*=5.3 Hz, 1H), 4.75 (s, 1H), 4.63 (s, 1H), 3.78 (s, 3H), 3.73 - 3.65 (m, 4H), 3.63 - 3.55 (m, 2H), 3.53 - 3.47 (m, 4H), 3.25 (t, *J*=6.4 Hz, 2H), 2.54 (td, *J*=10.9, 5.0 Hz, 1H), 2.21 - 2.11 (m, 2H), 2.11 (dd, *J*=17.6, 6.5 Hz, 1H), 1.95 - 0.85 (m, 21H), 1.71 (s, 3H), 1.02 (s, 6H), 0.97 (s, 3H), 0.92 (s, 6H).

Step 2: The title compound (solid, 63%) was prepared following the procedure described in step 2 for the preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-((2-(dimethylamino)ethyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoic acid. MS: m/e 759.7 $(M+H)^+$, 1.82 min (method 3). ^1H NMR (400MHz, METHANOL-d_4) δ 7.75 (d, *J*=8.3 Hz, 2H), 7.30 (d, *J*=16.1 Hz, 1H), 7.22 (d, *J*=8.5 Hz, 2H), 5.91 (d, *J*=16.1 Hz, 1H), 5.28 (dd, *J*=6.1, 1.6 Hz, 1H), 4.76 (d, *J*=1.5 Hz, 1H), 4.62 (s, 1H), 3.65 - 3.60 (m, 4H), 3.50 (t, *J*=6.5 Hz, 2H), 3.46 - 3.42 (m, 4H), 3.16 (t, *J*=7.3 Hz, 2H), 2.54 (td, *J*=11.0, 5.1 Hz, 1H), 2.14 (dd, *J*=17.2, 6.4 Hz, 1H), 2.01 (quin, *J*=6.8 Hz, 2H), 1.96 - 0.87 (m, 21H), 1.72 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H).

Example 5

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(methoxy(methyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1: Preparation of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(methoxy(methyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

To a solution of (E)-3-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

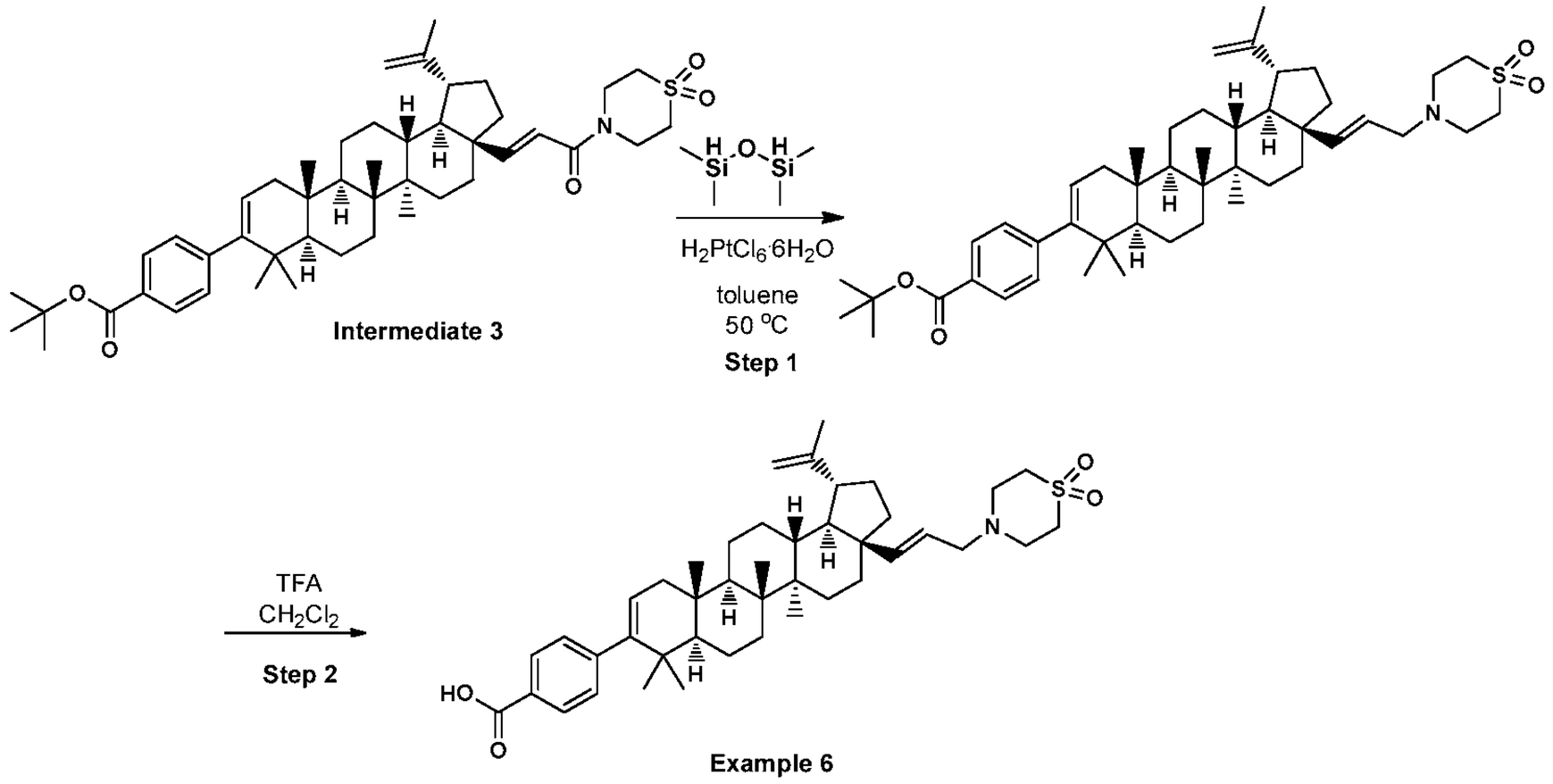
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)acrylic acid (100 mg, 0.16 mmol) and N,O-dimethylhydroxylamine hydrochloride (18 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added DIPEA (0.14 mL, 0.78 mmol) followed by HATU (89 mg, 0.23 mmol). The solution was stirred at RT for 1 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified by flash chromatography to give the title compound (101 mg, 95%) as a solid. MS: m/e 684.6 $(M+H)^+$, 3.12 min (method 3). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.89 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=17.3 Hz, 1H), 7.17 (d, *J*=8.5 Hz, 2H), 6.50 (d, *J*=17.1 Hz, 1H), 5.28 (dd, *J*=6.1, 1.6 Hz, 1H), 4.74 (d, *J*=1.3 Hz, 1H), 4.62 (s, 1H), 3.73 (s, 3H), 3.29 (s, 3H), 2.60 (td, *J*=11.1, 4.9 Hz, 1H), 2.10 (dd, *J*=17.1, 6.3 Hz, 1H), 1.98 - 0.86 (m, 21H), 1.72 (s, 3H), 1.56 (s, 9H), 1.02 (s, 6H), 0.97 (s, 3H), 0.92 (s, 6H).

Step 2: To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(methoxy(methyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (20 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.5 mL). The resulted solution was stirred at RT for 1 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified by Prep HPLC to give 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(methoxy(methyl)amino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (12 mg, 64%) as a solid. MS: m/e 628.5 $(M+H)^+$, 2.20 min (method 3). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.91 (d, *J*=8.3 Hz, 2H), 7.27 (d, *J*=16.1 Hz, 1H), 7.21 (d, *J*=8.5 Hz, 2H), 6.56 (d, *J*=16.1 Hz, 1H), 5.29 (dd, *J*=6.3, 1.8 Hz, 1H), 4.75 (d, *J*=2.0 Hz, 1H), 4.62 (s, 1H), 3.75 (s, 3H), 3.27 (s, 3H), 2.58 (td, *J*=10.9, 5.6 Hz, 1H), 2.15 (dd, *J*=17.3, 6.5 Hz, 1H), 1.99 - 0.88 (m, 21H), 1.73 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H).

Example 6

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)prop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1: Preparation of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)prop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

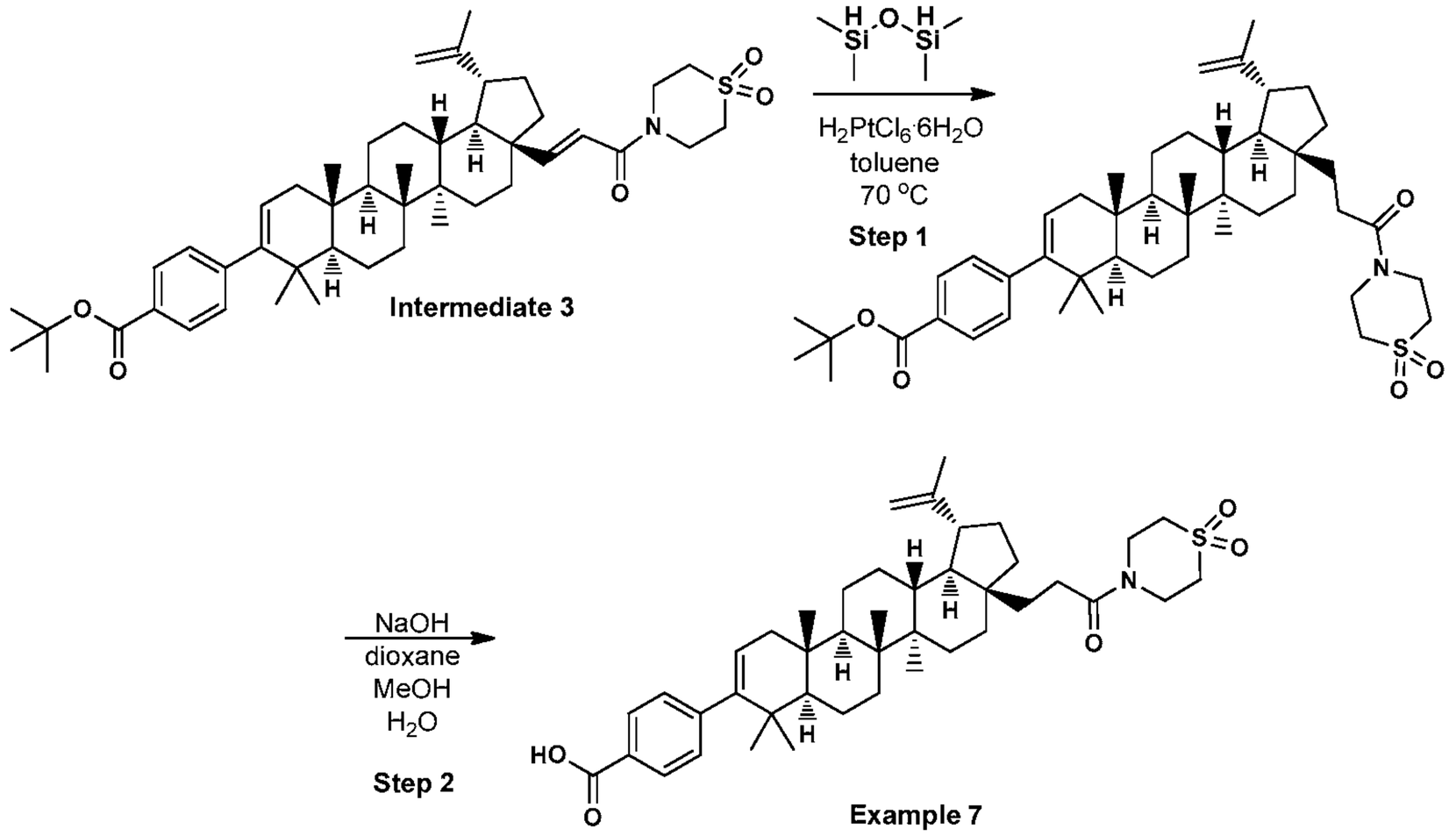
To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (15 mg, 0.020 mmol) in toluene (1 mL) was added 1,1,3,3-tetramethyldisiloxane (0.02 mL, 0.1 mmol) and chloroplatinic acid (0.04 M in THF) (0.05 mL, 0.002 mmol). The resulting brown solution was stirred at 50 °C for 24 h. The reaction mixture was filtered and the filtrate was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo* to give crude product without further purification. MS: m/e 744.6 $(M+H)^+$, 2.30 min (method 3).

Step 2: To a solution of crude *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)prop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate from step 1 (14 mg, 0.02 mmol) in CH_2Cl_2 (2 mL)

was added TFA (0.3 mL). The resulted solution was stirred at RT for 2 h. The reaction mixture was concentrated in *vacuo*. The crude mixture was purified by Prep HPLC to give 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)prop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (2 mg, 13%) as a solid. MS: m/e 688.5 $(M+H)^+$, 1.83 min (method 3). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.91 (d, *J*=8.3 Hz, 2H), 7.21 (d, *J*=8.3 Hz, 2H), 6.36 (d, *J*=15.8 Hz, 1H), 5.73 - 5.65 (m, 1H), 5.29 (dd, *J*=6.0, 1.5 Hz, 1H), 4.74 (d, *J*=2.0 Hz, 1H), 4.62 (s, 1H), 3.86 (d, *J*=7.0 Hz, 2H), 3.70 - 3.63 (m, 4H), 3.50 - 3.45 (m, 4H), 2.54 (td, *J*=11.2, 5.0 Hz, 1H), 2.15 (dd, *J*=17.2, 6.4 Hz, 1H), 1.97 - 0.85 (m, 21H), 1.72 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H).

Example 7

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1,1-dioxidothiomorpholino)-3-oxopropyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1: Preparation of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1,1-dioxidothiomorpholino)-3-oxopropyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

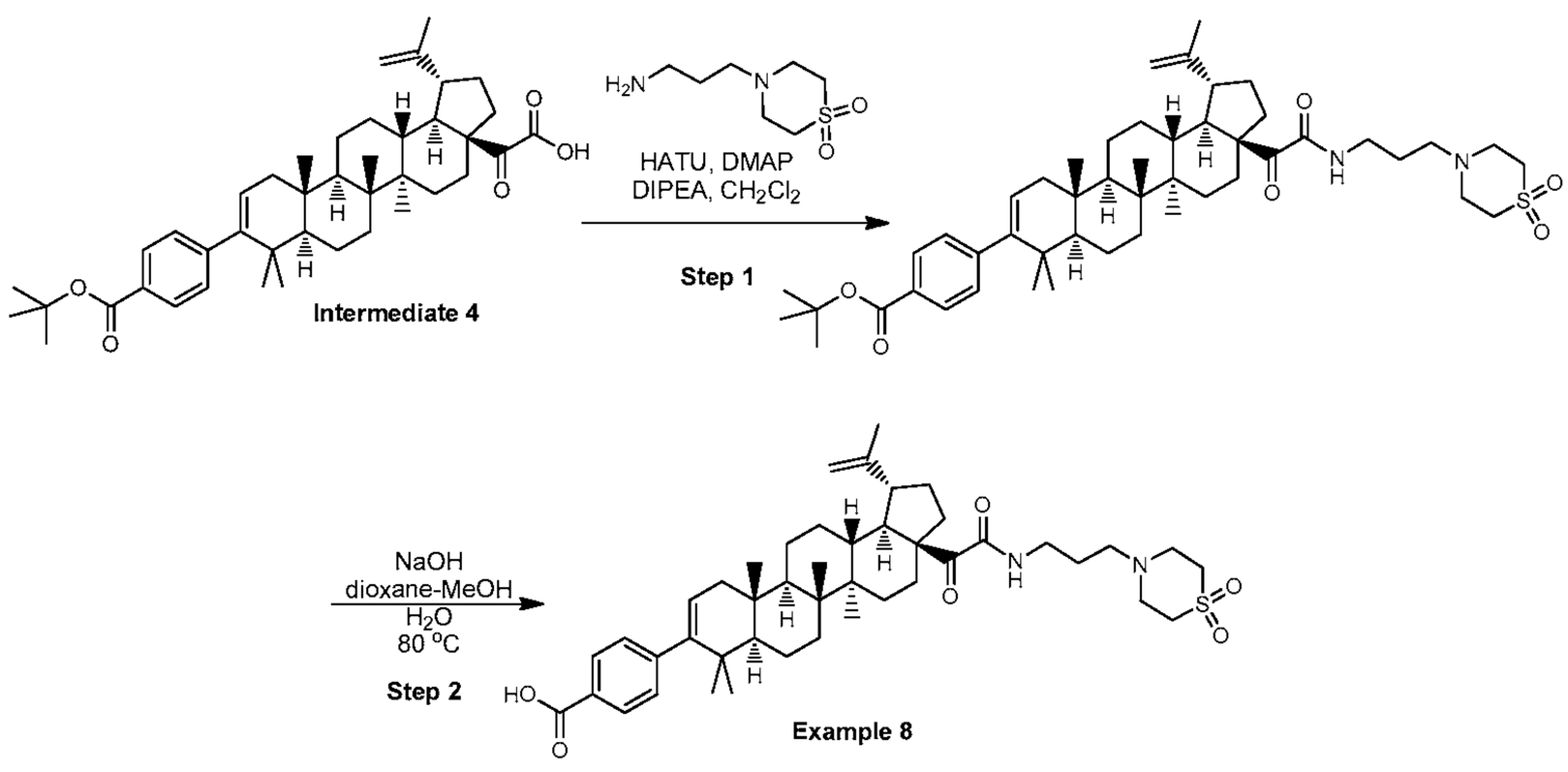
To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-(1,1-dioxidothiomorpholino)-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.066 mmol) in toluene (5 mL) was added 1,1,3,3-tetramethyldisiloxane (0.058 mL, 0.330 mmol) followed by chloroplatinic acid (0.04 M in THF) (0.082 mL, 3.30 μmol). The resulting brown solution was stirred at 70 °C for 24 h. The reaction mixture was filtered and the filtrate was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by flash chromatography to give the title compound (41 mg, 82%) as solid. MS: m/e 760.7 $(M+H)^+$, 2.88 min (method 1). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.89 (d, *J*=8.3 Hz, 2H), 7.18 (d, *J*=8.3 Hz, 2H), 5.28 (dd, *J*=6.1, 1.6 Hz, 1H), 4.72 (d, *J*=2.0 Hz, 1H), 4.61 (s, 1H), 4.17 - 4.09 (m, 2H), 4.03 - 3.96 (m, 2H), 3.10 - 3.05 (m, 4H), 2.50 (td, *J*=11.0, 5.6 Hz, 1H), 2.37 - 2.17 (m, 2H), 2.11 (dd, *J*=17.2, 6.4 Hz, 1H), 1.70 (s, 3H), 1.96 - 0.86 (m, 23H), 1.60 (s, 9H), 1.10 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

Step 2: To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1,1-dioxidothiomorpholino)-3-oxopropyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (step 1) (15 mg, 0.020 mmol) in dioxane (1 mL) and MeOH (0.5 mL) was added 1N NaOH (0.5 mL, 0.500 mmol). The resulting mixture was stirred at 50 °C for 24 h. The crude mixture was purified by Prep HPLC to give 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1,1-dioxidothiomorpholino)-3-oxopropyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (7 mg, 49%) as a solid. MS: m/e 704.5 $(M+H)^+$, 1.88 min (method 1). ^1H NMR (400MHz, CHLOROFORM-d) δ 8.00 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H), 5.31 (d, *J*=4.5 Hz, 1H), 4.72 (d, *J*=2.0 Hz, 1H), 4.61 (s, 1H), 4.19 - 4.10 (m, 2H), 4.04 - 3.98 (m, 2H), 3.12 - 3.06 (m, 4H), 2.50 (td, *J*=11.1, 5.9 Hz, 1H),

2.39 - 2.19 (m, 2H), 2.12 (dd, *J*=17.3, 6.3 Hz, 1H), 1.96 - 0.89 (m, 23H), 1.70 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H).

Example 8

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((3-(1,1-dioxidothiomorpholino)propyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1: Preparation of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((3-(1,1-dioxidothiomorpholino)propyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

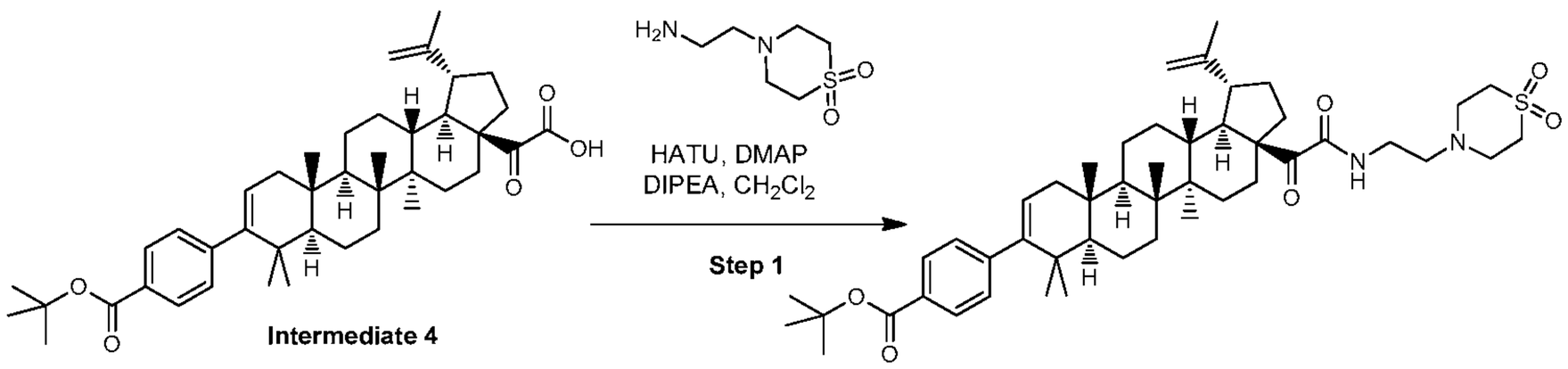
To a solution of 2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)-2-oxoacetic acid (Intermediate 4) (13 mg, 0.02 mmol) and 4-(3-aminopropyl)thiomorpholine 1,1-dioxide (8 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) was added DIPEA (0.02 mL, 0.1 mmol) followed by HATU (12 mg, 0.03 mmol). The resulting solution was stirred at RT for 2 days. LC/MS showed the reaction was incomplete with ~50% conversion. Additional 4-(3-aminopropyl)thiomorpholine 1,1-dioxide (16 mg, 0.08 mmol), HATU (24 mg, 0.06 mmol) and DMAP (3 mg, 0.025 mmol)

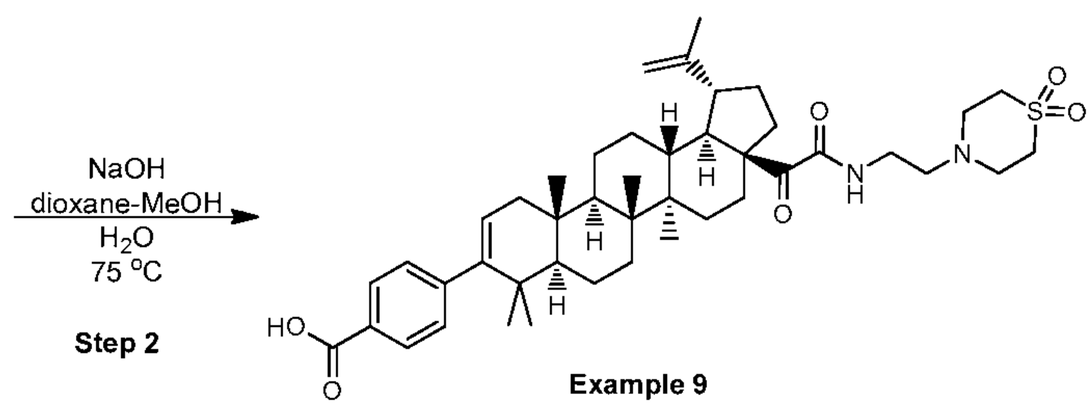
were added. The mixture was stirred at RT for 2 days. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a solid (16 mg) which was used in the next step without further purification. MS: m/e 817.6 $(M+H)^+$, 3.46 min (method 1).

Step 2: To a solution of crude from step 1, containing *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((3-(1,1-dioxidothiomorpholino)propyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (16 mg, 0.02 mmol) in 1,4-dioxane (2 mL) and MeOH (1 mL) was added 1 N NaOH (1 mL). The mixture was stirred at 80 °C for 8 h. The crude mixture was purified by Prep HPLC to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((3-(1,1-dioxidothiomorpholino)propyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (6 mg, 38% yield) as a solid. MS: m/e 761.5 $(M+H)^+$, 2.91 min (method 1). ^1H NMR (400MHz, METHANOL-d_4) δ 7.92 (d, *J*=8.5 Hz, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 5.30 (dd, *J*=6.0, 1.8 Hz, 1H), 4.72 (d, *J*=2.0 Hz, 1H), 4.61 (s, 1H), 3.65 - 3.58 (m, 4H), 3.47 - 3.41 (m, 4H), 3.15 - 3.08 (m, 2H), 2.94 (td, *J*=10.9, 4.8 Hz, 1H), 2.81 (dt, *J*=13.6, 2.9 Hz, 1H), 2.48 - 2.35 (m, 2H), 2.16 (dd, *J*=17.2, 6.4 Hz, 1H), 1.99 - 1.89 (m, 2H), 1.83 - 0.88 (m, 20H), 1.71 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H).

Example 9

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid





Step 1: Preparation of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

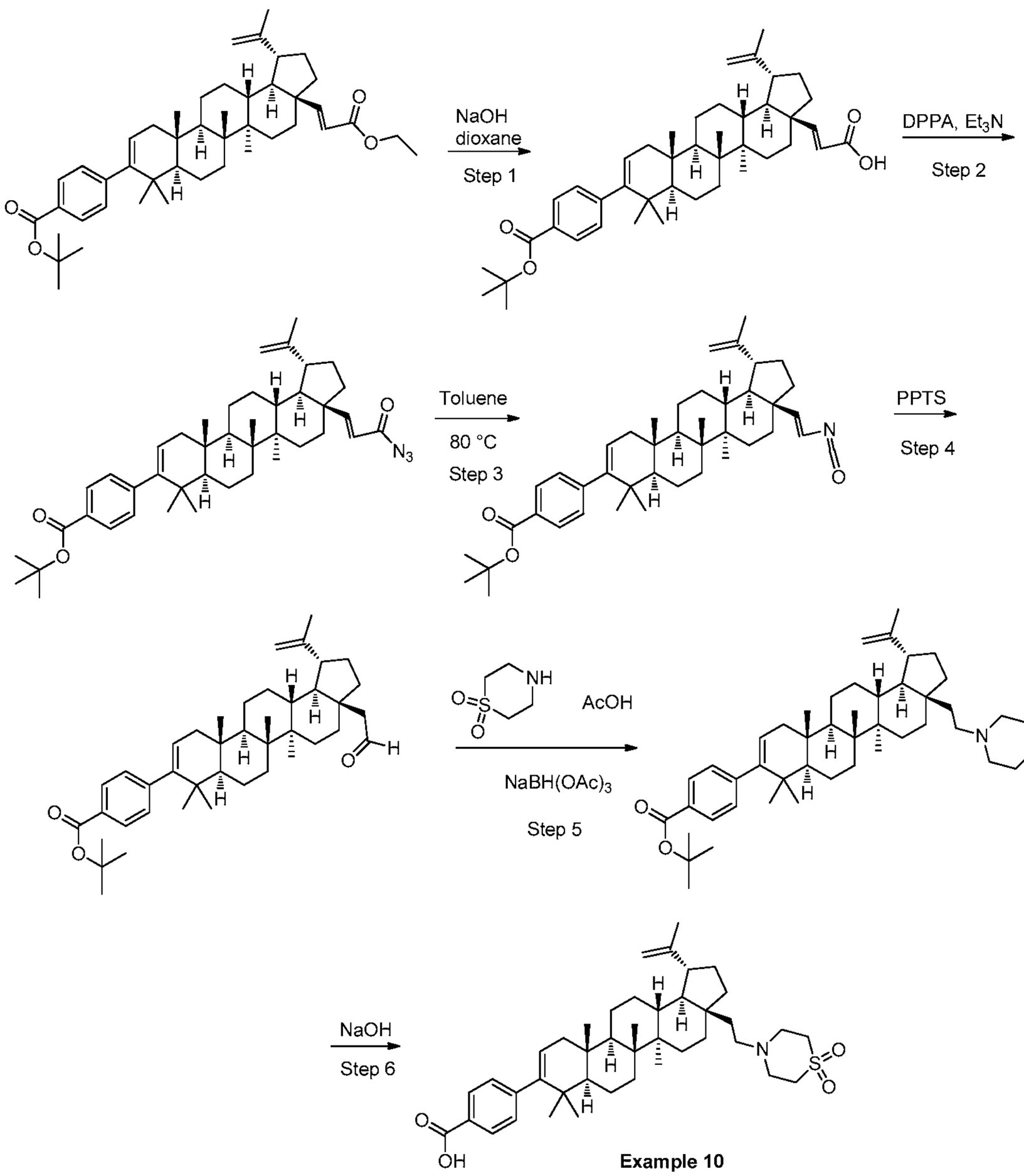
To a solution of 2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)-2-oxoacetic acid (Intermediate 4) (28 mg, 0.044 mmol), 4-(2-aminoethyl)thiomorpholine 1,1-dioxide (16 mg, 0.087 mmol) and DMAP (3 mg, 0.025 mmol) in DCM (2 mL) was added DIPEA (0.08 mL, 0.5 mmol) followed by HATU (25 mg, 0.07 mmol). The resulted solution was stirred at RT for 18 hours. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with H_2O (5 mL) followed by brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product as a solid. MS: m/e 803.6 $(M+H)^+$, 3.65 min (method 1).

Step 2: To a solution of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (35 mg, 0.044 mmol) in 1,4-dioxane (2 mL) and MeOH (1 mL) was added 1N NaOH (1 mL). The mixture was stirred at 75 °C for 4 h. The crude mixture was purified by Prep HPLC to give 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-2-oxoacetyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (5 mg, 15% yield) as a solid. MS: m/e 747.5 $(M+H)^+$, 2.99 min (method 1). ^1H NMR (400MHz, METHANOL-d_4) δ 7.92 (d, *J*=8.5 Hz, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 5.30 (dd, *J*=6.1, 1.4 Hz, 1H), 4.72 (d, *J*=1.8 Hz, 1H), 4.61 (s, 1H), 3.52 - 3.40 (m, 2H), 3.37 -3.32 (m, 2H), 3.26 - 3.20 (m, 4H), 2.99 - 2.91 (m, 3H), 2.82 (dt, *J*=13.7, 2.7 Hz, 1H), 2.46 - 2.36 (m, 2H), 2.19 - 2.11 (m, 1H), 1.81 - 0.84 (m, 20H), 1.71 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H).

Example 10

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,1-dioxidothiomorpholino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of (E)-3-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)acrylic acid

tert-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-ethoxy-3-oxoprop-1-enyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (300 mg, 0.448 mmol) was dissolved in dioxane (2 mL) and sodium hydroxide (1N, 2 mL) was added dropwise. The resulting solution was

stirred for 24 hours. The mixture was acidified to ~pH 4 adding HCl (1N). The volatile was removed under vacuum and the residue was extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to dryness. The crude material was purified by silica gel chromatography using ethyl acetate/hexanes (2-8%) first, followed by MeOH/CH_2Cl_2 (1-3%) to afford the title compound as a white solid (200 mg, 69%). MS: m/e 585.47 $(M-56+H)^+$, 3.89 min (method 6). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.94 - 7.80 (m, 2H), 7.43 (d, *J*=16.1 Hz, 1H), 7.24 - 7.08 (m, 2H), 5.97 (d, *J*=16.1 Hz, 1H), 5.31 - 5.28 (m, 1H), 4.77 (d, *J*=1.8 Hz, 1H), 4.65 (s, 1H), 2.56 (td, *J*=11.0, 5.0 Hz, 1H), 2.18 - 2.08 (m, 1H), 2.01 - 1.87 (m, 2H), 1.86 - 1.76 (m, 2H), 1.74 (s, 3H), 1.72 - 1.64 (m, 4H), 1.61 (s, 9H), 1.58 - 1.38 (m, 5H), 1.36 - 1.21 (m, 6H), 1.20 - 1.07 (m, 2H), 1.04 (s, 6H), 1.00 (s, 3H), 0.94 (s, 6H).

Step 2. Preparation of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-azido-3-oxoprop-1-en-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

To the solution of (E)-3-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(*tert*-butoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)acrylic acid (200 mg, 0.312 mmol) in DCM (5 mL) at 0 °C, was added DPPA (0.074 mL, 0.343 mmol) followed by triethylamine (0.065 mL, 0.468 mmol). The resulting solution was stirred for 4 hours and then concentrated under reduced pressure. The crude material was purified using silica gel eluted with mixtures of ethyl acetate/hexanes (1% - 4%) to furnish the title compound as a white solid (140 mg, 67.3%). MS: m/e 610.48 $(M-56+H)^+$, 4.86 min (method 6). ^1H NMR (400MHz, CHLOROFORM-d) δ 8.00 - 7.82 (m, 2H), 7.40 (d, *J*=16.1 Hz, 1H), 7.21 - 7.14 (m, 2H), 5.94 (d, *J*=16.1 Hz, 1H), 5.29 (dd, *J*=6.3, 1.8 Hz, 1H), 4.77 (d, *J*=1.8 Hz, 1H), 4.65 (d, *J*=1.5 Hz, 1H), 2.53 (d, *J*=5.0 Hz, 1H), 2.12 (dd, *J*=17.1, 6.5 Hz, 1H), 2.00 - 1.84 (m, 2H), 1.77 (br. s., 1H), 1.73 (s, 3H), 1.72 - 1.64 (m, 4H), 1.61 (s, 9H), 1.51 - 1.06 (m, 14H), 1.04 - 1.01 (m, 6H), 0.99 (s, 3H), 0.94 (s, 6H).

Step 3. Preparation of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-2-isocyanatovinyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-3-azido-3-oxoprop-1-enyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (140 mg, 0.21 mmol) in toluene (10 mL) was warmed to 80 °C for 3 hours. The solvent was removed under reduced pressure. The resulting residue yellow oil was purified using silica gel to give the titled compound as a white solid (140 mg, ~100%). MS: m/e 670.56 $(M+31+H)^+$, 3.98 min (method 6).

Step 4. Preparation of tert-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-oxoethyl)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

To the solution of *tert*-butyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((E)-2-isocyanatovinyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (160 mg, 0.251 mmol) in dioxane (10 mL) and water (10.00 mL), PPTS (31.5 mg, 0.125 mmol) was added. The resulting solution was stirred at room temperature for 30 min. A white solid floating on the top was observed. The mixture was concentrated under reduced pressure to remove the dioxane and the aqueous residue was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated to afford the title compound as a white solid (140 mg, 91%). The crude product was used in the next step without additional purification. MS: m/e 613.66 $(M+H)^+$, 4.06 min (method 6). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.86 (s, 1H), 8.04 - 7.78 (m, 2H), 7.23 - 7.00 (m, 2H), 5.29 (d, *J*=4.5 Hz, 1H), 4.73 (d, *J*=2.0 Hz, 1H), 4.63 - 4.48 (m, 1H), 2.66 - 2.53 (m, 1H), 2.45 - 2.31 (m, 1H), 2.11 (d, *J*=17.1 Hz, 2H), 2.07 - 1.95 (m, 1H), 1.94 - 1.82 (m, 2H), 1.80 - 1.65 (m, 4H), 1.72 (s, 3H), 1.61 (s, 9H), 1.55 - 1.38 (m, 7H), 1.27 (m, 4H), 1.12 (m, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 1.01 - 0.99 (s, 3H), 0.94 (s, 6H).

Step 5. Preparation of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,1-dioxidothiomorpholino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

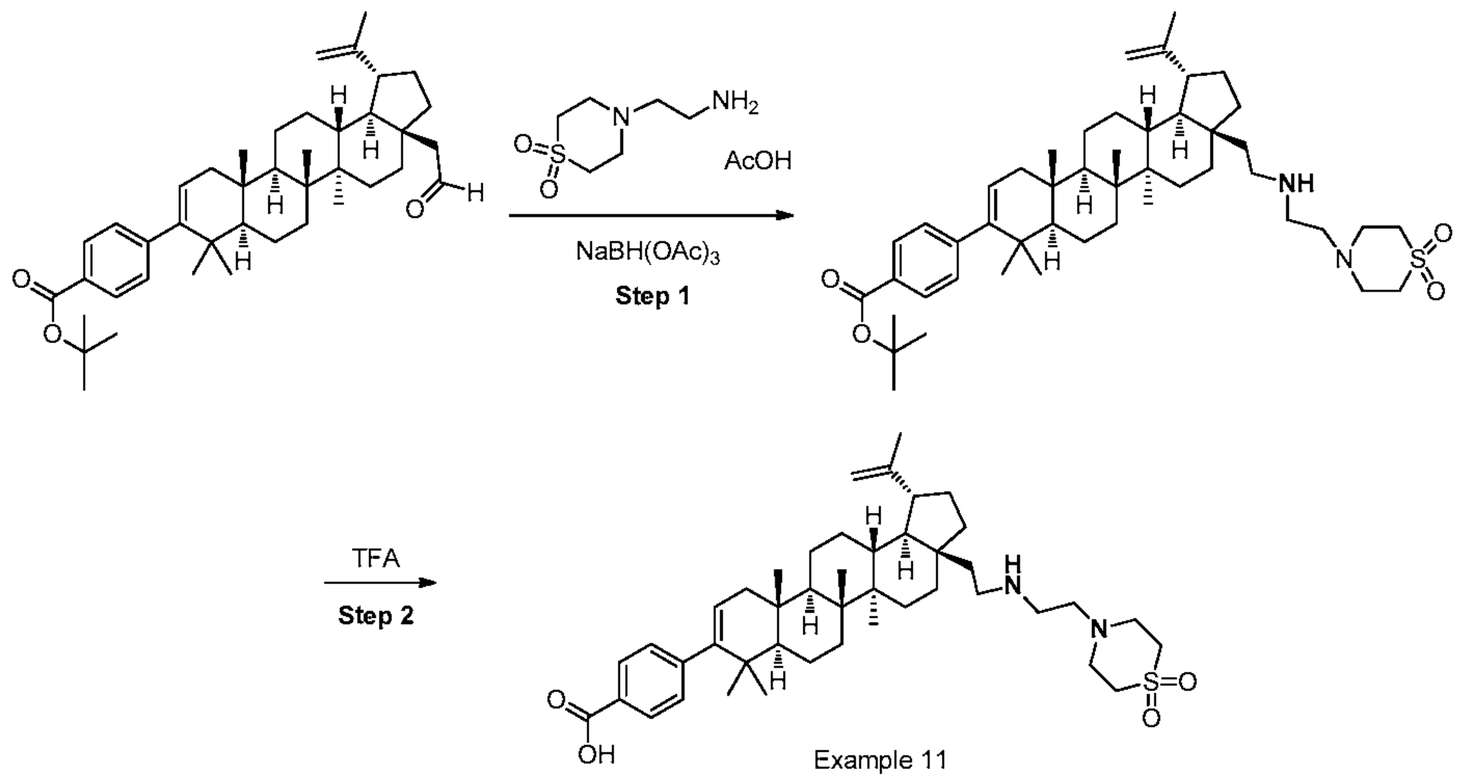
To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-oxoethyl)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.082 mmol) in DCE (2 mL) was added acetic acid (0.014 mL, 0.245 mmol) and thiomorpholine 1,1-dioxide (25.4 mg, 0.188 mmol). The mixture became cloudy at first but turned into clear solution 10 min later. The mixture was stirred at RT for 2 hours. Sodium triacetoxyborohydride (86 mg, 0.408 mmol) was added, and the stirring was continued for 72 hours. The resulting mixture was diluted with saturated $NaHCO_3$ (7 mL) and extracted with dichloromethane (3 x 7 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The crude product was purified on silica gel column, eluted with mixtures of hexane/acetone first, followed by MeOH/CH_2Cl_2 to afford the title compound as a white solid (50 mg, 83%). MS: m/e 732.73 $(M+H)^+$, 3.01 min (method 6). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.93 - 7.83 (m, 2H), 7.23 - 7.09 (m, 2H), 5.30 - 5.25 (m, 1H), 4.71 (d, *J*=2.0 Hz, 1H), 4.62 - 4.58 (m, 1H), 3.36 - 3.29 (m, 4H), 3.13 - 3.06 (m, 4H), 3.06 - 3.00 (m, 2H), 2.54 - 2.37 (m, 2H), 2.11 (dd, *J*=17.2, 6.4 Hz, 1H), 2.00 - 1.78 (m, 3H), 1.74 (m, 4H), 1.70 (s, 3H), 1.67 - 1.62 (m, 2H), 1.60 (s, 9H), 1.56 - 1.17 (m, 11H), 1.11 - 1.08 (m, 3H), 1.07 - 1.03 (m, 2H), 1.01 (s, 3H), 0.99 (s, 3H), 0.93 (s, 6H).

Step 6. To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,1-dioxidothiomorpholino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.068 mmole) in dioxane (2 mL) was added NaOH (1N, 0.5 mL, 0.500 mmol) .The reaction mixture was heated up to 70 °C for 5 hrs. The resulted solution was purified by prep HPLC (Method 1) to give 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,1-dioxidothiomorpholino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid as a white solid (16.7 mg, 33%). MS: m/e 676.69 $(M+H)^+$, 2.73 min (method 6). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.93 (d, *J*=8.0

Hz, 2H), 7.18 (d, *J*=8.3 Hz, 2H), 5.27 (d, *J*=4.5 Hz, 1H), 4.69 (s, 1H), 4.58 (s, 1H), 3.25 (br. s., 8H), 2.69 (br. s., 2H), 2.45 - 2.32 (m, 2H), 2.17 - 2.06 (m, 1H), 2.06 (s, 1H), 1.95 - 1.72 (m, 3H), 1.68 (s, 3H), 1.68 - 1.11 (m, 18H), 1.07 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H).

Example 11

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Example 11

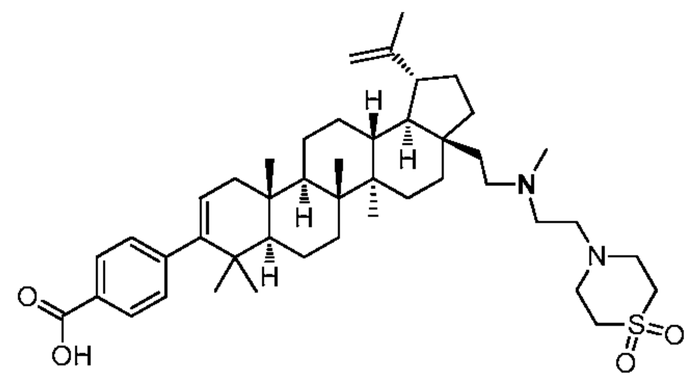
Step 1. Preparation of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

The titled compound was prepared in 79 % yield following the procedure described above in step 5 of the preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,1-dioxidothiomorpholino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, using 4-(2-aminoethyl)thiomorpholine 1,1-dioxide as the reactant. MS: m/e 775.79 $(M+H)^+$, 2.99 min (method 6).

Step 2: To a solution of *tert*-butyl 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (16 mg, 0.021 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.016 mL, 0.2 mmol) . The mixture was stirred at RT for 18 h. The mixture was concentrated under reduced pressure to afford an off white foam which was dissolved in MeOH (4 mL), and purified by prep HPLC (method 1). The fractions containing the desired product were combined and concentrated under reduced pressure to give the title compound as a white solid (10 mg, ~64%). MS: m/e 719.74 $(M+H)^+$, 2.71 min (method 6). ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.01 - 7.87 (m, 2H), 7.24 (d, *J*=8.5 Hz, 2H), 5.33 (d, *J*=4.5 Hz, 1H), 4.75 (d, *J*=2.0 Hz, 1H), 4.64 (s, 1H), 3.24 - 3.19 (m, 2H), 3.16 (d, *J*=6.3 Hz, 4H), 3.13 - 3.07 (m, 4H), 3.02 (dd, *J*=12.3, 4.3 Hz, 2H), 2.92 - 2.83 (m, 2H), 2.52 (d, *J*=5.8 Hz, 1H), 2.18 (dd, *J*=17.1, 6.5 Hz, 1H), 2.01 (d, *J*=11.5 Hz, 2H), 1.94 - 1.76 (m, 3H), 1.75 (s, 3H), 1.73 - 1.23 (m, 15H), 1.21 (s, 3H), 1.18 (m, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

Example 12

Preparation of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)(methyl)amino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



To a solution of 4-((1R,3aR,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(1,1-dioxidothiomorpholino)ethyl)amino)ethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (20 mg, 0.028 mmol) in MeOH (2 mL) was added formaldehyde (0.835 mg, 0.028 mmol) and acetic acid (1.670 mg, 0.028 mmol). A cloudy suspension was formed at first which turned clear after 10 min. The solution was stirred at RT for 19 minutes, then Sodium cyanoborohydride (1.748 mg, 0.028 mmol) was

added and the mixture was stirred for 2 hours. The resulted mixture was purified by prep HPLC (method 1) to give the title compound as a white solid (10 mg, 46.6%). MS: m/e 733.7$(M+H)^+$, 2.70 min (method 6). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.93 (d, *J*=8.0 Hz, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 5.31 (d, *J*=4.5 Hz, 1H), 4.75 (s, 1H), 4.64 (s, 1H), 3.30 - 3.06 (m, 12H), 3.04 - 2.83 (m, 5H), 2.52 (d, *J*=4.5 Hz, 1H), 2.15 (dd, *J*=16.9, 6.1 Hz, 1H), 2.05 - 1.75 (m, 5H), 1.73 (s, 3H), 1.72 - 1.20 (m, 18H), 1.18 (s, 3H), 1.08 (s, 3 H), 1.04 (s, 3H), 0.97 (s, 3H), 0.96 (br. s., 3H).

Section 2

LC/MS Method 1A

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 BEH C18 2.1 x 50 mm 1.7 micron

LC/MS Method 2A

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, 3 µm, 2.0 x 30 mm

Prep HPLC Method 1A

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

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

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

Column = Waters Sunfire 30x100 mm S5

Flow Rate = 40 mL/min

Prep HPLC Method 2A

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

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

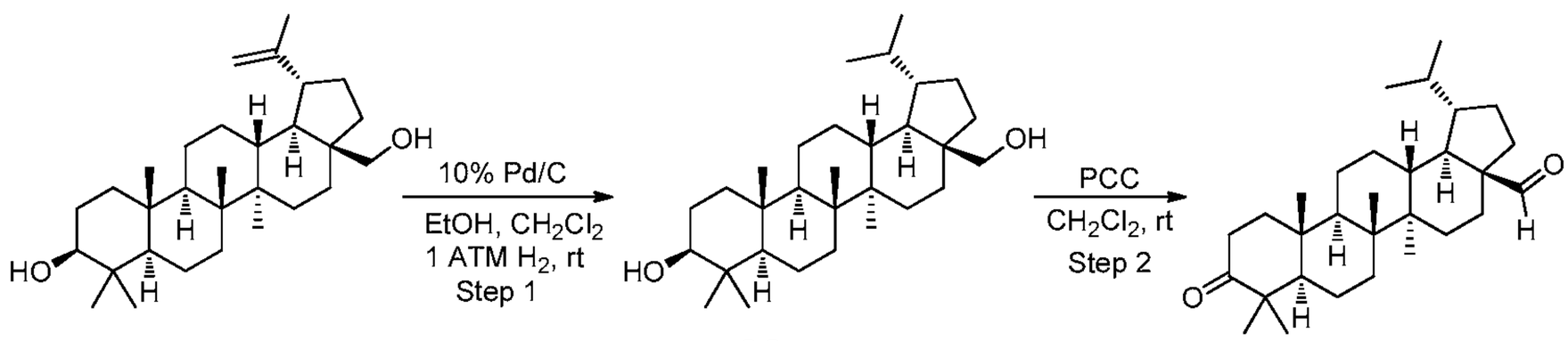
Solvent B = 90% ACN - 10% H_2O - 0.1% TFA

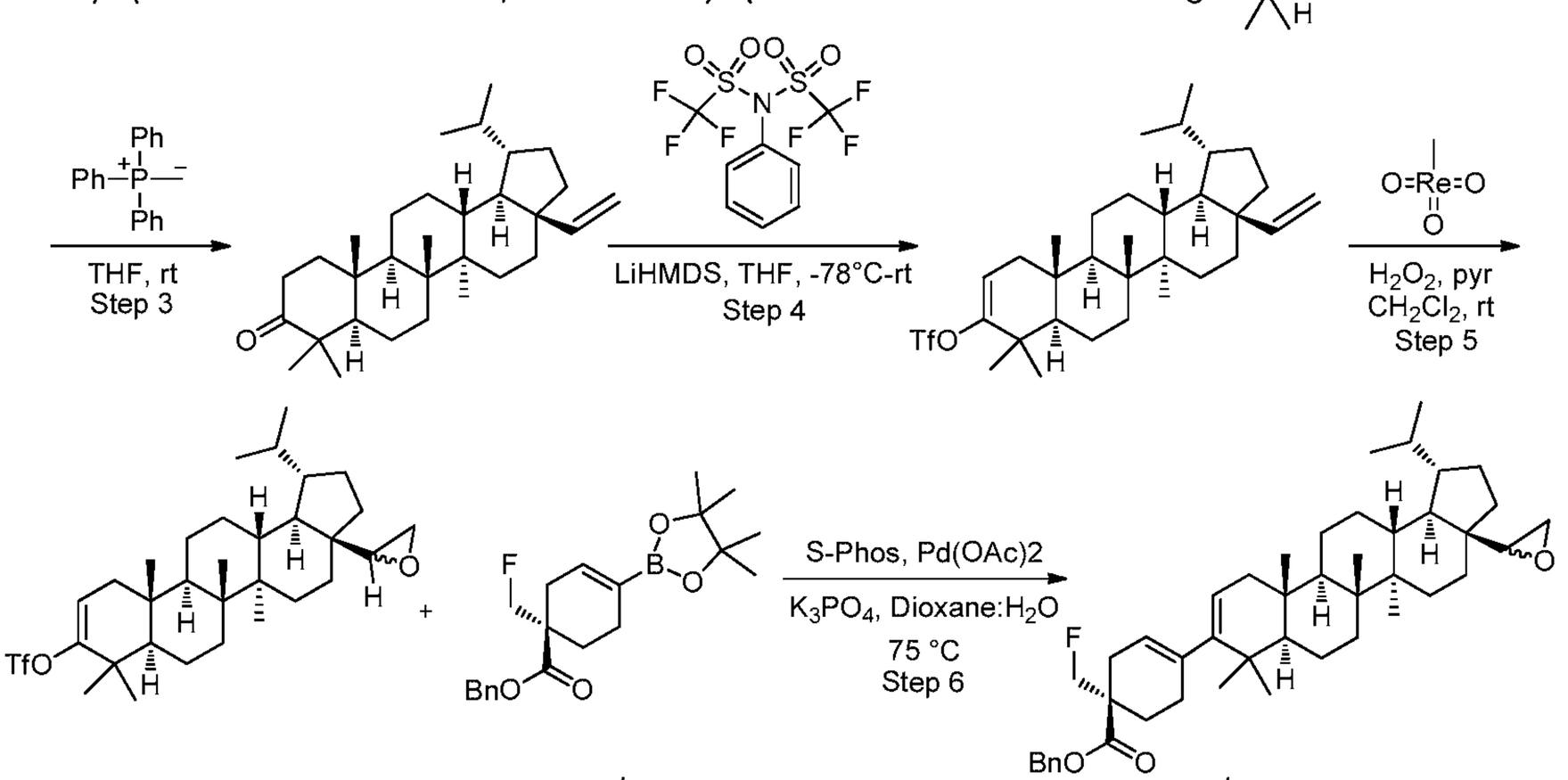
Column = Waters-Sunfire 30 x 100mm S5

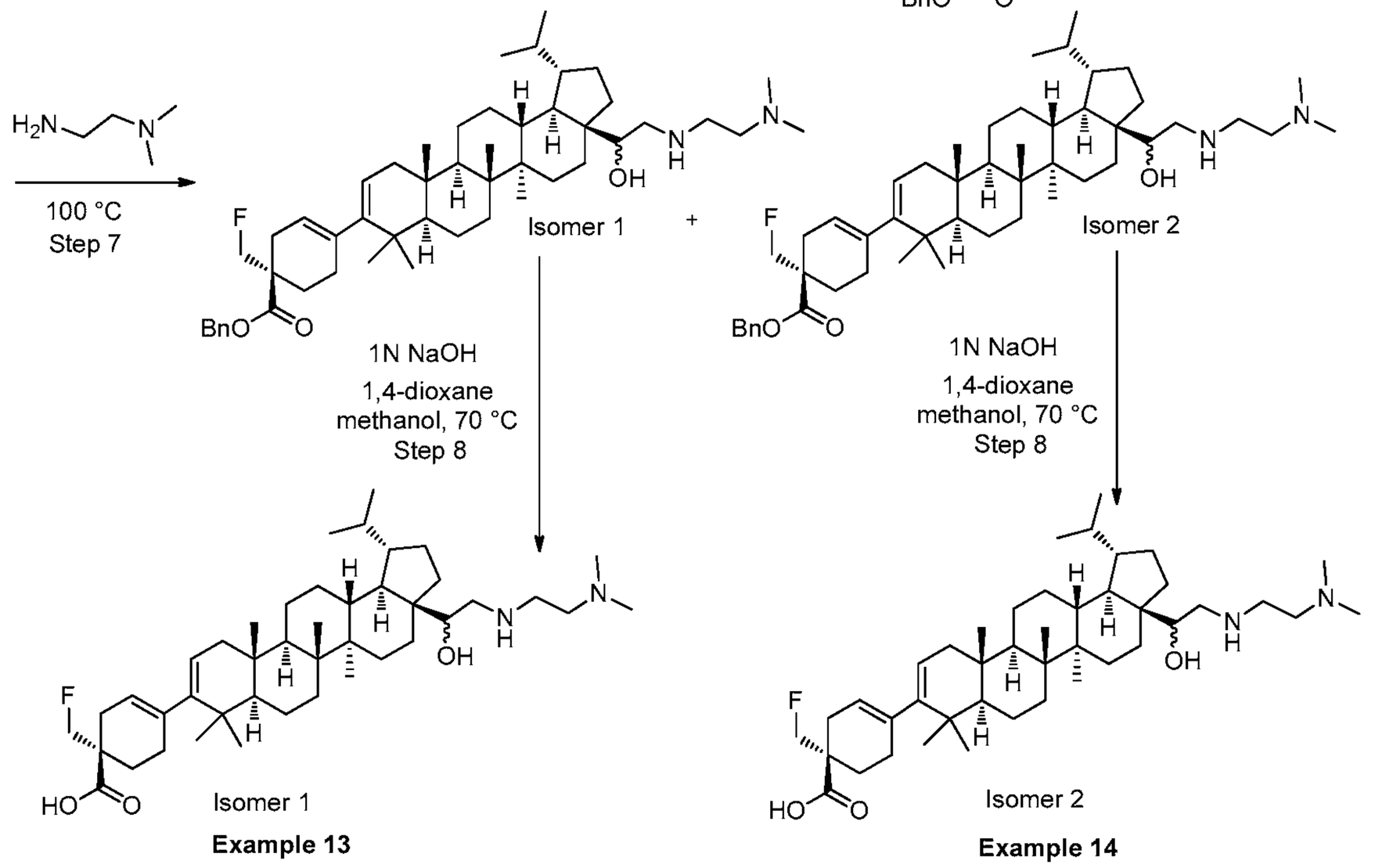
Flow Rate = 40 mL/min

Example 13 and Example 14

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







Example 13 **Example 14**

Step 1: Preparation of (1S,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-ol

To a flask containing a suspension of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-(hydroxymethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (10 g, 22.59 mmol) in ethanol (100 mL) and dichloromethane (100 mL) was added 10% palladium on carbon (1.202 g, 1.129 mmol). The mixture was stirred under 1 atm of hydrogen for 18 h, then was evacuated of hydrogen and celite was added. The mixture was carefully filtered over a pad of celite and washed with an ethanol and dichloromethane mixture (1:1). The filtrate was concentrated under reduced pressure to give 1.53 g product as a white solid. The remainder of the material still had not dissolved, so the celite pad was diluted with a mixture of chloroform and methanol and was stirred for several minutes. The mixture was again filtered and the filtrate was concentrated under reduced pressure. The solids that formed were diluted with water and collected by filtration. Then they were washed with water to give the title product (8.6 g, 19.3 mmol, 85% yield) as an off-white solid. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 3.79 (dd, *J*=10.6, 4.7 Hz, 1H), 3.32 (dd, *J*=10.9, 4.3 Hz, 1H), 3.21 (dt, *J*=11.0, 5.5 Hz, 1H), 1.94 - 1.78 (m, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 1.78 - 0.67 (m, 37H).

Step 2: Preparation of (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carbaldehyde

To a suspension of (1S,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-(hydroxymethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-ol (1.53 g, 3.44 mmol) in dichloromethane (100 mL) was added pyridinium chlorochromate (1.854 g, 8.60 mmol). The mixture was stirred for 16 h at rt then was filtered through a plug of silica gel and celite. The plug was washed with dichloromethane then with 1:1 ethyl acetate in hexanes. The filtrate was concentrated under reduced pressure to give the title compound (1.5 g, 3.4 mmol, 99 % yield) as an off-white solid. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 9.66 (d, *J*=1.3 Hz, 1H), 2.55 - 2.47 (m, 1H), 2.45 - 2.38 (m, 1H), 2.23 - 2.16 (m, 1H), 2.13 - 2.08 (m, 1H), 2.04 (td, *J*=12.1, 4.0 Hz, 1H), 1.96 - 1.86 (m, 2H), 1.77 - 1.67 (m, 2H), 1.08 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 1.57 - 0.93 (m, 17H), 0.89 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.8 Hz, 3H).

Step 3: Preparation of (1S,3aR,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-vinyloctadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one

A suspension of methyltriphenylphosphonium bromide (1.581 g, 4.42 mmol) in THF (15 mL) was cooled to 0 °C and potassium *tert*-butoxide (1M in THF) (4.77 mL, 4.77 mmol) was added. The mixture was removed from the ice bath and stirred for 30 minutes. To the mixture was added a solution of (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carbaldehyde (1.5 g, 3.40 mmol) in THF (15 mL). After 15 minutes of stirring, TLC showed no starting material remaining. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (3 x 20 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 0-25% ethyl acetate in hexanes gradient and an 80 g silica gel column. The fractions containing the product were combined and concentrated under reduced pressure to give the title product (1.1 g, 2.507 mmol, 73.7 % yield) as an off-white solid. ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 5.99 (dd, *J*=17.7, 11.1 Hz, 1H), 5.11 (dd, *J*=11.1, 1.2 Hz, 1H), 5.07 (dd, *J*=17.8, 1.6 Hz, 1H), 2.55 - 2.46 (m, 1H), 2.45 - 2.38 (m, 1H), 1.08 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.86 (d, *J*=6.8 Hz, 3H), 1.97 - 0.82 (m, 24H), 0.79 (d, *J*=6.8 Hz, 3H).

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

A solution of (1S,3aR,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-vinyloctadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (1.1 g, 2.507 mmol) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (0.985 g, 2.76 mmol) in THF (20 mL) was cooled to -78 °C and LiHMDS (1M in THF) (3.76 mL, 3.76 mmol) was added slowly. The mixture was stirred for 1h at -78 °C, then was removed from the ice bath and was warmed to rt. After 3 h of stirring at rt, the mixture was diluted with water (40 mL) and was extracted with ethyl acetate (3 x 40 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 0-5% ethyl acetate in hexanes gradient and an 80 g silica gel column. The fractions containing the product were combined and concentrated under reduced pressure to give the title compound (1.36 g, 2.383 mmol, 95 % yield) as a white solid. ^{1}H NMR

(500MHz, CHLOROFORM-d) δ = 5.99 (dd, *J*=17.7, 11.1 Hz, 1H), 5.57 (dd, *J*=6.8, 2.0 Hz, 1H), 5.12 (dd, *J*=11.1, 1.3 Hz, 1H), 5.07 (dd, *J*=17.8, 1.6 Hz, 1H), 2.18 (dd, *J*=17.1, 6.9 Hz, 1H), 1.13 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 1.93 - 0.90 (m, 23H), 0.87 (d, *J*=6.9 Hz, 3H), 0.79 (d, *J*=6.6 Hz, 3H). ^{19}F NMR (471MHz, CHLOROFORM-d) δ -74.84 (s, 1F).

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

This reaction was modified from the epoxidation procedure in *J. Am. Chem. Soc*. 1997, *119*, 6189-6190. To a flask containing (1S,3aR,5aR,5bR,7aR,11aR,11bR,13aR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-vinyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (1.36 g, 2.383 mmol) and methyltrioxorhenium(VII) (0.030 g, 0.119 mmol) was added dichloromethane (15 mL) followed by pyridine (0.023 mL, 0.286 mmol) and finally hydrogen peroxide (30%) (0.365 mL, 3.57 mmol) dropwise. The mixture was stirred at rt for 24 h, then an additional 365 μL of hydrogen peroxide was added and the mixture was further stirred at rt. After an additional 7 days of stirring at rt, the mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were treated with 10 mg of MnO_2, then were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product showed clean conversion of the starting material to the expected epoxide (65:35 mixture of diastereomers) by 1H NMR. The crude product was passed through a plug of silica gel and celite (washed with DCM, then 1:1 EtOAc:hexanes) and the filtrate was concentrated under reduced pressure to give 1.36g of the expected product as a 65:35 mixture of diastereoisomers. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 5.60 - 5.57 (m, 1H), 3.09 - 3.07 (m, 0.35H), 3.07-3.05 (m, 0.65H), 2.80 - 2.77 (m, 0.65H), 2.73 - 2.70 (m, 0.35H), 2.74 - 2.69 (m, 1H), 2.64 - 2.60 (m, 3H), 2.25 - 2.16 (m, 1H), 2.23 - 2.16 (m, 1H), 2.14 - 0.75 (m, 44H).

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

To vial containing (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-(oxiran-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (1.06 g, 1.806 mmol) was added (S)-benzyl 1-(fluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.845 g, 2.258 mmol), phosphoric acid, potassium salt (1.150 g, 5.42 mmol), palladium (II) acetate (0.020 g, 0.090 mmol), and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-phos) (0.056 g, 0.135 mmol). The mixture was flushed with nitrogen, then the vial was sealed and heated to 75°C. After 16 h of heating, the mixture was cooled to rt and was partially concentrated under reduced pressure. The mixture was diluted with water (25 mL) and extracted with dichloromethane (3 x 25 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% EtOAc in hexanes gradient and an 80g silica gel column. The fractions containing the product were combined and concentrated under reduced pressure to give the product as a white foam (0.65:0.35 ratio of epoxide isomers). The crude was carried to the next step with no additional purification. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.39 - 7.30 (m, 5H), 5.33 (br. s., 1H), 5.22 - 5.15 (m, 2H), 5.14 (d, *J*=5.8 Hz, 1H), 4.61 - 4.46 (m, 2H), 3.10 (t, *J*=3.4 Hz, 0.35H), 3.07 (t, *J*=3.2 Hz, 0.65H), 2.79 (t, *J*=4.5 Hz, 0.65H), 2.71 (t, *J*=4.5 Hz, 0.35H), 2.65 - 2.56 (m, 2H), 2.22 - 0.74 (m, 50H).

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

To a vial containing of (S)-benzyl 1-(fluoromethyl)-4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-

3a-(oxiran-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.1 g, 0.146 mmol) was added N,N-dimethylethylenediamine (0.5 mL, 4.54 mmol). The mixture was heated to 100 °C overnight for 87 h then was cooled to rt and was purified by prep HPLC (method 1). The fractions containing each of the two isomers that were separated were concentrated under reduced pressure to give isomer 1 (5.7 mg,) and isomer 2 (10.2 mg) as their respective TFA salts.

Isomer 1: LC/MS: m/e 773.45 $(M+H)^+$, 1.62 min (method 1A). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.39 - 7.29 (m, 5H), 5.32 (br. s., 1H), 5.21 - 5.14 (m, 2H), 5.13 (dd, *J*=6.1, 1.7 Hz, 1H), 4.61 - 4.45 (m, 2H), 4.30 (d, *J*=10.9 Hz, 1H), 3.73 - 3.49 (m, 4H), 3.27 (d, *J*=10.4 Hz, 1H), 3.09 (t, *J*=11.7 Hz, 1H), 2.93 (s, 6H), 2.60 (d, *J*=17.3 Hz, 1H), 1.02 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.83 (d, *J*=7.1 Hz, 3H), 0.76 (d, *J*=6.8 Hz, 3H), 2.21 - 0.71 (m, 31H).

Isomer 2: LC/MS: m/e 773.45 $(M+H)^+$, 1.63 min (method 1A). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.41 - 7.31 (m, 5H), 5.34 (br. s., 1H), 5.22 - 5.16 (m, 2H), 5.15 (dd, *J*=6.0, 1.6 Hz, 1H), 4.63 - 4.45 (m, 3H), 3.72 - 3.52 (m, 4H), 3.19 (d, *J*=11.7 Hz, 1H), 3.11 - 3.04 (m, 1H), 2.95 (s, 6H), 2.62 (d, *J*=17.2 Hz, 1H), 1.05 (s, 3H), 0.99 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.84 (d, *J*=6.9 Hz, 3H), 0.77 (d, *J*=6.8 Hz, 3H), 2.24 - 0.68 (m, 31H).

Step 8:

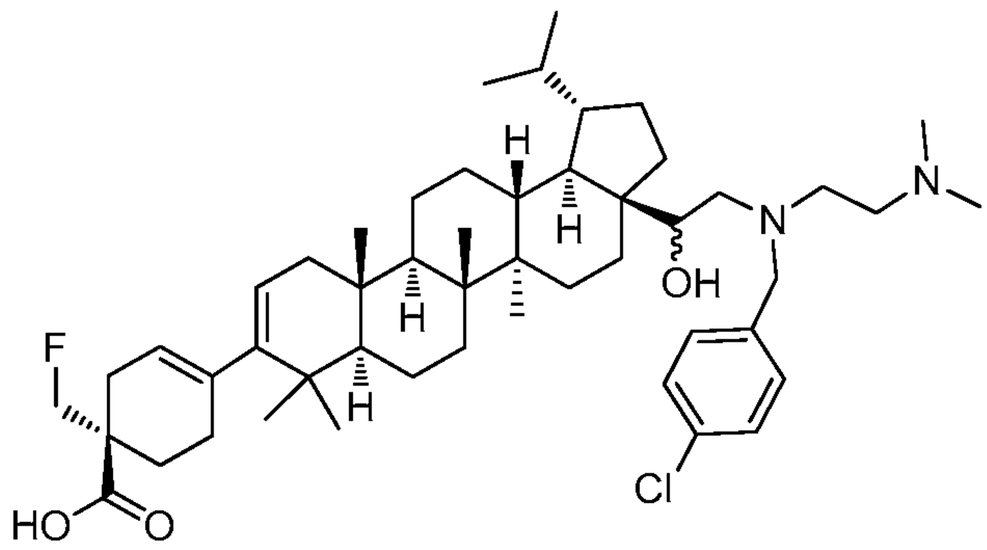
Example 20: Representative procedure for (S)-4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid, Isomer 1: To a solution of isomer 1 from step 7 (5.7 mg) in 1,4-dioxane (1 mL) and methanol (0.2 mL) was added sodium hydroxide (1.0N) (0.037 mL, 0.037 mmol). The mixture was heated to 70 °C for 8h then was cooled to rt and stirred overnight. The mixture was purified by prep HPLC (method 2A). The fractions containing the product were combined and concentrated under reduced pressure to give the product as a clear film.

Prep HPLC retention time, method 2A = 8.8 minutes. 2.0 mg of isomer 2 was isolated as the TFA salt of the title compound. Stereochemistry of the alcohol was not assigned. LC/MS: m/e 683.9 $(M+H)^+$, 1.81 min (method 2A). ^{1}H NMR (500MHz, Acetic acid-d_4) δ 5.37 (br. s., 1H), 5.23 (d, *J*=4.4 Hz, 1H), 4.62 - 4.45 (m, 2H), 4.36 (d, *J*=10.7 Hz, 1H), 3.86 - 3.78 (m, 1H), 3.76 - 3.64 (m, 3H), 3.56 (d, *J*=9.9 Hz, 1H), 3.25 (t, *J*=11.9 Hz, 1H), 2.99 (s, 6H), 2.59 (d, *J*=15.9 Hz, 1H), 1.10 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.86 (d, *J*=6.9 Hz, 3H), 2.33 - 0.84 (m, 29H), 0.80 (d, *J*=6.6 Hz, 3H).

Example 21: Isomer 2 was prepared using the same procedure, only starting with 10.2 mg of the benzyl ester and 0.066 mL of 1N NaOH for the reaction. Prep HPLC retention time, method 2A = 9.3 minutes. 3.9 mg of isomer 2 was isolated as the TFA salt of the title compound. Stereochemistry of the alcohol was not assigned. LC/MS: m/e 683.9 $(M+H)^+$, 1.83 min (method 2A). ^{1}H NMR (500MHz, Acetic acid-d_4) δ 5.37 (br. s., 1H), 5.23 (d, *J*=4.6 Hz, 1H), 4.63 - 4.45 (m, 3H), 3.83 - 3.65 (m, 4H), 3.39 (d, *J*=12.3 Hz, 1H), 3.30 - 3.20 (m, 1H), 3.01 (s, 6H), 2.59 (d, *J*=17.2 Hz, 1H), 1.11 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 2.32 - 0.89 (m, 29H), 0.86 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.6 Hz, 3H).

Example 15

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



To a suspension of (S)-4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid, isomer 1 (0.028 g) in methanol (1.0 mL) and acetic acid (0.1 mL) was added 4-chlorobenzaldehyde (6.34 mg, 0.045 mmol) followed by borane-2-picoline complex (4.82 mg, 0.045 mmol). The mixture was stirred at rt for 16 h, then an additional 6 mg of 4-chlorobenzaldehyde was added followed by 5 mg of borane-2-picoline complex. The mixture was stirred at rt for an additional 5 days, then was diluted with methanol, filtered, and purified by prep HPLC to afford the title compound as a white solid (14.3 mg). ^{1}H NMR (500MHz, Acetic acid-d_4) δ 7.65 (d, *J*=8.4 Hz, 2H), 7.52 (d, *J*=8.4 Hz, 2H), 5.37 (br. s., 1H), 5.25 - 5.21 (m, 1H), 4.65 (d, *J*=13.1 Hz, 1H), 4.62 - 4.46 (m, 2H), 4.41 (d, *J*=12.9 Hz, 1H), 4.19 - 4.06 (m, 2H), 4.00 - 3.91 (m, 1H), 3.87 - 3.79 (m, 2H), 3.42 (d, *J*=12.5 Hz, 1H), 3.25 (t, *J*=12.3 Hz, 1H), 2.97 (s, 6H), 2.59 (d, *J*=16.4 Hz, 1H), 0.86 (d, *J*=6.8 Hz, 3H), 0.75 (d, *J*=6.6 Hz, 3H), 2.34 - 0.67 (m, 44H).

Example 16

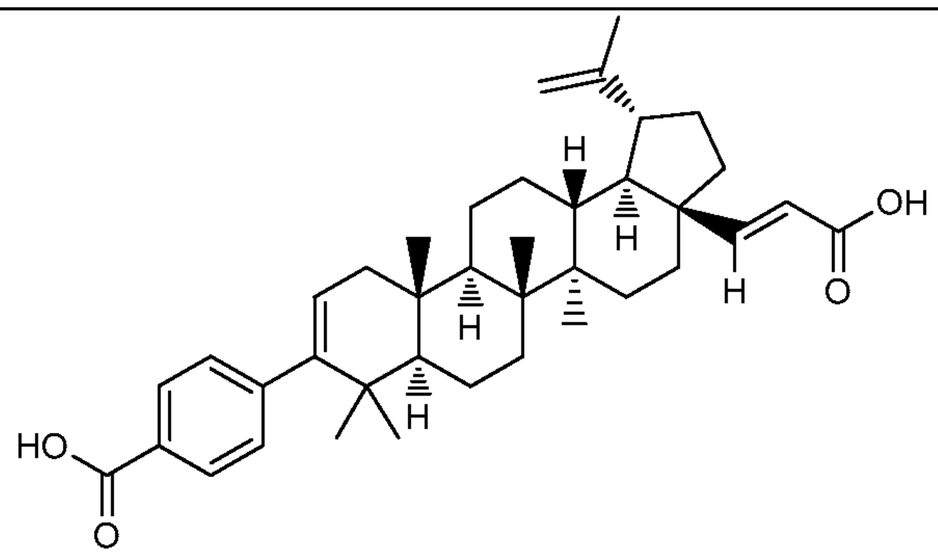
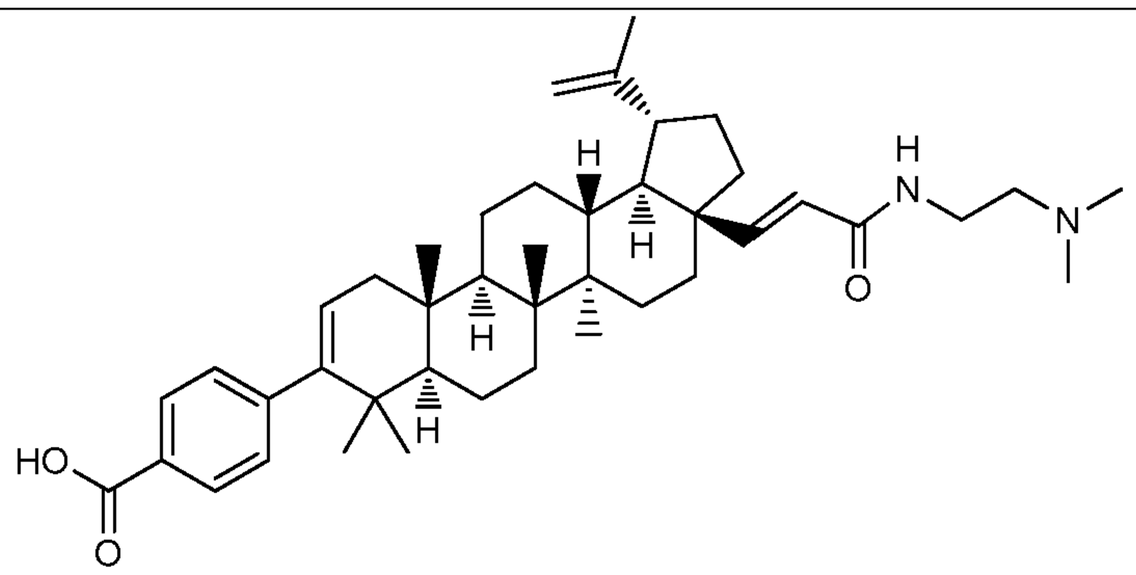
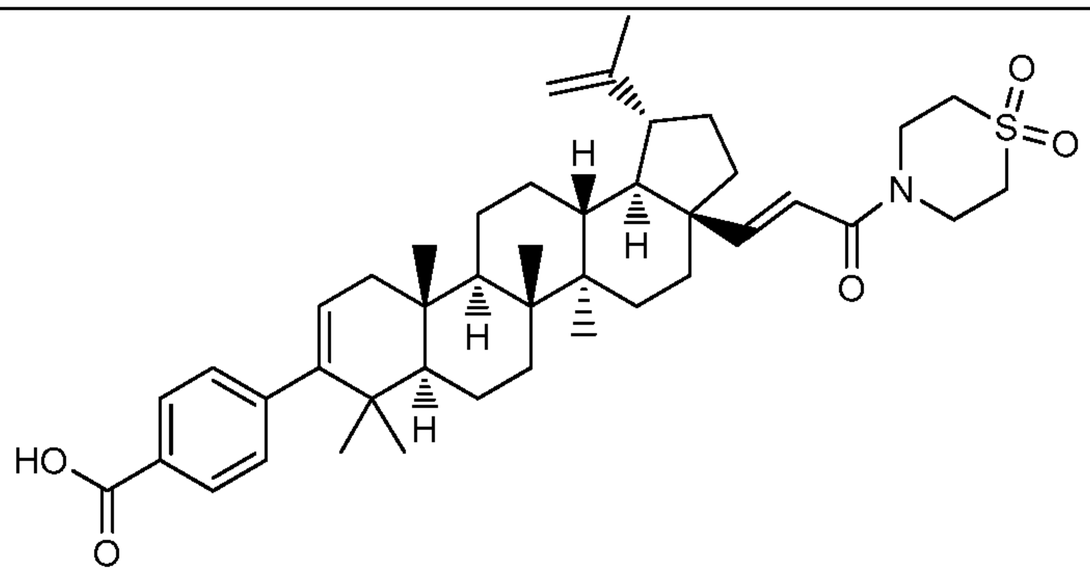
Preparation of (S)-4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid, isomer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

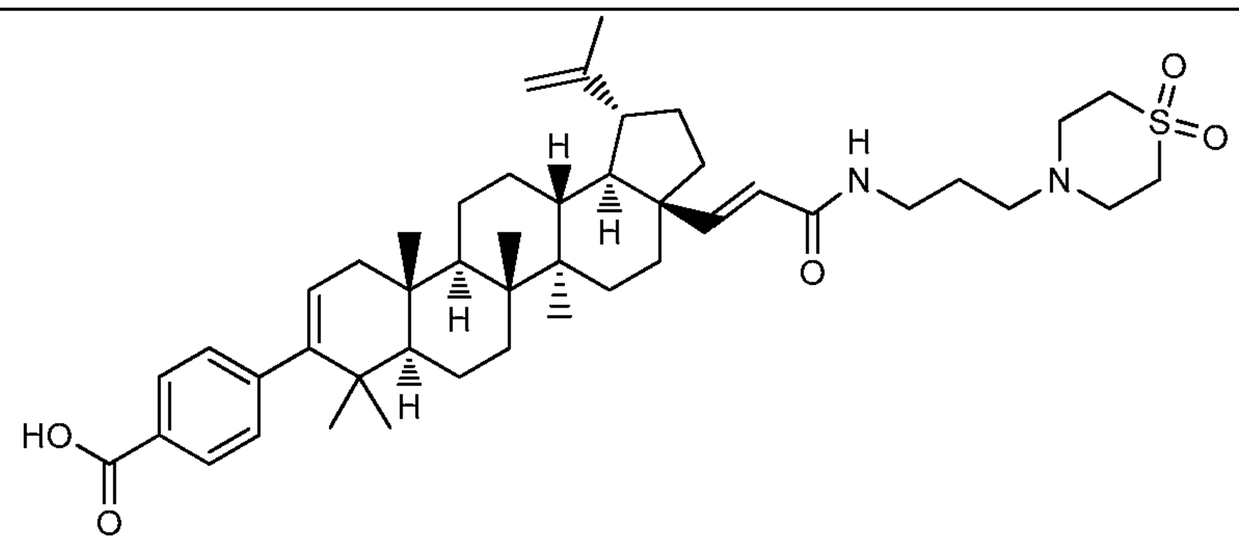
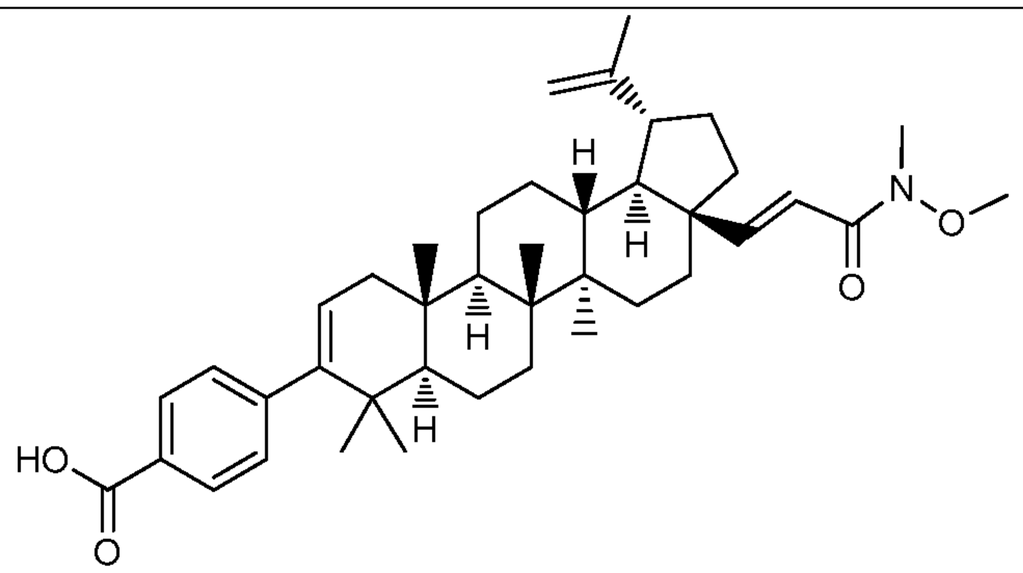
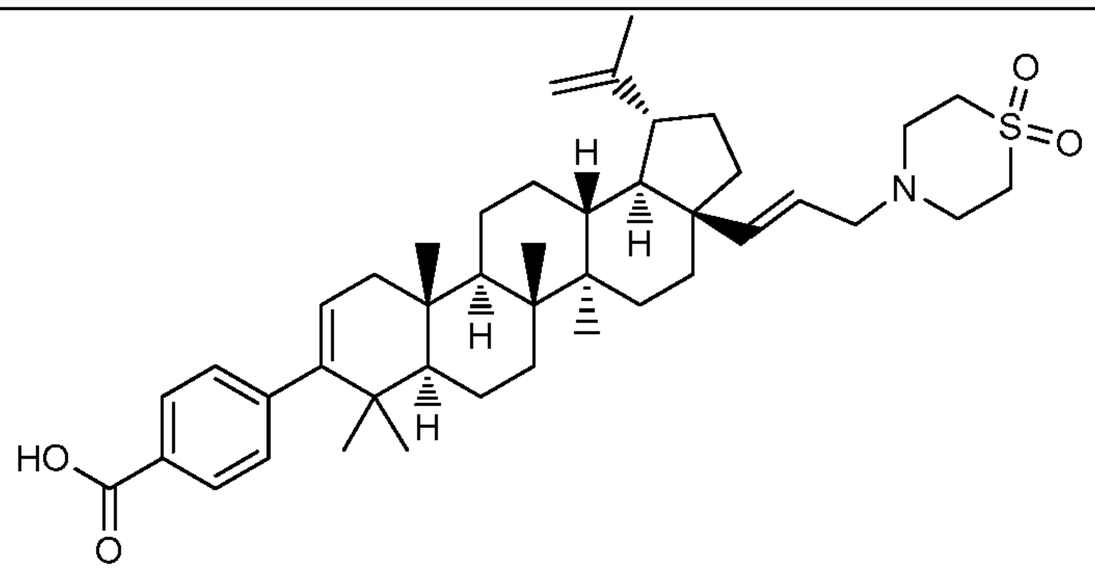
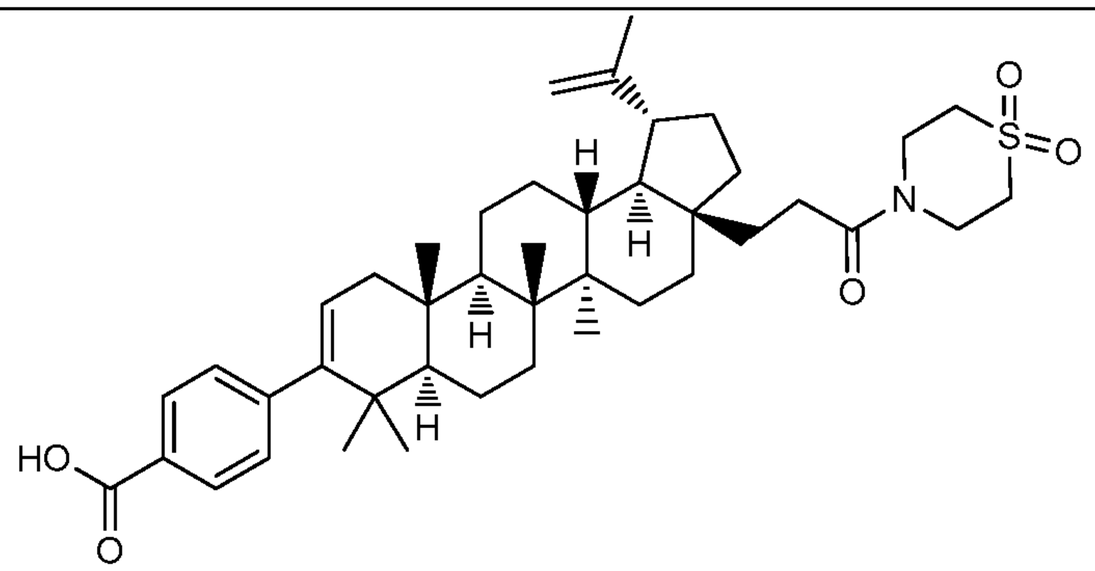
The title compound was prepared using the same procedure described above for its diastereoisomer, only using (S)-4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-(dimethylamino)ethyl)amino)-1-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(fluoromethyl)cyclohex-3-enecarboxylic acid as the starting material. After 16 h of stirring, an additional 10 mg of 4-chlorobenzaldehyde and 7.5 mg of borane-2-picoline complex was added to the mixture. Work up and purification were performed as indicated above for its diastereoisomer to provide the title compound as a white solid (19.2 mg). ^{1}H NMR (500MHz, Acetic acid-d_4) δ 7.67 (d, *J*=8.4 Hz, 2H), 7.50 (d, *J*=8.5 Hz, 2H), 5.37 (br. s., 1H), 5.22 (d, *J*=4.6 Hz, 1H), 4.69 (d, *J*=12.8 Hz, 1H), 4.62 - 4.43 (m, 3H), 4.07 - 3.98 (m, 3H), 3.92 - 3.85 (m, 2H), 3.53 - 3.36 (m, 2H), 3.01 (s, 6H), 2.59 (d, *J*=17.0 Hz, 1H), 0.84 (d, *J*=6.8 Hz, 3H), 0.75 (d, *J*=6.8 Hz, 3H), 2.37 - 0.65 (m, 44H).

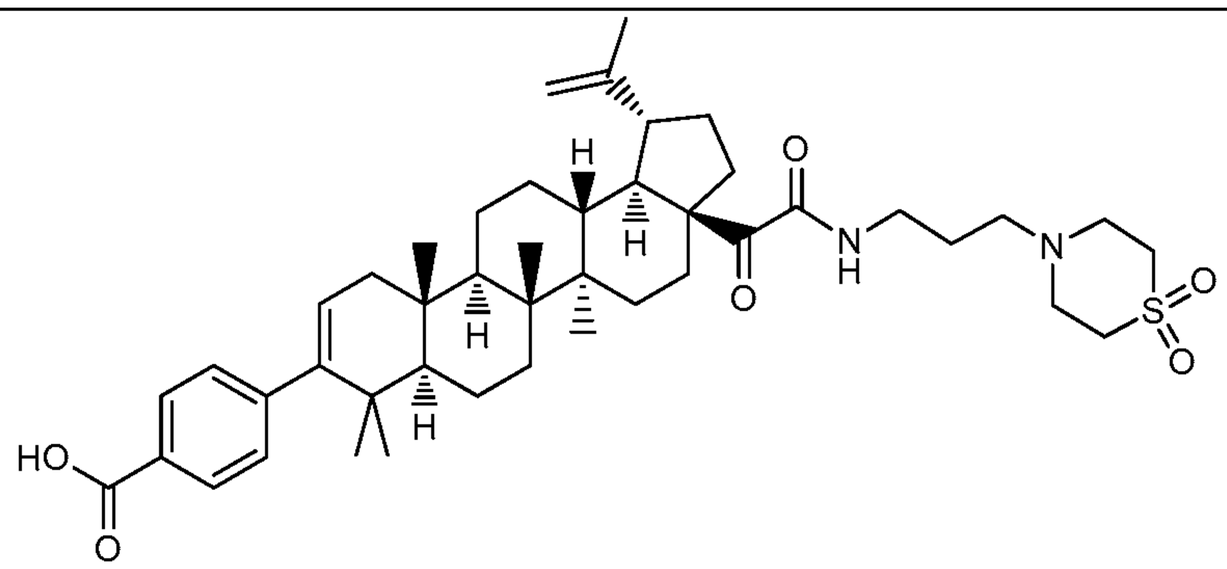
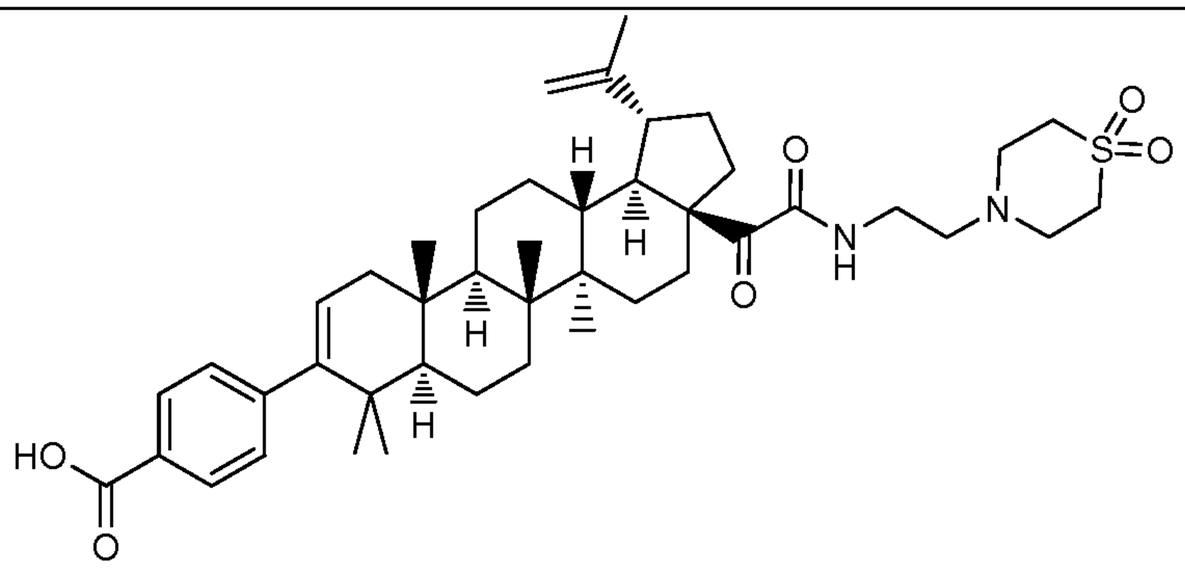
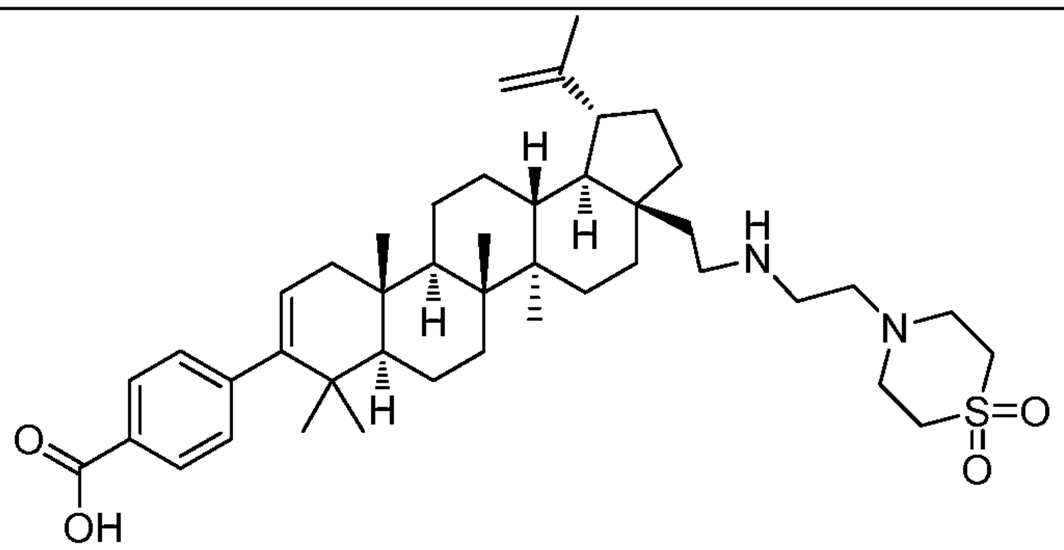
HIV cell culture assay - MT-2 cells and 293T cells were obtained from the NIH AIDS Research and Reference Reagent Program. MT-2 cells were propagated in RPMI 1640 media supplemented with 10% heat inactivated fetal bovine serum, 100 µg/mL penicillin G and up to 100 units/mL streptomycin. The 293T cells 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}

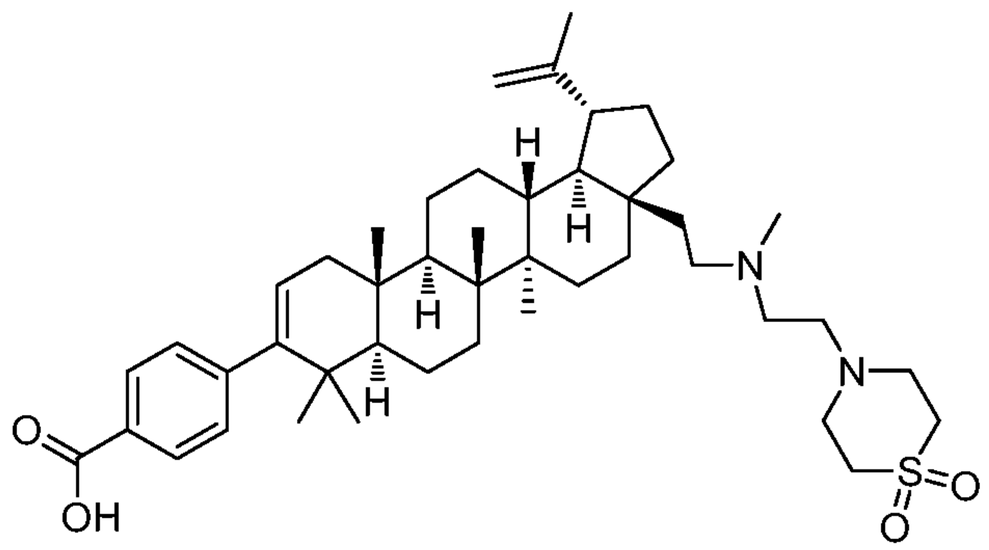
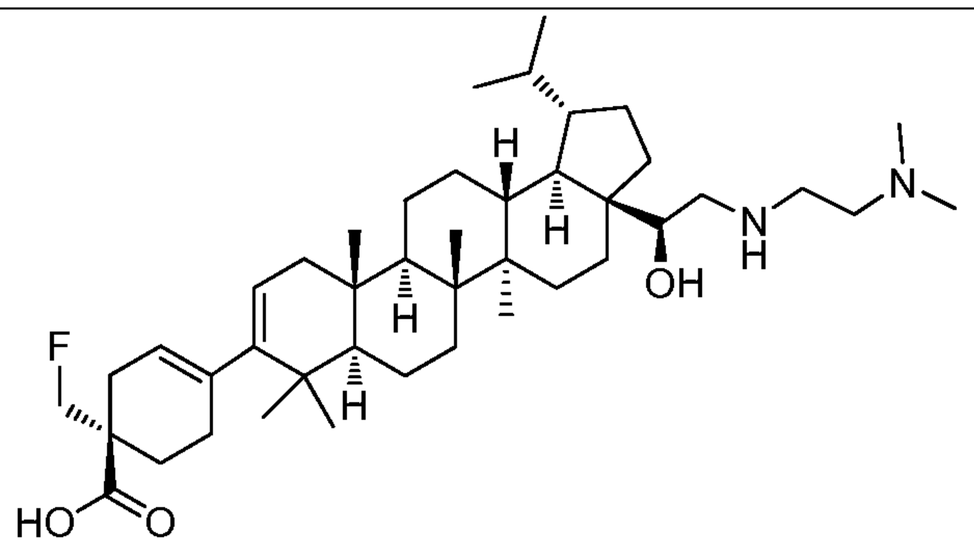
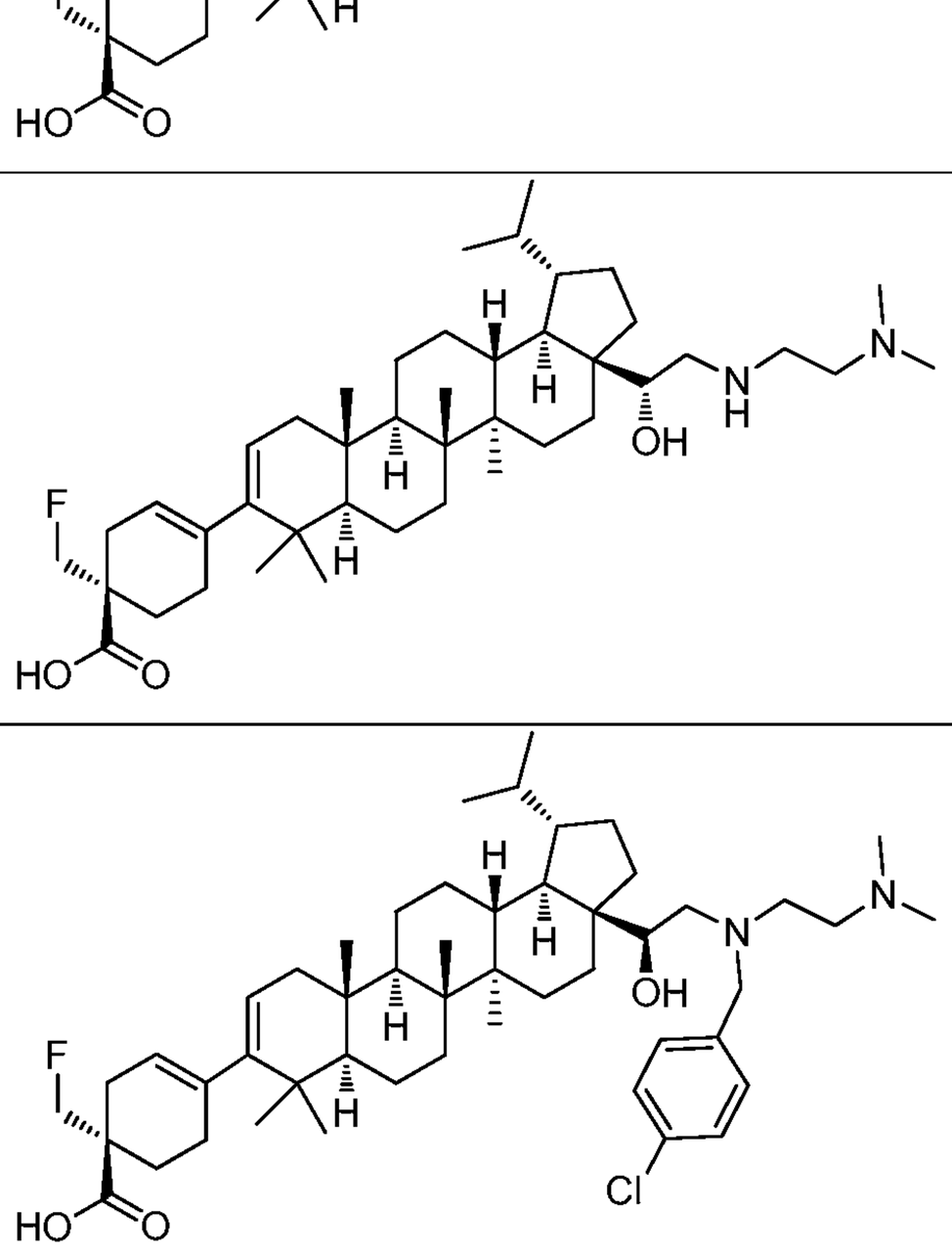
Compounds with EC_{50} >0.1 µM	Compounds with $EC_{50} \leq 0.1$ µM
Group "B"	Group "A"

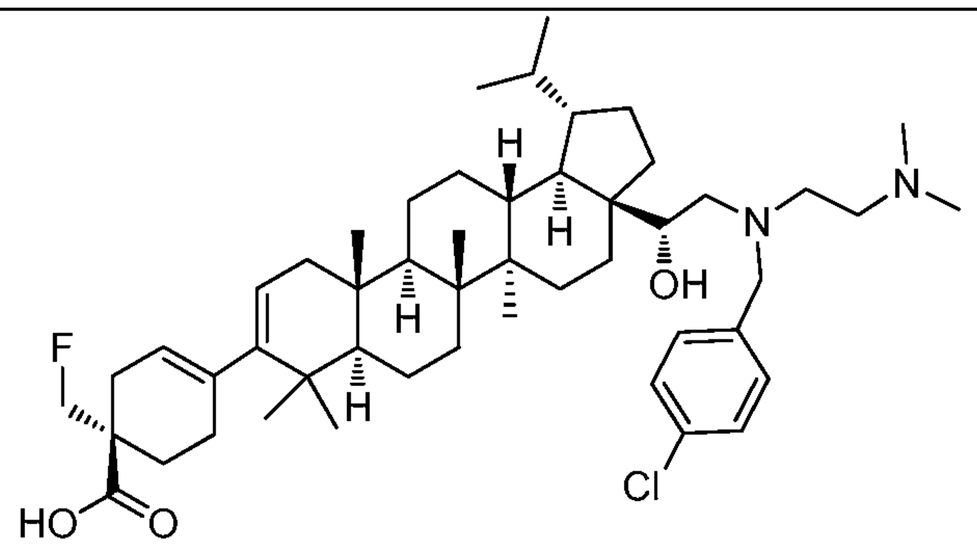
TABLE 1

Example #	Structure	WT EC50 μM
1		0.02
2		B
3		A

4		B
5		A
6		A
7		5.66E-03

8		A
9		A
10		A
11		1.24E-03

12		A
13		A
14		A
15		A

16		0.13

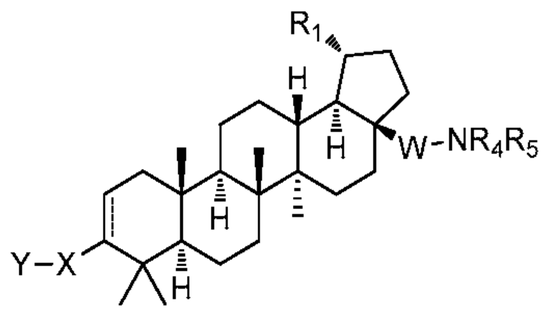
The foregoing description is merely illustrative and should not be understood to limit the scope or underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from 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:

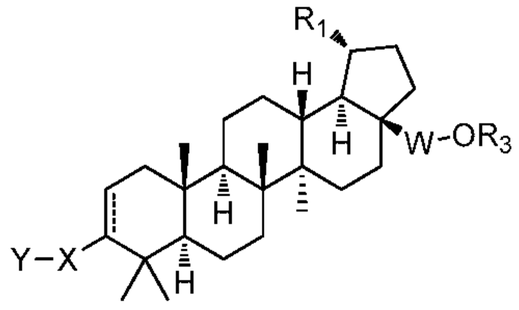
1. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

a compound of formula I



Formula I ;

and a compound of formula II



Formula II ;

wherein R_1 is isopropenyl or isopropyl;

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;

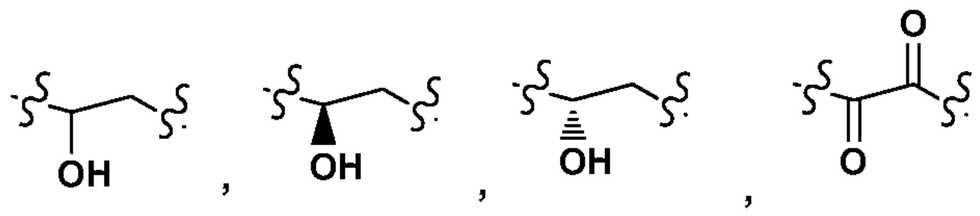
wherein X is substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{1-6}haloalkyl, -CN, -NR_8R_9, -$COOR_2$, -$CONR_2R_2$ and -C_{1-6} alkyl-Q;

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 benzyl;

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;

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



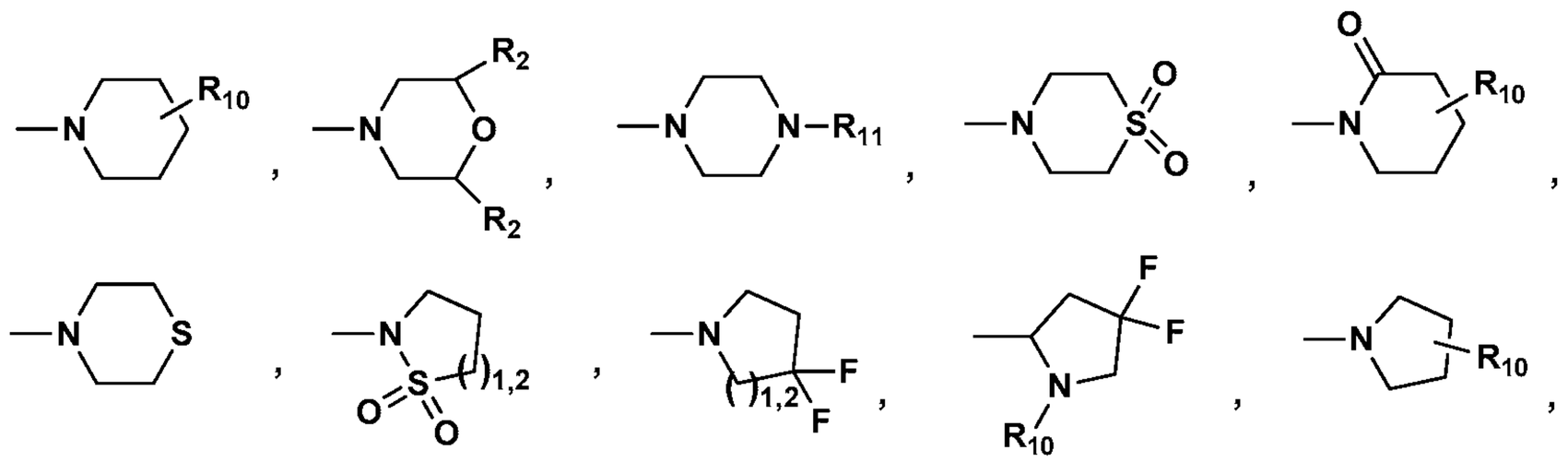
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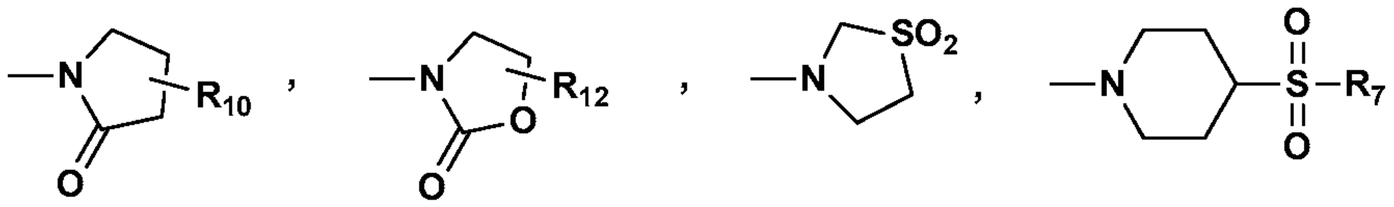
R_3 is –H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or benzyl;

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 -$SO_2NR_2R_2$;

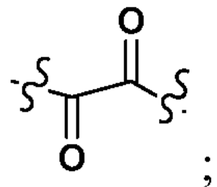
Q_1 is selected from the group of heteroaryl, substituted heteroaryl,
halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

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 -$SO_2NR_2R_2$;
or R_4 and R_5 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_4 or R_5 can be selected from the group of $-COR_6$, $-COCOR_6$,$-SO_2R_7$ and $-SO_2NR_2R_2$, and with the further proviso that R_4 or R_5 cannot be $-COR_6$ or $-COCOR_6$ when W is $-C_{2-6}$ alkyl-CO-, $-C_{2-6}$ alkenyl-CO-, or ;

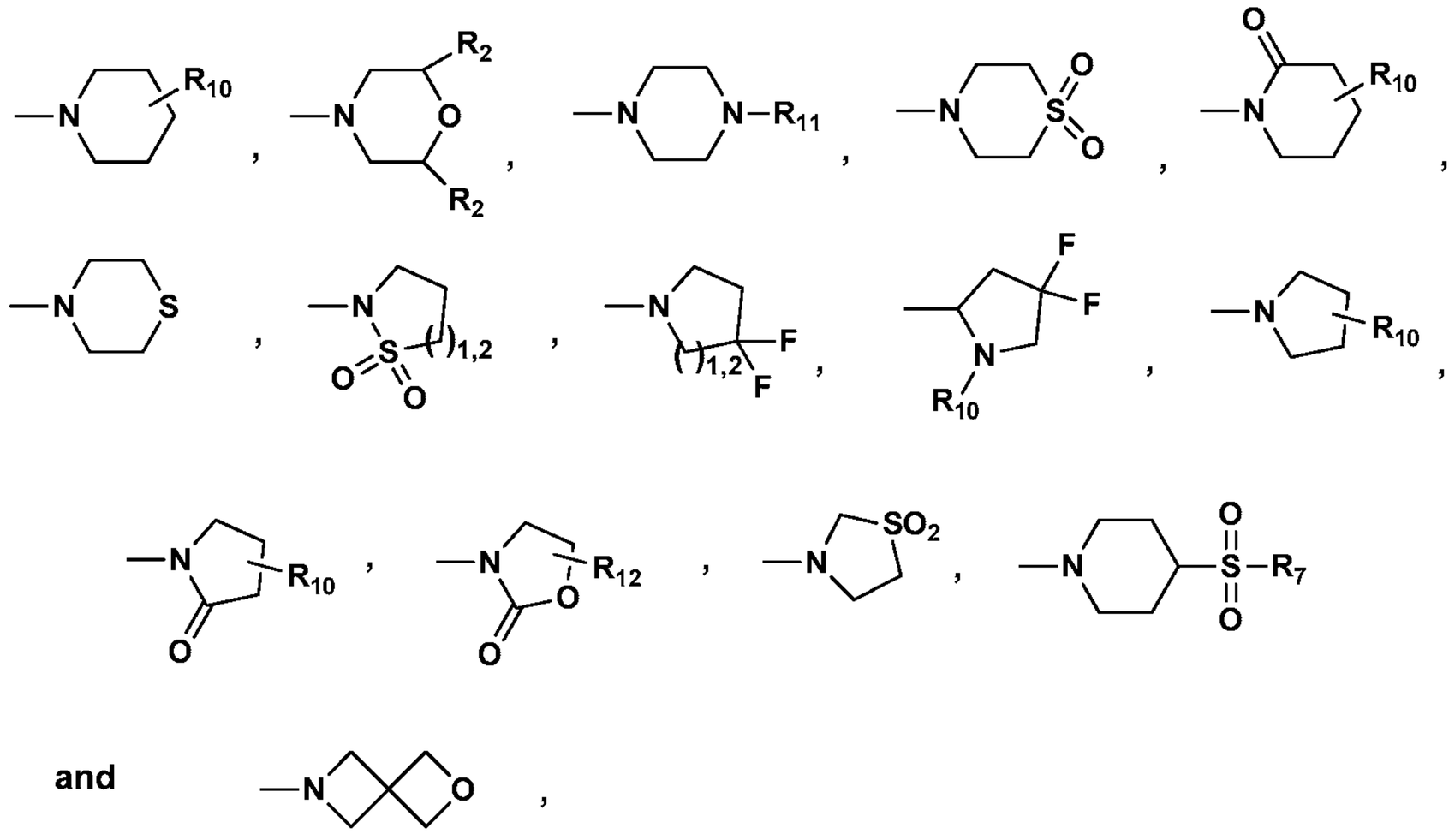
R_6 is selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-substitutedalkyl, $-C_{3-6}$ cycloalkyl, $-C_{3-6}$ substitutedcycloalkyl-Q_2, $-C_{1-6}$ alkyl-Q_2, $-C_{1-6}$ alkyl-substitutedalkyl-Q_2,$-C_{3-6}$ cycloalkyl-Q_2, aryl-Q_2, $-NR_2R_2$, and $–OR_2$;

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

R_{11} 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, -$COONR_2R_2$, -SOR_7, and -$SONR_2R_2$; and

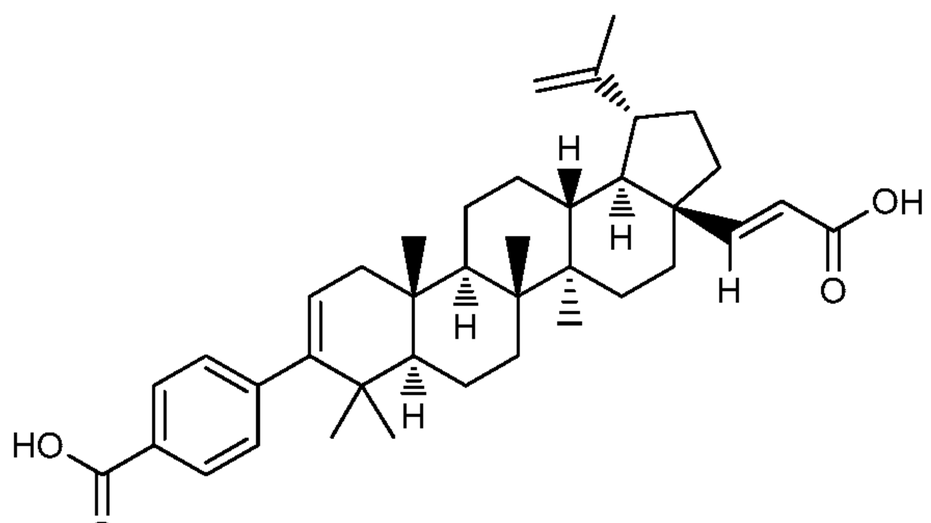
R_{12} is selected from the group of -H, -C_{1-6} alkyl, -$COOR_3$, and aryl.

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

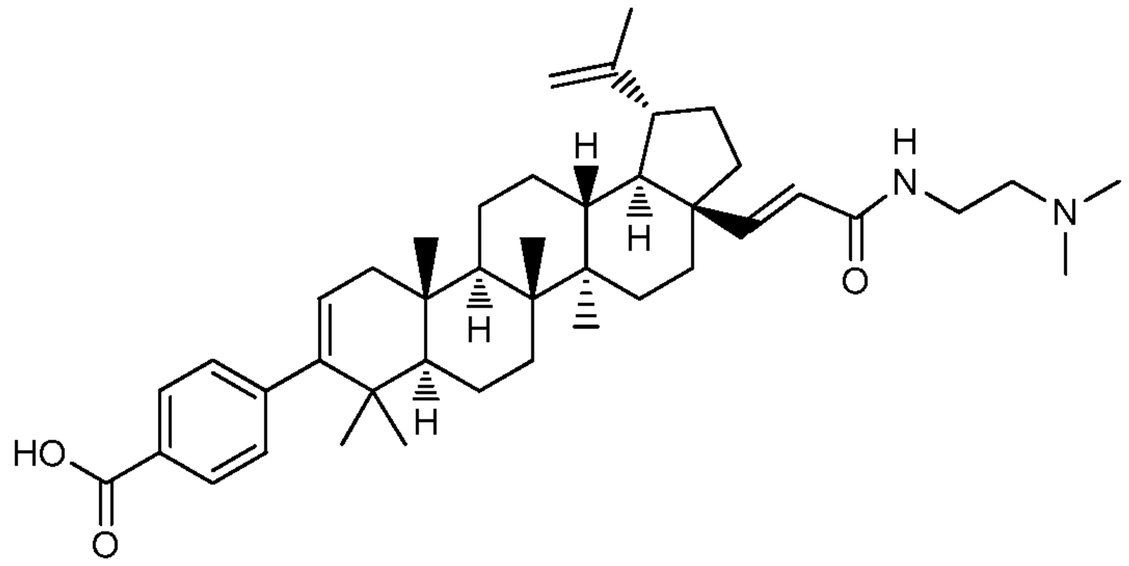
3. The compound as claimed in claim 2, wherein Y is –COOH.

4. The compound as claimed in claim 3, wherein said compound is a compound of Formula I.

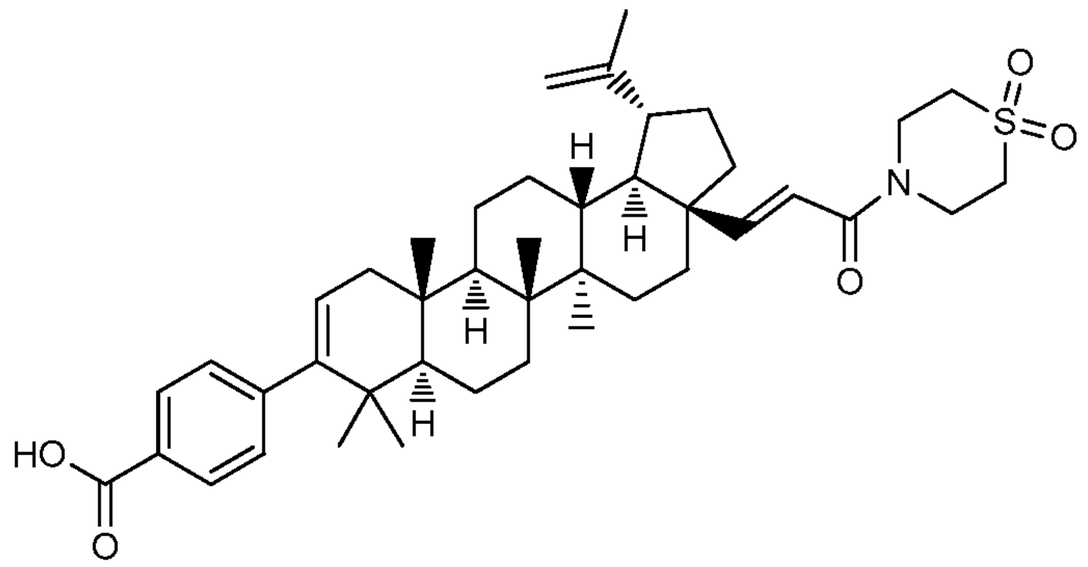
5. A compound, including pharmaceutically acceptable salts thereof, which is



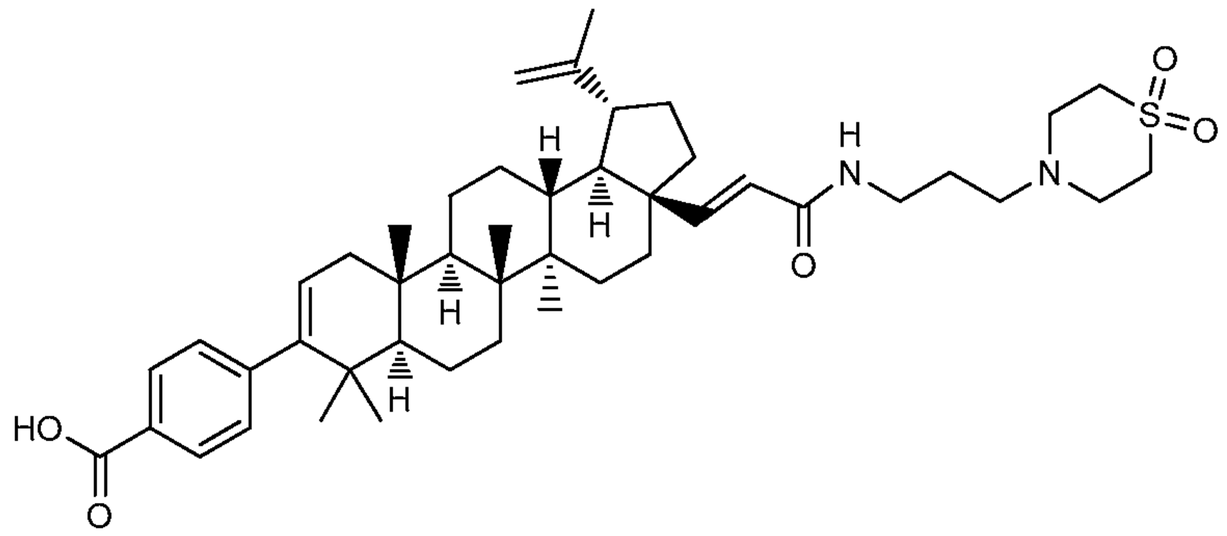
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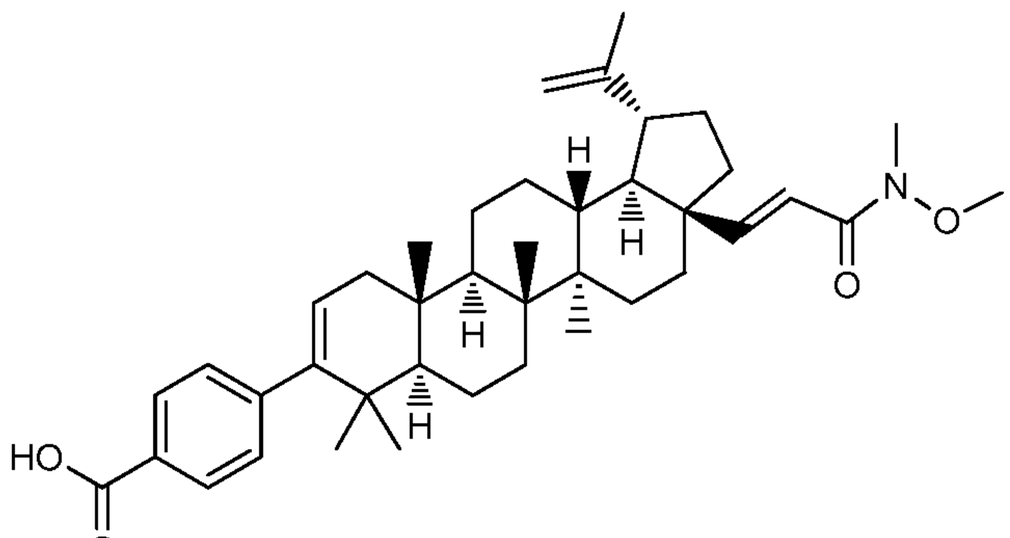
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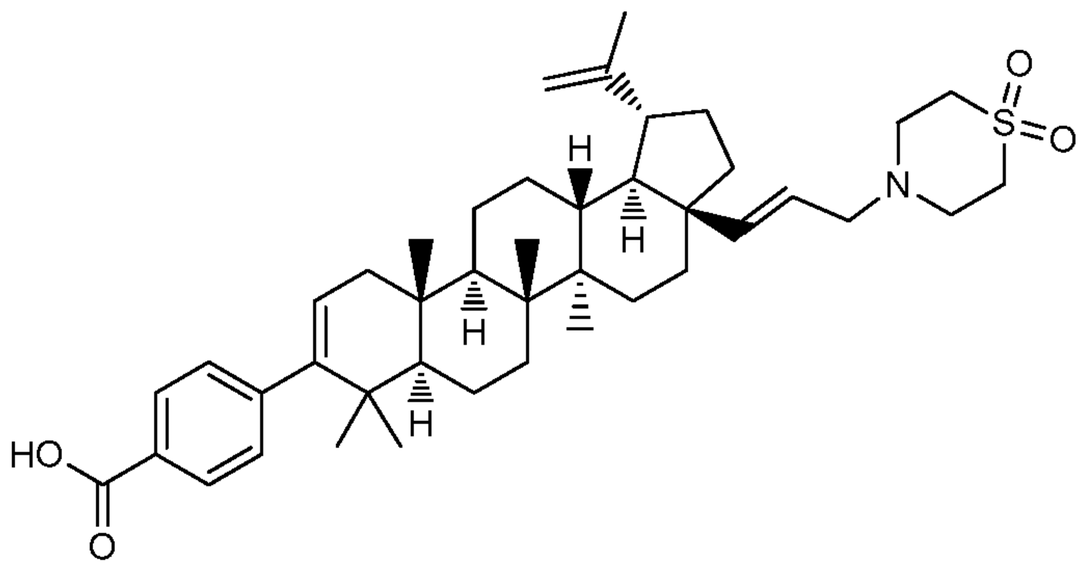
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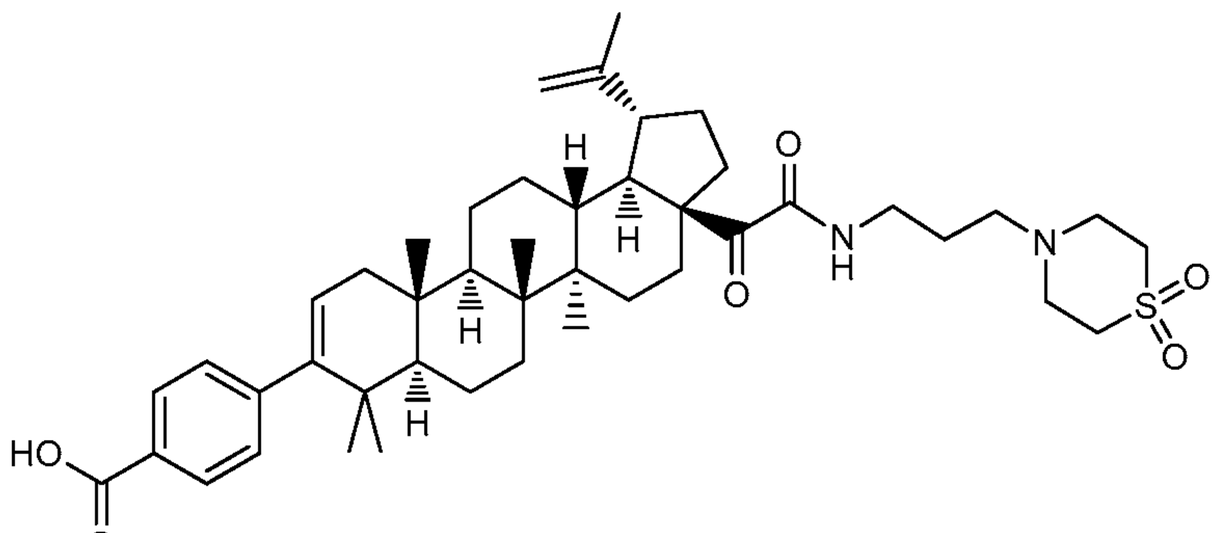


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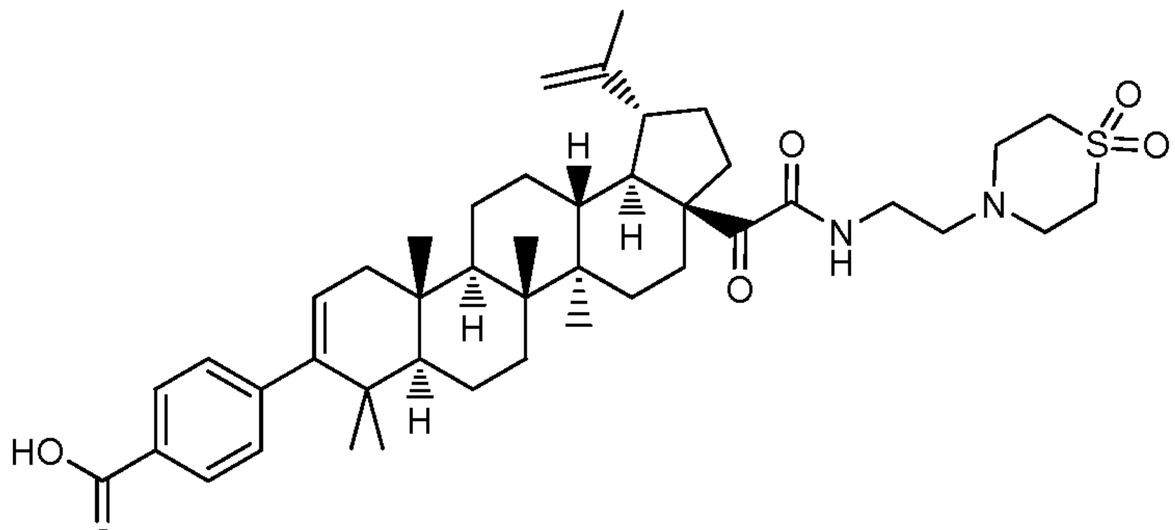
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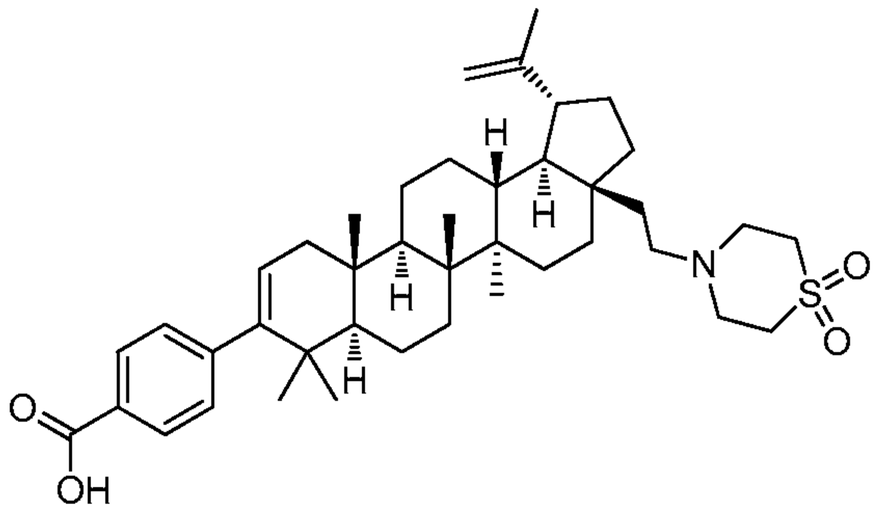
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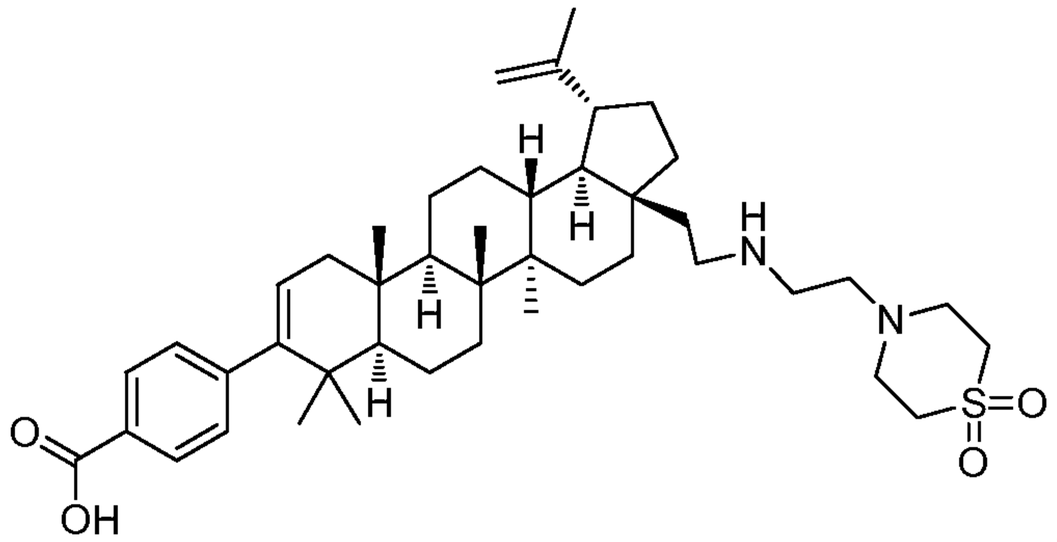
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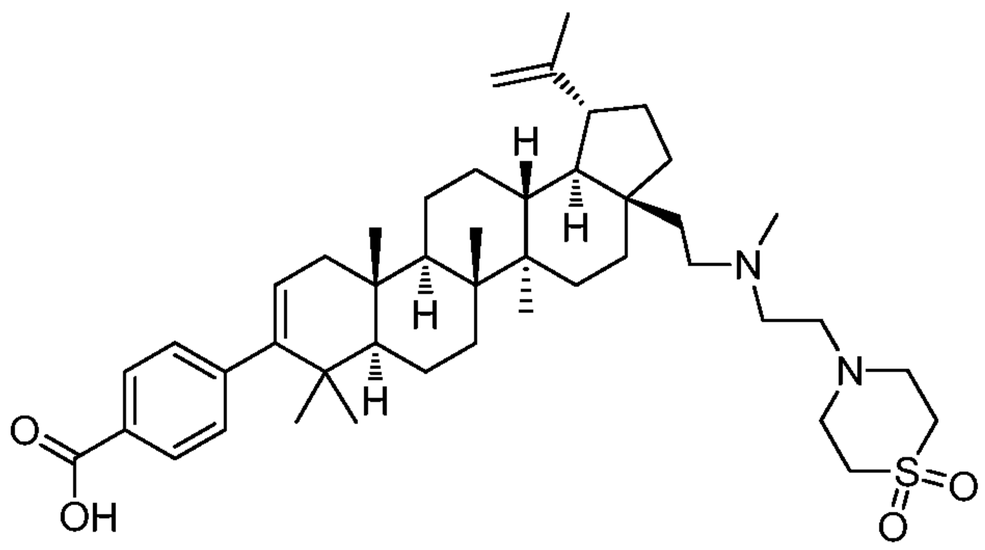
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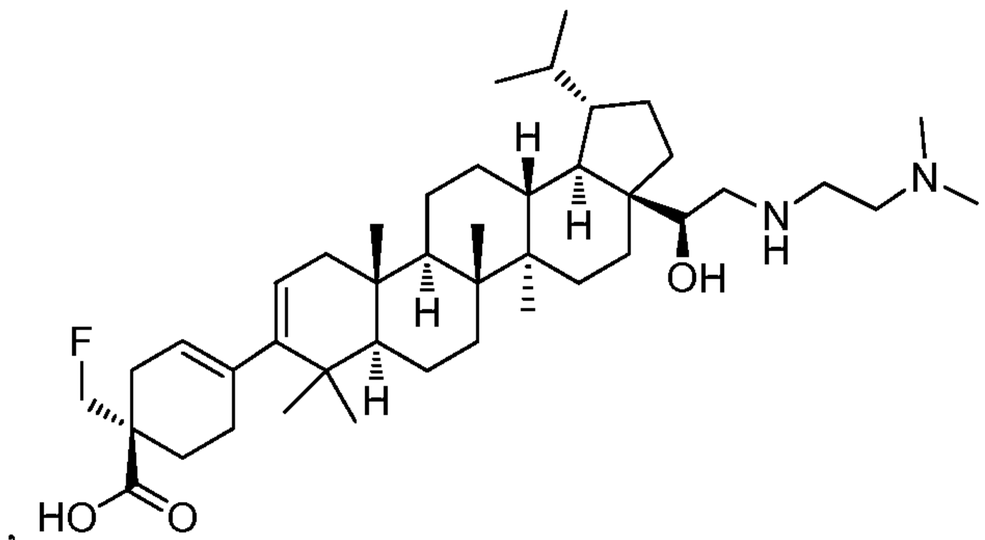


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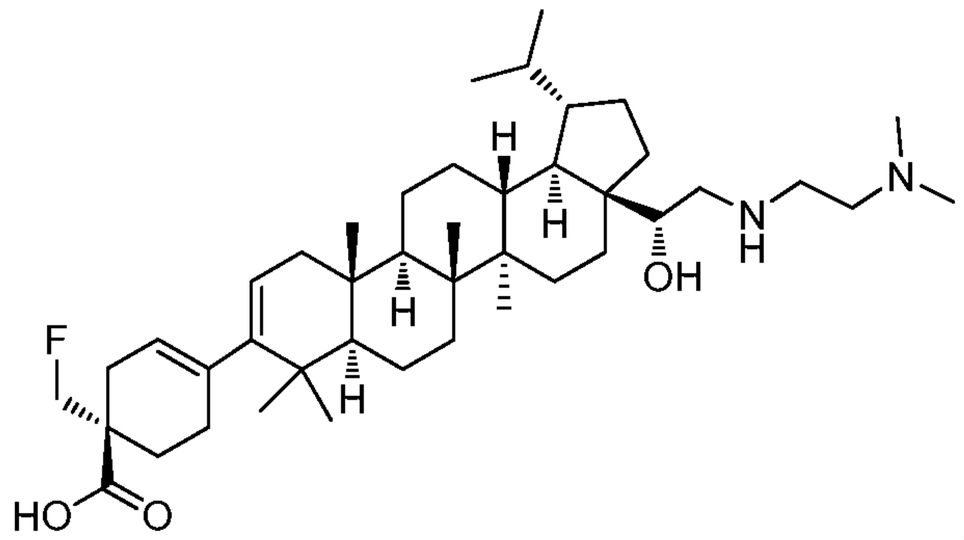


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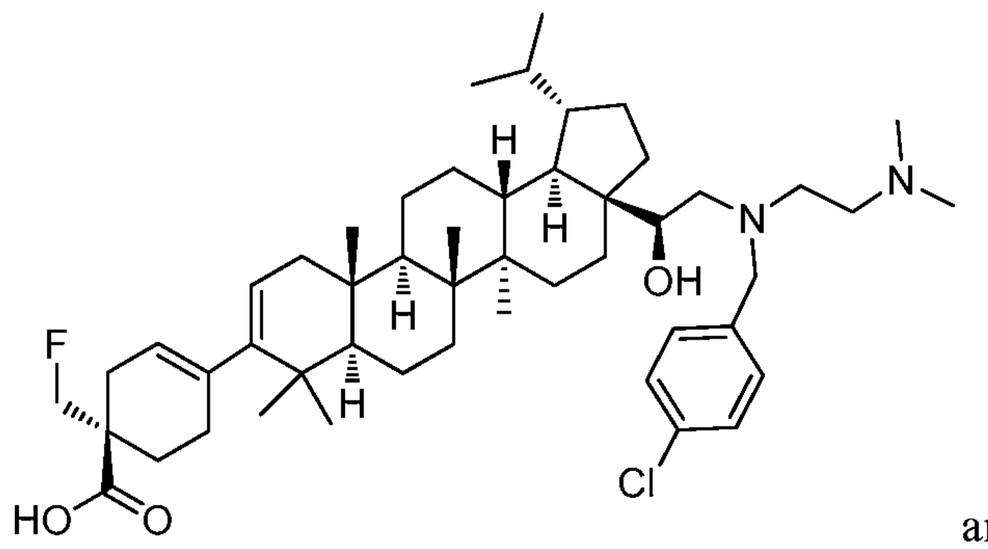




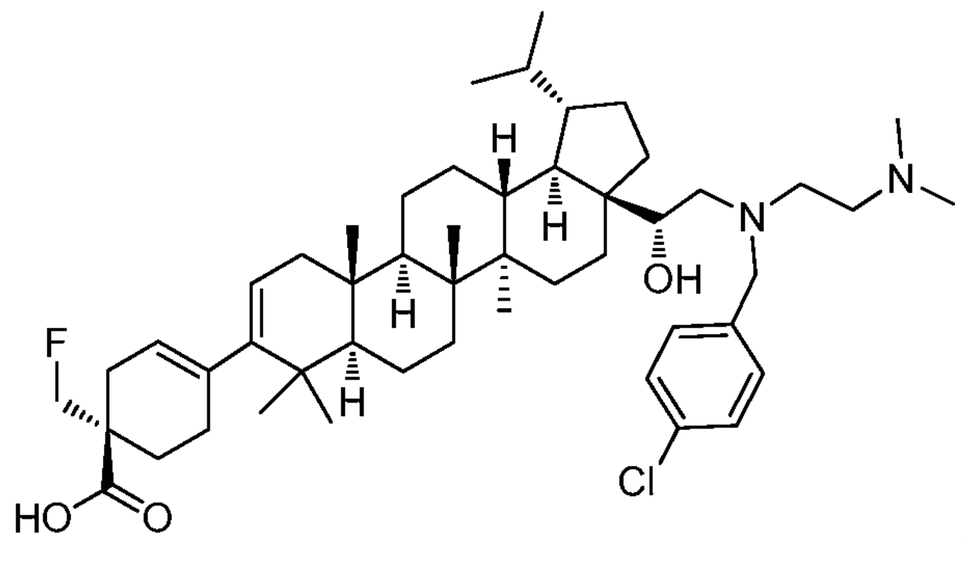
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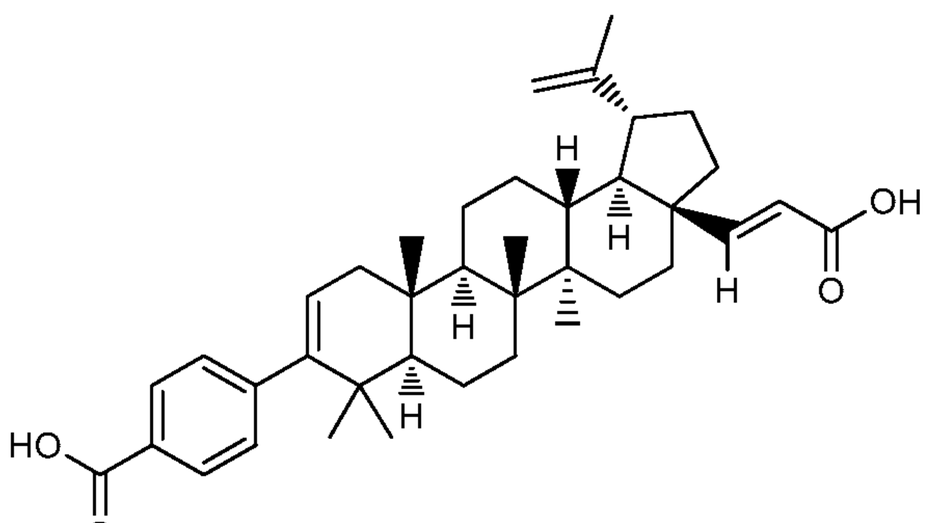


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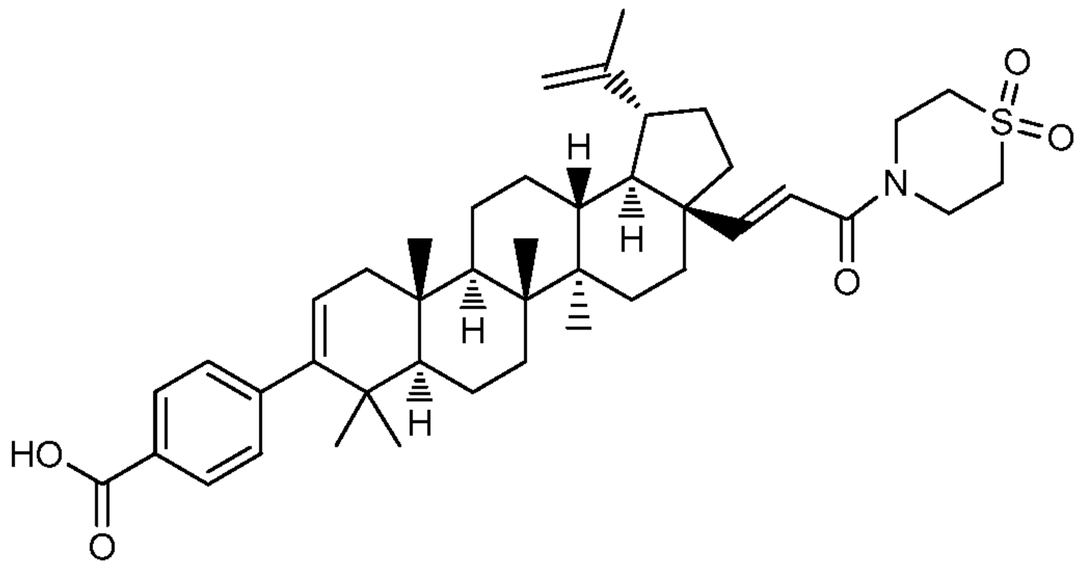


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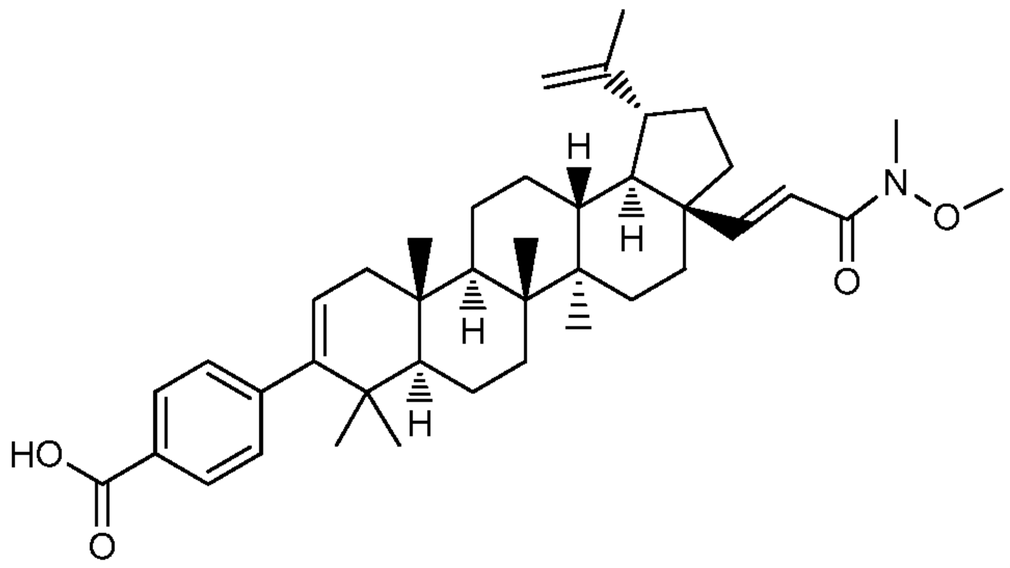
6. A compound, including pharmaceutically acceptable salts thereof, which is



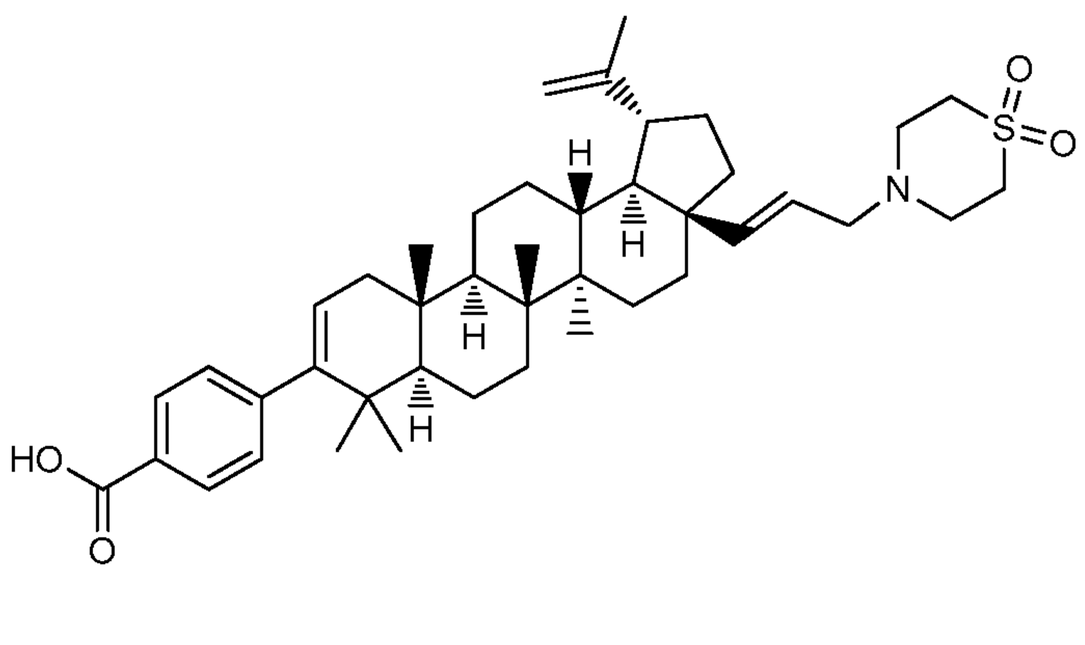
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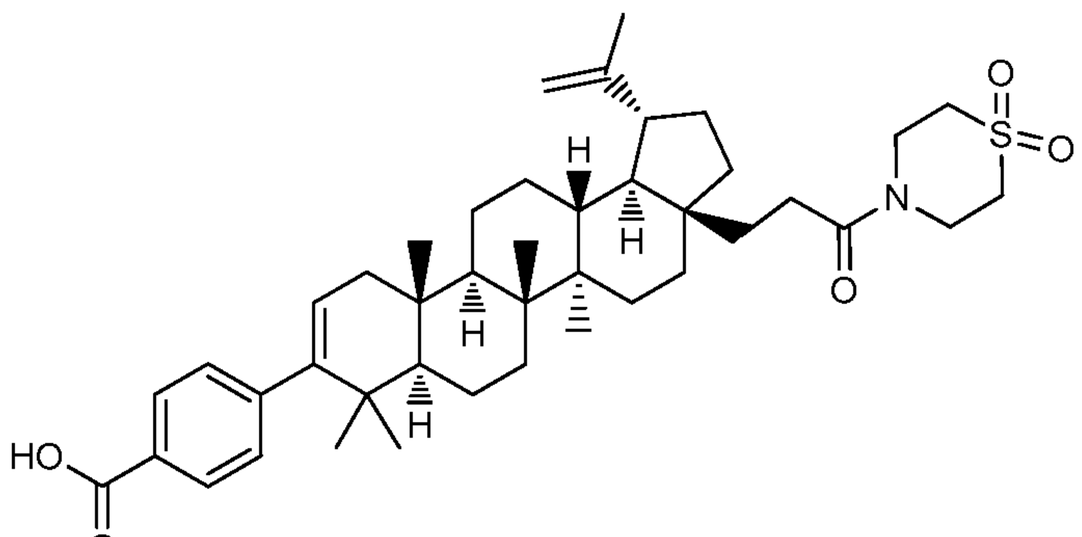
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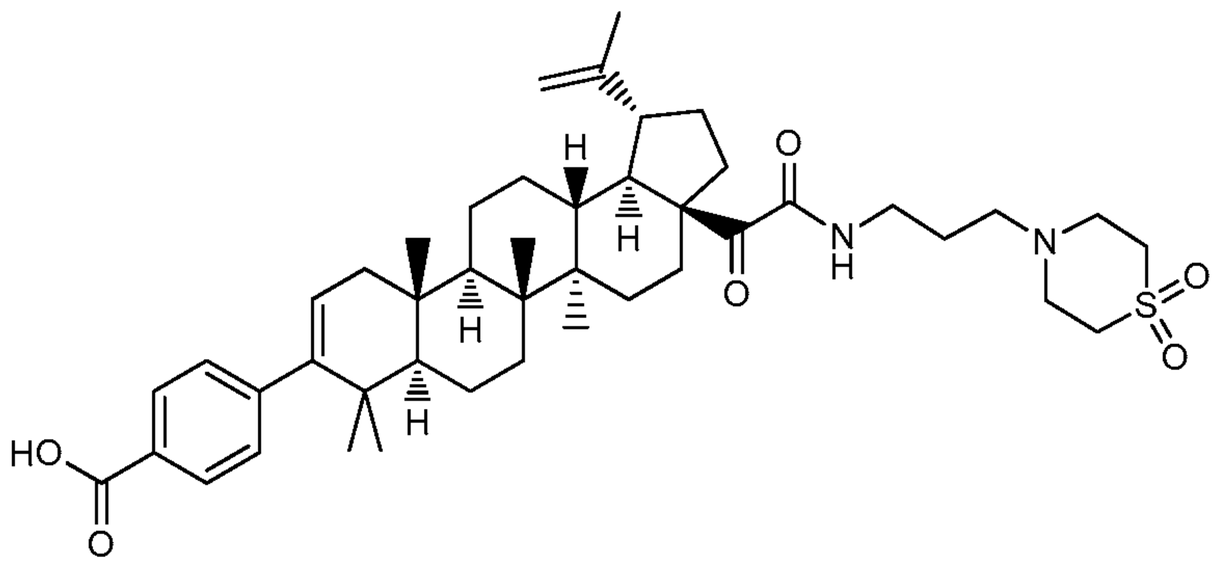
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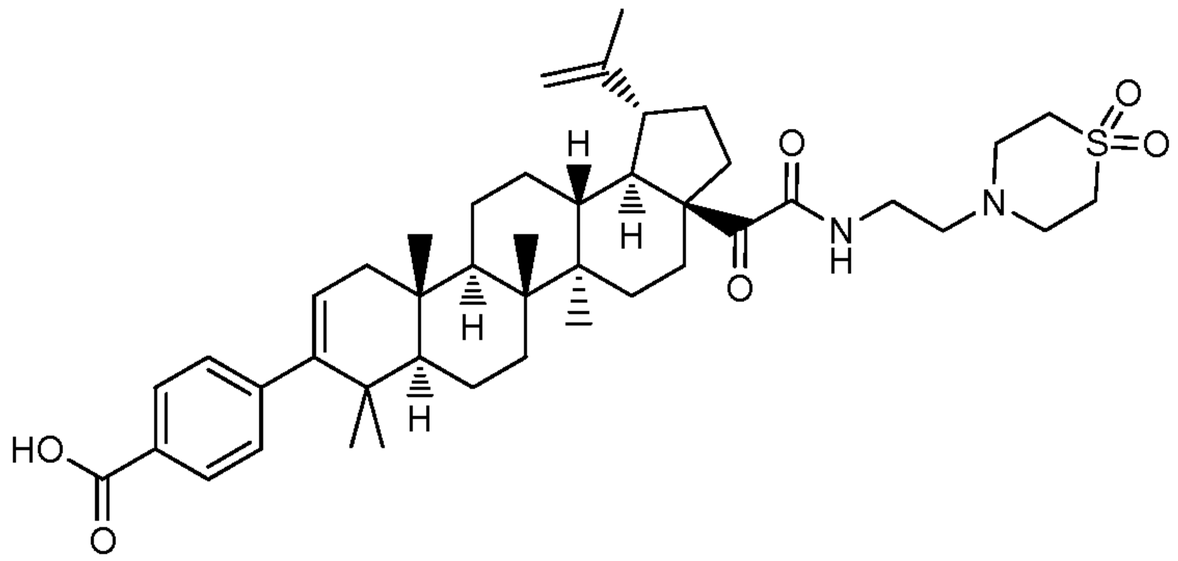
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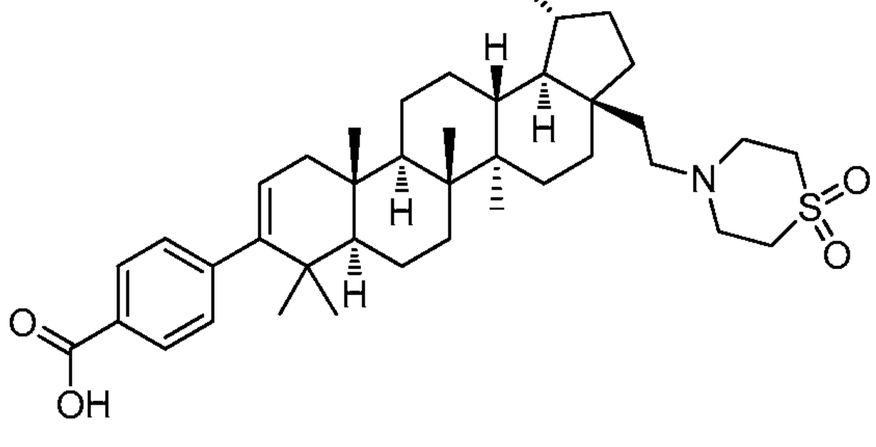
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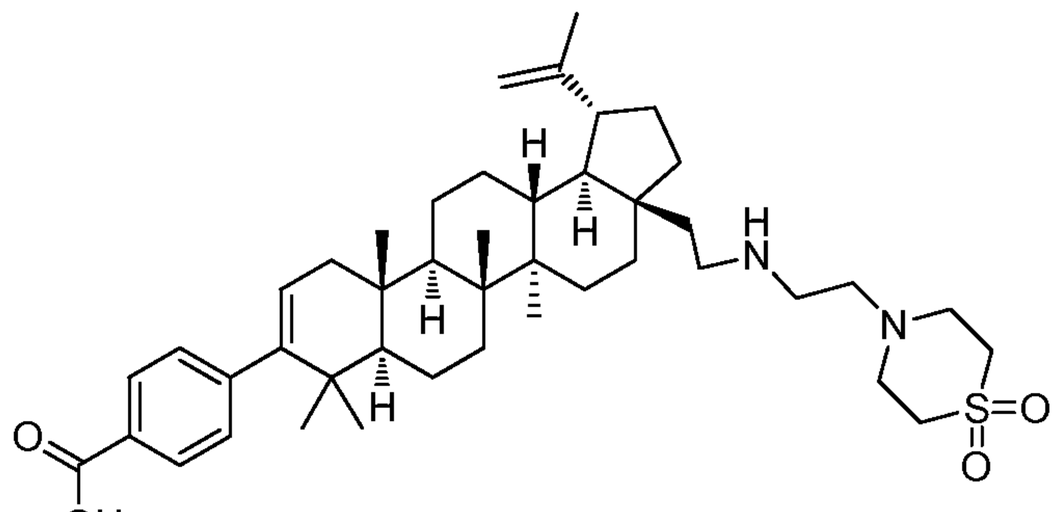
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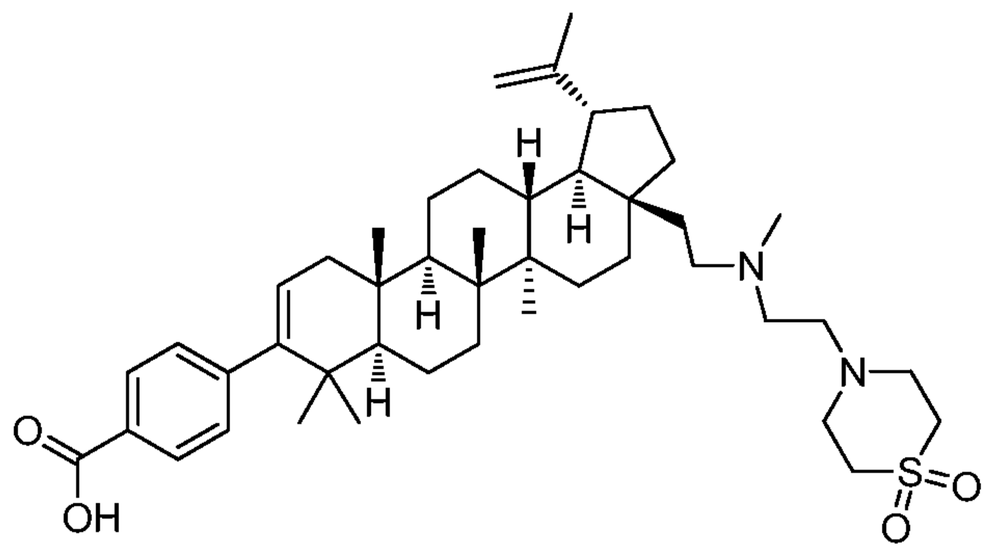
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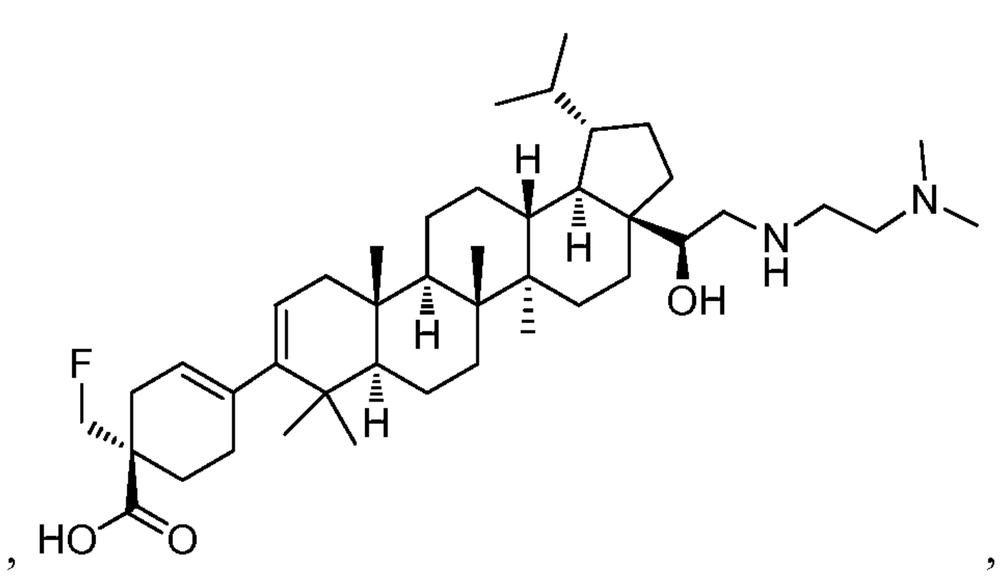
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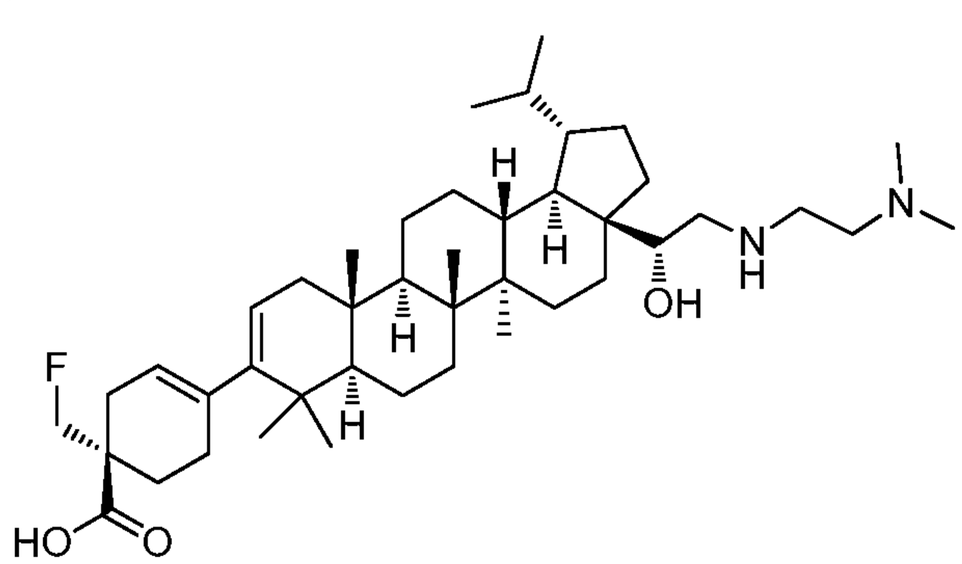
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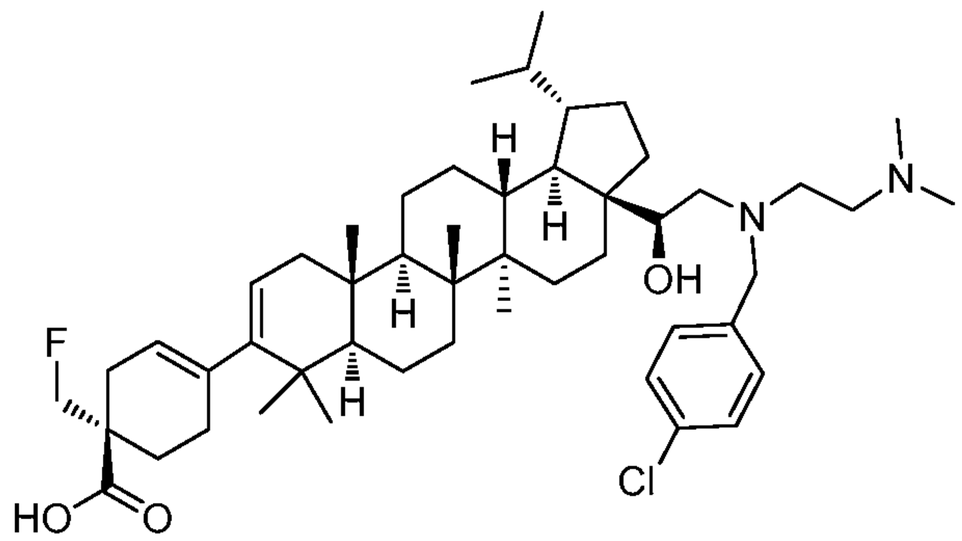


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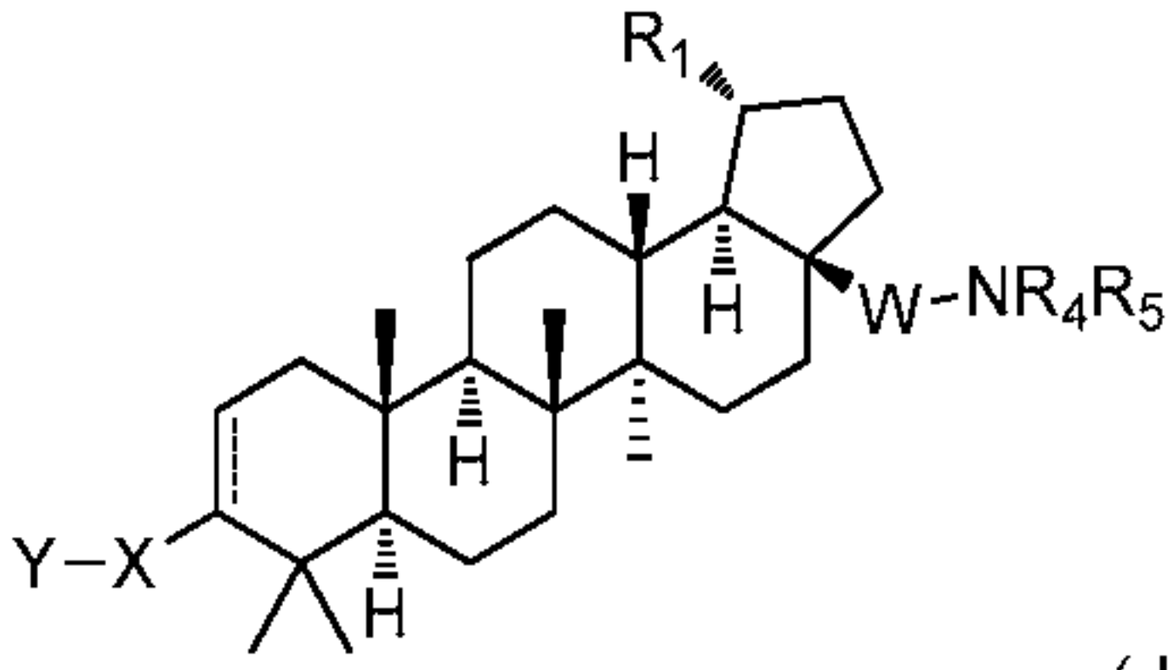


7. A composition which comprises an HIV ameliorating amount of one or more compounds as claimed in claim 1, together with one or more pharmaceutically acceptable carriers, excipients, and/or diluents.

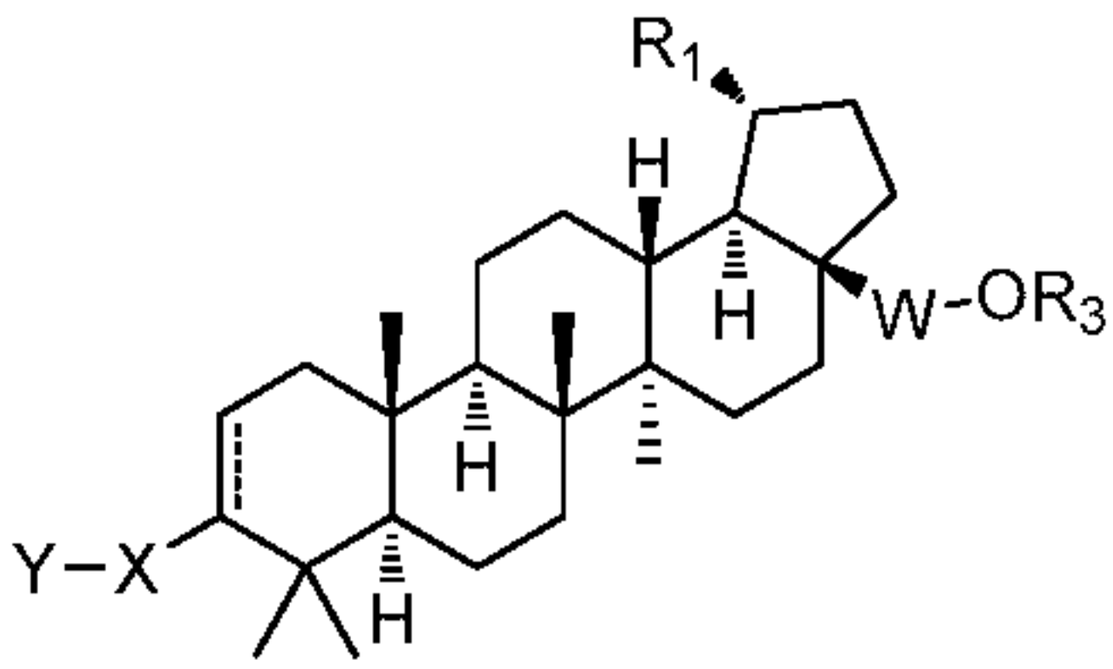
8. A composition which comprises an HIV ameliorating amount of one or more compounds as claimed in claim 5, together with one or more pharmaceutically acceptable carriers, excipients, and/or diluents.

9. 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.

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 5, together with one or more pharmaceutically acceptable carriers, excipients, and/or diluents.



(I)



(II)