

C-17 AND C-3 MODIFIED TRITERPENOIDS WITH HIV MATURATION
INHIBITORY ACTIVITY

5 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
10 pharmaceutical compositions containing same, as well as to methods for their preparation.

BACKGROUND OF THE INVENTION

15 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
20 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),
25 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:
30 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.

5 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

10 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

15 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

20 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

25 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, US 7,354,924 and US 2005/0209246 are illustrative of HIV attachment inhibitors.

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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,
5 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
10 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
15 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., Gos. Nauchnyi Tsentr Virusol. Biotekhnol. "Vector" 9:485-491 (2001)).

20 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
25 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
30 MATURATION INHIBITORS" USSN 13/151,706 filed on June 2, 2011 and "C-28 AMIDES OF MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,722, filed on June 2, 2011. Reference is also made to the application entitled "C-28 AMINES OF C-3 MODIFIED

BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS” USSN 61/437,870, filed on January 31, 2011.

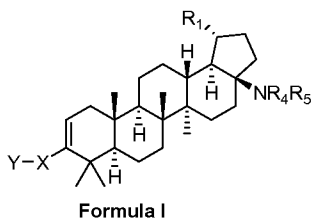
What is now needed in the art are new compounds which are useful as HIV
5 maturation inhibitors, as well as new pharmaceutical compositions containing these
compounds.

SUMMARY OF THE INVENTION

10 The present invention provides compounds of Formulas I, II, and III 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 – III are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

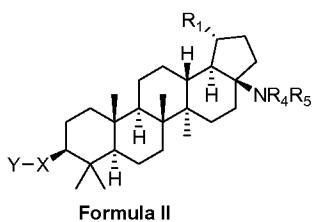
One embodiment of the present invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

20 a compound of formula I



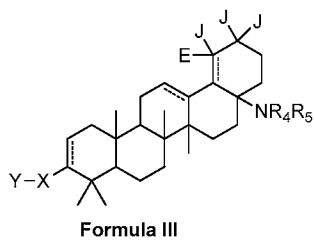
a compound of formula II

25



; and

a compound of formula III



5

wherein R_1 is isopropenyl or isopropyl;

J and E are $-H$ or $-CH_3$, and E is absent when the double bond is present;

- 10 X is a phenyl or heteroaryl ring 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, and $-COOR_2$;

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

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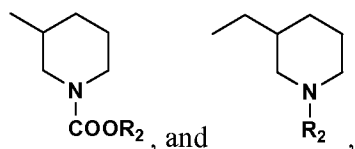
Y is selected from the group of $-COOR_2$, $-C(O)NR_2SO_2R_3$, $-C(O)NHSO_2NR_2R_2$, $-NR_2SO_2R_2$, $-SO_2NR_2R_2$, $-C_{3-6}$ cycloalkyl- $COOR_2$, $-C_{2-6}$ alkenyl- $COOR_2$, $-C_{2-6}$ alkynyl- $COOR_2$, $-C_{1-6}$ alkyl- $COOR_2$, $-NHC(O)(CH_2)_n-COOR_2$, $-SO_2NR_2C(O)R_2$, $-tetrazole$, and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

- 20 wherein $n=1-6$;

R_3 is $-C_{1-6}$ alkyl or $-alkylsubstituted\ C_{1-6}$ alkyl;

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, $-$

- 25 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, $-COR_6$, $-COCOR_6$, $-SO_2R_7$, $-SO_2NR_2R_2$,



wherein Q₁ is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF₃, -OR₂, -COOR₂, -NR₈R₉, -CONR₁₀R₁₁ and -SO₂R₇;

5

R₅ is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₁₀, -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

with the proviso that only one of R₄ or R₅ can be selected from the group of -COR₆, -

10

COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

or R₄ and R₅ are taken together with the adjacent N to form



R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆

15

cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -NR₁₃R₁₄, and -OR₁₅;

wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

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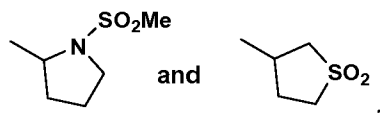
R₇ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, aryl, and heteroaryl;

R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆

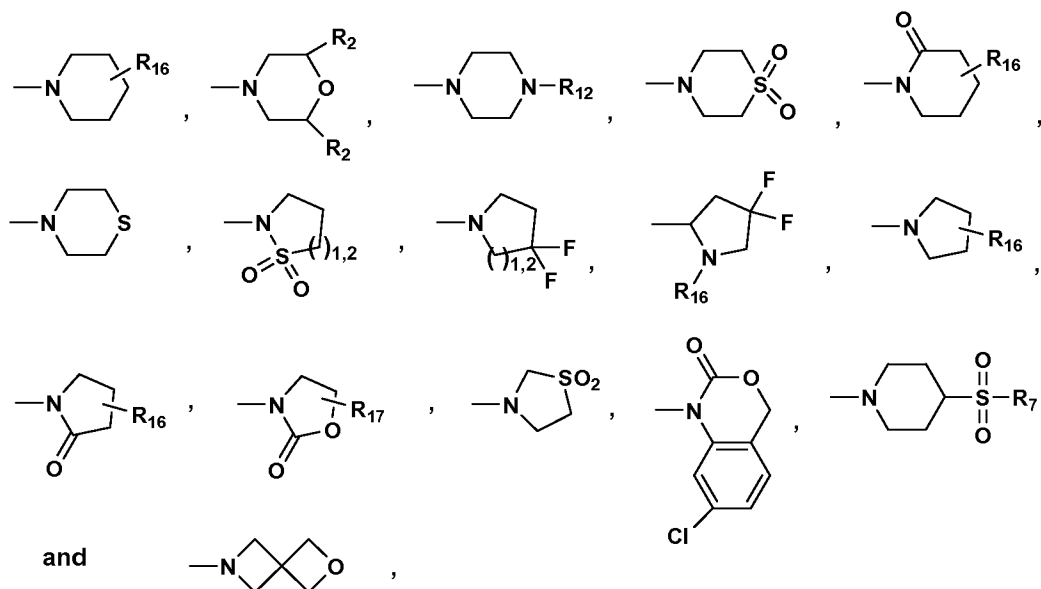
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substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-Q₂, and -COOR₃,

and R₈ and R₉ can also be independently selected from the group of



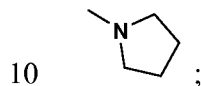
or R₈ and R₉ are taken together with the adjacent N to form a cycle selected from the group of:



5 with the proviso that only one of R₈ or R₉ can be -COOR₃;

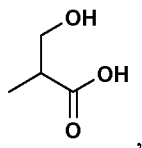
R₁₀ and R₁₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl and -C₃₋₆ cycloalkyl,

or R₁₀ and R₁₁ are taken together with the adjacent N to form a cycle such as



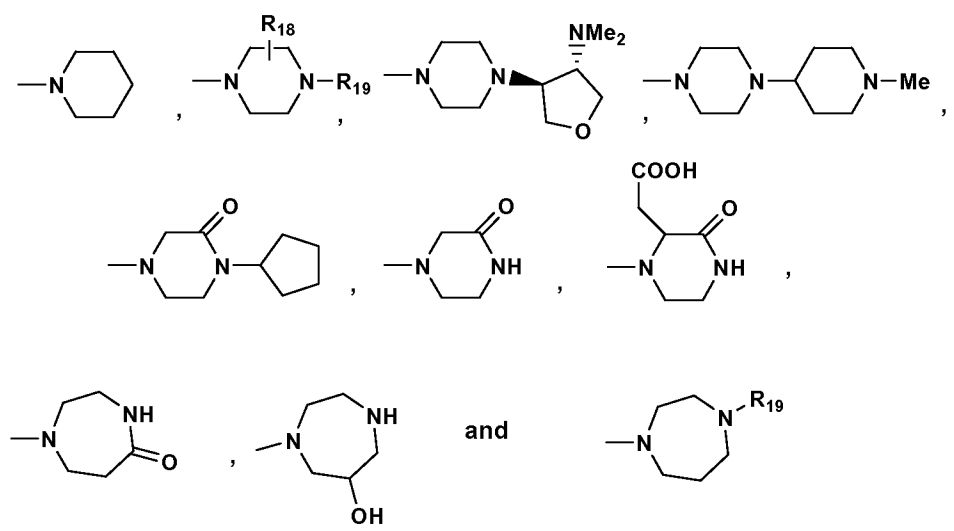
R₁₂ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ alkyl-OH; -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -COR₇, -COONR₂₂R₂₃, -SOR₇, and -SONR₂₄R₂₅;

15 R₁₃ and R₁₄ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃, C₁₋₆ substituted alkyl-Q₃ and



or R₁₃ and R₁₄ are taken together with the adjacent N to form a cycle selected from the group of:

20



Q₃ is selected from the group of heteroaryl, substituted heteroaryl, -NR₂₀R₂₁, -CONR₂R₂, -COOR₂, -OR₂, and -SO₂R₃;

5

R₁₅ is selected from the group of -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃ and -C₁₋₆ substituted alkyl-Q₃;

R₁₆ is selected from the group of -H, -C₁₋₆ alkyl, -NR₂R₂, and -COOR₃;

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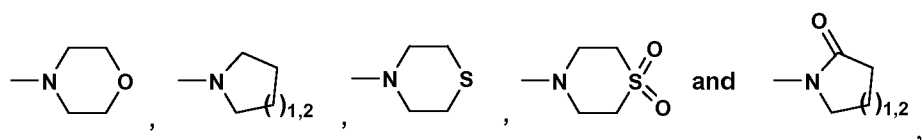
R₁₇ is selected from the group of -H, -C₁₋₆ alkyl, -COOR₃, and aryl;

R₁₈ is selected from the group of -COOR₂ and -C₁₋₆ alkyl-COOR₂;

15 R₁₉ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-Q₄, -COR₃, -COOR₃, wherein Q₄ is selected from the group of -NR₂R₂ and -OR₂;

R₂₀ and R₂₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ substituted alkyl-OR₂, and -COR₃,

20 or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of

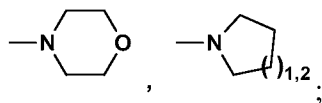


with the proviso that only one of R₂₀ or R₂₁ can be -COR₃;

R₂₂ and R₂₃ are independently selected from the group of H, -C₁₋₆ alkyl, -C₁₋₆

5 substituted alkyl, and -C₁₋₆ cycloalkyl,

or R₂₂ and R₂₃ are taken together with the adjacent N to form a cycle selected from the group of



R₂₄ and R₂₅ are independently from the group of H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl,

10 -C₁₋₆ alkyl-Q₅, -C₁₋₆ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

and Q₅ is selected from the group of halogen and SO₂R₃.

In a further embodiment, there is provided a method for treating mammals
 15 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, II, III above, and one or more pharmaceutically acceptable carriers, excipients or diluents. Optionally, the compound of Formulas I, II, and/or III can be administered in combination with an
 20 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
 25 comprising an antiviral effective amount of a compound which is selected from the group of compounds of Formulas I, II, and III, and one or more pharmaceutically acceptable carriers, excipients, and diluents; and optionally 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
 30 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, II, and III herein.

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

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

DETAILED DESCRIPTION OF THE EMBODIMENTS

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

15 *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:

20

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

The term “C₁₋₆ 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.

25

“C₁–C₄ fluoroalkyl” refers to F-substituted C₁–C₄ alkyl wherein at least one H atom is substituted with F atom, and each H atom can be independently substituted by F atom;

30

“Halogen” 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
 5 unsubstituted. When substituted the substituted group(s) is 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,
 10 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.

As used herein, 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
 20 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,
 25 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,
 30 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.

As used herein, 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 azetidiny, piperidyl, piperaziny, imidazoliny, thiazolidiny, 3-pyrrolidin-1-yl, morpholiny, thiomorpholiny and tetrahydropyrany. 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 an 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, 5 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, 10 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.

15

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 20 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 25 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 30 defined herein.

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

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

5 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.

10 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.

15 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.

20 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.

25 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.

30 A “trihalomethanecarbonyl” group refers to a $\text{Z}_3\text{CC(=O)C}$ - group with said Z being a halogen.

A “C-carboxy” group refers to a --C(=O)OR 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
 5 hydrogen.

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

10 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.

15 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.

20 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.

25 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
 30 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.

5

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.

10 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.

15 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.

20

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.

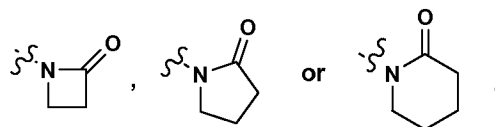
25

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.

30 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



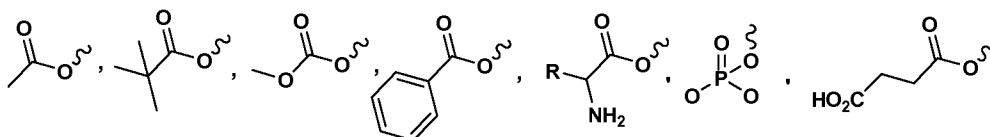
Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

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.

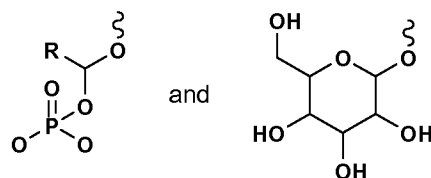
As stated above, the compounds of the invention also include “prodrugs”. The term “prodrug” as used herein encompasses both the term “prodrug esters” and the term “prodrug ethers”. The term “prodrug esters” as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of Formula I with either alkyl, alkoxy, or aryl substituted acylating agents or phosphorylating agent employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, amino acid esters, phosphates, half acid esters such as malonates, succinates or glutarates, and the like. In certain embodiments, amino acid esters may be especially preferred.

Examples of such prodrug esters include



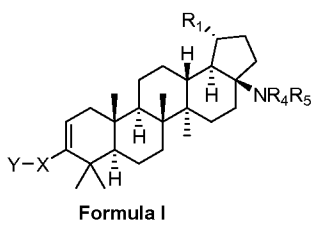
The term “prodrug ethers” include both phosphate acetals and O-glucosides.

Representative examples of such prodrug ethers include

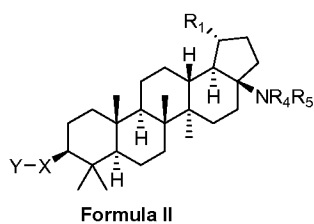


As set forth above, the invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

a compound of formula I

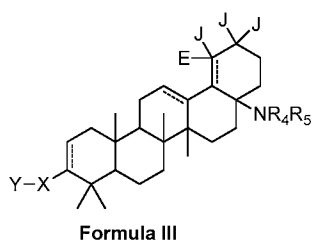


a compound of formula II



; and

5 a compound of formula III



;

wherein R₁ is isopropenyl or isopropyl;

10

J and E are -H or -CH₃, and E is absent when the double bond is present;

X is a phenyl or heteroaryl ring substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C₁₋₆ alkyl, -C₁₋₆ alkoxy, and

15 -COOR₂;

R₂ is -H, -C₁₋₆ alkyl, -alkylsubstituted C₁₋₆ alkyl or-arylsubstituted C₁₋₆ alkyl;

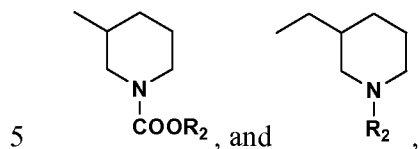
Y is selected from the group of -COOR₂, -C(O)NR₂SO₂R₃, -C(O)NHSO₂NR₂R₂,

20 -NR₂SO₂R₂, -SO₂NR₂R₂, -C₃₋₆ cycloalkyl-COOR₂, -C₂₋₆ alkenyl-COOR₂, -C₂₋₆ alkynyl-COOR₂, -C₁₋₆ alkyl-COOR₂, -NHC(O)(CH₂)_n-COOR₂, -SO₂NR₂C(O)R₂, -tetrazole, and -CONHOH,

wherein n=1-6;

25 R₃ is -C₁₋₆ alkyl or -alkylsubstituted C₁₋₆ alkyl;

R₄ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-C(OR₃)₂-C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-Q₁, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₁, aryl, heteroaryl, substituted heteroaryl, -COR₆, -COCOR₆, -SO₂R₇, -SO₂NR₂R₂,



wherein Q₁ is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF₃, -OR₂, -COOR₂, -NR₈R₉, -CONR₁₀R₁₁ and -SO₂R₇;

- 10 R₅ is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₁₀, -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

with the proviso that only one of R₄ or R₅ can be selected from the group of -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

- 15 or R₄ and R₅ are taken together with the adjacent N to form



R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆ cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -NR₁₃R₁₄, and -OR₁₅;

- 20

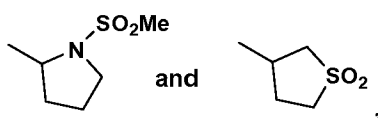
wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

- 25 R₇ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, aryl, and heteroaryl;

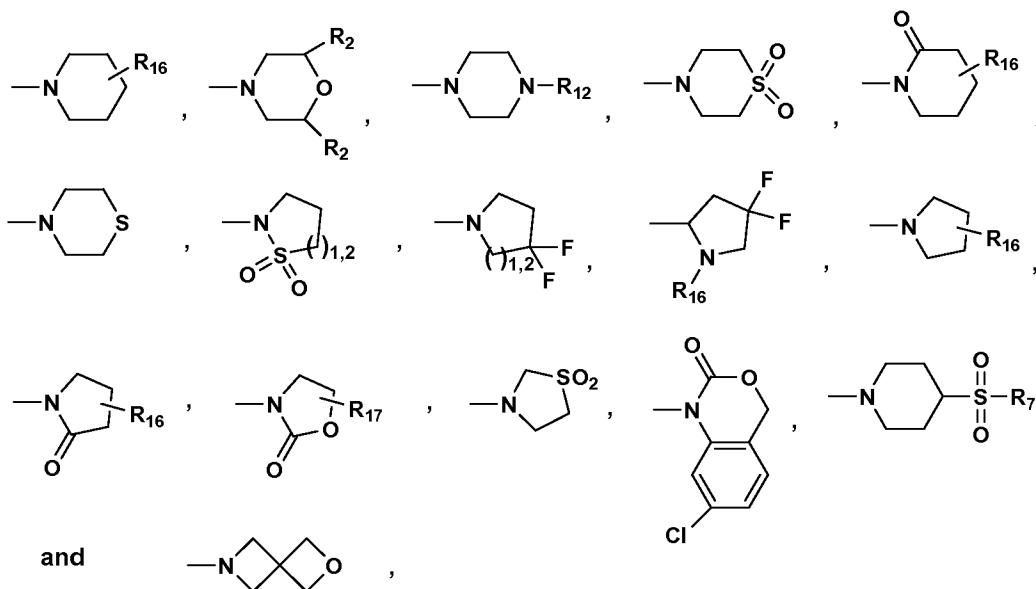
R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-

- 30 Q₂, and -COOR₃,

and R₈ and R₉ can also be independently selected from the group of



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

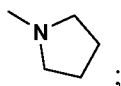


5

with the proviso that only one of R_8 or R_9 can be $-\text{COOR}_3$;

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

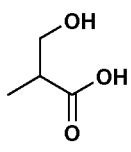
10 or R_{10} and R_{11} are taken together with the adjacent N to form a cycle such as



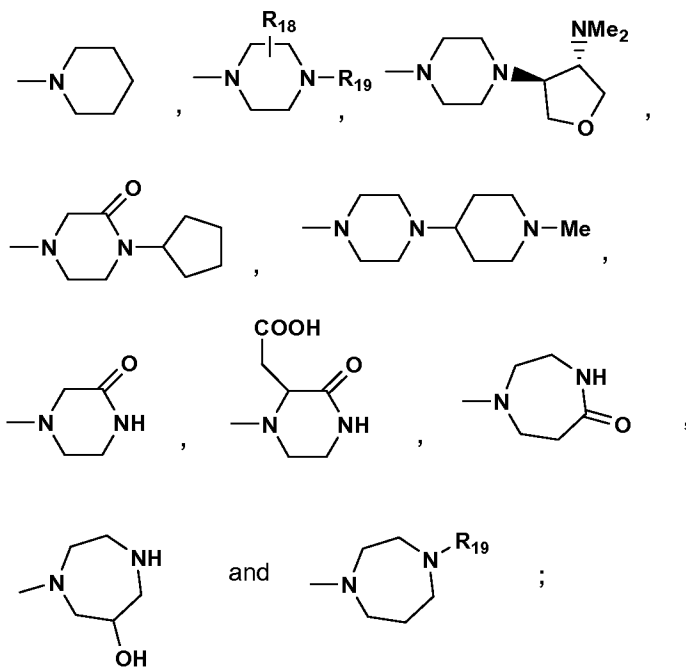
R_{12} is selected from the group of $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkyl-OH, $-\text{C}_{1-6}$ substituted alkyl, $-\text{C}_{3-6}$ cycloalkyl, $-\text{COR}_7$, $-\text{COONR}_{22}\text{R}_{23}$, $-\text{SOR}_7$, and $-\text{SONR}_{24}\text{R}_{25}$;

15

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



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



5

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

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

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

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

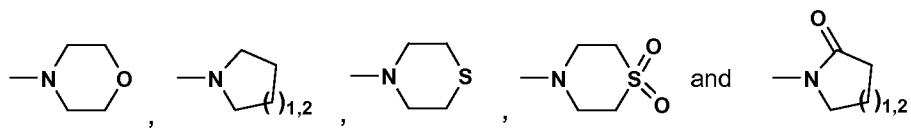
R_{18} is selected from the group of $-COOR_2$ and $-C_{1-6}$ alkyl- $COOR_2$;

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

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

R_{20} and R_{21} are independently selected from the group of $-H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ substituted alkyl- OR_2 , and $-COR_3$,

- 5 or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of

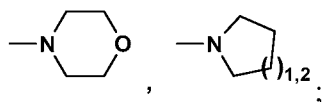


with the proviso that only one of R_{20} or R_{21} can be $-COR_3$;

10

R_{22} and R_{23} are independently selected from the group of H , $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, and $-C_{1-6}$ cycloalkyl,

or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



15

R_{24} and R_{25} are independently from the group of H , $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl- Q_5 , $-C_{1-6}$ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

and Q_5 is selected from the group of halogen and SO_2R_3 .

20

Even more preferred compounds include those wherein R_1 is isopropenyl.

More preferred compounds include those which are encompassed by Formula I. Of these, those wherein X is a phenyl ring are even more preferred. Even more preferred are compounds of Formula I wherein X is a phenyl ring and Y is in the para position.

25

Also preferred are compounds of Formula I wherein A is at least one member selected from the group of $-H$, $-OH$, $-halo$, $-C_{1-3}$ alkyl, and $-C_{1-3}$ alkoxy, wherein $-halo$ is selected from the group of $-Cl$, $-F$ and $-Br$, with $-F$ being more preferred. It is even more preferred that A is $-H$.

30

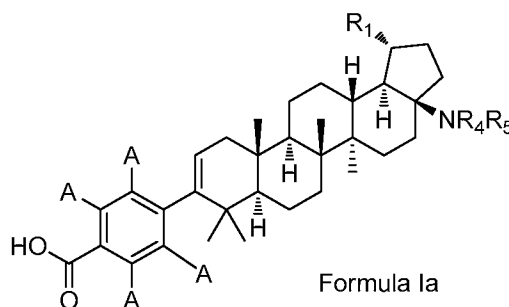
Also preferred are compounds of Formula I wherein Y is $-\text{COOR}_2$, and more preferably $-\text{COOH}$.

Also preferred are compounds wherein R_4 is selected from the group of $-\text{H}$,
 5 $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkyl- Q_1 , and $-\text{COR}_6$. Especially preferred are compounds wherein R_4 is $-\text{C}_{1-6}$ alkyl- Q_1 or $-\text{COR}_6$.

It is also preferred that R_5 is $-\text{H}$.

10 In addition, it is preferred that Q_1 is $-\text{NR}_8\text{R}_9$.

In another preferred embodiment there is provided a compound of Formula Ia below wherein X is a phenyl ring and Y is $-\text{COOH}$ in the para position:

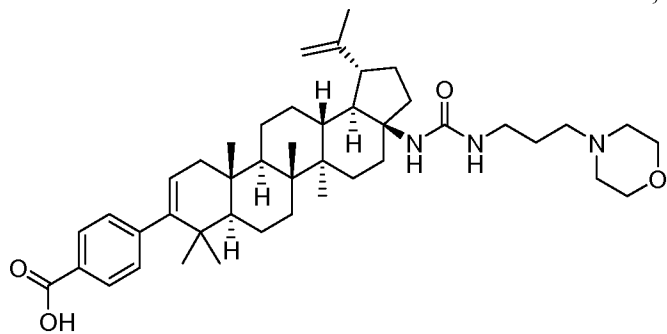
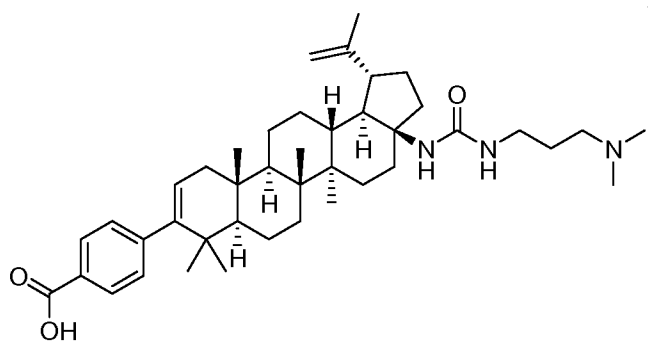
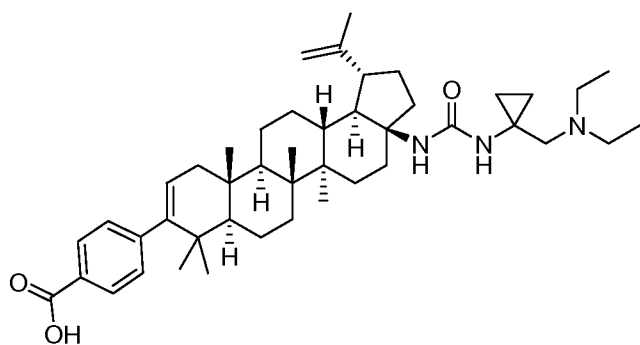
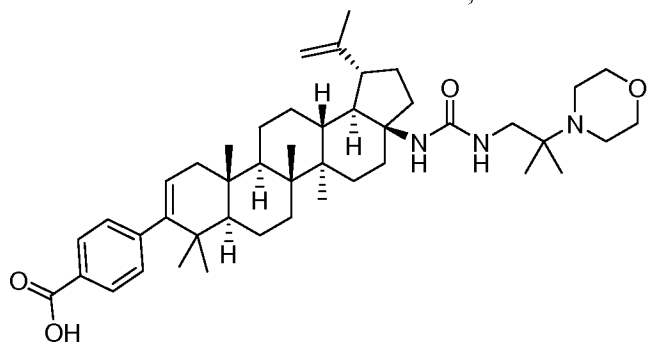
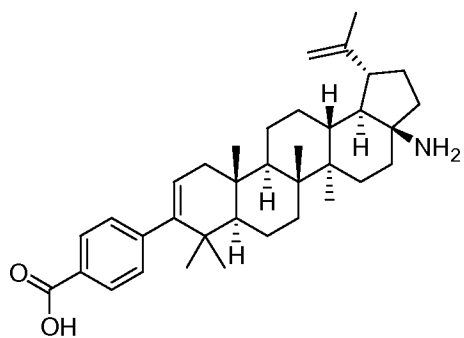


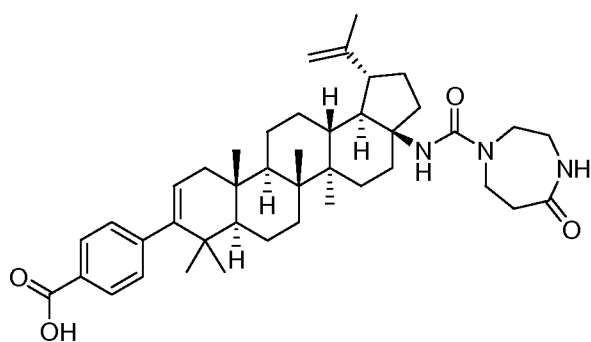
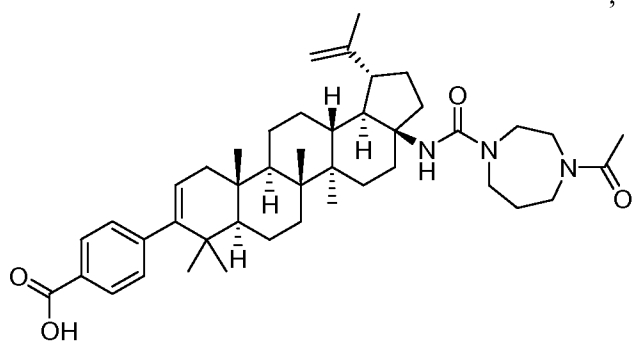
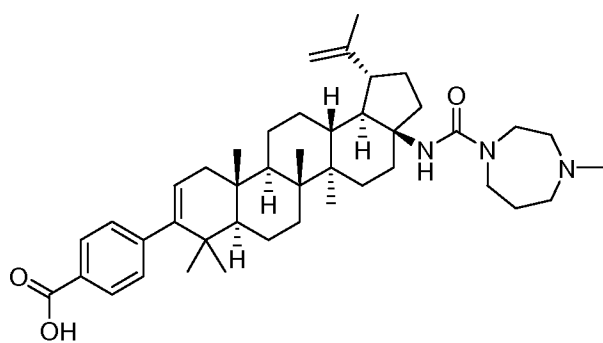
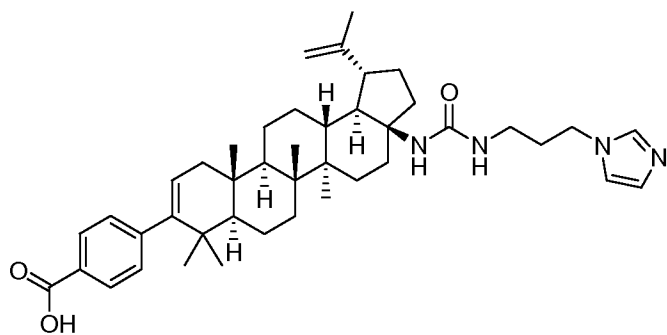
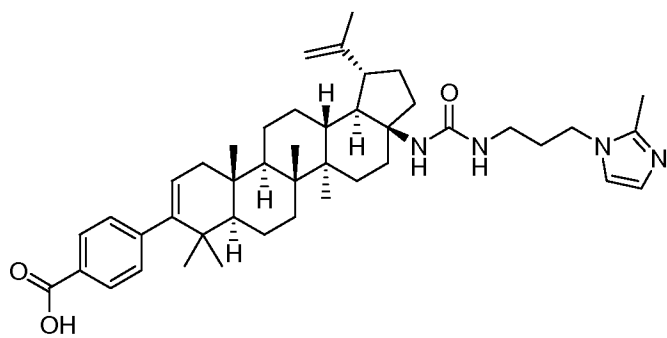
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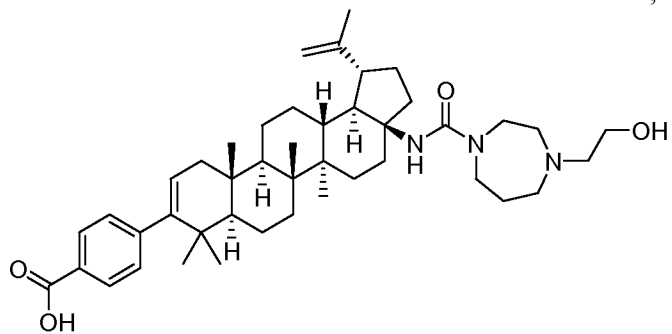
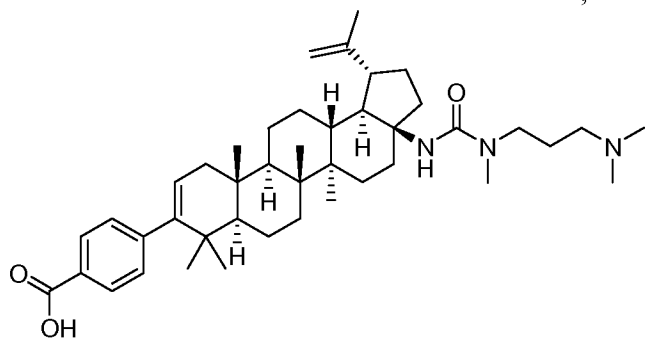
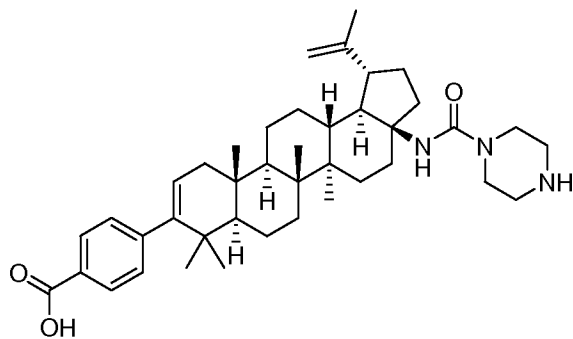
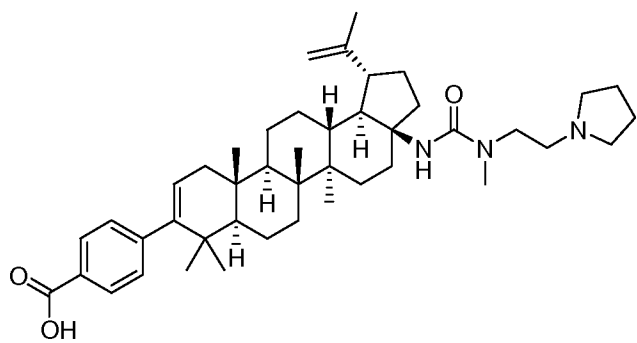
In this embodiment, it is also preferred that A is at least one member selected from the group of $-\text{H}$, $-\text{halo}$, $-\text{OH}$, $-\text{C}_{1-3}$ alkyl and $-\text{C}_{1-3}$ alkoxy. It is particularly preferred that A is at least one member selected from the group of $-\text{H}$, $-\text{fluoro}$, $-\text{chloro}$, $-\text{OH}$,
 20 $-\text{methyl}$ and $-\text{methoxy}$, with $-\text{H}$ being even more preferred.

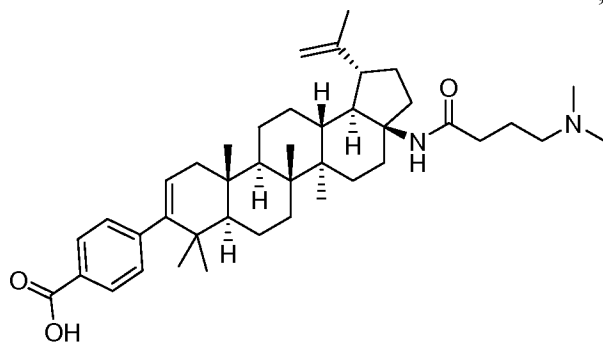
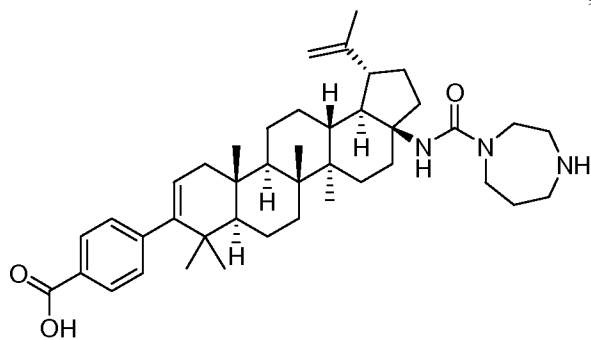
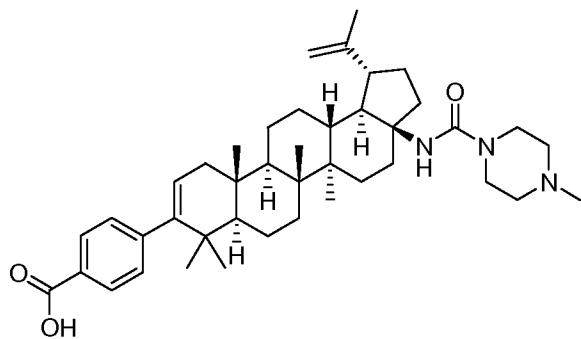
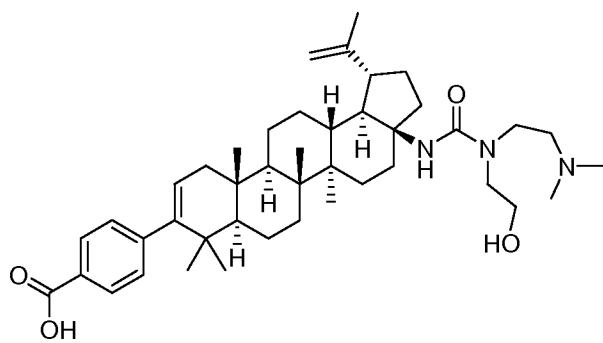
In addition, in a further embodiment of the invention compounds of Formula II are preferred, as are compounds of Formula III.

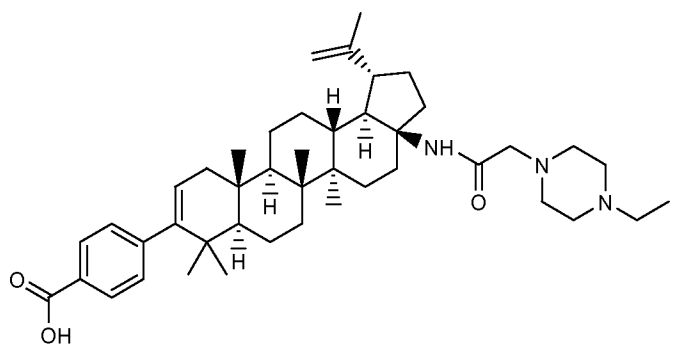
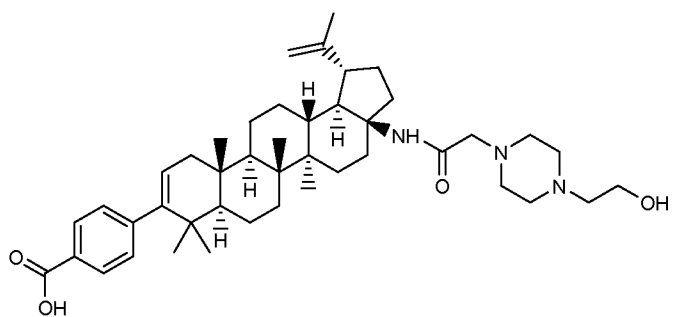
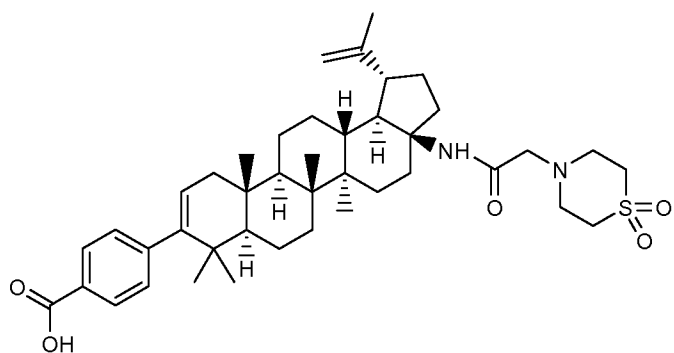
25 Other compounds, including pharmaceutically acceptable salts thereof, which are preferred as part of the invention include the following:



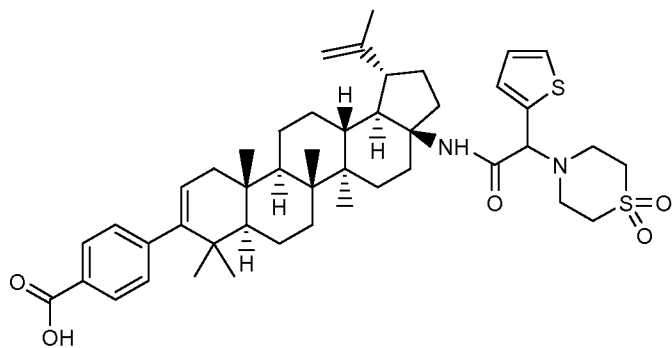
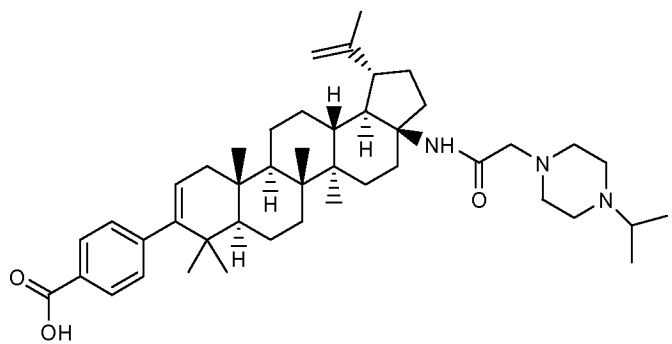
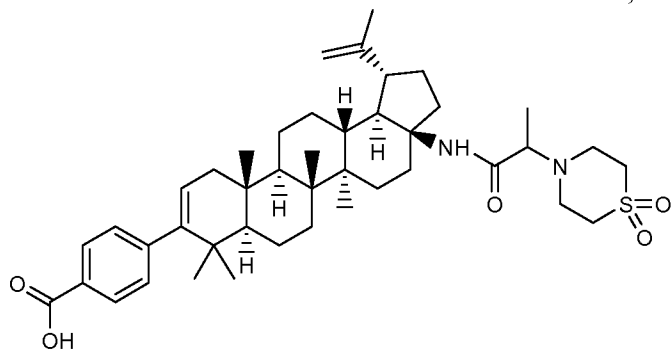
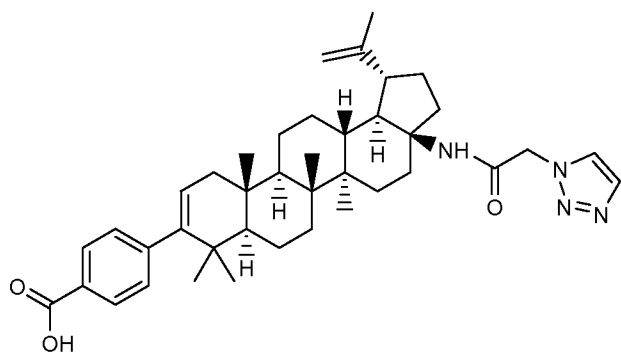


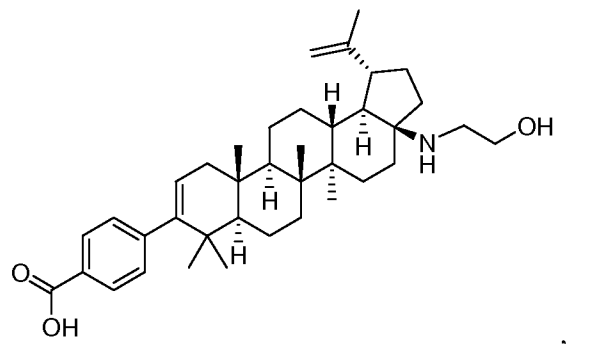
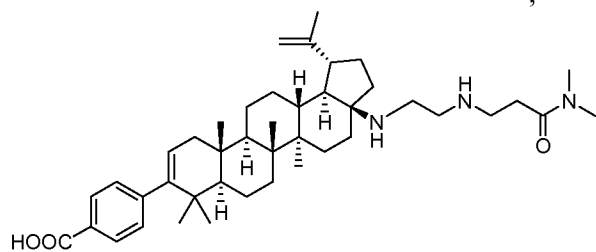
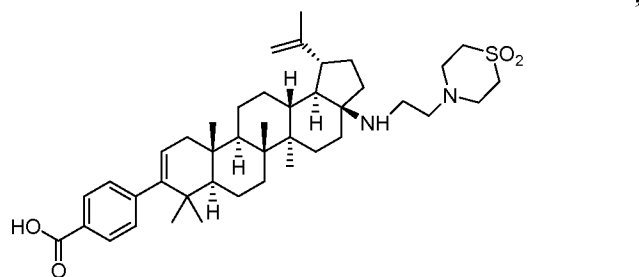
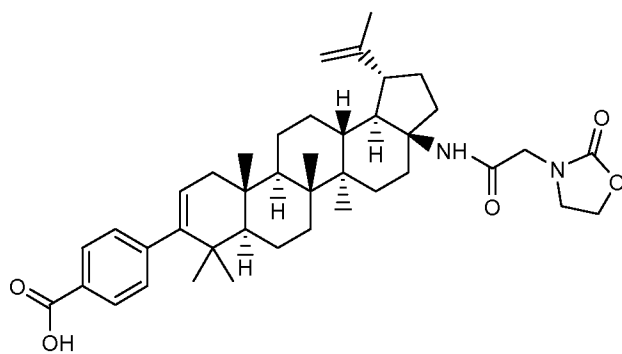


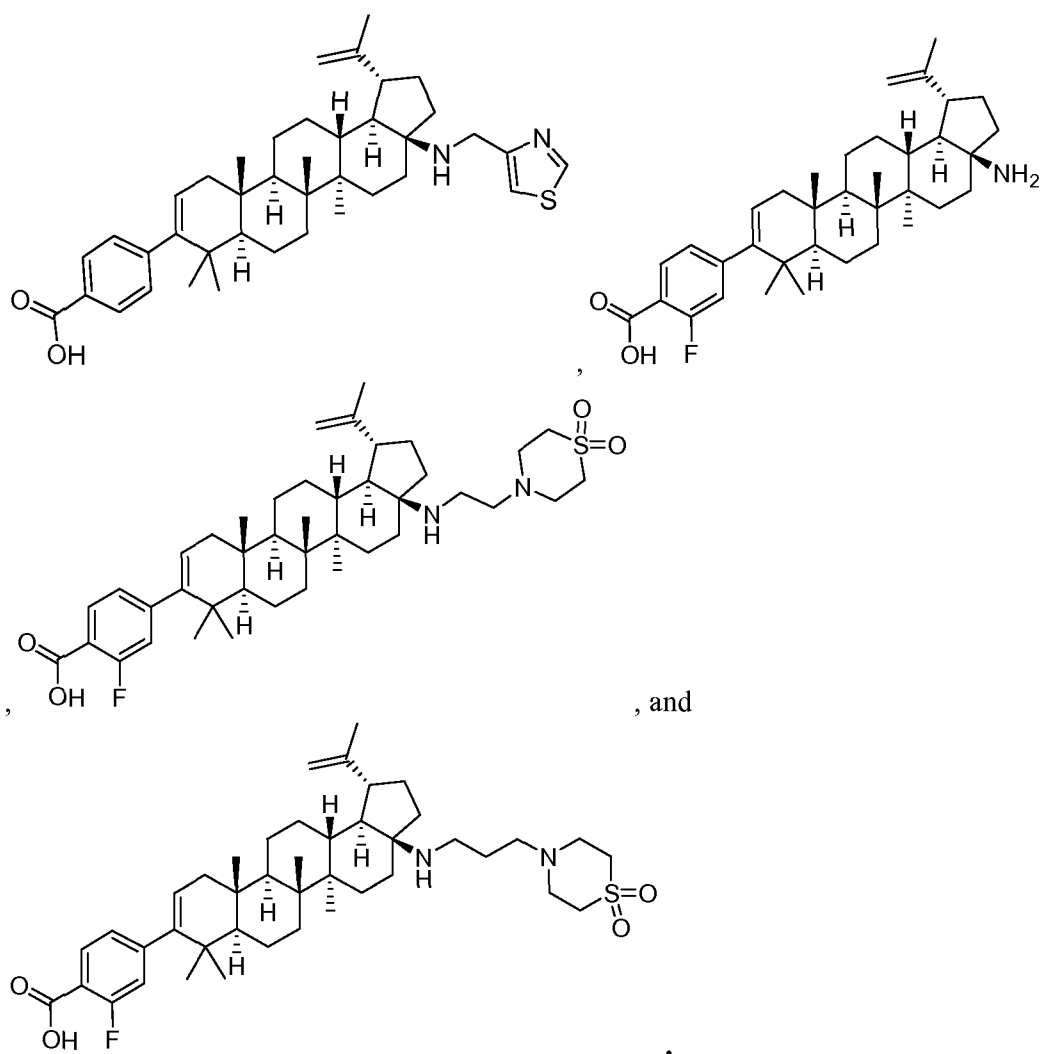




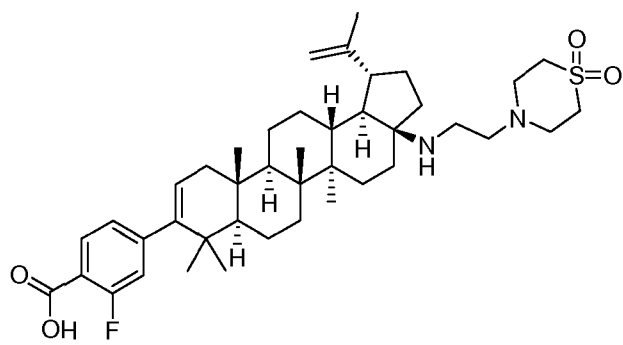
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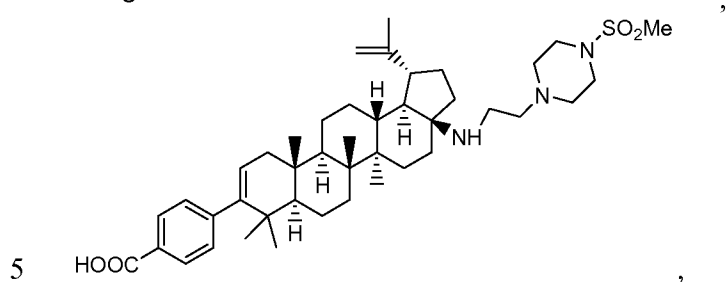
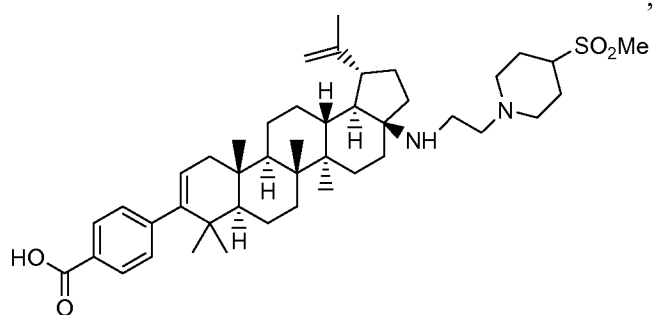
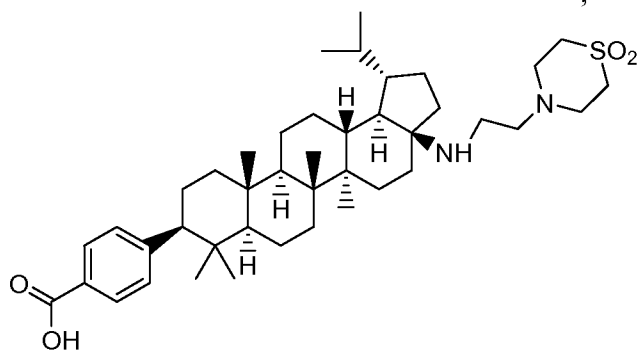
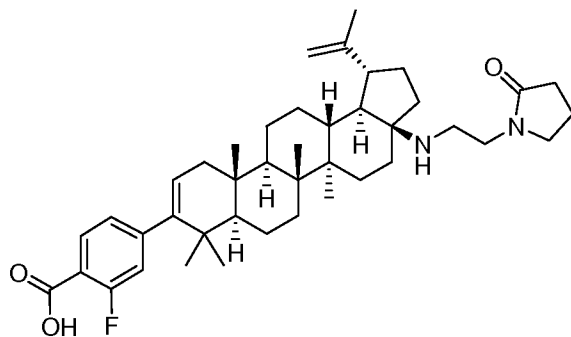
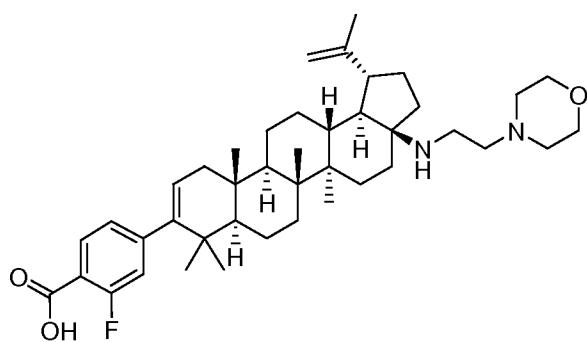


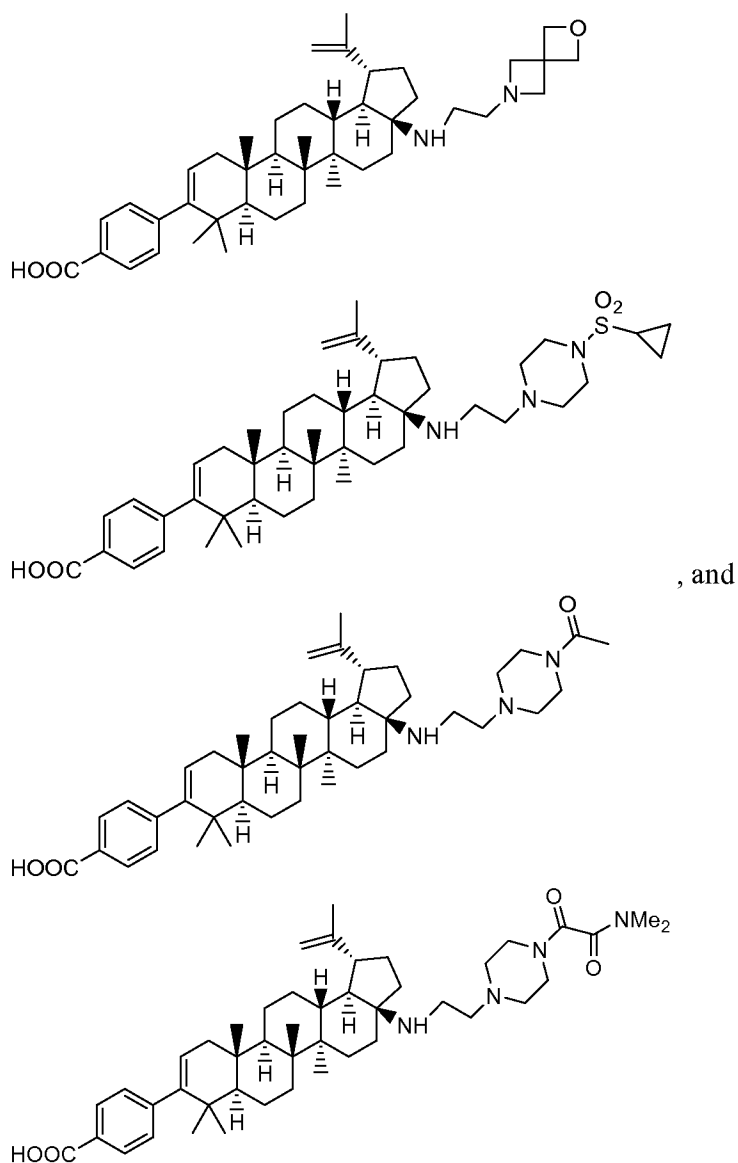




Also preferred are the following compounds, including pharmaceutically acceptable salts thereof:







5

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

15

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

5 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 the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied
10 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, ameliorating or healing diseases associated with HIV infection.

15 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
20 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
25 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.

30

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.

5 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.

15

Also contemplated herein are combinations of the compounds of Formulas I, II, and /or III 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:

20

ANTIVIRALS

	<i>Drug Name</i>	<i>Manufacturer</i>	<i>Indication</i>
5	097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse trans- criptase (RT) inhibitor)
10			
	Amprenavir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
15			
	Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
20	Acemannan	Carrington Labs (Irving, TX)	ARC
	Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC
25			
	AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
	AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
30			
	Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection ARC, PGL HIV positive, AIDS
35			
	Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
40			
	Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC

5	Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
	AR177	Aronex Pharm	HIV infection, AIDS, ARC
10	Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
15	BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
	CI-1012	Warner-Lambert	HIV-1 infection
20	Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
	Curdlan sulfate	AJI Pharma USA	HIV infection
25	Cytomegalovirus Immune globin	MedImmune	CMV retinitis
	Cytovene	Syntex	Sight threatening
30	Ganciclovir		CMV peripheral CMV retinitis
	Darunavir	Tibotec- J & J	HIV infection, AIDS, ARC (protease inhibitor)
35	Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
40	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
5	DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
10	Efavirenz (DMP 266, Sustiva [®]) (-)-6-Chloro-4-(S)- cyclopropylethynyl- 4(S)-trifluoro-	Bristol Myers Squibb	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
15	methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one, STOCRINE		
20	EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
	Etravirine	Tibotec/ J & J	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
25			
	Famciclovir	Smith Kline	herpes zoster, herpes simplex
30	GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
35	HBV097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
40			
	Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
45	Recombinant Human Interferon Beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC

	Interferon alfa-n3	Interferon Sciences	ARC, AIDS
5	Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
10	ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
	KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
15	Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
20	Lobucavir	Bristol-Myers Squibb	CMV infection
25	Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
	Nevirapine	Boehringer Ingelheim	HIV infection, AIDS, ARC (RT inhibitor)
30	Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
35	Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
40	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
5	RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
	Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
10	Saquinavir	Hoffmann- LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
15	Stavudine; d4T Didehydrodeoxy- Thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
20	Tipranavir	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)
	Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
25	Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
	VX-478	Vertex	HIV infection, AIDS, ARC
30	Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
35	Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
40	Tenofovir disoproxil, fumarate salt (Viread [®])	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
45	Emtriva [®] (Emtricitabine) (FTC)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)

5	Combivir [®]	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
10	Abacavir succinate (or Ziagen [®])	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
15	Reyataz [®] (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDS, protease inhibitor
20	Fuzeon [®] (Enfuvirtide or T-20)	Roche / Trimeris	HIV infection AIDS, viral Fusion inhibitor
25	Lexiva [®] (or Fosamprenavir calcium)	GSK/Vertex	HIV infection AIDS, viral protease inhibitor
30	Selzentry Maraviroc; (UK 427857)	Pfizer	HIV infection AIDS, (CCR5 antagonist, in development)
35	Trizivir [®]	GSK	HIV infection AIDS, (three drug combination)
40	Sch-417690 (vicriviroc)	Schering-Plough	HIV infection AIDS, (CCR5 antagonist, in development)
45	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)
5	Integrase Inhibitor GS917/JTK-303 Elvitegravir	Gilead/Japan Tobacco	HIV Infection AIDs in development
10	Triple drug combination Atripla [®]	Gilead/Bristol-Myers Squibb	Combination of Tenofovir disoproxil fumarate salt (Viread [®]), Emtriva [®] (Emtricitabine), and Sustiva [®] (Efavirenz)
15	Festinavir [®] 4'-ethynyl-d4T	Oncolys BioPharma BMS	HIV infection AIDs in development
20	CMX-157 Lipid conjugate of nucleotide tenofovir	Chimerix	HIV infection AIDs
25	GSK1349572 Integrase inhibitor	GSK	HIV infection AIDs

IMMUNOMODULATORS

30	<i>Drug Name</i>	<i>Manufacturer</i>	<i>Indication</i>
	AS-101	Wyeth-Ayerst	AIDS
	Bropirimine	Pharmacia Upjohn	Advanced AIDS
35	Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
40	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)
5	Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
10	Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
15	Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
20	HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
	IL-2	Cetus	AIDS, in combination w/AZT
	Interleukin-2	Hoffman-LaRoche	AIDS, ARC, HIV, in combination w/AZT
25	IL-2 Interleukin-2	Immunex	
	IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
30	Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
35	IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
	IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
40	Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
	Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS

	Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
5	MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
10	Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
	Remune	Immune Response Corp.	Immunotherapeutic
15	rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
20	rCD4-IgG hybrids		AIDS, ARC
	Recombinant Soluble Human CD4	Biogen	AIDS, ARC
25	Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
30	SK&F106528 Soluble T4	Smith Kline	HIV infection
	Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
35	Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

40	<i>Drug Name</i>	<i>Manufacturer</i>	<i>Indication</i>
	Clindamycin with	Pharmacia Upjohn	PCP

	Primaquine		
5	Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
	Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
10	Ornidyl Eflornithine	Merrell Dow	PCP
15	Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
	Trimethoprim		Antibacterial
	Trimethoprim/sulfa		Antibacterial
20	Piritrexim	Burroughs Wellcome	PCP treatment
25	Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
	Spiramycin	Rhone-Poulenc diarrhea	Cryptosporidial
30	Intraconazole- R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
	Trimetrexate	Warner-Lambert	PCP
35	Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
40	Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
	Recombinant Human	Serono	AIDS-related

	Growth Hormone		wasting, cachexia
5	Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
	Testosterone	Alza, Smith Kline	AIDS-related wasting
10	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 2005/0209246.

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 600mg 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.

15

In such combinations the compound 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).

20

GENERAL CHEMISTRY (METHODS OF SYNTHESIS)

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

25

Abbreviations

30

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:

- Bz₂O = benzoic anhydride
- 5 TBTU = O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
- HATU = 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium
hexafluorophosphate methanaminium
- 10 DCE = dichloroethane
- DCM = dichloromethane
- CDI = carbonyl diimidazole
- 15 prep. HPLC = preparative high performance liquid chromatography
- rt = room temperature
- DIPEA = diisopropylethylamine
- 20 DMAP = 4-dimethylaminopyridine
- DMSO = dimethylsulfoxide
- 25 THF = tetrahydrofuran
- KHMDS = potassium bis(trimethylsilyl)amide
- min = minute(s)
- 30 h = hour(s)
- sat. = saturated
- 35 TEA = triethylamine
- EtOAc = ethyl acetate
- TFA = trifluoroacetic acid
- 40 PCC = pyridinium chlorochromate
- TLC = thin layer chromatography
- 45 Tf₂NPh = (trifluoromethylsulfonyl)methanesulfonamide
- dioxane = 1,4-dioxane
- PG = protective group
- 50

atm = atmosphere(s)

mol = mole(s)

5 mmol= milimole(s)

mg = milligram(s)

μg = microgram(s)

10

μl = microliter(s)

μm = micrometer(s)

15

mm= millimeter(s)

HOAc= acetic acid

MeOH= methanol

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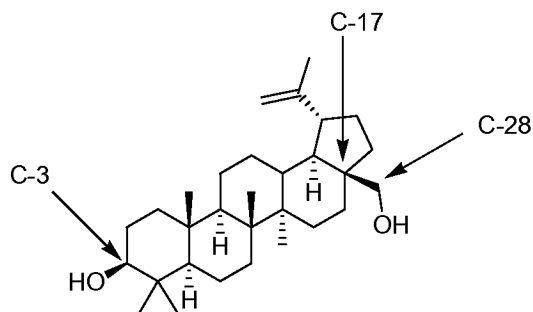
DMF= *N,N*-dimethylformamide

TBAF= tetrabutylammonium fluoride

TBDMSCl= *tert*-butyldimethylsilyl chloride

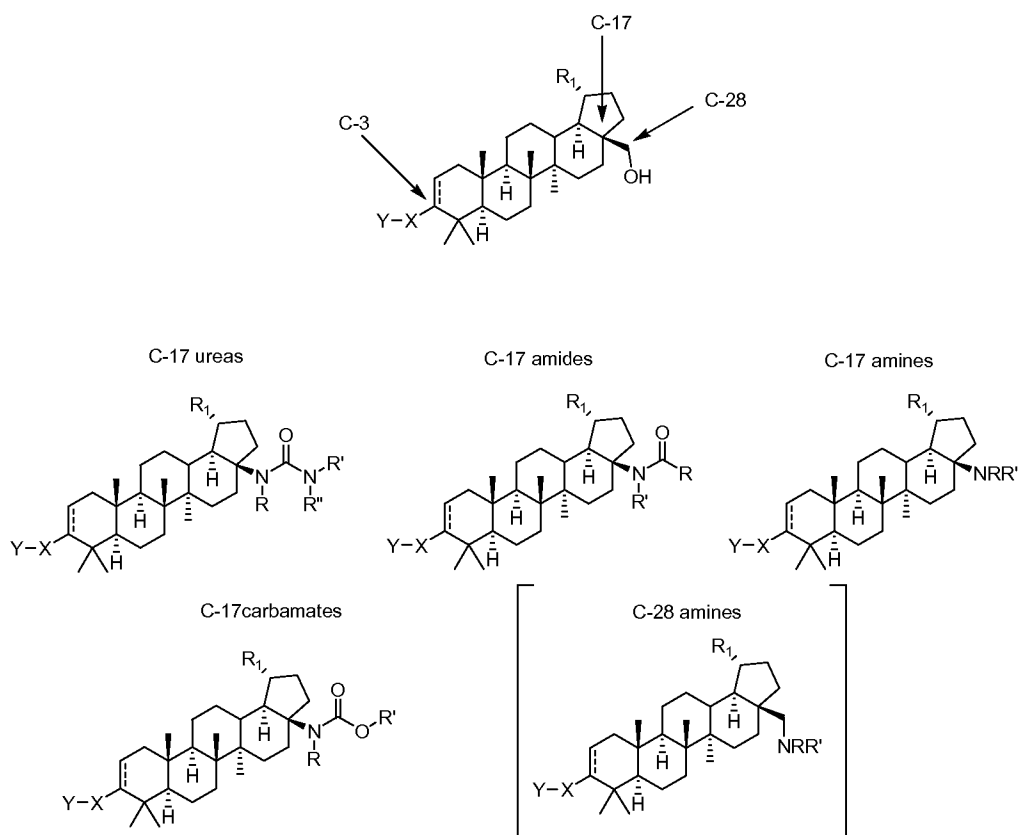
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The terms “C-3” and “C-28” refer to certain positions of a triterpene core as numbered in accordance with IUPAC rules (positions depicted below with respect to an illustrative triterpene: betulin):



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



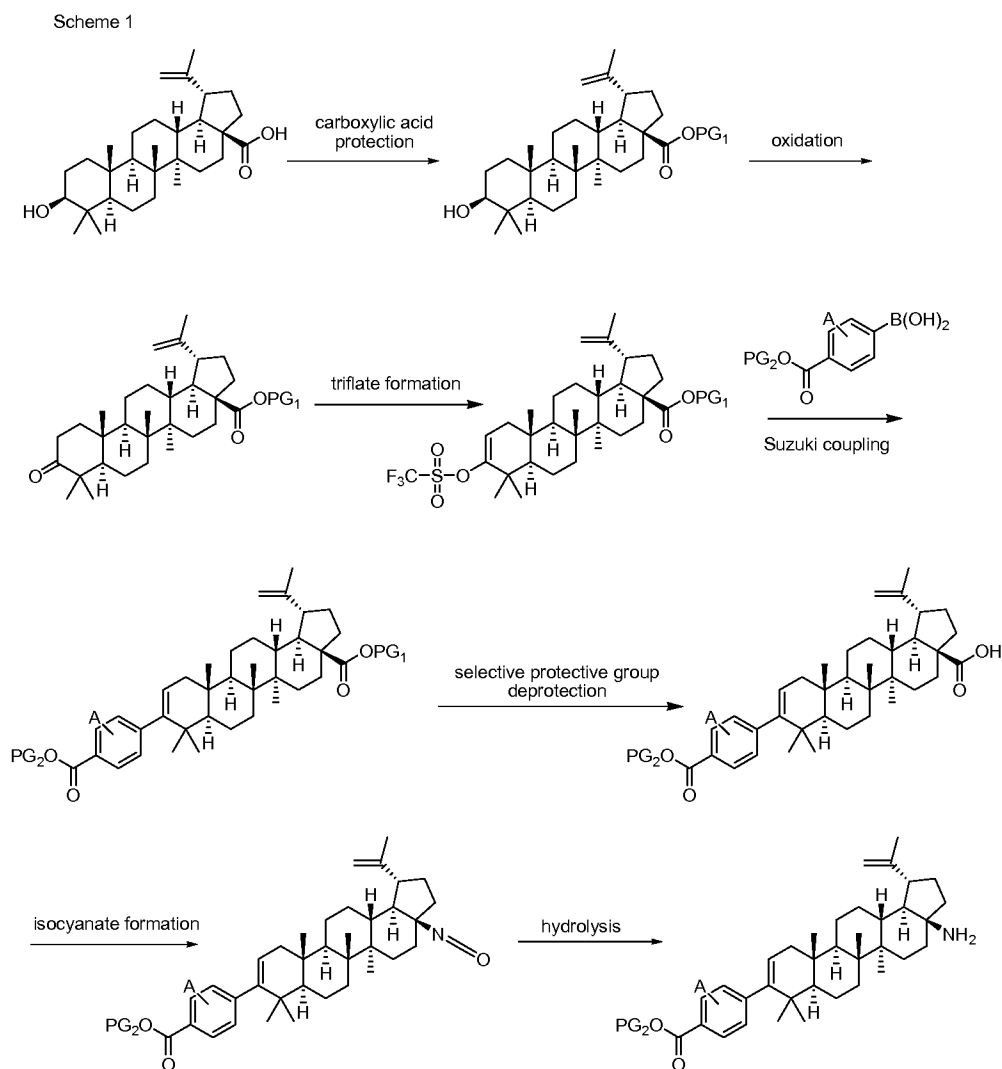
Preparation of Compounds of Formulas I, II, and III General Chemistry Schemes:

Preparation of Compounds of Formulas I, II and III General Chemistry Schemes:

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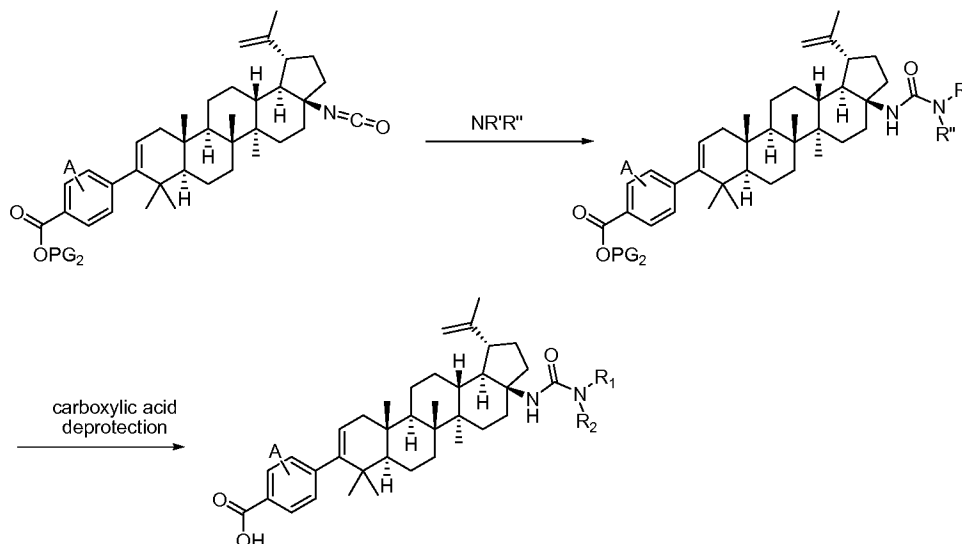
Compounds of Formula I can be prepared from commercially available (Aldrich, others) betulinic acid by chemistry described in the following schemes. Compounds of Formula II and III are described thereafter.

10 General reaction schemes are set forth as follows:



Scheme 1 describes the preparation of the key intermediate C-17 primary amine from betulinic acid. The carboxylic acid present in betulinic acid was protected with a suitable protective group. Standard oxidation (i.e. PCC, Dess-Martin) of the C-3 hydroxyl group produces the C-3 ketone which is then converted into the triflate using conditions known to those skilled in the art. Palladium-catalyzed cross coupling with a boronic acid derivative (Stille coupling using stannanes can also be used) afforded the corresponding C-3-modified betulinic acid derivatives. The C-28 carboxylic ester was then selectively deprotected and submitted to Curtius rearrangement conditions to afford the C-17 primary amine. This reaction can be carried out in one single step or stepwise via isolation of the isocyanate intermediate, as shown in Scheme 1.

Scheme 2

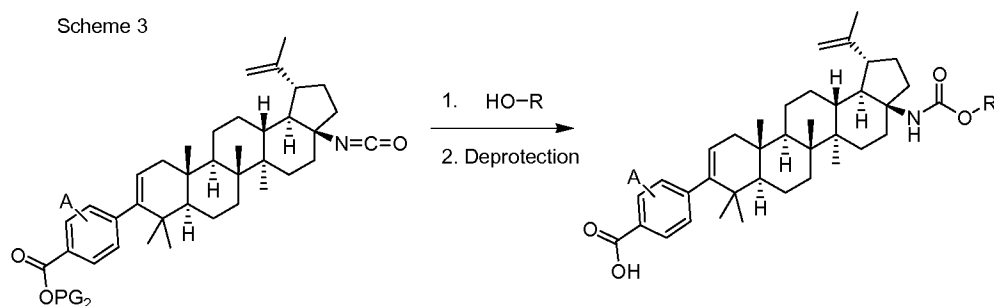


The isocyanate can be further modified to prepare ureas as shown in Scheme 2.

Addition of an amine to a solution of the isocyanate in a solvent such as THF or dioxane in the presence of Hunig's base or TEA at room temperature or heating if necessary, affords the corresponding C-17 urea. Hydrolysis of the benzoic ester affords the benzoic acid derivative.

5

Scheme 3

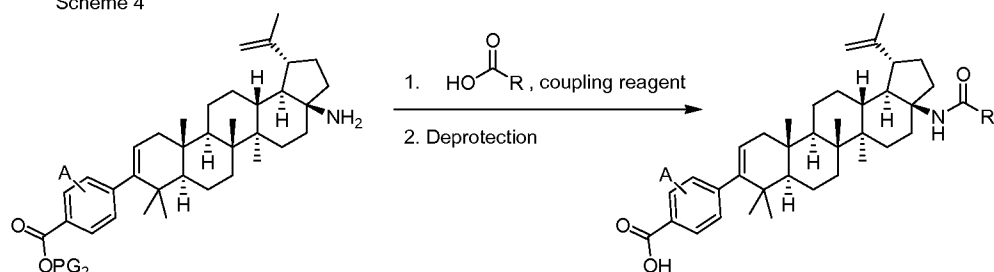


Similarly, carbamates can be prepared by adding an alcohol to the isocyanate in a solution of THF or dioxane in the presence of a base such as sodium hydride at room temperature or heating when necessary followed by hydrolysis of the carboxylic ester. The deprotection may also happen under the conditions of the first reaction, so no additional step may be needed.

The C-17 primary amine can be further modified using standard methods, known to those skill in the art. Some examples are shown in the following schemes.

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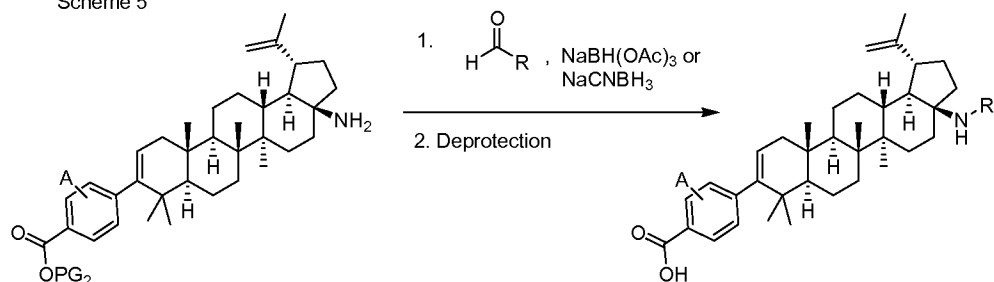
Scheme 4



C-17 amides can be prepared by reacting a carboxylic acid with the C-17 primary amine in the presence of an adequate coupling reagent such as HATU, DCC, and others known to those skilled in the art, in the presence of a base such as Hunig's base, TEA, etc., in the appropriate solvent (DCM, THF, DMF, etc.). Hydrolysis of the carboxylic ester affords the benzoic acid. Alternatively, some amides can be prepared by treating the C-17 primary amine with the corresponding carboxylic acid chloride reagent instead of an acid. Similarly, sulfonamides can be prepared from the C-17 primary amine by using a sulfonyl chloride as the sulfonylating agent.

10

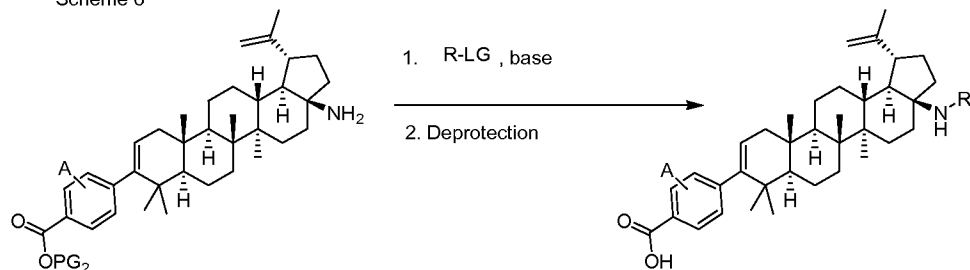
Scheme 5



The C-17 primary amine can be treated with an aldehyde under reductive amination conditions (e.g. $\text{NaBH}(\text{OAc})_3$) in the presence of AcOH/NaOAc or $\text{Ti}(\text{OPr})_4$ in a solvent such as THF, 1,4-dioxane, DCE or DCM) to afford C-17 secondary amines. Hydrolysis of the carboxylic ester renders the benzoic acid compound.

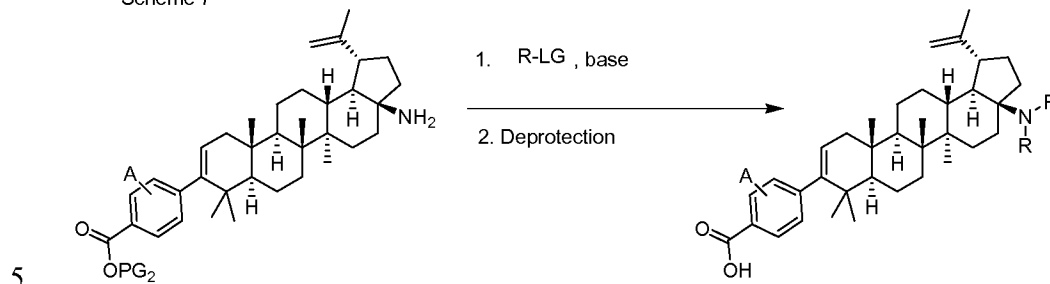
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Scheme 6



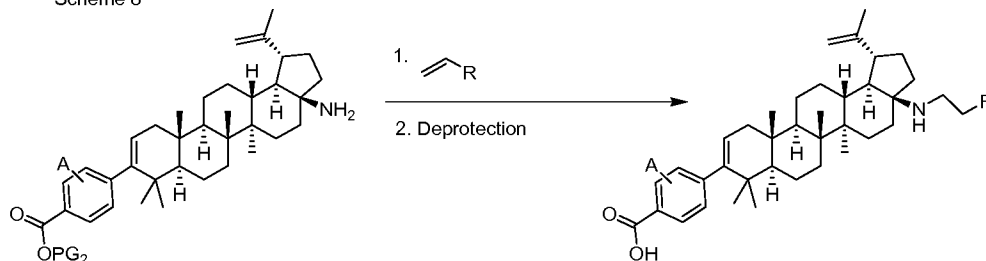
Some C-17 amines can be prepared by alkylation of the C-17 primary amine with an alkylating agent (R-LG), where LG is a leaving group such as, but not limited to Br, Cl, I, mesylate, tosylate or triflate in the presence of a base. Heating may be needed in some cases. Hydrolysis of the carboxylic ester renders the benzoic acid product.

Scheme 7



In some cases, by prolonging the reaction times and heating the reaction mixture, the dialkylated product can also be formed.

Scheme 8



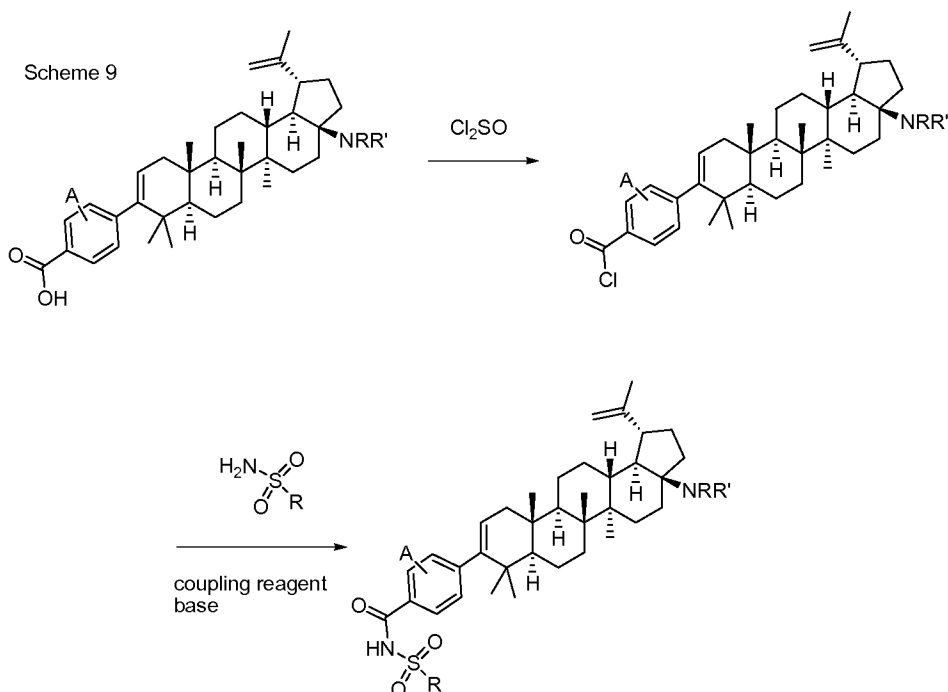
- 10 Alternatively, some C-17 amines can be prepared by 1,4-addition to Michael acceptors followed by hydrolysis of the ester.

Substituents R, R' and R'' may contain functional groups (i.e. COOH, COOR, OH, NHR) that can be further modified by methods known to those skilled in the art. The

- 15 modification can be carried out before or after the final deprotection of the carboxylic acid is performed depending on the nature of the functional group.

Alternatively, the C-17 secondary amine can be further modified (i.e. alkylated, acylated, sulfonylated, etc.) using some of the methods described above or other

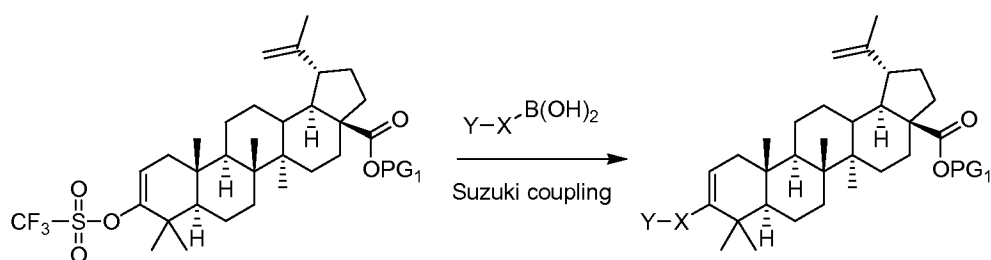
- 20 standard methods known to those skilled in the art. Saturation of the isopropenyl group can be accomplished by hydrogenation under standard conditions of the final products.



The benzoic acid can be further modified by methods known to those skilled in the art. An example of such modifications is shown in scheme 9: The free benzoic acid
 5 can be converted into the corresponding acid chloride and then treated with the corresponding nucleophile, for example a sulfonyl amide or urea sulfamide, in the presence of a base to afford a sulfonyl amide or acylsulfamide derivative.

Compounds of formula I where the modification in the C-3 position differs from
 10 benzoic acid can be prepared by selecting the corresponding boronic acid in the palladium-catalyzed cross coupling step shown in Scheme 1 (Scheme 10). Then the C-28 position can be modified using the chemistry methods described in the above schemes to obtain the corresponding C-17 amino derivatives.

Scheme 10



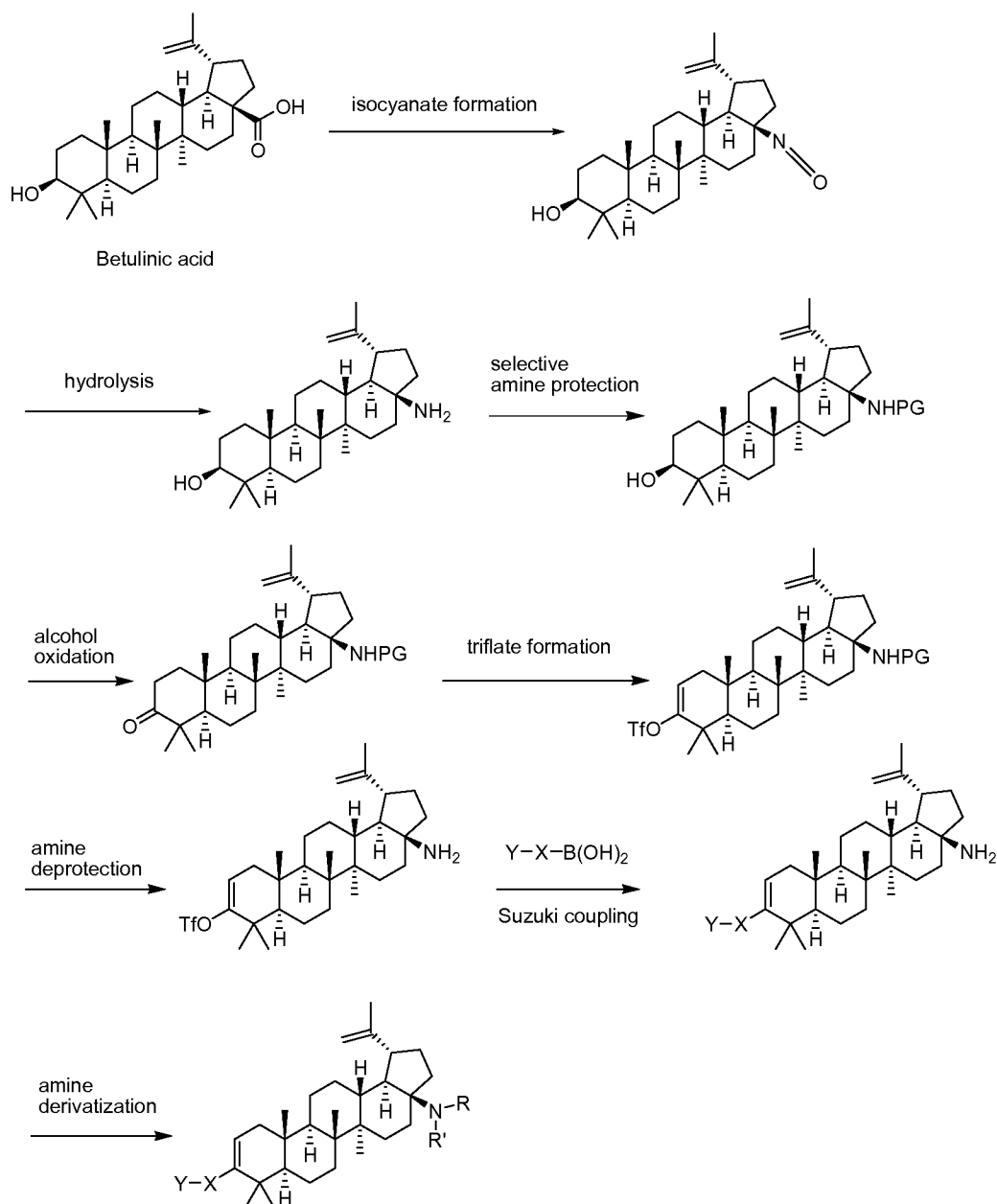
15

Alternatively, compounds of formula I can be prepared from betulinic acid as described in Scheme 11. Curtius rearrangement of betulinic acid can be accomplished without protection of the C-3 hydroxyl group to render the C-17 isocyanate which upon acid hydrolysis affords the C-17 amine. The C-17 amine is then selectively
5 protected with an amine protective group (i.e F-moc, Boc) to then perform the oxidation of the C-3 hydroxy group to a ketone under standard conditions (i.e. PCC, Dess-Martin reagent, etc). Conversion of the ketone into its triflate can be accomplished by methods known to those skilled in the art. The protective group in the amino group is then taken off to produce the C-17 unsubstituted amine.
10 Installation of the C-3 moiety is accomplished via Suzuki coupling of the triflate with the corresponding boronic acid as described above. The C-17 amino group can then be derivatized as shown above in previous schemes (alkylation, acylation, etc).

15

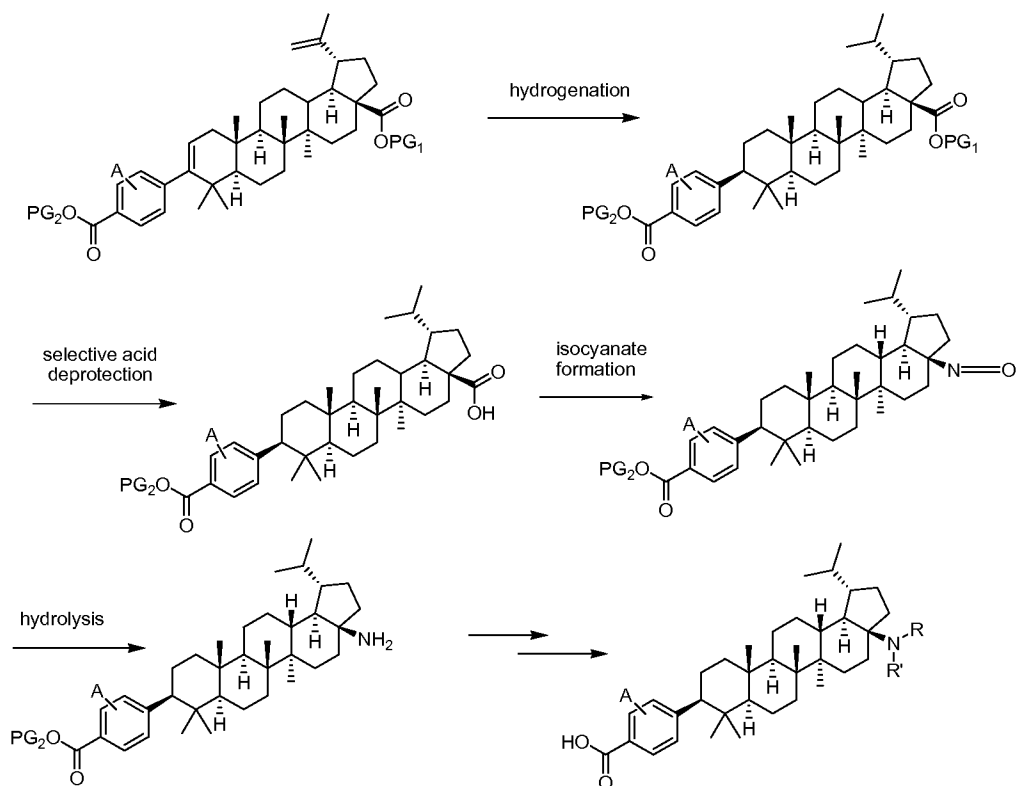
20

Scheme 11



Compounds of formula II can be prepared using the chemistry methods described above for compounds of formula I, with one extra step which consists of saturation of the double bonds, as shown below in Scheme 12:

Scheme 12



Compounds of formula III can be prepared in the same manner described above for compounds of formula I and II using oleanolic or ursolic acid as starting materials

5 instead of betulinic acid.

EXAMPLES

The following examples illustrate typical syntheses of the compounds of

10 Formulas I, II and III 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

15 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). ¹H 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 δ TMS = 0. The following internal references were used for the residual protons in the following solvents: CDCl₃ (δ _H 7.26), CD₃OD (δ _H 3.30), Acetic-d₄ (*Acetic Acid d₄*) (δ _H 11.6, 2.07), DMSO mix or DMSO-D₆-CDCl₃ (δ _H 2.50 and 8.25) (ratio 75%:25%), and DMSO-D₆ (δ _H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (*J*) is in Hertz. All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

LC/MS methods:

Method 1

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 4 mL / min
Wavelength = 220 nm
Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate
Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate
Column = Phenomenex Luna C18, 5 μ m, 3.0 x 50 mm

Method 2

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 μ m, 2.0 x 30 mm

Method 3

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

Flow Rate = 4 mL / min

5 Wavelength = 220 nm

Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate

Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate

Column = Waters Xbridge C18, 5 μ m, 4.6 x 50 mm

10 Method 4

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

Flow Rate = 0.8 mL / min

Wavelength = 220 nm

15 Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate

Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate

Column = Waters Xbridge C18, 3.5 μ m, 2.1 x 50 mm

Method 5

20

Start%B = 15, Final%B = 100 over 2 minute gradient, hold at 100%B

Flow Rate = 1 mL / min

Wavelength = 220 nm

Solvent A = 95% water, 5% acetonitrile, 10 mM ammonium acetate

25 Solvent B = 5% water, 95% acetonitrile, 10 mM ammonium acetate

Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

Method 6

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

Flow Rate = 1 ml/min

Wavelength = 220 nm

Solvent A = 95% water, 5% acetonitrile, 10mM ammonium acetate

Solvent B = 5% water, 95% acetonitrile, 10mM ammonium acetate

35 Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

Method 7

Start%B = 25, Final%B = 100 over 2 minute gradient, hold at 100%B

Flow Rate = 1 ml/min

Wavelength = 220 nm

Solvent A = 95% water, 5% acetonitrile, 10mM ammonium acetate

5 Solvent B = 5% water, 95% acetonitrile, 10mM ammonium acetate

Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

Method 8

Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B

10 Flow Rate = 5 ml/min

Wavelength = 220 nm

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

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

Column = Phenomenex Luna C18, 10 μ m 3.0 x 50 mm

15

Method 9

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

Flow Rate = 1 ml/min

Wavelength = 220 nm

20 Solvent A = 95% water, 5% acetonitrile, 10 mM ammonium acetate

Solvent B = 5% water, 95% acetonitrile, 10 mM ammonium acetate

Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

Method 10

25 Start%B = 0, 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, 10 mM ammonium acetate

Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate

30 Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

Method 11

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

Flow Rate = 1 mL / min

Wavelength = 220 nm

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

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

- 5 Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

Method 12

Start%B = 30, Final%B = 100 over 1 minute gradient

Flow Rate = 0.8 mL / min

- 10 Wavelength = 220 nm

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

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

Column = Xbridge Phenyl 2.1 x 50 mm 2.5 μ m

- 15 Method 13

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

Flow Rate = 0.8 mL / min

Wavelength = 254 nm

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

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

Column = Xbridge Phenyl 2.1 x 50 mm 2.5 μ m

Method 14

Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B

- 25 Flow Rate = 1 mL / min

Wavelength = 220 nm

Solvent A = 95% water, 5% acetonitrile, 10 mM ammonium acetate

Solvent B = 5% water, 95% acetonitrile, 10 mM ammonium acetate

Column = Waters BEH C18, 1.7 μ m, 2.0 x 50 mm

- 30

Method 15

Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B

Flow Rate = 0.5 mL / min

Wavelength = 220 nm

Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate

Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate

Column = Waters BEH C18, 1.7 μ m, 2.0 x 50 mm

5

Method 16

Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B

Flow Rate = 1 mL / min

10 Wavelength = 220 nm

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

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

Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

15 Method 17

Start%B = 10%, Final%B = 100 over 1 minute gradient, hold at 100%B

Flow Rate = 0.8 mL / min

Wavelength = 220 nm

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

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

Column = Phenomenex-luna , 2.0 x 30 mm, 3.0 μ m

Prep HPLC methods:

25

Prep HPLC Method 1

Start%B = 35, Final%B = 100 over 10 minute gradient, hold at 100%B for 8 minutes

Flow Rate = 100 mL / min

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

30 Solvent B = 10% water, 90% acetonitrile, 0.1% TFA

Column = Phenomenex Luna C8(2), 10 μ m, 50 x 250 mm (100A)

Prep HPLC Method 2

Start%B = 15, Final%B = 100 over 12 minute gradient, hold at 100%B for 6 minutes

35 Flow Rate = 50 mL / min

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

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

Column = Waters Sunfire C18, 5 μ m, 30 x 100 mm

5 Prep HPLC Method 3

Start%B = 20, Final%B = 100 over 8 minute gradient, hold at 100%B for 10 minutes

Flow Rate = 50 mL / min

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

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

10 Column = Waters Sunfire C18, 5 μ m, 30 x 100 mm

Prep HPLC Method 4

Start%B = 20, Final%B = 100 over 15 minute gradient, hold at 100%B for 8 minutes

Flow Rate = 100 mL / min

15 Solvent A = 90% water, 10% acetonitrile, 0.1% TFA

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

Column = Phenomenex Luna C8(2), 10 μ m, 50 x 250 mm (100A)

Prep HPLC Method 5:

20 Start%B = 15, Final%B = 100 over 20 minute gradient, hold at 100%B for 4 minutes

Flow Rate = 50 mL / min

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

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

Column = Waters Sunfire C18, 5 μ m, 30 x 100 mm

25

Prep HPLC Method 6

Start%B = 30, Final%B = 100 over 20 minute gradient, hold at 100%B for 6 minutes

Flow Rate = 40 mL / min

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

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

Column = Phenomenex Luna C18(2), 5 μ m, 30 x 100 mm

Prep HPLC Method 7

Start%B = 0, Final%B = 100 over 30 minute gradient, hold at 100%B for 8 minutes

Flow Rate = 50 mL / min

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

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

- 5 Column = Waters Xbridge Phenyl, 5 μ m, 30 x 100 mm

Prep HPLC Method 8

Start%B = 0, Final%B = 100 over 15 minute gradient, hold at 100%B for 10 minutes

Flow Rate = 50 mL / min

- 10 Solvent A = 90% water, 10% acetonitrile, 0.1% TFA

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

Column = Waters Xbridge Phenyl, 5 μ m, 30 x 100 mm

Prep HPLC Method 9

- 15 Start%B = 30, Final%B = 100 over 20 minute gradient, hold at 100%B for 10 minutes

Flow Rate = 50 mL / min

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

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

Column = Waters Sunfire C18, 5 μ m, 30 x 100 mm

20

Prep HPLC Method 10

Start%B = 0, Final%B = 100 over 20 minute gradient, hold at 100%B for 4 minutes

Flow Rate = 50 mL / min

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

- 25 Solvent B = 10% water, 90% acetonitrile, 0.1% TFA

Column = Waters Xbridge Phenyl, 5 μ m, 30 x 100 mm

Prep HPLC Method 11

Start % B = 20, Final % B = 100 over 10 min gradient, hold at 100% B for 15 min

- 30 Flow Rate = 50 ml/min

Wavelength = 220

Solvent Pair = Water - Methanol- TFA

Solvent A = 90% Water -10% Methanol-0.1% TFA

Solvent B = 10% Water -90% Methanol-0.1% TFA

Column = Waters Sunfire C18, 5 μ m, 30 x 150 mm

Analytical HPLC Methods:

5

Analytical HPLC Method 1

Start % B = 10

Final % B = 100

Gradient Time = 15 min

10 Flow Rate = 1 ml/min

Wavelength1 = 220

Wavelength2 = 254

Solvent A = 10mM amm. bicarb (pH=9.5)/95%water/5%methanol

Solvent B = 10mM amm. bicarb (pH=9.5)/5%water/95%methanol

15 Column = Xbridge Phenyl 3.5 μ m, 3.0x150mm

Analytical HPLC Method 2

Start % B = 10

Final % B = 100

20 Gradient Time = 15 min

Flow Rate = 1 ml/min

Wavelength1 = 220

Wavelength2 = 254

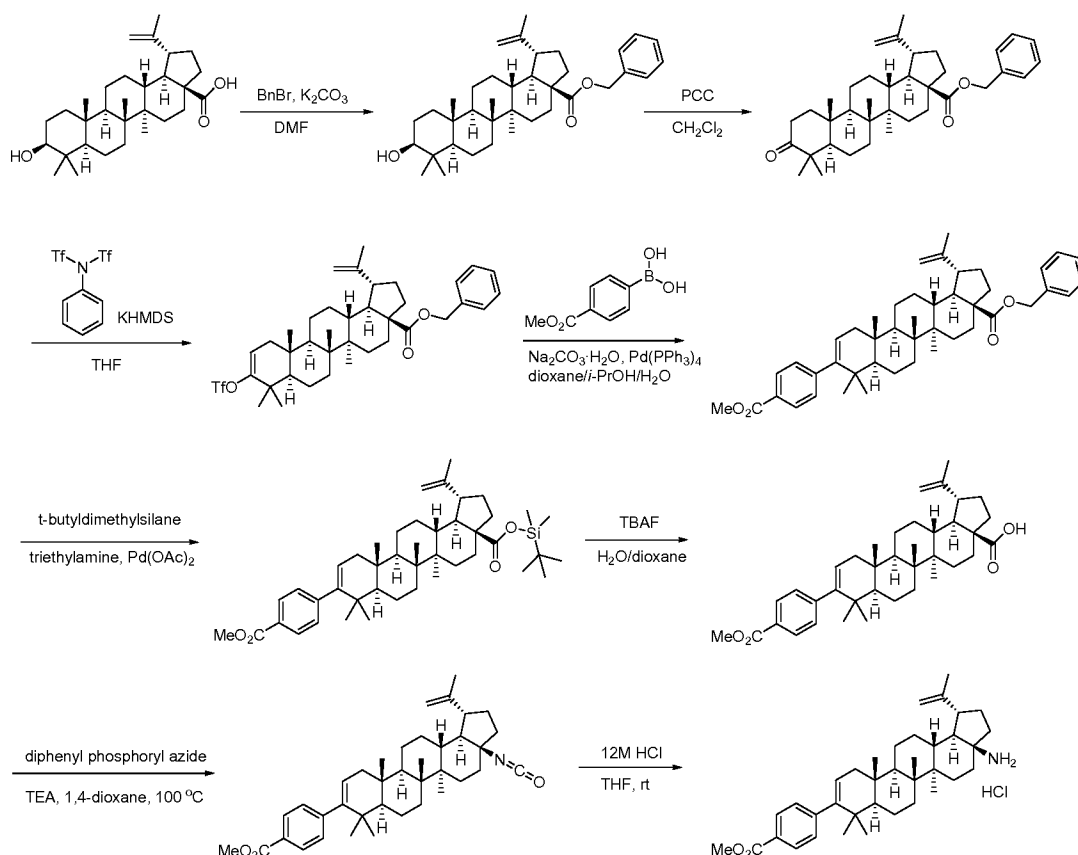
Solvent A = 0.1%TFA/95%water/5%acetonitrile

25 Solvent B = 0.1%TFA/5%water/95%acetonitrile

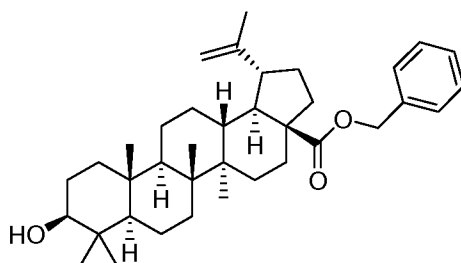
Column = Xbridge Phenyl 3.5 μ m, 3.0x150mm

Preparation of compounds:

30



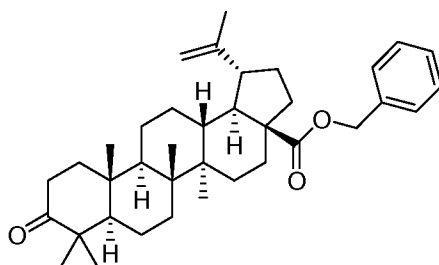
Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-benzyl 9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



To a suspension of betulinic acid (12 g, 26.3 mmol) and potassium carbonate (7.26 g, 52.6 mmol) in DMF (150 mL) was added benzyl bromide (3.28 mL, 27.6 mmol). The mixture was heated to 60 °C for 3.5 h, and then it was cooled to rt. Solids started to precipitate upon cooling. The mixture was diluted water (200 mL) and the solids that formed were collected by filtration to give the title compound (13.92 g, 25.5 mmol, 97% yield) as a white solid. ¹H NMR (500 MHz,

CHLOROFORM-d) δ ppm 7.39-7.28 (m, 5 H), 5.16-5.06 (m, 2 H), 4.71 (d, $J=1.83$ Hz, 1 H), 4.59 (s, 1 H), 3.17 (ddd, $J=11.44, 5.65, 5.49$ Hz, 1 H), 3.01 (td, $J=10.99, 4.88$ Hz, 1 H), 2.27 (ddd, $J=12.36, 3.20, 3.05$ Hz, 1 H), 2.21-2.13 (m, 1 H), 1.93 - 1.81 (m, 2 H), 1.67 (s, 3 H), 0.95 (s, 3 H), 0.93 (s, 3 H), 1.71 - 0.82 (m, 20 H), 0.79 (s, 3 H), 0.75 (s, 3 H), 0.74 (s, 3 H).

Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



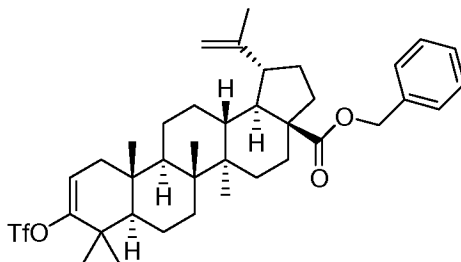
10

To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-benzyl 9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (7.1 g, 12.98 mmol) in dichloromethane (100 mL) was added PCC (4.20 g, 19.48 mmol). After stirring for five minutes, the mixture turned a deep crimson color. The mixture was further stirred for 5.5 h. The mixture was filtered through a pad of celite and silica gel which was washed with dichloromethane and then with a 1:1 mixture of ethyl acetate: hexanes. The filtrate was concentrated under reduced pressure to give the title compound (6.92 g, 12.7 mmol, 98% yield) as a white foam. ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.38 - 7.28 (m, 5 H), 5.17 - 5.06 (m, 2 H), 4.72 (d, $J=1.83$ Hz, 1 H), 4.59 (s, 1 H), 3.01 (td, $J=10.99, 4.88$ Hz, 1 H), 2.51 - 2.43 (m, 1 H), 2.42 - 2.34 (m, 1 H), 2.28 (dt, $J=12.59, 3.17$ Hz, 1 H), 2.21 (td, $J=12.28, 3.51$ Hz, 1 H), 1.94 - 1.82 (m, 3 H), 1.67 (s, 3 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 1.73 - 0.95 (m, 17 H), 0.94 (s, 3 H), 0.89 (s, 3 H), 0.78 (s, 3 H).

25

Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(trifluoromethylsulfonyloxy)-

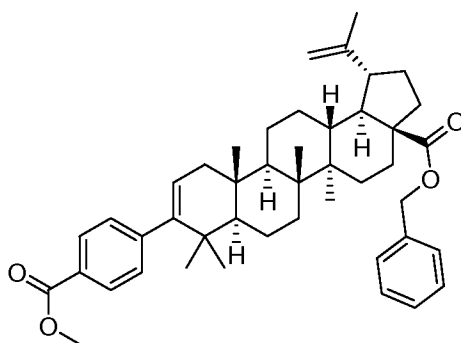
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



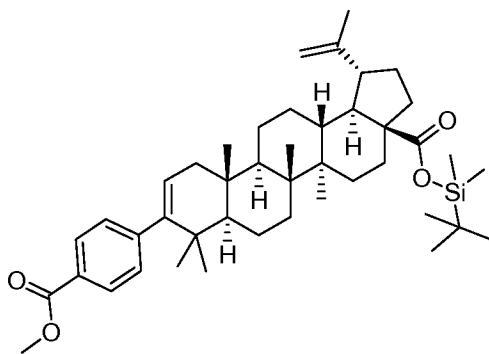
5 A solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (29.0 g, 53.2 mmol) in THF (200 mL) was cooled to -78 °C. To the solution was added KHMDS (0.5 M in toluene) (213 mL, 106 mmol). The yellow solution was stirred at -78 °C for 25 minutes and a solution
10 of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl)sulfonyl methanesulfonamide (20.92 g, 58.6 mmol) in THF (70 mL) and toluene (30 mL) was added via cannula. The solution was stirred at -78 °C for 3 h. Then, an additional 1.0 g of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl)sulfonyl methanesulfonamide was added and the mixture was stirred at -78 °C. After stirring for 1 h, the mixture was quenched with water
15 (300 mL) and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried with MgSO₄. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (40.0 g, 59.1 mmol) as a yellow solid. Product R_f = 0.57 by silica gel TLC, 5% EtOAc in hexanes, visualized using Hanessian's stain. ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.29-7.41 (m, 5 H), 5.54 (dd, *J* = 6.71, 1.53 Hz, 1 H), 5.13-5.18 (m, 1 H), 5.05-5.12 (m, 1 H), 4.72 (d, *J* = 1.53 Hz, 1 H), 4.59 (s, 1 H), 3.02 (td, *J* = 10.99, 4.58 Hz, 1 H), 2.25-2.31 (m, 1 H), 2.22 (td, *J* = 12.21, 3.36 Hz, 1 H), 2.14 (dd, *J* = 17.09, 6.71 Hz, 1 H), 1.81-1.96 (m, 2 H), 1.67 (s, 3 H), 1.10 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.91-1.77 (m, 17 H), 0.88 (s, 3 H), 0.77 (s, 3 H).

25

Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 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]chrysene-3a-carboxylate.



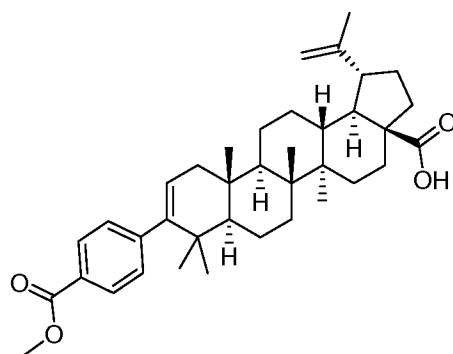
- To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(trifluoromethylsulfonyloxy)-
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (6.21 g, 9.18 mmol) in dioxane (25 mL) was added 2-propanol (25 mL) and water (15 mL) followed by sodium carbonate monohydrate (3.42 g, 27.5 mmol), 4-methoxycarbonylphenylboronic acid (2.478 g, 13.77 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.318 g, 0.275 mmol).
- 10 The flask was attached to a reflux condenser, flushed with N₂ and heated to reflux overnight. The mixture was then cooled to rt and diluted with water (75 mL). The mixture was extracted with ethyl acetate (3 x 75 mL) and washed with brine (75 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated under reduced pressure. The residue was adsorbed to silica gel and purified by silica
- 15 gel flash chromatography using a 0-20% ethyl acetate in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give the title compound (4.16 g, 6.28 mmol, 68.4% yield) as a white foam. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.92 (d, *J*=8.24 Hz, 2 H), 7.40 - 7.29 (m, 5 H), 7.19 (d, *J*=8.24 Hz, 2 H), 5.28 (dd, *J*=6.10, 1.83 Hz, 1 H),
- 20 5.19 - 5.07 (m, 2 H), 4.73 (d, *J*=1.83 Hz, 1 H), 4.60 (s, 1 H), 3.90 (s, 3 H), 3.04 (td, *J*=10.91, 4.73 Hz, 1 H), 2.20 - 2.32 (m, 2 H), 2.09 (dd, *J*=17.24, 6.26 Hz, 1 H), 1.95 - 1.82 (m, 2 H), 1.69 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.91 (s, 3 H), 1.75 - 0.87 (m, 17 H), 0.82 (s, 3 H).
- 25 Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-*tert*-butyldimethylsilyl 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]chrysene-3a-carboxylate.



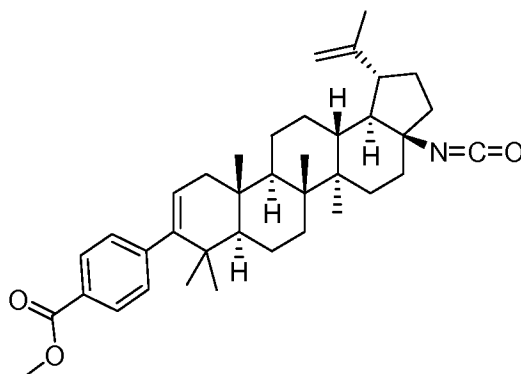
To a solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (3.82 g, 5.76 mmol) in dichloroethane (100 mL) was added triethylamine (1.285 mL, 9.22 mmol), *tert*-butyldimethylsilane (1.912 mL, 11.52 mmol), and palladium(II) acetate (0.647 g, 2.88 mmol). The mixture was flushed with N₂ and heated to 60 °C. After 2 h, the reaction was cooled to rt, filtered
 10 through a pad of celite and silica gel to remove the solids which were washed with 25% EtOAc in hexanes. The filtrate was concentrated under reduced pressure and treated with acetic acid (25 mL), THF (10 mL) and water (3 mL). After stirring for 1 h the solids formed were collected by filtration and washed with water to give the title compound (3.62 g, 5.27 mmol, 91% yield) as a white solid. ¹H NMR (400 MHz,
 15 *CHLOROFORM-d*) δ ppm 7.94 (d, *J*=8.28 Hz, 2 H), 7.21 (d, *J*=8.28 Hz, 2 H), 5.30 (dd, *J*=6.15, 1.63 Hz, 1 H), 4.75 (d, *J*=1.76 Hz, 1 H), 4.62 (s, 1 H), 3.92 (s, 4 H), 3.08 (td, *J*=10.92, 4.27 Hz, 1 H), 2.35 - 2.22 (m, 2 H), 2.17 - 2.06 (m, 1 H), 2.02 - 1.84 (m, 2 H), 1.71 (s, 3 H), 1.01 (s, 6 H), 0.99 (br. s., 3 H), 0.98 (s, 9 H), 0.94 (s, 6 H), 1.78 - 0.90 (m, 16 H), 0.32 - 0.28 (m, 6 H).

20

Preparation of (1R,3aS,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]chrysene-3a-carboxylic acid.



- To solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR, 13aR,13bR)-*tert*-butyldimethylsilyl 9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-
- 5 (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-carboxylate (3.12 g, 4.54 mmol) in dioxane (25 mL) was added TBAF (75% wt in water) (2.375 g, 6.81 mmol) and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with 1N HCl (25 mL) and water (5 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic layers were
- 10 dried over Na₂SO₄, filtered, and partially concentrated under reduced pressure to about 10 mL volume. To the partially concentrated mixture was added 1N HCl (50 mL). The solids that formed were collected by filtration and washed with water to give the title compound (2.58 g, 4.50 mmol, 99% yield) as a white solid. LCMS: m/e 571.47 (M-H)⁻, 3.60 min (method 1). ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
- 15 9.80 (br. s., 1 H), 7.92 (d, *J*=8.24 Hz, 2 H), 7.18 (d, *J*=8.24 Hz, 2 H), 5.32 - 5.26 (m, 1 H), 4.75 (s, 1 H), 4.62 (br. s., 1 H), 3.90 (s, 3 H), 3.07 - 2.99 (m, 1 H), 2.33 - 2.21 (m, 2 H), 2.10 (dd, *J*=17.09, 6.10 Hz, 1 H), 2.06 - 1.94 (m, 2 H), 1.70 (s, 3 H), 1.01 (br. s., 3 H), 1.00 (br. s., 3 H), 0.98 (s, 3 H), 0.91 (s, 6 H), 1.79 - 0.89 (m, 17 H).
- 20 Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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.

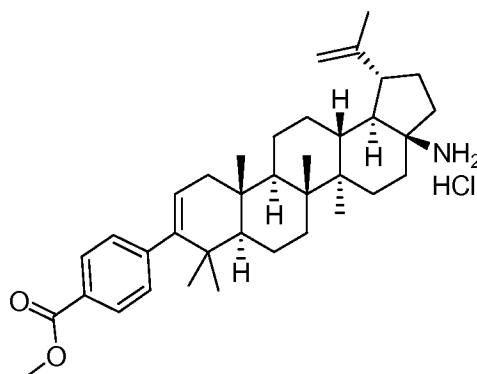


To a slurry of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (10 g, 17.46 mmol) in 1,4-dioxane (200 mL) was added triethylamine (4.38 mL, 31.4 mmol) followed by diphenyl phosphoryl azide (5.82 mL, 26.2 mmol). The resulting white slurry was heated to 100 °C. After 5 h, the reaction was allowed to cool to rt and was then diluted with EtOAc and
 10 washed with 1N NaOH (2 x 70 mL). The combined aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to a slurry (75 mL) which was stored in a refrigerator overnight. The slurry was filtered and the white solid product was washed with Et₂O. The liquid filtrate was concentrated to a yellow slurry which was filtered and washed with Et₂O
 15 to give more white solid product. The two batches of white solid were combined and dried *in vacuo* to give the title compound (8.6 g, 15.09 mmol, 86% yield) as a white solid. ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.0 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=4.6 Hz), 4.8 (1 H, s), 4.7 (1 H, s), 3.9 (3 H, s), 2.6 (1 H, td, *J*=10.8, 5.8 Hz), 2.1 - 2.2 (2 H, m), 1.8 - 2.0 (4 H, m), 1.7 - 1.8 (1 H, m), 1.7 (3 H, s), 1.5 - 1.7 (5 H, m), 1.4 - 1.5 (5 H, m), 1.3 - 1.4 (2 H, m), 1.2 - 1.3 (2 H, m), 1.1 (3 H, s), 1.1 - 1.1 (1 H, m), 1.0 (3 H, s), 1.0 (3 H, s), 1.0 (3 H, br. s.), 1.0 (3 H, br. s.).
 20 ¹³C NMR (CHLOROFORM-*d*) δ ppm 14.2, 15.4, 16.2, 19.2, 19.5, 20.8, 21.0, 24.7, 27.4, 29.0, 29.2, 33.3, 36.0, 37.2, 39.0, 39.0, 40.3, 41.5, 41.8, 47.8, 49.0, 49.2, 51.7, 52.6, 66.8, 71.3, 110.2, 121.3, 123.7, 127.6, 128.2, 129.8, 146.0, 148.4, 148.6, 166.9.

25

Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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.



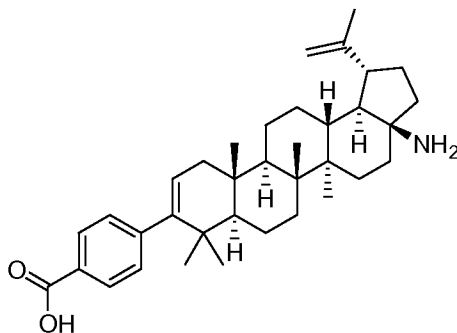
5

To a cloudy solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 (5.47 g, 9.60 mmol) in THF (100 mL) was added concentrated hydrochloric acid (19.83 mL, 240 mmol). The resulting homogeneous mixture was stirred at rt for 72 h, the reaction mixture was concentrated to dryness to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, HCl (4.98 g, 8.58 mmol, 89% yield) as a white solid. LCMS: m/e 544.5 ($M+H$)⁺, 3.26 min (method 6). ¹H NMR (500 MHz, 1:1 *CDCl*₃:*MeOD*, *MeOD* lock) δ ppm 7.9 (2 H, d, $J=8.5$ Hz), 7.3 (1 H, t, $J=7.8$ Hz), 7.2 (2 H, d, $J=8.5$ Hz), 7.1 (1 H, t, $J=7.3$ Hz), 5.3 (1 H, d, $J=4.6$ Hz), 4.8 (1 H, s), 4.7 (1 H, br. s.), 3.9 (2 H, s), 3.6 (2 H, dt, $J=15.6, 6.6$ Hz), 3.3 (1 H, dt, $J=3.1, 1.6$ Hz), 2.6 (1 H, td, $J=11.0, 6.1$ Hz), 2.1 (1 H, dd, $J=17.1, 6.4$ Hz), 2.0 (1 H, d, $J=13.4$ Hz), 1.9 - 2.0 (1 H, m), 1.8 - 1.9 (2 H, m), 1.7 - 1.7 (3 H, m), 1.6 - 1.7 (3 H, m), 1.5 - 1.6 (3 H, m), 1.5 - 1.5 (2 H, m), 1.4 (1 H, br. s.), 1.3 - 1.4 (1 H, m), 1.2 - 1.3 (1 H, m), 1.1 - 1.2 (2 H, m), 1.1 - 1.1 (1 H, m), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 (3 H, s), 0.9 (3 H, s).

25

Example 1

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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

The title compound was formed as a byproduct during the preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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. Purification by reverse phase preparative HPLC gave an off-white solid (100 mg, 3.5% yield) mono-TFA salt.

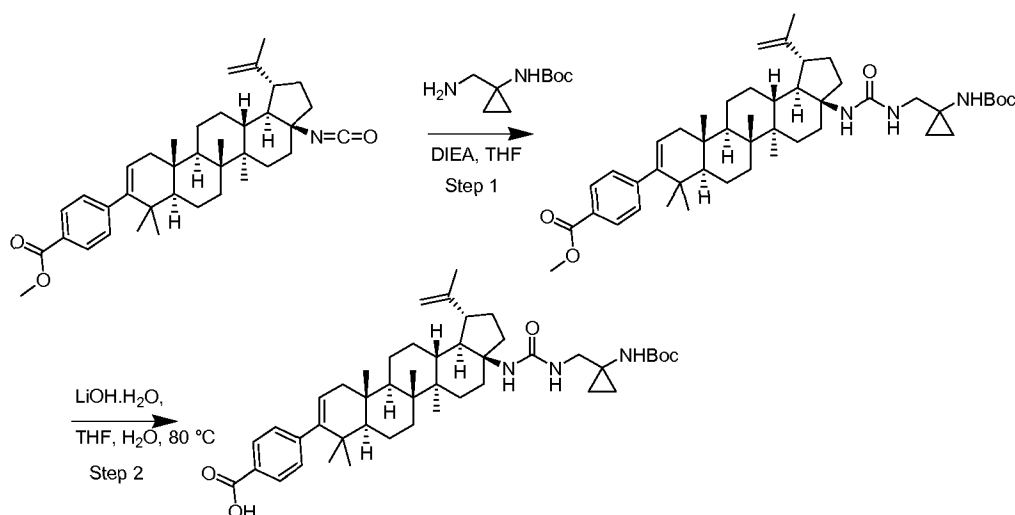
LCMS: m/z 530 ($M+H^+$), retention time 2.29 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 1.02 (s, 3 H) 1.06 (s, 3 H) 1.09 - 1.22 (m, 4 H) 1.22 - 1.30 (m, 1 H) 1.30 - 1.47 (m, 3 H) 1.49 - 1.57 (m, 4 H) 1.58 - 1.72 (m, 6 H) 1.73 (s, 3 H) 1.74 - 1.91 (m, 4 H) 1.91 - 1.99 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.51 - 2.63 (m, 1 H) 4.71 (s, 1 H) 4.81 (s, 1 H) 5.29 (d, $J=4.88$ Hz, 1 H) 7.20 (d, $J=8.24$ Hz, 2 H) 7.92 (d, $J=8.24$ Hz, 2 H).

15

Section 1. Ureas

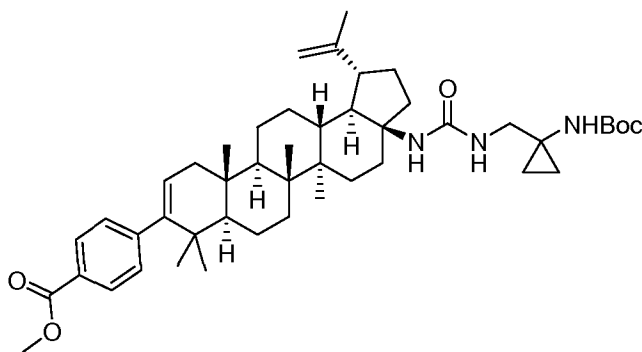
Example 2

- 5 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylamino)-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.



10

Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylamino)-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.

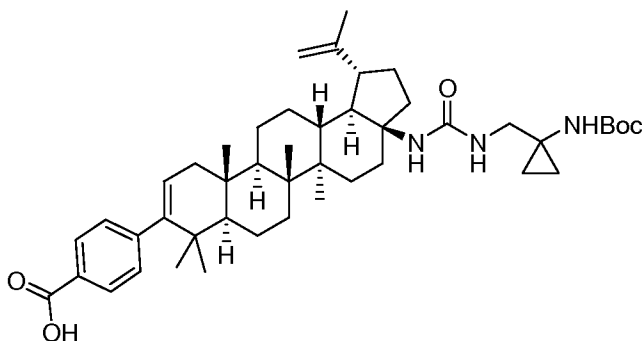


15

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 (600 mg, 1.053 mmol) and *N,N*-diisopropylethylamine (0.734 mL, 4.21 mmol) in THF (6 mL) was added *tert*-butyl 1-(aminomethyl)cyclopropylcarbamate (294 mg, 1.579 mmol). The resulting mixture was stirred at rt. After 16 h, the solvent was concentrated. The crude material was dissolved in THF (1 mL) and MeOH (2 mL), filtered and purified by reverse phase preparative HPLC (method 1) to give the title compound (499.5 mg, 58% yield) as a white solid. LCMS: m/e 756.7 ($M+H$)⁺, 2.75 min (method 7). ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.0 (2 H, d, $J=8.5$ Hz), 7.2 (2 H, d, $J=8.5$ Hz), 5.3 - 5.3 (1 H, m), 5.1 (1 H, br. s.), 4.8 (1 H, s), 4.7 (1 H, s), 3.9 (3 H, s), 3.5 - 3.5 (1 H, m), 3.4 (1 H, d, $J=14.3$ Hz), 2.8 (1 H, br. s.), 2.6 (1 H, d, $J=12.8$ Hz), 2.4 (1 H, dd, $J=12.2, 8.2$ Hz), 2.1 (1 H, dd, $J=17.4, 6.4$ Hz), 1.9 - 2.1 (2 H, m), 1.8 (1 H, d, $J=13.4$ Hz), 1.7 - 1.8 (1 H, m), 1.7 (3 H, s), 1.7 - 1.7 (2 H, m), 1.5 - 1.7 (3 H, m), 1.5 (9 H, s), 1.4 - 1.5 (5 H, m), 1.2 - 1.3 (1 H, m), 1.1 - 1.2 (2 H, m), 1.1 (3 H, s), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 (6 H, s), 0.8 - 0.9 (3 H, m). ¹³C NMR (*CHLOROFORM-d*) δ ppm 14.1, 15.4, 16.1, 19.0, 19.5, 20.7, 20.8, 24.8, 27.0, 28.1, 29.1, 29.2, 29.4, 31.4, 33.2, 35.1, 36.0, 36.6, 37.2, 40.4, 41.4, 41.6, 46.0, 49.1, 49.6, 51.7, 52.5, 77.3, 80.1, 109.9, 123.7, 127.6, 128.2, 129.8, 146.0, 148.4, 149.2, 167.0.

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylamino)-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.

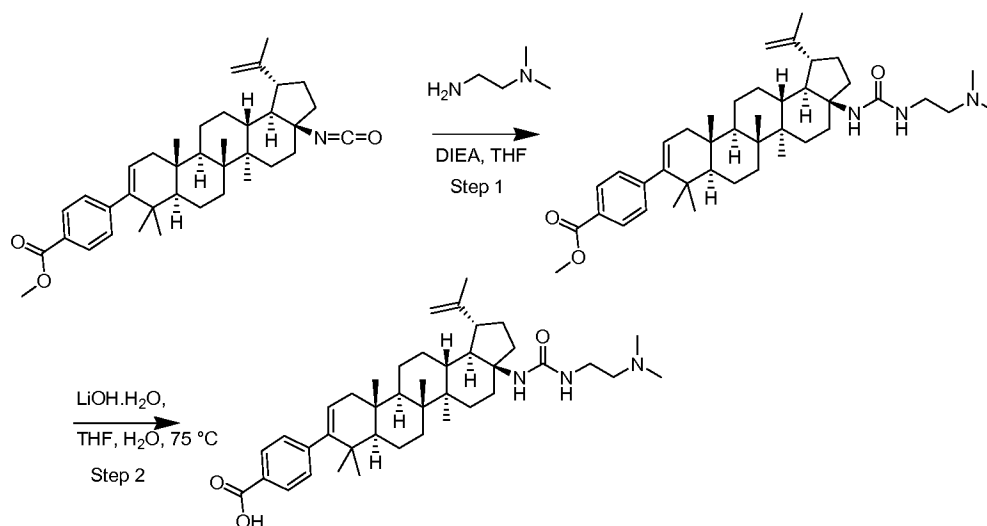


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

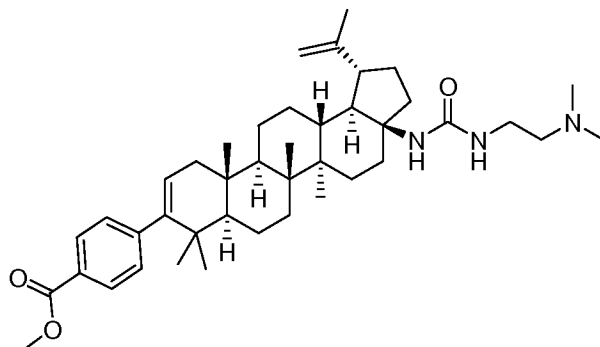
octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (91 mg, 0.12 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (20.2 mg, 0.481 mmol) in water (1.00 mL). The reaction mixture was stirred at 80 °C for 3 h. The reaction was concentrated and purified by reversed phase preparative HPLC using prep HPLC method 2. HPLC fractions containing product peaks were treated with saturated aqueous NaHCO₃ solution (100 mL), combined and concentrated. The resulting residue was triturated with H₂O (8 mL) and extracted with a mixture of THF (30 mL) and EtOAc (50 mL). The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated to give the title compound (58.1 mg, 0.069 mmol, 57.7% yield) as a white solid. LCMS: m/e 742.6 (M+H)⁺, 2.13 min (method 6). ¹H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=7.9 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=6.1 Hz), 4.8 (1 H, s), 4.6 (1 H, s), 3.9 - 4.0 (1 H, m), 3.3 (2 H, d, *J*=9.5 Hz), 2.7 (1 H, br. s.), 2.6 (1 H, d, *J*=13.4 Hz), 2.4 (1 H, dd, *J*=11.7, 8.7 Hz), 2.2 (1 H, dd, *J*=17.2, 6.3 Hz), 1.9 - 2.0 (3 H, m), 1.7 - 1.8 (2 H, m), 1.7 (3 H, s), 1.7 - 1.7 (1 H, m), 1.5 - 1.6 (3 H, m), 1.5 - 1.5 (6 H, m), 1.5 (9 H, s), 1.4 (2 H, d, *J*=2.1 Hz), 1.2 - 1.4 (6 H, m), 1.2 (3 H, s), 1.1 - 1.1 (2 H, m), 1.0 (6 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 - 0.9 (1 H, m). ¹³C NMR (*MeOD*) δ ppm 11.2, 13.9, 15.5, 16.1, 18.4, 18.6, 20.0, 20.7, 21.6, 23.9, 25.6, 27.5, 27.8, 29.1, 29.1, 29.8, 29.9, 30.0, 33.8, 35.7, 36.5, 37.6, 37.7, 40.8, 41.9, 42.1, 49.9, 49.9, 53.3, 63.8, 67.3, 79.2, 109.5, 124.1, 128.7, 130.1, 146.8, 150.4, 157.5, 159.2.

Example 3

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-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.



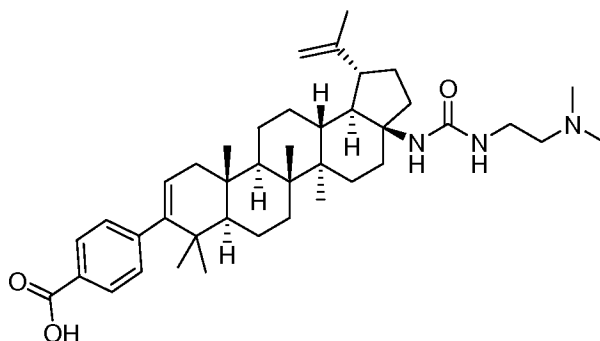
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 (610.0 mg, 1.071 mmol) in THF (10 mL) was added *N,N*-diisopropylethylamine (0.559 mL, 3.21 mmol) and *N,N*-dimethylethylenediamine (0.353 mL, 3.21 mmol). The reaction mixture was stirred at 25 °C. After 18 h, the reaction mixture was diluted with EtOAc (50 mL) and treated with 1N HCl (5 mL). The mixture was concentrated to a paste and then triturated with EtOAc, filtered and washed with Et₂O. The white solid was saved and the liquid filtrate was concentrated and the trituration and filtration steps were

repeated twice more. The combined white solid product was dried in a vacuum oven to give the title compound (650.0 mg, 0.958 mmol, 90% yield). LCMS: m/e 658.4 $(M+H)^+$, 4.25 min (method 8). ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.9 (2 H, d, $J=8.5$ Hz), 7.2 (2 H, d, $J=8.2$ Hz), 5.3 (1 H, dd, $J=6.3$, 1.7 Hz), 4.8 (1 H, s), 4.6 (1 H, s), 3.9 (3 H, s), 3.7 - 3.8 (1 H, m), 3.5 - 3.6 (1 H, m), 3.2 (2 H, br. s.), 2.9 (6 H, br. s.), 2.7 - 2.7 (1 H, m), 2.6 (1 H, d, $J=13.4$ Hz), 2.4 (1 H, dd, $J=11.6$, 8.2 Hz), 2.1 (1 H, dd, $J=17.2$, 6.3 Hz), 2.0 - 2.1 (1 H, m), 1.8 - 1.9 (1 H, m), 1.8 (1 H, d, $J=12.8$ Hz), 1.7 (3 H, s), 1.7 (1 H, d, $J=6.7$ Hz), 1.6 - 1.7 (1 H, m), 1.5 - 1.6 (2 H, m), 1.5 (4 H, d, $J=2.7$ Hz), 1.3 - 1.4 (5 H, m), 1.2 - 1.3 (1 H, m), 1.1 (3 H, s), 1.0 - 1.1 (2 H, m), 1.0 (3 H, s), 1.0 - 1.0 (3 H, m), 0.9 (6 H, s). ^{13}C NMR (*CHLOROFORM-d*) δ ppm 14.2, 15.8, 16.3, 18.4, 19.2, 19.5, 20.7, 21.1, 25.0, 27.1, 29.1, 29.5, 29.6, 33.3, 35.3, 35.4, 36.0, 37.2, 37.3, 40.3, 41.4, 41.7, 43.4, 46.7, 49.3, 51.7, 52.6, 53.4, 58.9, 63.9, 77.3, 109.8, 123.9, 127.6, 128.2, 129.8, 145.9, 148.5, 149.4, 157.5, 167.0.

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-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 cloudy solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-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 (0.255 g, 0.388 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (0.049 g, 1.16 mmol) in water (1.00 mL). The reaction mixture was heated to 75 °C for 18 h. Then, the reaction was treated with 1N HCl (1 mL) and concentrated *in vacuo*, absorbed onto silica gel (3.5

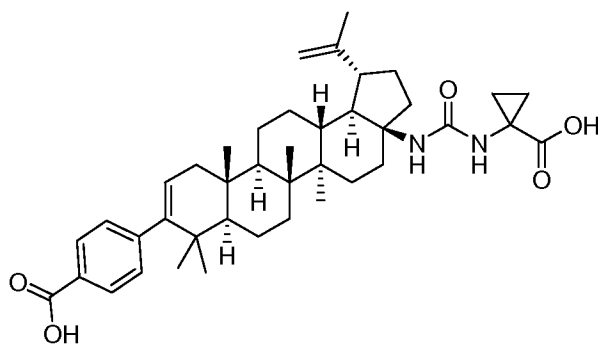
g), loaded onto a silica gel column (12 g cartridge) and eluted with 90:10 DCM:MeOH to give the title compound (237 mg, 0.368 mmol, 95% yield) as a white solid. LCMS: m/e 644.4 ($M+H$)⁺, 3.95 min (method 8). ¹H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, $J=8.2$ Hz), 7.2 (2 H, d, $J=8.2$ Hz), 5.9 (1 H, s), 5.3 - 5.3 (1 H, m), 4.8 (1 H, d, $J=1.8$ Hz), 4.6 (1 H, s), 3.7 - 3.8 (1 H, m), 3.4 - 3.6 (2 H, m), 3.4 (1 H, s), 3.2 - 3.3 (2 H, m), 2.9 (6 H, s), 2.7 (1 H, td, $J=11.1, 5.0$ Hz), 2.6 (1 H, dd, $J=10.2, 3.2$ Hz), 2.4 (1 H, dd, $J=12.1, 8.1$ Hz), 2.2 (1 H, dd, $J=17.4, 6.4$ Hz), 1.9 - 2.0 (2 H, m), 1.8 (1 H, d, $J=13.4$ Hz), 1.7 (3 H, s), 1.7 (1 H, br. s.), 1.7 - 1.7 (1 H, m), 1.6 - 1.6 (2 H, m), 1.5 - 1.6 (4 H, m), 1.4 - 1.4 (5 H, m), 1.3 - 1.4 (3 H, m), 1.2 (3 H, s), 1.1 - 1.1 (1 H, m), 1.0 - 1.1 (6 H, m), 1.0 (3 H, s), 1.0 (3 H, s). ¹³C NMR (*MeOD*) δ ppm 14.5, 16.3, 16.8, 19.2, 20.6, 21.3, 22.2, 26.3, 28.2, 29.7, 30.4, 30.5, 34.5, 36.2, 36.4, 37.1, 38.2, 38.4, 41.5, 42.6, 42.8, 43.6, 48.1, 49.0, 49.3, 49.3, 50.4, 50.6, 54.0, 55.6, 59.9, 64.9, 110.3, 111.1, 124.8, 129.3, 130.7, 147.5, 150.9, 160.4.

15

Example 4

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1-carboxycyclopropyl)ureido)-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



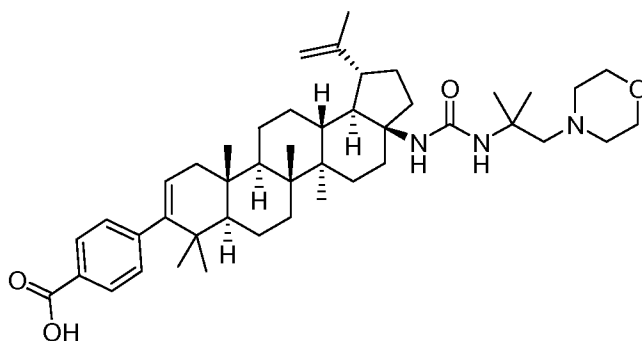
The title compound was prepared in 25% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-

25

3a-(3-(2-(dimethylamino)ethyl)ureido)-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, except 1-aminocyclopropane-1-carboxylic
 acid ethyl ester hydrochloride was used instead of *N,N*-dimethylethylenediamine in
 5 Step 1. LCMS: m/e 657.3 ($M+H$)⁺, 4.18 min (method 8). ¹H NMR (500 MHz,
MeOD) δ ppm 7.9 (2 H, d, $J=8.2$ Hz), 7.2 (2 H, d, $J=8.2$ Hz), 5.3 - 5.3 (1 H, m), 4.8 (1
 H, br. s.), 4.6 (1 H, br. s.), 3.7 - 3.8 (1 H, m), 3.6 - 3.6 (1 H, m), 3.5 - 3.6 (1 H, m), 2.5
 - 2.7 (2 H, m), 2.4 (1 H, dd, $J=12.1, 8.4$ Hz), 2.2 (1 H, dd, $J=17.1, 6.4$ Hz), 2.0 (1 H,
 d, $J=11.9$ Hz), 1.9 (2 H, dt, $J=6.6, 3.2$ Hz), 1.8 - 1.9 (2 H, m), 1.7 - 1.8 (4 H, m), 1.4 -
 10 1.7 (7 H, m), 1.4 (3 H, td, $J=13.1, 4.0$ Hz), 1.3 (3 H, t, $J=11.7$ Hz), 1.2 (3 H, s), 1.1 -
 1.1 (3 H, m), 1.1 (3 H, d, $J=2.4$ Hz), 1.0 (3 H, s), 1.0 (2 H, s), 0.9 (1 H, m).

Example 5

15 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-3a-(3-(2-methyl-1-morpholinopropan-2-yl)ureido)-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.



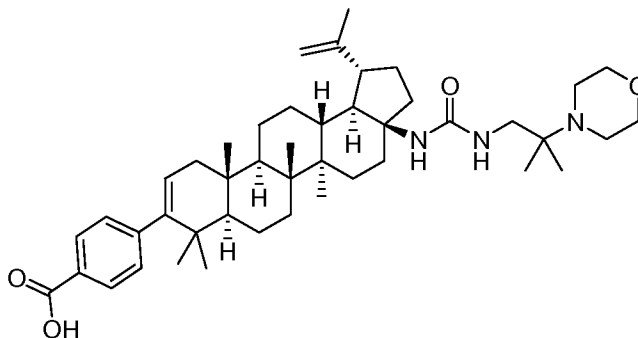
20

The title compound was prepared in 16% yield from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 following the same procedure
 25 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 3a-(3-(2-(dimethylamino)ethyl)ureido)-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, except 2-methyl-2-morpholinopropan-1-

amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: *m/e* 714.3 ($M+H$)⁺, 3.97 min (method 8). ¹H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=4.6 Hz), 4.7 (1 H, br. s.), 2.5 - 2.7 (1 H, m), 2.2 (1 H, dd, *J*=16.9, 6.0 Hz), 2.1 (1 H, dd, *J*=13.3, 9.9 Hz), 1.9 - 2.0 (2 H, m), 1.8 - 1.9 (3 H, m), 1.8 (3 H, br. s.), 1.7 - 1.8 (1 H, m), 1.6 - 1.7 (5 H, m), 1.5 - 1.6 (3 H, m), 1.4 (2 H, d, *J*=13.4 Hz), 1.3 - 1.4 (1 H, m), 1.2 (3 H, br. s.), 1.1 (3 H, br. s.), 1.1 (3 H, br. s.), 1.0 (3 H, br. s.), 1.0 (3 H, br. s.).

Example 6

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

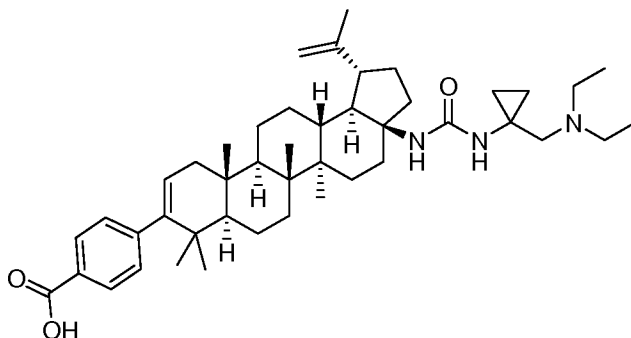


The title compound was prepared in 20% yield from methyl 4-((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,11*aS*,11*bR*,13*aR*,13*bR*)-3*a*-isocyanato-5*a*,5*b*,8,8,11*a*-pentamethyl-1-(prop-1-en-2-yl)-2,3,3*a*,4,5,5*a*,5*b*,6,7,7*a*,8,11,11*a*,11*b*,12,13,13*a*,13*b*-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,11*aS*,11*bR*,13*aR*,13*bR*)-3*a*-(3-(2-(dimethylamino)ethyl)ureido)-5*a*,5*b*,8,8,11*a*-pentamethyl-1-(prop-1-en-2-yl)-2,3,3*a*,4,5,5*a*,5*b*,6,7,7*a*,8,11,11*a*,11*b*,12,13,13*a*,13*b*-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl)benzoic acid, except 2-methyl-2-morpholinopropan-1-amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: *m/e* 714.3 ($M+H$)⁺, 3.95 min (method 8). ¹H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=6.1 Hz), 4.8 (1 H, s), 4.7 (1 H, s), 4.1 (2 H, d, *J*=12.2 Hz), 3.7 - 3.9 (2 H, m), 3.5 - 3.6 (2 H, m), 3.4 - 3.5 (2 H, m), 3.2 (2 H,

t, $J=11.9$ Hz), 2.6 - 2.7 (2 H, m), 2.4 (1 H, dd, $J=12.1$, 8.4 Hz), 2.2 (1 H, dd, $J=17.1$, 6.1 Hz), 2.0 (1 H, t, $J=10.8$ Hz), 1.8 - 1.9 (1 H, m), 1.8 (1 H, br. s.), 1.7 (3 H, s), 1.7 (1 H, td, $J=13.3$, 3.4 Hz), 1.6 - 1.6 (2 H, m), 1.5 - 1.6 (4 H, m), 1.4 - 1.5 (3 H, m), 1.4 - 1.4 (6 H, m), 1.3 (1 H, d, $J=9.5$ Hz), 1.1 (3 H, s), 1.1 (3 H, br. s.), 1.1 (3 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s).

Example 7

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1-
 10 ((diethylamino)methyl)cyclopropyl)ureido)-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.



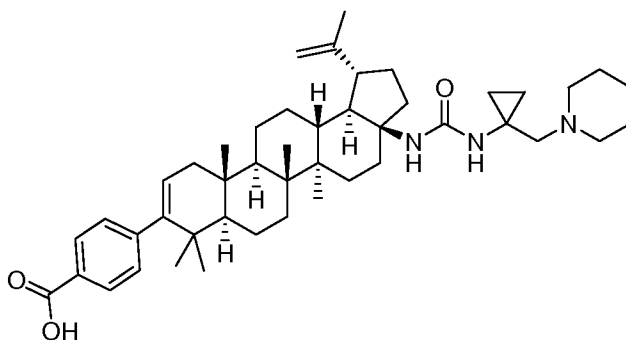
15 The title compound was prepared in 25% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 20 3a-(3-(2-(dimethylamino)ethyl)ureido)-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, except 1-((diethylamino)methyl)cyclopropanamine, 2 HCl was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 698.3 ($M+H$)⁺, 3.97 min (method 8).
 25 ¹H NMR (500 MHz, *MeOD*) δ ppm 7.9 - 8.0 (2 H, m), 7.2 - 7.3 (2 H, m), 5.3 (1 H, dd, $J=4.0$, 1.8 Hz), 4.8 (1 H, br. s.), 4.7 (1 H, br. s.), 3.2 - 3.3 (4 H, m), 2.6 (1 H, d, $J=12.8$ Hz), 2.5 - 2.6 (1 H, m), 2.3 - 2.4 (1 H, m), 2.2 (1 H, dd, $J=16.0$, 5.3 Hz), 1.9 - 2.0 (1 H, m), 1.7 - 1.8 (3 H, m), 1.7 (3 H, br. s.), 1.6 - 1.7 (4 H, m), 1.5 (4 H, d, $J=7.3$ Hz),

1.4 - 1.5 (2 H, m), 1.4 (8 H, dd, $J=7.0, 5.2$ Hz), 1.3 (2 H, br. s.), 1.1 - 1.2 (1 H, m), 1.1 (3 H, br. s.), 1.1 (6 H, br. s.), 1.0 (3 H, d, $J=1.5$ Hz), 1.0 (3 H, br. s.), 0.9 (3 H, br. s.).

Example 8

5

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(1-(piperidin-1-ylmethyl)cyclopropyl)ureido)-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.



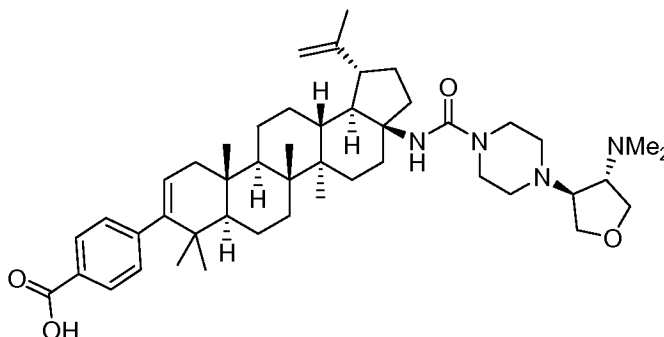
10

The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-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, except 1-(piperidin-1-ylmethyl)cyclopropanamine, 2 HCl was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 710.6 ($M+H$)⁺, 2.00 min (method 6). ¹H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, $J=7.9$ Hz), 7.2 (2 H, d, $J=7.9$ Hz), 5.3 (1 H, d, $J=4.9$ Hz), 4.8 (1 H, s), 4.7 (1 H, s), 3.5 - 3.7 (2 H, m), 3.3 (1 H, s), 3.2 - 3.3 (2 H, m), 3.0 (2 H, ddd, $J=12.0, 8.5, 3.7$ Hz), 2.6 (1 H, d, $J=13.4$ Hz), 2.6 (1 H, td, $J=10.9, 5.0$ Hz), 2.4 (1 H, dd, $J=11.9, 8.2$ Hz), 2.2 (1 H, dd, $J=17.1, 6.4$ Hz), 1.9 - 2.1 (3 H, m), 1.7 - 1.9 (5 H, m), 1.7 (3 H, s), 1.7 - 1.7 (1 H, m), 1.5 - 1.7 (8 H, m), 1.3 - 1.5 (6 H, m), 1.2 - 1.2 (1 H, m), 1.1 (1 H, d, $J=4.0$ Hz), 1.1 (3 H, s), 1.1 (6 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 - 0.9 (2 H, m).

25

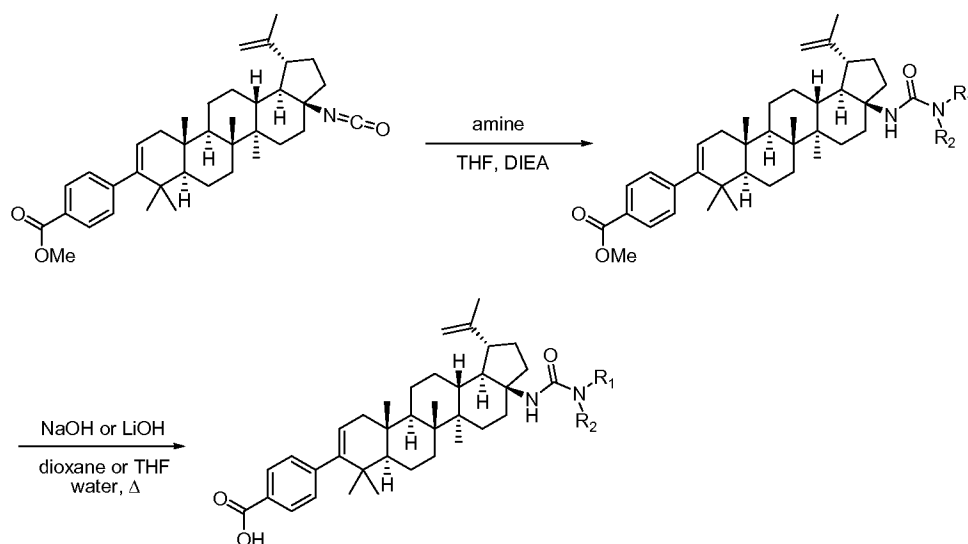
Example 9

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-((3S,4S)-4-(dimethylamino)tetrahydrofuran-3-yl)piperazine-1-carboxamido)-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.



The title compound was prepared in 20% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-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, except (3S,4S)-N,N-dimethyl-4-(piperazin-1-yl)tetrahydrofuran-3-amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 755.6 ($M+H$)⁺, 1.85 min (method 6). ¹H NMR (500MHz, *METHANOL-d*₄) δ = 7.93 (d, J = 8.2 Hz, 2 H), 7.23 (d, J = 8.2 Hz, 2 H), 5.31 (d, J = 6.1 Hz, 1 H), 4.78 (s, 1 H), 4.64 (br. s., 1 H), 4.09 (d, J = 3.4 Hz, 1 H), 4.05 (d, J = 4.9 Hz, 2 H), 4.02 (td, J = 3.5, 6.8 Hz, 1 H), 3.96 (td, J = 5.1, 10.1 Hz, 1 H), 3.73 (d, J = 5.2 Hz, 1 H), 3.56 - 3.41 (m, 4 H), 2.96 (s, 6 H), 2.87 - 2.66 (m, 5 H), 2.59 (d, J = 13.1 Hz, 1 H), 2.45 (dd, J = 8.7, 11.7 Hz, 1 H), 2.16 (dd, J = 6.4, 17.1 Hz, 1 H), 1.97 - 1.90 (m, 1 H), 1.90 - 1.82 (m, 1 H), 1.82 - 1.74 (m, 2 H), 1.73 (s, 3 H), 1.66 - 1.54 (m, 3 H), 1.51 (d, J = 12.5 Hz, 4 H), 1.45 - 1.26 (m, 6 H), 1.23 - 1.15 (m, 2 H), 1.13 (s, 3 H), 1.10 (d, J = 13.4 Hz, 2 H), 1.06 (s, 3 H), 1.04 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

General Procedure for C-17 Urea Formation:



5 Step 1: General procedure for the preparation of C-17 urea methyl esters.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 in THF (approximately 0.1 M) was added

- 10 Hunig's base (3-9 equiv.) and the amine (3 equiv.). The mixture was stirred at rt for 2-72 h. The reaction mixture was concentrated and redissolved in a mixture of THF and methanol and often a couple drops of water were added. The mixture was filtered and purified by reverse phase preparative HPLC.

15 Step 2: General Procedures for hydrolysis of the benzoic ester using NaOH or LiOH·H₂O.

The C-17 urea formed in Step 1 above was dissolved in either 1,4-dioxane or THF to give approximately a 0.1M solution. Aqueous 1N NaOH (4 eq.) was added to the mixture and it was heated to 50-85 °C. After heating for 2-48 h, the mixture was

20 cooled to rt. The crude mixture was purified by reverse phase preparative HPLC.

Alternatively, the ester hydrolysis can be carried out as follows: The C-17 urea formed in Step 1 above was dissolved in either 1,4-dioxane or THF to give approximately a 0.1M solution. To the solution was added water (ratio 4:1 or 5:1

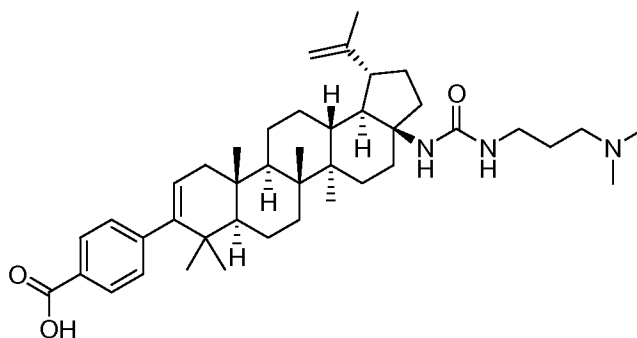
organic 1,4-dioxane or THF: water) followed by LiOH·H₂O (5-12 equiv.). The mixture was heated to 50-85 °C. After heating for as little as 60 seconds to as long as 24 h, the mixture was cooled to rt. The crude mixture was purified by reverse phase preparative HPLC.

5

Example 10

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(dimethylamino)propyl)ureido)-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.

10



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N,N*-dimethylpropane-1,3-diamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (60 mg, 32.7% yield). LCMS: *m/z* 658 (M+H⁺), retention time 1.86 min (method 2). ¹H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.11 - 1.13 (m, 1 H), 1.15 (s, 3 H), 1.17 - 1.22 (m, 1 H), 1.28 - 1.48 (m, 5 H), 1.48 - 1.64 (m, 6 H), 1.64 - 1.83 (m, 7 H), 1.83 - 2.01 (m, 4 H), 2.18 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.37 (dd, *J*=12.21, 8.24 Hz, 1 H), 2.58 - 2.68 (m, 2 H), 2.90 (s, 6 H), 3.13 (td, *J*=7.02, 1.83 Hz, 2 H), 3.25 (td, *J*=6.49, 0.76 Hz, 1 H), 4.66 (s, 1 H), 4.78 (d, *J*=1.53 Hz, 1 H), 5.33 (dd, *J*=6.10, 1.22 Hz, 1 H), 7.25 (m, *J*=8.24 Hz, 2 H), 7.95 (m, *J*=8.24 Hz, 2 H).

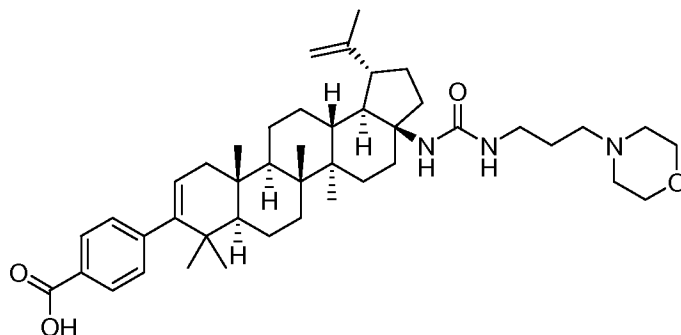
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Example 11

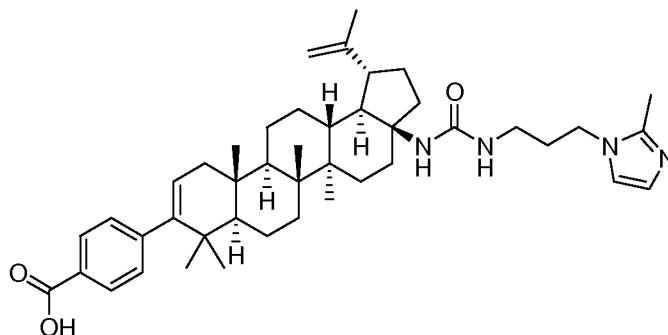
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-morpholinopropyl)ureido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 3-morpholinopropan-1-amine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (85 mg, 43% yield). LCMS: m/z 700 ($M+H^+$), retention time 1.89 min (method 2). ^1H NMR
 15 (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.11 - 1.13 (m, 1 H), 1.15 (s, 3 H), 1.17 - 1.21 (m, 1 H), 1.28 - 1.47 (m, 5 H), 1.50 - 1.63 (m, 6 H), 1.64 - 1.72 (m, 1 H), 1.74 (br. s., 1 H), 1.75 (s, 3 H), 1.76 - 1.83 (m, 2 H), 1.87 (td, $J=12.21, 3.36$ Hz, 1 H), 1.91 - 1.99 (m, 3 H), 2.18 (dd, $J=17.09, 6.41$ Hz, 1 H), 2.35 (dd, $J=12.05, 8.09$ Hz, 1 H), 2.58 - 2.67 (m, 2 H), 3.11 - 3.20 (m, 4 H), 3.25 - 3.31 (m,
 20 2 H), 3.45 (t, $J=12.97$ Hz, 2 H), 3.81 (t, $J=12.51$ Hz, 2 H), 4.11 (d, $J=12.82$ Hz, 2 H), 4.66 (s, 1 H), 4.78 (s, 1 H), 5.33 (dd, $J=6.10, 1.83$ Hz, 1 H), 7.24 (m, $J=8.55$ Hz, 2 H), 7.95 (m, $J=8.55$ Hz, 2 H).

Example 12

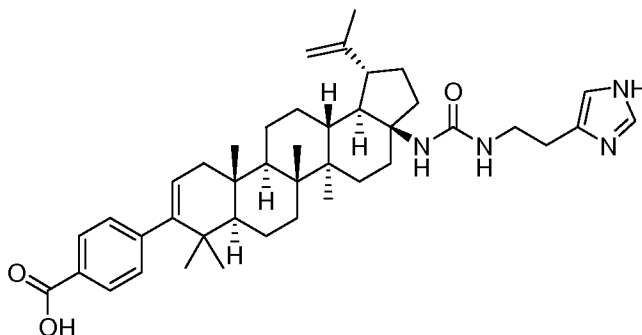
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(2-methyl-1H-imidazol-1-yl)propyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 3-(2-methyl-1H-imidazol-1-yl)propan-1-amine dihydrochloride as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (40 mg, 21% yield). LCMS: m/z 709 ($M+H^+$), retention time 1.83 min (method 2). ^1H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.12 (d, $J=13.43$ Hz, 1 H), 1.15 (s, 3 H), 1.17 - 1.22 (m, 1 H), 1.27 - 1.46 (m, 5 H), 1.47 - 1.64 (m, 6 H), 1.66 - 1.82 (m, 7 H), 1.83 - 1.98 (m, 2 H), 2.04 (quin, $J=6.94$ Hz, 2 H), 2.18 (dd, $J=17.09, 6.41$ Hz, 1 H), 2.38 (dd, $J=12.36, 8.09$ Hz, 1 H), 2.58 - 2.65 (m, 2 H), 2.66 (s, 3 H), 3.18 (t, $J=6.71$ Hz, 2 H), 4.18 (t, $J=7.17$ Hz, 2 H), 4.66 (s, 1 H), 4.78 (d, $J=1.83$ Hz, 1 H), 5.33 (dd, $J=6.26, 1.68$ Hz, 1 H), 7.24 (m, $J=8.55$ Hz, 2 H), 7.47 (d, $J=1.83$ Hz, 1 H), 7.59 (d, $J=2.14$ Hz, 1 H), 7.95 (m, $J=8.24$ Hz, 2 H).

Example 13

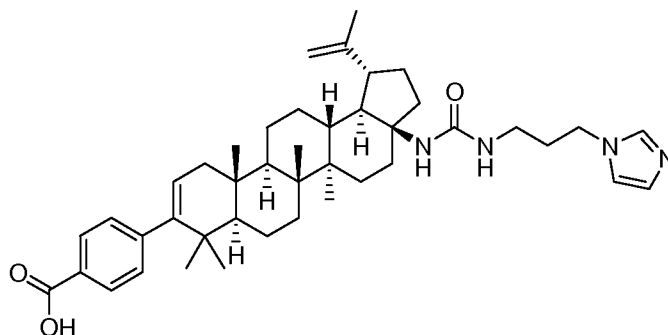
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-4-yl)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using histamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (23 mg, 11% yield). LCMS: m/z 667 ($M+H^+$), retention time 1.79 min (method 2). ^1H NMR (500 MHz, *MeOD*) δ ppm
 15 0.97 (s, 3 H), 0.99 (s, 3 H), 1.05 (s, 3 H), 1.06 (s, 3 H), 1.07 - 1.11 (m, 1 H), 1.12 (s, 3 H), 1.13 - 1.20 (m, 1 H), 1.26 - 1.45 (m, 5 H), 1.49 - 1.68 (m, 7 H), 1.71 (d, $J=11.60$ Hz, 1 H), 1.74 (s, 3 H), 1.75 - 1.94 (m, 4 H), 2.17 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.31 (dd, $J=12.36$, 8.09 Hz, 1 H), 2.54 - 2.64 (m, 2 H), 2.90 (t, $J=6.71$ Hz, 2 H), 3.45 (t, $J=6.87$ Hz, 2 H), 4.65 (s, 1 H), 4.76 (d, $J=1.83$ Hz, 1 H), 5.33 (dd, $J=6.10$, 1.83 Hz, 1
 20 H), 7.24 (d, $J=8.24$ Hz, 2 H), 7.34 (s, 1 H), 7.94 (d, $J=8.24$ Hz, 2 H), 8.84 (d, $J=1.22$ Hz, 1 H).

Example 14

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(1H-imidazol-1-yl)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 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.



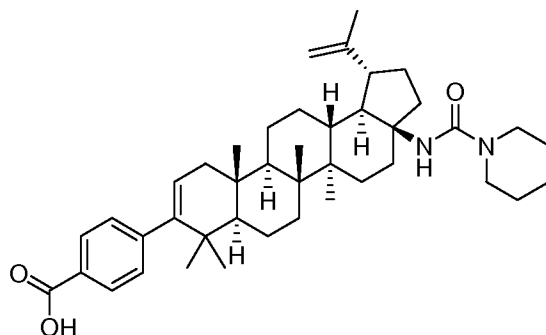
10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 3-(1H-imidazol-1-yl)propan-1-amine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (109 mg, 53% yield). LCMS: m/z 681 ($M+H^+$), retention time 1.82 min (method 2). ^1H NMR
 15 (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.06 (s, 6 H), 1.09 - 1.14 (m, 1 H), 1.15 (s, 3 H), 1.17 - 1.21 (m, 1 H), 1.27 - 1.46 (m, 5 H), 1.47 - 1.63 (m, 6 H), 1.64 - 1.73 (m, 2 H), 1.75 (s, 3 H), 1.76 - 1.82 (m, 2 H), 1.83 - 2.00 (m, 2 H), 2.07 (qd, $J=7.07$, 6.87 Hz, 2 H), 2.18 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.39 (dd, $J=12.36$, 8.09 Hz, 1 H), 2.58 - 2.68 (m, 2 H), 3.11 - 3.23 (m, 2 H), 4.31 (t, $J=6.87$ Hz, 2 H), 4.66 (s, 1 H),
 20 4.78 (d, $J=1.83$ Hz, 1 H), 5.33 (dd, $J=6.10$, 1.83 Hz, 1 H), 7.24 (m, $J=8.54$ Hz, 2 H), 7.60 (t, $J=1.53$ Hz, 1 H), 7.71 (t, $J=1.68$ Hz, 1 H), 7.94 (m, $J=8.54$ Hz, 2 H), 9.00 (s, 1 H).

25

Example 15

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidine-1-carboxamido)-1-(prop-1-en-2-yl)-

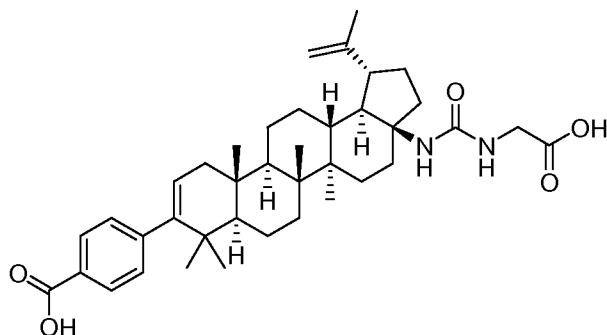
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using piperidine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (10 mg, 6% yield). LCMS: m/z 641 ($M+H^+$), retention time 2.67 min (method 2). ^1H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 3 H), 1.08 (s, 3 H), 1.12 (dt, $J=13.81, 3.17$ Hz, 1 H), 1.16 (s, 3 H), 1.17 - 1.22 (m, 1 H), 1.28 - 1.47 (m, 5 H), 1.48 - 1.65 (m, 11 H), 1.65 - 1.70 (m, 2 H), 1.71 - 1.90 (m, 7 H), 1.91 - 2.02 (m, 1 H), 2.14 - 2.21 (m, 1 H), 2.49 (dd, $J=12.36, 8.09$ Hz, 1 H), 2.59 - 2.71 (m, 2 H), 3.35 - 3.48 (m, 4 H), 4.63 - 4.67 (m, 1 H), 4.80 (d, $J=1.83$ Hz, 1 H), 5.33 (dd, $J=6.10, 1.83$ Hz, 1 H), 7.25 (m, $J=8.24$ Hz, 2 H), 7.94 (m, $J=8.24$ Hz, 2 H).
- 15
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Example 16

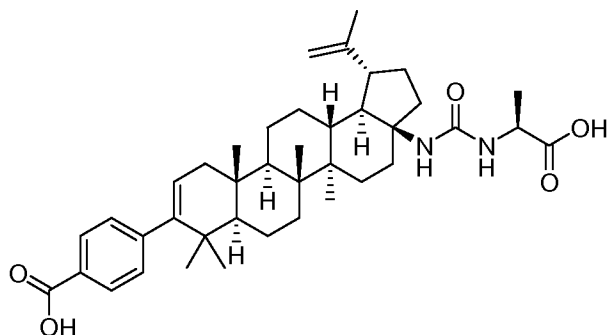
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(carboxymethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using glycine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (59 mg, 45% yield). LCMS: m/z 631 ($M+H^+$), retention time 2.17 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.95 (s, 3 H), 1.02 (s, 6 H), 1.04 - 1.11 (m, 2 H), 1.12 (s, 3 H), 1.23 - 1.41 (m, 5 H), 1.42 - 1.61 (m, 6 H), 1.65 (t, $J=11.60$ Hz, 1 H), 1.68 - 1.79 (m, 6 H), 1.85 (td, $J=12.21, 3.36$ Hz, 1 H), 1.92 - 2.05 (m, 1 H), 2.13 (dd, $J=17.09, 6.41$ Hz, 1 H), 2.36 (dd, $J=12.36, 8.09$ Hz, 1 H), 2.55 - 2.66 (m, 2 H), 3.80 - 3.95 (m, 2 H), 4.58 - 4.64 (m, 1 H), 4.74 (d, $J=1.83$ Hz, 2 H), 5.29 (dd, $J=6.26, 1.68$ Hz, 1 H), 7.19 - 7.23 (m, 2 H), 7.91 - 7.95 (m, 2 H).

Example 17

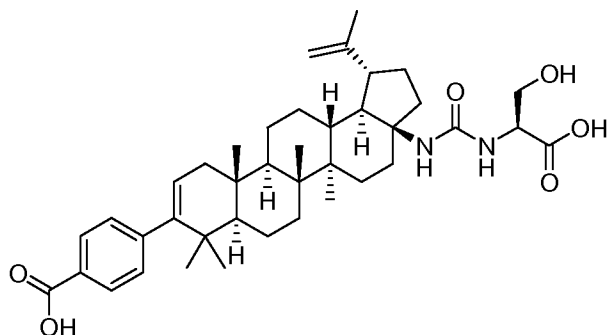
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using L-alanine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (74 mg, 54% yield). LCMS: m/z 645 ($M+H^+$), retention time 2.26 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 0.99 (s, 6 H), 1.02 - 1.09 (m, 2 H), 1.10 (s, 3 H), 1.19 - 1.35 (m, 5 H), 1.37 (d, $J=7.32$ Hz, 3 H), 1.39 - 1.57 (m, 6 H), 1.63 (t, $J=11.60$ Hz, 1 H), 1.66 - 1.76 (m, 6 H), 1.76 - 1.85 (m, 1 H), 1.88 - 1.99 (m, 1 H), 2.11 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.35 (dd, $J=12.36$, 8.09 Hz, 1 H), 2.50 - 2.61 (m, 2 H), 4.28 (q, $J=7.02$ Hz, 1 H), 4.61 (br. s., 1 H), 4.72 (br. s., 1 H), 5.26 - 5.31 (m, 1 H), 7.20 (d, $J=8.24$ Hz, 2 H), 7.92 (d, $J=8.55$ Hz, 2 H).

Example 18

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxy-2-hydroxyethyl)ureido)-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.

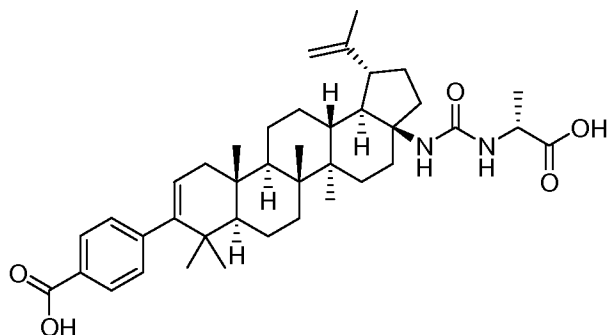


- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using L-serine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (70 mg, 48% yield). LCMS: m/z 661 ($M+H^+$), retention time 2.19 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.93 (s, 3 H), 0.99 (br. s., 3 H), 1.00 (s, 3 H), 1.03 - 1.09 (m, 2 H), 1.11 (s, 3 H), 1.21 - 1.41 (m, 5 H), 1.41 - 1.57 (m, 6 H), 1.64 (t, $J=11.60$ Hz, 1 H), 1.67 - 1.77 (m, 6 H), 1.84 (td, $J=12.21, 3.36$ Hz, 1 H), 1.88 - 1.99 (m, 1 H), 2.11 (dd, $J=17.09, 6.41$ Hz, 1 H), 2.35 (dd, $J=12.21, 8.24$ Hz, 1 H), 2.54 - 2.63 (m, 2 H), 3.80 (dd, $J=10.99, 3.66$ Hz, 1 H), 3.93 (dd, $J=10.99, 4.27$ Hz, 1 H), 4.37 (t, $J=3.97$ Hz, 1 H), 4.61 (br. s., 1 H), 4.72 (d, $J=1.53$ Hz, 1 H), 5.28 (dd, $J=6.26, 1.68$ Hz, 1 H), 7.20 (m, $J=8.54$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

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Example 19

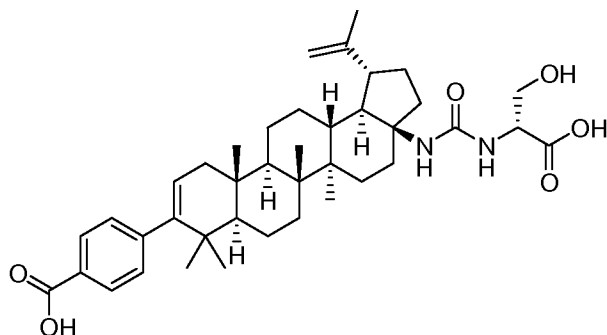
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *D*-alanine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (68 mg, 50% yield). LCMS: m/z 645 ($M+H^+$), retention time 2.23 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 6 H), 1.03 - 1.14 (m, 5 H), 1.20 - 1.36 (m, 5 H), 1.37 (d, $J=7.02$ Hz, 3 H), 1.40 - 1.58 (m, 6 H), 1.58 - 1.68 (m, 2 H), 1.68 - 1.75 (m, 5 H), 1.75 - 1.83 (m, 1 H), 1.92 - 2.03 (m, 1 H), 2.11 (dd, $J=17.09, 6.41$ Hz, 1 H), 2.34 (dd, $J=12.21, 8.24$ Hz, 1 H), 2.51 - 2.60 (m, 2 H), 4.27 (q, $J=7.32$ Hz, 1 H), 4.60 (br. s., 2 H), 4.72 (d, $J=1.53$ Hz, 1 H), 5.28 (dd, $J=6.10, 1.53$ Hz, 1 H), 7.20 (m, $J=8.55$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 20

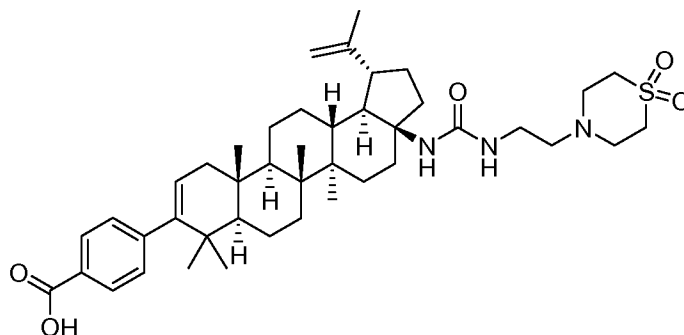
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxy-2-hydroxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *D*-serine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (51 mg, 34% yield). LCMS: m/z 661 ($M+H^+$), retention time 2.11 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.92 (br. s., 6 H), 0.98 (br. s., 6 H), 1.02 - 1.14 (m, 5 H), 1.17 - 1.38 (m, 5 H), 1.39 - 1.58 (m, 6 H), 1.58 - 1.75 (m, 7 H), 1.76 - 1.86 (m, 1 H), 1.90 - 2.04 (m, 1 H), 2.04 - 2.13 (m, 1 H), 2.36 (t, $J=9.77$ Hz, 1 H), 2.56 (d, $J=12.51$ Hz, 2 H), 3.81 (d, $J=10.99$ Hz, 1 H), 3.94 (d, $J=10.99$ Hz, 1 H), 4.35 (d, $J=2.44$ Hz, 1 H), 4.60 (br. s., 1 H), 4.71 (br. s., 1 H), 5.28 (br. s., 1 H), 7.19 (m, $J=7.32$ Hz, 2 H), 7.92 (m, $J=7.63$ Hz, 2 H).

Example 21

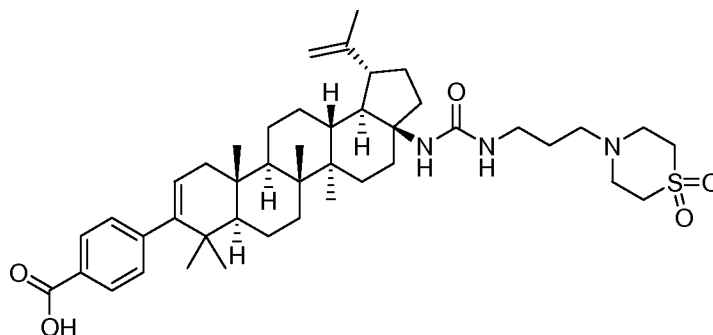
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 4-(2-aminoethyl)thiomorpholine 1,1-dioxide as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (121 mg, 74% yield). LCMS: m/z 734 ($M+H^+$), retention time 2.49 min
- 15 (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.95 (s, 3 H), 1.02 (br. s., 3 H), 1.03 (br. s., 3 H), 1.10 (s, 3 H), 1.11 - 1.17 (m, 2 H), 1.21 - 1.60 (m, 11 H), 1.63 - 1.82 (m, 8 H), 1.86 - 2.00 (m, 1 H), 2.13 (dd, $J=17.24$, 6.26 Hz, 1 H), 2.35 (dd, $J=12.05$, 8.39 Hz, 1 H), 2.52 - 2.63 (m, 2 H), 3.20 (br. s., 2 H), 3.39 - 3.52 (m, 6 H), 3.69 (br. s., 4 H), 4.63 (s, 1 H), 4.75 (d, $J=1.22$
- 20 Hz, 1 H), 5.29 (d, $J=4.58$ Hz, 1 H), 7.21 (m, $J=8.24$ Hz, 2 H), 7.93 (m, $J=8.24$ Hz, 2 H).

Example 22

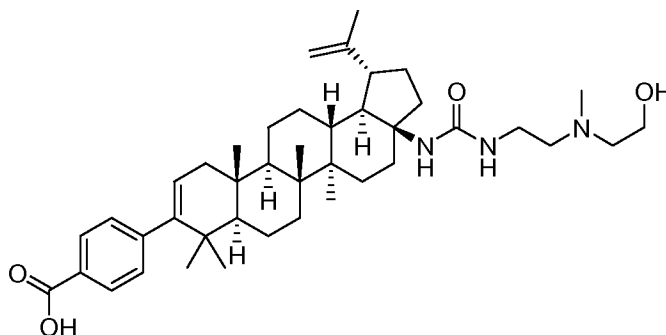
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxido-4-thiomorpholinyl)propyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 4-(3-aminopropyl)thiomorpholine 1,1-dioxide as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (115 mg, 59% yield). LCMS: m/z 748 ($M+H^+$), retention time 2.44 min
- 15 (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.95 (s, 3 H), 0.96 (s, 3 H), 1.02 (br. s., 3 H), 1.03 (br. s., 3 H), 1.11 (s, 3 H), 1.12 - 1.18 (m, 2 H), 1.24 - 1.44 (m, 5 H), 1.44 - 1.60 (m, 6 H), 1.63 - 1.80 (m, 8 H), 1.85 - 1.99 (m, 3 H), 2.14 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.32 (dd, $J=12.05$, 8.09 Hz, 1 H), 2.52 - 2.63 (m, 2 H), 3.14 (t, $J=7.02$ Hz, 2 H), 3.19 - 3.30 (m, 2 H), 3.50 (d, $J=4.58$
- 20 Hz, 4 H), 3.65 (d, $J=5.19$ Hz, 4 H), 4.63 (s, 1 H), 4.75 (s, 1 H), 5.27 - 5.32 (m, 1 H), 7.21 (m, $J=8.24$ Hz, 2 H), 7.93 (m, $J=8.24$ Hz, 2 H).

Example 23

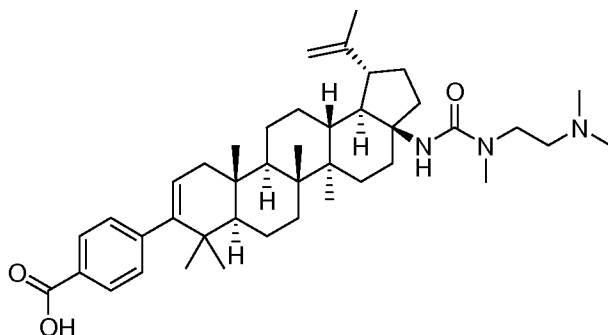
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-((2-hydroxyethyl)(methyl)amino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-((2-aminoethyl)(methyl)amino)ethanol as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (43 mg, 69% yield). LCMS: m/z 674 ($M+H^+$), retention time 2.41 min (method 11). ^1H
- 15 NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 1.08 (s, 3 H), 1.08 - 1.15 (m, 2 H), 1.22 - 1.39 (m, 5 H), 1.40 - 1.56 (m, 6 H), 1.59 - 1.79 (m, 8 H), 1.85 - 1.99 (m, 1 H), 2.11 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.35 (br. s., 1 H), 2.48 - 2.61 (m, 2 H), 2.96 (s, 3 H), 3.09 - 3.61 (m, 6 H), 3.87 (t, $J=5.19$ Hz, 2 H), 4.61 (br. s., 1 H), 4.73 (br. s., 1 H),
- 20 5.24 - 5.31 (m, 1 H), 7.20 (d, $J=8.24$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 24

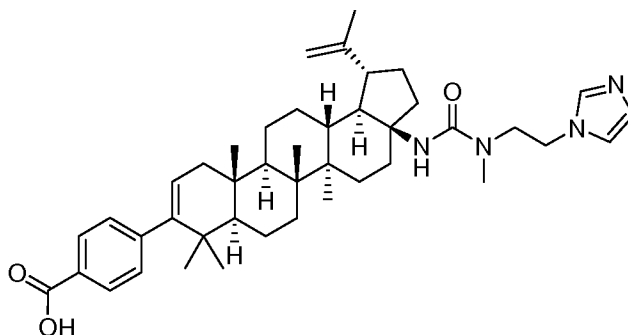
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1,N2*-trimethylethane-1,2-diamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (34 mg, 57% yield). LCMS: m/z 658 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.10 (s, 3 H), 1.10 - 1.20 (m, 2 H), 1.20 - 1.28 (m, 1 H), 1.31 - 1.42 (m, 4 H), 1.44 - 1.58 (m, 7 H), 1.62 - 1.80 (m, 7 H), 1.88 - 2.01 (m, 1 H), 2.12 (dd, $J=17.09$, 6.10 Hz, 1 H), 2.41 - 2.56 (m, 3 H), 2.92 (s, 6 H), 3.03 (s, 3 H), 3.18 - 3.31 (m, 2 H), 3.51 (ddd, $J=15.11$, 5.95, 5.80 Hz, 1 H), 3.73 - 3.83 (m, 1 H), 4.54 (s, 1 H), 4.64 (br. s., 1 H), 4.75 (s, 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, $J=8.24$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 25

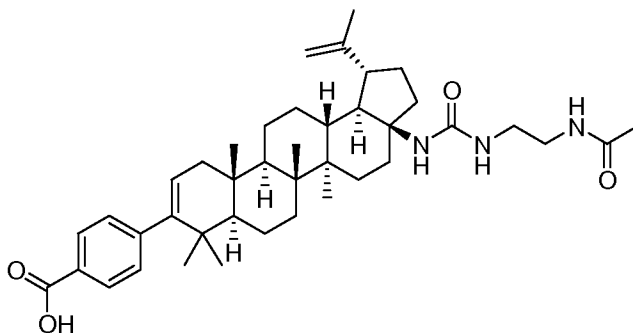
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-1-yl)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(1H-imidazol-1-yl)-N-methylethanamine, 2 HCl as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (35 mg, 56% yield). LCMS: m/z 681 ($M+H^+$), retention time 2.39 min (method
- 15 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.02 (s, 3 H), 1.09 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.23 - 1.42 (m, 5 H), 1.43 - 1.54 (m, 6 H), 1.54 - 1.60 (m, 1 H), 1.61 - 1.76 (m, 7 H), 1.80 - 1.94 (m, 1 H), 2.12 (dd, $J=17.24$, 6.26 Hz, 1 H), 2.29 (dd, $J=12.67$, 8.09 Hz, 1 H), 2.35 - 2.51 (m, 2 H), 3.01 (s, 3 H), 3.65 (dt, $J=14.57$, 5.84 Hz, 1 H),
- 20 3.79 - 3.89 (m, 1 H), 4.33 - 4.43 (m, 2 H), 4.64 (br. s., 1 H), 4.74 (br. s., 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, $J=8.55$ Hz, 2 H), 7.41 (t, $J=1.53$ Hz, 1 H), 7.51 (t, $J=1.68$ Hz, 1 H), 7.92 (d, $J=8.24$ Hz, 2 H), 8.88 (d, $J=1.22$ Hz, 1 H).

Example 26

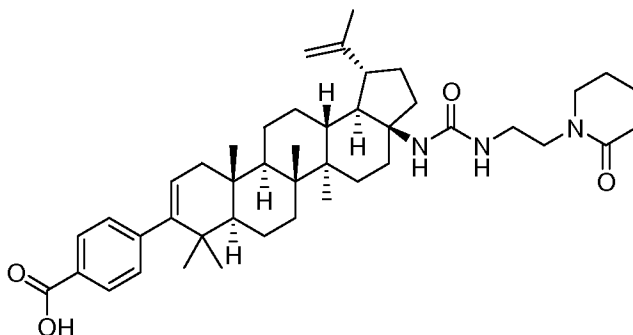
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-
acetamidoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-aminoethyl)acetamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (24 mg, 48% yield). LCMS: m/z 658 ($M+H^+$), retention time 2.73 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 1.04 - 1.15 (m, 5 H), 1.21 - 1.41 (m, 6 H), 1.41 - 1.58 (m, 6 H), 1.58 - 1.67 (m, 2 H), 1.70 (s, 3 H), 1.70 - 1.82 (m, 3 H), 1.86 - 1.94 (m, 1 H), 1.96 (s, 3 H), 2.11 (dd, $J=17.40, 6.41$ Hz, 1 H), 2.34 (dd, $J=12.05, 8.09$ Hz, 1 H), 2.49 - 2.61 (m, 2 H), 3.19 - 3.27 (m, 4 H), 4.61 (br. s., 1 H), 4.72 (s, 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, $J=8.55$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 27

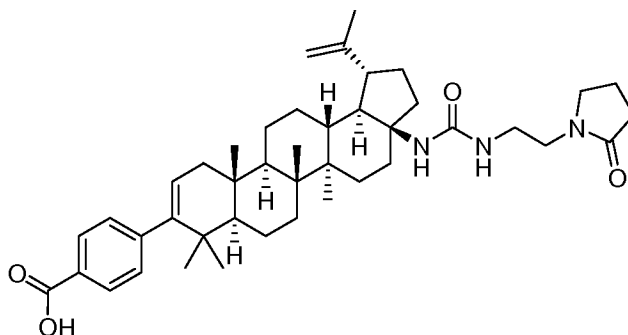
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(2-oxopiperidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(2-aminoethyl)piperidin-2-one hydrobromide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (37 mg, 68% yield). LCMS: m/z 698 ($M+H^+$), retention time 2.83 min (method 11). ^1H NMR
 15 (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 6 H), 1.04 - 1.14 (m, 5 H), 1.21 - 1.41 (m, 5 H), 1.41 - 1.58 (m, 6 H), 1.58 - 1.67 (m, 2 H), 1.70 (s, 3 H), 1.70 - 1.85 (m, 7 H), 1.86 - 1.97 (m, 1 H), 2.11 (dd, $J=17.09$, 6.10 Hz, 1 H), 2.29 - 2.39 (m, 3 H), 2.50 - 2.61 (m, 2 H), 3.30 - 3.32 (m, 1 H), 3.40 (t, $J=5.34$ Hz, 2 H), 3.45 (t, $J=5.95$ Hz, 2 H), 4.61 (br. s., 1 H),
 20 4.72 (br. s., 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, $J=8.24$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 28

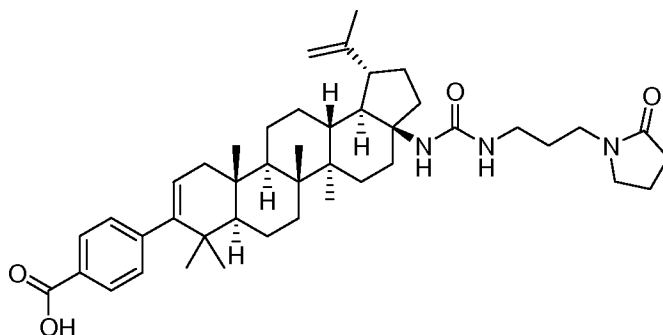
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(2-oxopyrrolidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(2-aminoethyl)pyrrolidin-2-one oxalic acid salt as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (37 mg, 67% yield). LCMS: m/z 684 ($M+H^+$), retention time 2.78 min (method 11). ^1H NMR
 15 (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 6 H), 1.04 - 1.15 (m, 5 H), 1.21 - 1.41 (m, 6 H), 1.41 - 1.59 (m, 6 H), 1.59 - 1.67 (m, 2 H), 1.67 - 1.81 (m, 6 H), 1.86 - 1.97 (m, 1 H), 2.00 - 2.08 (m, 2 H), 2.11 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.33 (dd, $J=12.36$, 8.09 Hz, 1 H), 2.38 (t, $J=8.09$ Hz, 2 H), 2.50 - 2.60 (m, 2 H), 3.28 - 3.32 (m, 2 H), 3.53 (t, $J=7.32$ Hz, 2 H), 4.61 (s,
 20 1 H), 4.72 (d, $J=1.53$ Hz, 1 H), 5.28 (dd, $J=5.95$, 1.68 Hz, 1 H), 7.20 (m, $J=8.54$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 29

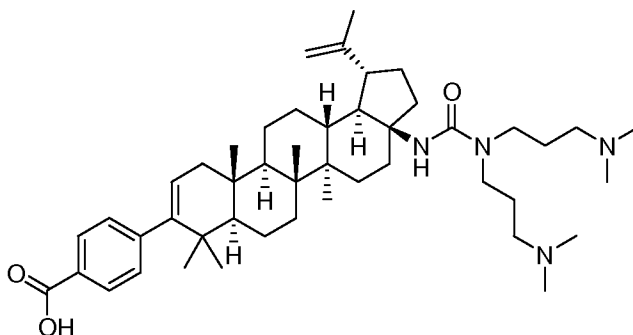
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(2-oxopyrrolidin-1-yl)propyl)ureido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(3-aminopropyl)pyrrolidin-2-one as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (38 mg, 69% yield). LCMS: m/z 698 ($M+H^+$), retention time 2.79 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (s, 3 H), 1.04 - 1.16 (m, 5 H), 1.21 - 1.41 (m, 5 H), 1.41 - 1.59 (m, 6 H), 1.59 - 1.76 (m, 9 H), 1.80 (td, $J=12.21$, 3.05 Hz, 1 H), 1.88 - 2.00 (m, 1 H), 2.03 - 2.16 (m, 3 H), 2.36 (dd, $J=12.21$, 8.24 Hz, 1 H), 2.42 (t, $J=8.09$ Hz, 2 H), 2.51 - 2.64 (m, 2 H), 3.09 (t, $J=6.56$ Hz, 2 H), 3.25 - 3.38 (m, 2 H), 3.47 (t, $J=7.17$ Hz, 2 H), 4.61 (s, 1 H), 4.73 (d, $J=1.53$ Hz, 1 H), 5.25 - 5.32 (m, 1 H), 7.20 (m, $J=8.24$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 30

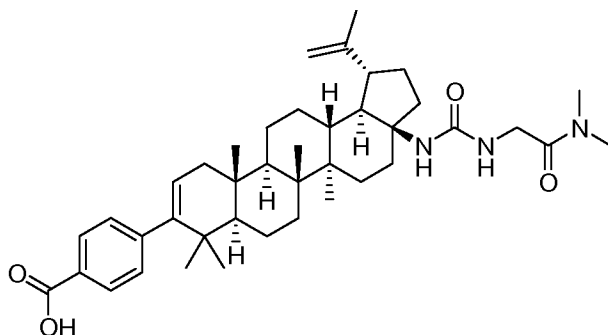
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-bis(3-(dimethylamino)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*1-(3-(dimethylamino)propyl)-*N*3,*N*3-dimethylpropane-1,3-diamine as the reactant amine. The bis-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (15 mg, 20% yield). LCMS: m/z 743 ($M+H^+$), retention
 15 time 2.27 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.09 (s, 3 H), 1.11 - 1.19 (m, 2 H), 1.26 (d, $J=6.71$ Hz, 1 H), 1.30 - 1.44 (m, 3 H), 1.44 - 1.62 (m, 8 H), 1.63 - 1.81 (m, 7 H), 1.83 - 1.95 (m, 1 H), 2.02 (br. s., 4 H), 2.13 (dd, $J=17.09, 6.41$ Hz, 1 H), 2.41 (dd, $J=12.51, 8.24$ Hz, 1 H), 2.51 (td, $J=10.91, 5.04$ Hz,
 20 1 H), 2.59 (d, $J=13.43$ Hz, 1 H), 2.89 (s, 12 H), 3.13 (t, $J=7.02$ Hz, 4 H), 3.34 - 3.43 (m, 4 H), 4.76 (s, 1 H), 5.26 - 5.33 (m, 1 H), 7.20 (m, $J=8.55$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 31

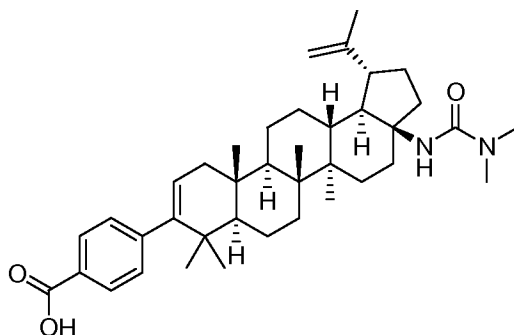
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)-2-oxoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-amino-*N,N*-dimethylacetamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (7 mg, 14% yield). LCMS: m/z 658 ($M+H^+$), retention time 2.77 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.01 (s, 6 H), 1.05 - 1.16 (m, 5 H), 1.21 - 1.41 (m, 6 H), 1.41 - 1.57 (m, 6 H), 1.60 - 1.78 (m, 7 H), 1.84 (td, $J=12.28$, 3.51 Hz, 1 H), 1.91 - 2.01 (m, 1 H), 2.12 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.36 (dd, $J=12.21$, 7.93 Hz, 1 H), 2.55 - 2.64 (m, 2 H), 2.98 (s, 3 H), 3.03 (s, 3 H), 3.89 - 4.07 (m, 2 H), 4.61 (d, $J=1.22$ Hz, 1 H), 4.73 (d, $J=1.83$ Hz, 1 H), 5.29 (dd, $J=6.10$, 1.83 Hz, 1 H), 7.20 (d, $J=8.54$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 32

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-dimethylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 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.

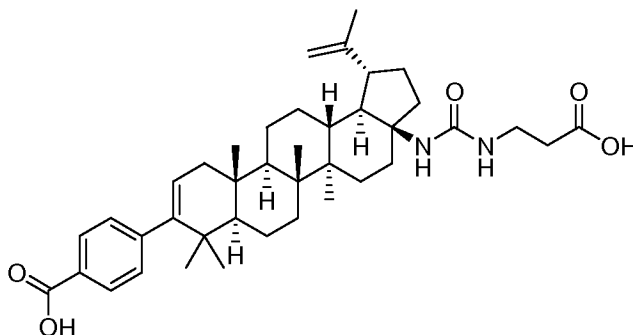


10 The title compound was formed as a byproduct during the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)-2-oxoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. Hydrolysis of the penultimate methyl ester
 15 by the general procedure as described and purification by reverse phase preparative HPLC gave a white solid (13 mg, 29% yield). LCMS: m/z 601 ($M+H^+$), retention time 2.90 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.10 (s, 3 H), 1.11 - 1.19 (m, 2 H), 1.24 - 1.44 (m, 6 H), 1.45 - 1.60 (m, 7 H), 1.61 - 1.66 (m, 1
 20 H), 1.69 (d, $J=5.49$ Hz, 2 H), 1.71 (s, 3 H), 1.72 - 1.78 (m, 2 H), 1.91 - 2.01 (m, 1 H), 2.12 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.42 - 2.52 (m, 2 H), 2.56 (dt, $J=13.20$, 3.32 Hz, 1 H), 2.95 (s, 6 H), 4.63 (d, $J=1.53$ Hz, 1 H), 4.74 (d, $J=1.83$ Hz, 1 H), 5.29 (dd, $J=6.26$,
 1.68 Hz, 1 H), 7.20 (m, $J=8.24$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

25

Example 33

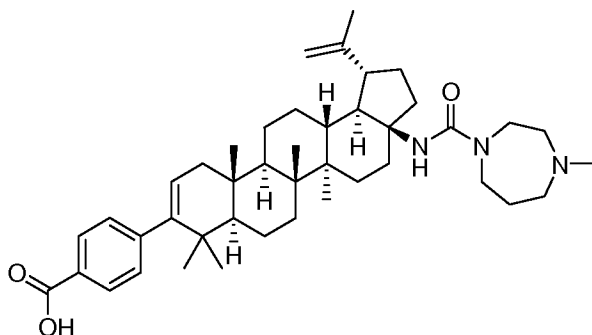
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using methyl-3-aminopropanoate HCl as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (33 mg, 67% yield). LCMS: m/z 645 ($M+H^+$), retention time 2.69 min (method 11). ^1H NMR (500 MHz, 1:1
 15 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H), 0.94 (s, 3 H), 1.00 (s, 6 H), 1.03 - 1.14 (m, 5 H), 1.21 - 1.40 (m, 5 H), 1.40 - 1.58 (m, 6 H), 1.58 - 1.67 (m, 2 H), 1.67 - 1.75 (m, 5 H), 1.75 - 1.83 (m, 1 H), 1.87 - 1.98 (m, 1 H), 2.11 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.34 (dd, $J=12.05$, 8.09 Hz, 1 H), 2.49 (t, $J=6.26$ Hz, 2 H), 2.51 - 2.63 (m, 2 H), 3.37 (td, $J=6.33$, 3.81 Hz, 2 H), 4.60 (s, 1 H), 4.72 (d, $J=1.83$
 20 Hz, 1 H), 5.28 (dd, $J=6.10$, 1.53 Hz, 1 H), 7.20 (m, $J=8.54$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 34

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-methyl-1,4-diazepane-1-carboxamido)-1-(prop-1-en-2-yl)-
 5 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.

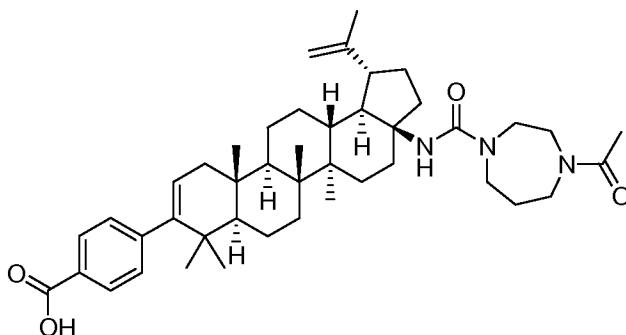


- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-methyl-1,4-diazepane as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (30 mg, 48% yield). LCMS: m/z 670 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 6 H), 1.00 (s, 3 H),
 15 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.22 (m, 3 H), 1.22 - 1.45 (m, 5 H), 1.45 - 1.64 (m, 8 H), 1.64 - 1.81 (m, 7 H), 1.87 - 2.01 (m, 1 H), 2.12 (dd, $J=17.19$, 6.40 Hz, 1 H), 2.33 (br. s., 2 H), 2.40 - 2.53 (m, 2 H), 2.58 (d, $J=13.30$ Hz, 1 H), 2.92 (s, 3 H), 3.54 (br. s., 2 H), 4.64 (s, 1 H), 4.75 (d, $J=1.00$ Hz, 1 H), 5.26 - 5.33 (m, 1 H), 7.20 (m, $J=8.28$
 20 Hz, 2 H), 7.92 (m, $J=8.28$ Hz, 2 H).

Example 35

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetyl-1,4-

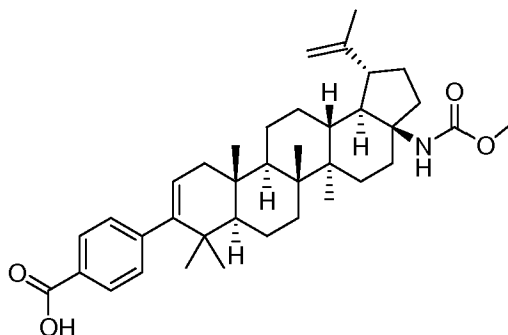
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-[1,4-diazepan-1-yl]ethanone as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (27 mg, 48% yield). LCMS: m/z 698 ($M+H^+$), retention time 2.74 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.01 (s, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.19 (m, 2 H), 1.21 - 1.66 (m, 14 H), 1.67 - 1.78 (m, 6 H), 1.85 - 2.02 (m, 3 H), 2.11 (s, 2 H), 2.12 - 2.17 (m, 2 H), 2.34 - 2.50 (m, 2 H), 2.54 - 2.64 (m, 1 H), 3.41 - 3.48 (m, 2 H), 3.50 - 3.64 (m, 5 H), 4.63 (br. s., 1 H), 4.75 (d, $J=9.16$ Hz, 1 H), 5.29 (d, $J=4.58$ Hz, 1 H), 7.20 (d, $J=8.24$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).
- 15
- 20

Example 36

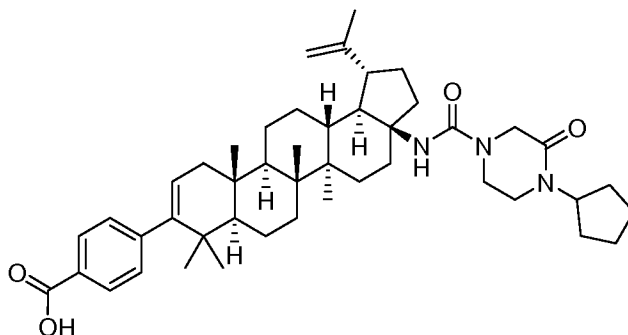
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(methoxycarbonylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was formed as a byproduct during the urea formation step in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetyl-1,4-diazepane-1-carboxamido)-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. Hydrolysis of the penultimate methyl ester by the general procedure as described and purification by reverse phase preparative HPLC gave a white solid (6 mg, 13% yield). LCMS: m/z 588 ($M+H^+$), retention time 3.07 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.01 (s, 3 H), 1.09 (s, 3 H), 1.09 - 1.16 (m, 2 H), 1.23 - 1.27 (m, 1 H), 1.28 - 1.44 (m, 5 H), 1.45 - 1.57 (m, 6 H), 1.59 - 1.77 (m, 9 H), 1.88 - 2.00 (m, 1 H), 2.12 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.28 - 2.39 (m, 1 H), 2.45 - 2.58 (m, 2 H), 3.62 (br. s., 3 H), 4.62 (d, $J=1.53$ Hz, 1 H), 4.74 (d, $J=1.83$ Hz, 1 H), 5.29 (dd, $J=6.26$, 1.68 Hz, 1 H), 7.20 (d, $J=8.24$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 37

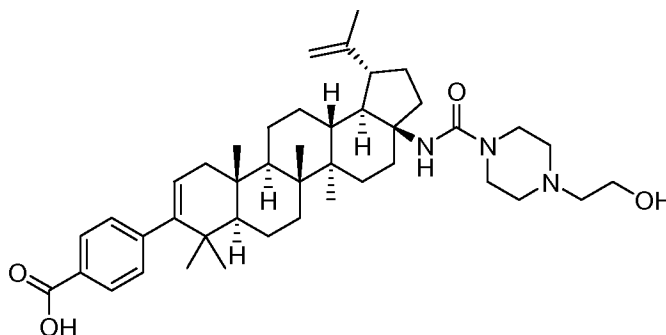
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-cyclopentyl-3-oxopiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-cyclopentylpiperazin-2-one, HCl, 0.5 H₂O as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (18 mg, 28% yield). LCMS: *m/z* 724 (M+H⁺), retention time 2.97 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of CDCl₃ and MeOD, MeOD lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.11 - 1.19 (m, 2 H), 1.24 (d, *J*=8.85 Hz, 1 H), 1.30 - 1.42 (m, 4 H), 1.43 - 1.60 (m, 10 H), 1.62 - 1.67 (m, 2 H), 1.67 - 1.80 (m, 9 H), 1.82 - 1.90 (m, 2 H), 1.90 - 2.00 (m, 1 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.40 - 2.60 (m, 3 H), 3.35 - 3.41 (m, 2 H), 3.53 - 3.68 (m, 2 H), 3.94 - 4.04 (m, 1 H), 4.04 - 4.13 (m, 1 H), 4.63 (br. s., 1 H), 4.75 (s, 1 H), 4.90 (quin, *J*=8.47 Hz, 1 H), 5.25 - 5.31 (m, 1 H), 5.34 - 5.38 (m, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 38

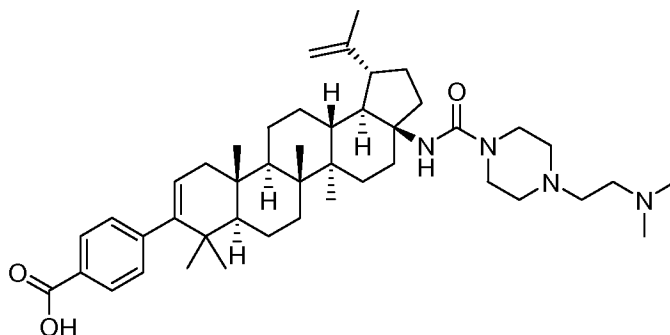
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hydroxyethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(piperazin-1-yl)ethanol as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (12 mg, 18% yield). LCMS: m/z 686 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.24 - 1.28 (m, 1 H), 1.32 - 1.43 (m, 4 H), 1.44 - 1.59 (m, 7 H), 1.67 - 1.80 (m, 7 H), 1.86 - 1.98 (m, 1 H), 2.12 (dd, $J=17.24$, 6.26 Hz, 1 H), 2.42 (dd, $J=12.36$, 8.09 Hz, 1 H), 2.53 - 2.65 (m, 2 H), 3.23 - 3.29 (m, 3 H), 3.92 (dd, $J=5.95$, 4.43 Hz, 2 H), 4.75 (d, $J=1.53$ Hz, 1 H), 5.29 (dd, $J=6.10$, 1.83 Hz, 1 H), 7.20 (m, $J=8.24$ Hz, 2 H), 7.92 (m, $J=8.54$ Hz, 2 H).

Example 39

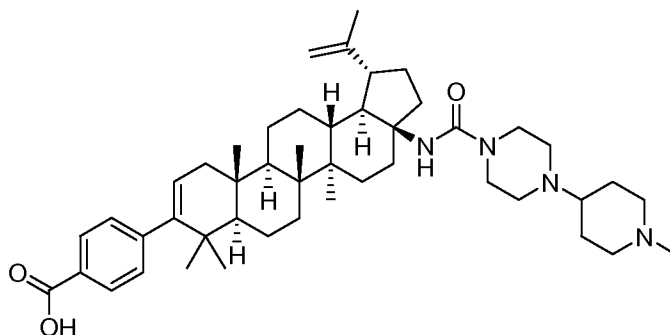
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-(dimethylamino)ethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N,N*-dimethyl-2-(piperazin-1-yl)ethanamine as the reactant amine. The bis-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (15 mg, 19% yield). LCMS: m/z 713 ($M+H^+$), retention time 2.44 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.20 (m, 2 H), 1.24 - 1.44 (m, 7 H), 1.44 - 1.62 (m, 7 H), 1.64 - 1.79 (m, 7 H), 1.88 - 2.00 (m, 1 H), 2.12 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.44 (dd, $J=12.21$, 8.24 Hz, 1 H), 2.51 (dt, $J=10.15$, 5.15 Hz, 1 H), 2.57 (d, $J=13.12$ Hz, 1 H), 2.73 (br. s., 4 H), 2.87 - 2.99 (m, 8 H), 3.39 - 3.55 (m, 4 H), 4.75 (s, 1 H), 5.29 (d, $J=4.58$ Hz, 1 H), 7.20 (m, $J=8.24$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 40

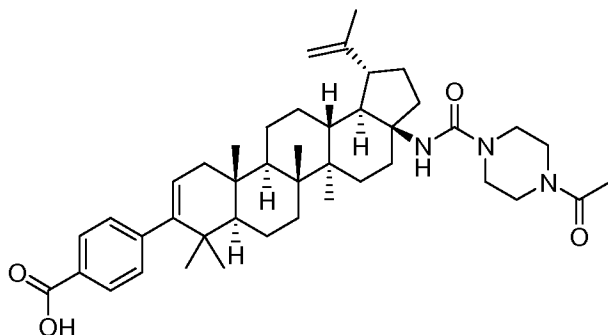
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-(1-methylpiperidin-4-yl)piperazine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(1-methylpiperidin-4-yl)piperazine as the reactant amine. The bis-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (48 mg, 61% yield). LCMS: m/z 739 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.23 - 1.28 (m, 1 H), 1.29 - 1.44 (m, 4 H), 1.44 - 1.64 (m, 9 H), 1.65 - 1.79 (m, 7 H), 1.87 - 1.99 (m, 1 H), 1.99 - 2.08 (m, 2 H), 2.12 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.40 - 2.60 (m, 3 H), 2.77 - 2.93 (m, 5 H), 3.03 - 3.13 (m, 1 H), 3.35 (br. s., 4 H), 3.47 (br. s., 4 H), 3.99 - 4.15 (m, 2 H), 4.63 (s, 1 H), 4.75 (d, $J=1.22$ Hz, 1 H), 5.29 (dd, $J=6.10$, 1.53 Hz, 1 H), 7.20 (m, $J=8.54$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 41

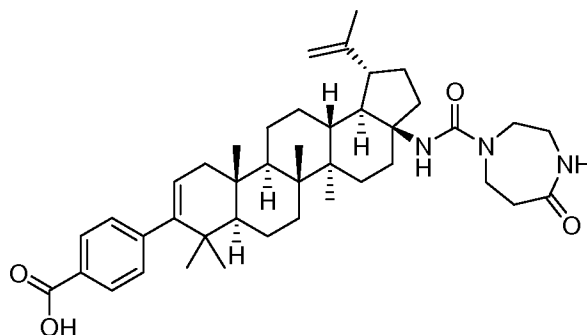
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-
acetylpiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described
above for the C-17 urea formation and subsequent ester hydrolysis using 1-(piperazin-
1-yl)ethanone as the reactant amine. The product was isolated after reverse phase
preparative HPLC purification as a white solid (6 mg, 11% yield). LCMS: m/z 684
($M+H^+$), retention time 2.81 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of
15 $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H), 0.94 (s, 3 H), 1.01 (s, 3 H),
1.04 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.20 (m, 2 H), 1.24 - 1.28 (m, 2 H), 1.29 - 1.45 (m,
4 H), 1.45 - 1.62 (m, 7 H), 1.64 - 1.79 (m, 7 H), 1.89 - 2.00 (m, 1 H), 2.08 - 2.16 (m, 4
H), 2.46 (dd, $J=12.36$, 8.09 Hz, 1 H), 2.52 (td, $J=10.60$, 5.34 Hz, 1 H), 2.58 (ddd,
 $J=13.35$, 3.36, 3.13 Hz, 1 H), 3.35 - 3.48 (m, 3 H), 3.49 - 3.60 (m, 3 H), 3.60 - 3.73
20 (m, 2 H), 4.75 (d, $J=1.53$ Hz, 1 H), 5.29 (dd, $J=6.10$, 1.53 Hz, 1 H), 7.20 (m, $J=8.54$
Hz, 2 H), 7.92 (m, $J=8.54$ Hz, 2 H).

Example 42

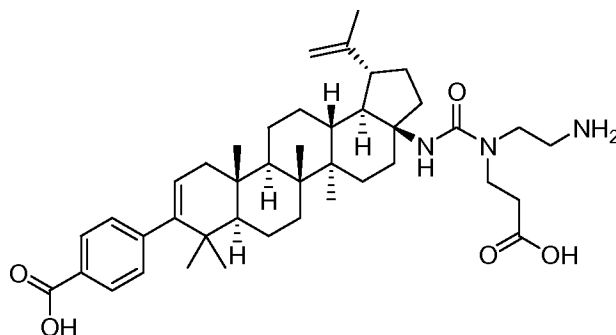
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(5-oxo-1,4-diazepane-1-carboxamido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1,4-diazepan-5-one as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (26 mg, 46% yield). LCMS: m/z 670 ($M+H^+$), retention time 2.70 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of
 15 $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.19 (m, 2 H), 1.26 (dd, $J=7.17, 3.20$ Hz, 1 H), 1.31 - 1.43 (m, 5 H), 1.45 - 1.54 (m, 6 H), 1.55 - 1.60 (m, 2 H), 1.63 - 1.80 (m, 7 H), 1.88 - 1.99 (m, 1 H), 2.13 (dd, $J=16.94, 6.26$ Hz, 1 H), 2.44 - 2.53 (m, 2 H), 2.60 (ddd, $J=13.50, 2.82, 2.59$ Hz, 1 H), 2.68 (t, $J=5.19$ Hz, 2 H), 3.49 - 3.68 (m, 4 H), 4.57 (s, 1
 20 H), 4.75 (d, $J=1.53$ Hz, 1 H), 5.29 (dd, $J=6.10, 1.53$ Hz, 1 H), 7.20 (d, $J=8.54$ Hz, 2 H), 7.92 (d, $J=8.54$ Hz, 2 H).

Example 43

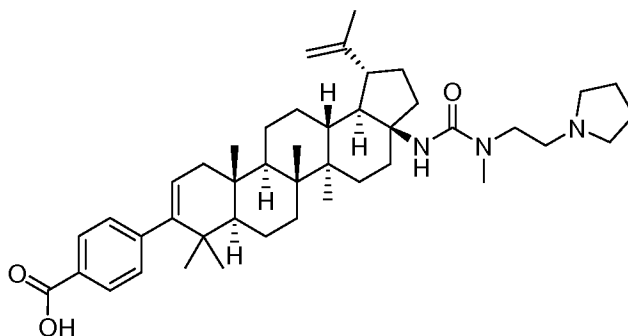
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoethyl)-3-(2-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 10 The title compound was formed as a byproduct during the ester hydrolysis step in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(5-oxo-1,4-diazepane-1-carboxamido)-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. Purification by reverse phase preparative
- 15 HPLC gave a white solid (10 mg, 15% yield) mono-TFA salt. LCMS: m/z 688 ($M+H^+$), retention time 2.40 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 6 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.07 - 1.17 (m, 5 H), 1.23 - 1.42 (m, 7 H), 1.44 - 1.62 (m, 7 H), 1.67 - 1.81 (m, 6 H), 1.84 - 2.00 (m, 2 H), 2.13 (dd, $J=17.39, 6.41$ Hz, 1 H), 2.38 (dd, $J=11.90, 7.93$ Hz, 1 H),
- 20 2.51 - 2.58 (m, 1 H), 2.59 - 2.66 (m, 1 H), 2.66 - 2.73 (m, 1 H), 2.77 (td, $J=10.83, 4.58$ Hz, 1 H), 2.99 - 3.10 (m, 2 H), 3.36 - 3.46 (m, 3 H), 3.76 (ddd, $J=15.56, 9.31, 3.81$ Hz, 1 H), 4.76 (d, $J=1.83$ Hz, 1 H), 5.29 (dd, $J=6.10, 1.53$ Hz, 1 H), 7.20 (m, $J=8.24$ Hz, 2 H), 7.92 (m, $J=8.24$ Hz, 2 H).

Example 44

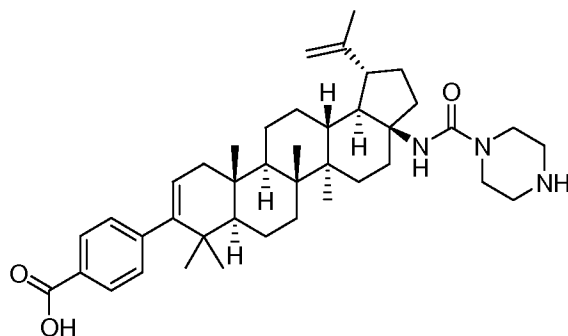
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-methyl-3-(2-(pyrrolidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using *N*-methyl-2-(pyrrolidin-1-yl)ethanamine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (34 mg, 54% yield) mono-TFA salt. LCMS: m/z 684 ($M+H^+$), retention time 2.41 min (method 11). ^1H
 NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3
 15 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.10 (s, 3 H), 1.10 - 1.21 (m, 2 H), 1.26 (dd, $J=10.68$, 2.75 Hz, 1 H), 1.32 - 1.43 (m, 4 H), 1.45 - 1.59 (m, 7 H), 1.62 - 1.81 (m, 8 H), 1.87 - 2.00 (m, 1 H), 2.08 (br. s., 4 H), 2.12 (dd, $J=17.09$, 6.41 Hz, 1
 H), 2.41 - 2.57 (m, 3 H), 3.03 (s, 3 H), 3.06 (br. s., 2 H), 3.25 - 3.39 (m, 2 H), 3.52 (dt, $J=14.65$, 6.26 Hz, 1 H), 3.63 - 3.83 (m, 3 H), 4.64 (br. s., 1 H), 4.75 (s, 1 H), 5.26 -
 20 5.32 (m, 1 H), 7.20 (d, $J=7.93$ Hz, 2 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 45

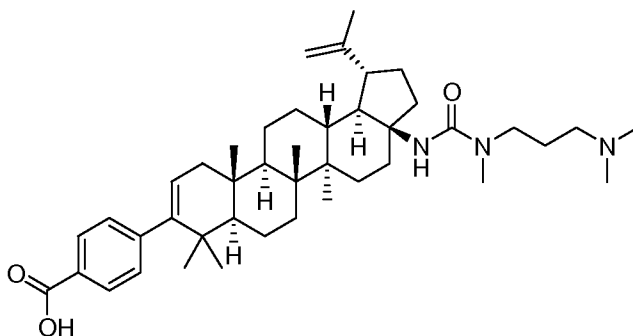
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperazine-1-carboxamido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using 1-(piperazin-1-yl)ethanone as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (5 mg, 8% yield) mono-TFA salt.
 LCMS: m/z 642 ($M+H^+$), retention time 2.42 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H),
 15 1.00 (s, 3 H), 1.04 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.26 (dd, $J=8.09$, 2.29 Hz, 1 H), 1.29 - 1.44 (m, 4 H), 1.44 - 1.51 (m, 4 H), 1.51 - 1.62 (m, 3 H), 1.67 - 1.80 (m, 7 H), 1.87 - 1.97 (m, 1 H), 2.12 (dd, $J=17.09$, 6.41 Hz, 1 H), 2.43 (dd, $J=12.36$, 8.09 Hz, 1 H), 2.53 - 2.63 (m, 2 H), 3.13 - 3.27 (m, 4 H), 3.55 - 3.68 (m, 4 H), 4.75 (d, $J=1.53$ Hz, 1 H), 4.95 (s, 1 H), 5.29 (dd, $J=6.10$, 1.53 Hz, 1 H), 7.20 (d, $J=8.54$ Hz, 2
 20 H), 7.92 (d, $J=8.24$ Hz, 2 H).

Example 46

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(dimethylamino)propyl)-3-methylureido)-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.

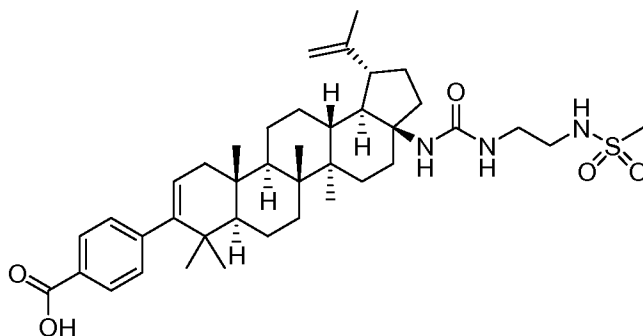


The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1,N3*-trimethylpropane-1,3-diamine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (21 mg, 31% yield) mono-TFA salt. LCMS: m/z 672 ($M+H^+$), retention time 1.86 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.05 (s, 3 H) 1.07 - 1.20 (m, 5 H) 1.24 - 1.29 (m, 2 H) 1.33 - 1.39 (m, 2 H) 1.40 - 1.59 (m, 9 H) 1.62 - 1.80 (m, 7 H) 1.88 - 2.02 (m, 3 H) 2.13 (dd, $J=17.09, 6.41$ Hz, 1 H) 2.43 (dd, $J=12.51, 8.24$ Hz, 1 H) 2.46 - 2.55 (m, 2 H) 2.87 (s, 6 H) 2.98 - 3.10 (m, 5 H) 3.34 - 3.49 (m, 2 H) 4.76 (d, $J=1.22$ Hz, 1 H) 5.29 (dd, $J=6.10, 1.83$ Hz, 1 H) 7.20 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.24$ Hz, 2 H).

20

Example 47

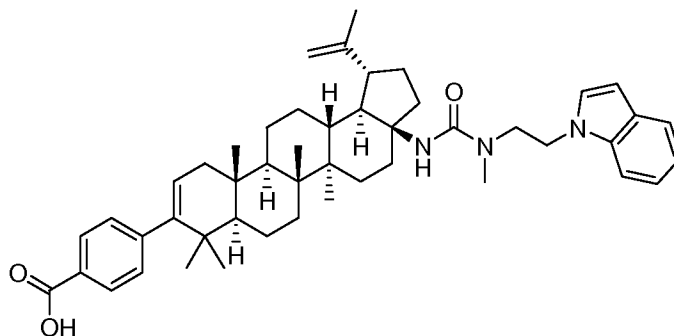
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(methylsulfonamido)ethyl)ureido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-aminoethyl)methanesulfonamide hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (28 mg, 51% yield). LCMS: m/z 694 ($M+H^+$), retention time 2.17 min (method 2). ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3
 15 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.04 - 1.16 (m, 5 H) 1.23 - 1.43 (m, 6 H) 1.45 - 1.56 (m, 5 H) 1.59 - 1.83 (m, 8 H) 1.87 - 2.00 (m, 1 H) 2.11 (dd, $J=17.19$, 6.40 Hz, 1 H) 2.36 (dd, $J=12.05$, 8.28 Hz, 1 H) 2.49 - 2.63 (m, 2 H) 2.95 (s, 3 H) 3.09 - 3.17 (m, 2 H) 3.20 - 3.30 (m, 2 H) 4.61 (s, 1 H) 4.72 (d, $J=1.76$ Hz, 1 H) 5.29 (dd, $J=6.02$, 1.51 Hz, 1 H) 7.20 (m, $J=8.28$ Hz, 2 H) 7.92 (m, $J=8.28$ Hz, 2 H).

Example 48

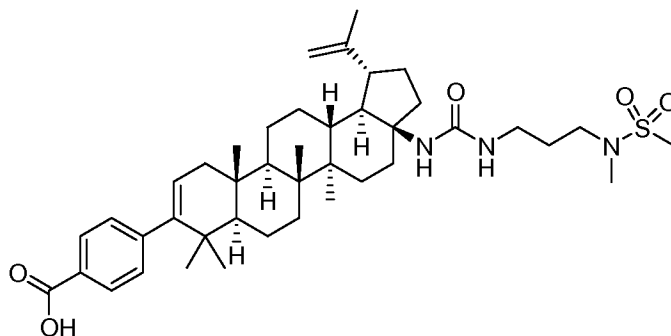
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-indol-1-yl)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(1H-indol-1-yl)-*N*-methylethanamine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (30 mg, 39% yield) mono-TFA salt. LCMS: m/z 730 ($M+H^+$), retention time 2.73 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H) 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 0.97 (s, 3 H) 0.99 (s, 3 H) 1.01 - 1.12 (m, 2 H) 1.21 - 1.29 (m, 3 H) 1.32 - 1.37 (m, 2 H) 1.38 - 1.53 (m, 7 H) 1.54 - 1.73 (m, 7 H) 1.79 - 1.92 (m, 1 H) 2.09 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.19 (td, $J=10.61$, 4.43 Hz, 1 H) 2.42 (s, 3 H) 2.48 - 2.57 (m, 2 H) 3.60 (ddd, $J=14.50$, 5.49, 5.34 Hz, 1 H) 3.71 (ddd, $J=14.65$, 5.65, 5.34 Hz, 1 H) 4.28 - 4.39 (m, 2 H) 4.60 (br. s., 1 H) 4.69 (s, 1 H) 5.27 (d, $J=6.10$ Hz, 1 H) 6.51 (d, $J=3.05$ Hz, 1 H) 7.05 - 7.12 (m, 2 H) 7.15 - 7.22 (m, 3 H) 7.38 (d, $J=8.24$ Hz, 1 H) 7.61 (d, $J=7.93$ Hz, 1 H) 7.92 (d, $J=8.24$ Hz, 2 H).

Example 49

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(*N*-methylmethanesulfonamido)propyl)ureido)-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.

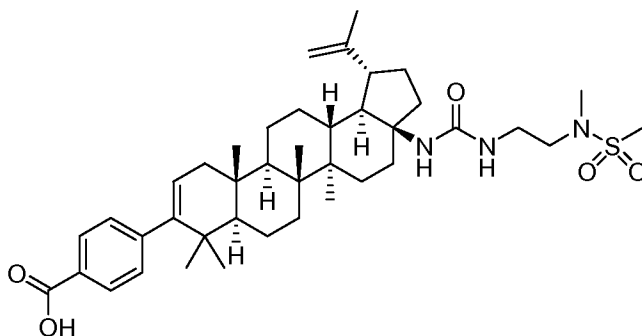


The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(3-aminopropyl)-*N*-methylmethanesulfonamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (36 mg, 62% yield). LCMS: m/z 730 ($M+H^+$), retention time 2.25 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.05 - 1.15 (m, 5 H) 1.21 - 1.41 (m, 5 H) 1.41 - 1.59 (m, 6 H) 1.62 - 1.81 (m, 10 H) 1.88 - 1.99 (m, 1 H) 2.11 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.35 (dd, $J=12.36$, 8.09 Hz, 1 H) 2.50 - 2.63 (m, 2 H) 2.85 (s, 3 H) 2.86 (s, 3 H) 3.12 - 3.23 (m, 4 H) 4.61 (s, 1 H) 4.72 (d, $J=1.53$ Hz, 1 H) 5.25 - 5.32 (m, 1 H) 7.20 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.24$ Hz, 2 H).

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Example 50

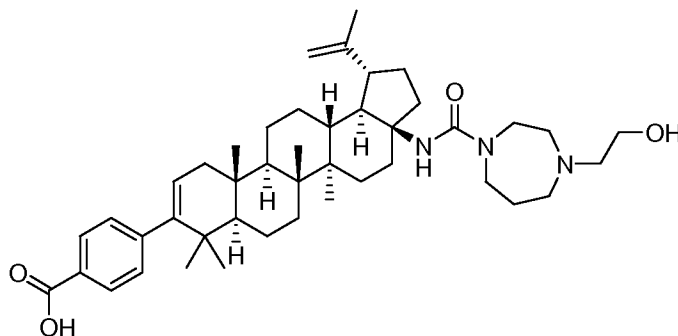
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(N-methylmethanesulfonamido)ethyl)ureido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-aminoethyl)-*N*-methylmethanesulfonamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (37 mg, 65% yield). LCMS: m/z 708 ($M+H^+$), retention time 2.25 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H)
 15 0.94 (s, 3 H) 1.00 (s, 6 H) 1.04 - 1.15 (m, 5 H) 1.21 - 1.41 (m, 5 H) 1.41 - 1.58 (m, 6 H) 1.59 - 1.75 (m, 7 H) 1.75 - 1.83 (m, 1 H) 1.88 - 2.00 (m, 1 H) 2.11 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.36 (dd, $J=12.36$, 8.09 Hz, 1 H) 2.51 - 2.64 (m, 2 H) 2.86 (s, 3 H) 2.91 (s, 3 H) 3.18 - 3.25 (m, 2 H) 3.31 (t, $J=5.49$ Hz, 2 H) 4.61 (s, 1 H) 4.72 (d, $J=1.53$ Hz, 1 H) 5.28 (dd, $J=6.26$, 1.68 Hz, 1 H) 7.20 (d, $J=8.54$ Hz, 2 H) 7.92 (d, $J=8.24$ Hz, 2
 20 H).

Example 51

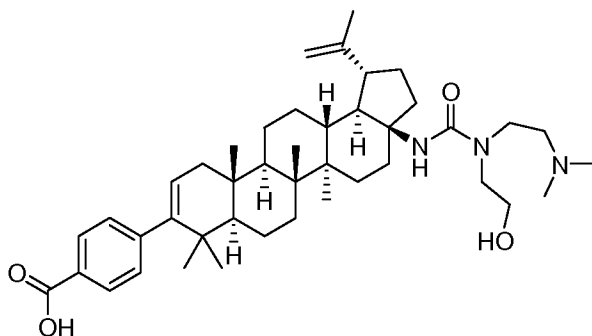
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hydroxyethyl)-1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,4-diazepan-1-yl)ethanol as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (49 mg, 72% yield) mono-TFA salt. LCMS: m/z 700 ($M+H^+$), retention time 1.77 min (method 2). ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.04 (s, 3 H) 1.09 (s, 3 H) 1.10 - 1.18 (m, 2 H) 1.18 - 1.64 (m, 13 H) 1.64 - 1.82 (m, 7 H) 1.85 - 2.01 (m, 1 H) 2.12 (dd, $J=17.19, 6.40$ Hz, 1 H) 2.29 - 2.41 (m, 2 H) 2.41 - 2.53 (m, 2 H) 2.58 (d, $J=13.30$ Hz, 1 H) 3.25 - 3.32 (m, 2 H) 3.35 - 3.63 (m, 6 H) 3.69 - 4.00 (m, 4 H) 4.64 (br. s., 1 H) 4.75 (s, 1 H) 5.29 (d, $J=4.77$ Hz, 1 H) 7.19 (m, 2 H) 7.91 (m, 2 H).

Example 52

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)-3-(2-hydroxyethyl)ureido)-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.

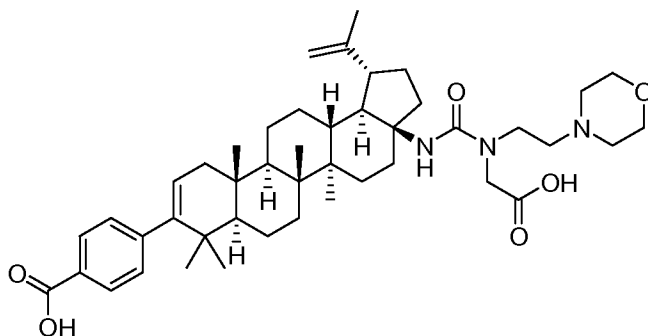


The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(2-(dimethylamino)ethylamino)ethanol as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (35 mg, 51% yield) mono-TFA salt. LCMS: m/z 688 ($M+H^+$), retention time 1.79 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.01 (br. s., 3 H) 1.02 (br. s., 3 H) 1.06 - 1.18 (m, 5 H) 1.20 - 1.66 (m, 12 H) 1.66 - 1.81 (m, 7 H) 1.81 - 2.01 (m, 2 H) 2.12 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.37 (dd, $J=12.05$, 8.09 Hz, 1 H) 2.46 - 2.61 (m, 2 H) 2.93 (s, 6 H) 3.21 - 3.31 (m, 2 H) 3.48 - 3.61 (m, 3 H) 3.72 - 3.79 (m, 2 H) 4.61 (br. s., 1 H) 4.74 (br. s., 1 H) 5.23 - 5.35 (m, 1 H) 7.20 (d, $J=8.24$ Hz, 2 H) 7.92 (d, $J=8.24$ Hz, 2 H).

20

Example 53

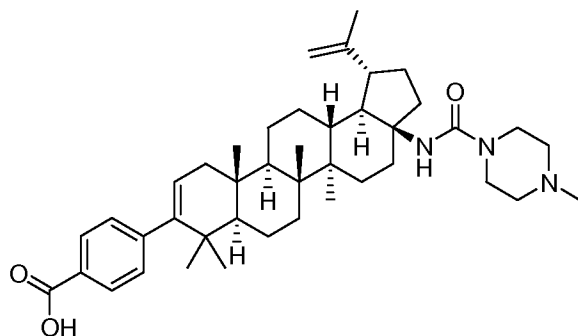
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(carboxymethyl)-3-(2-morpholinoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using ethyl 2-(2-morpholinoethylamino)acetate as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (5 mg, 6% yield) mono-TFA salt. LCMS: m/z 744 ($M+H^+$), retention time 1.81 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.10 (d, $J=2.44$ Hz, 1 H) 1.11 - 1.16 (m, 4 H) 1.19 - 1.64 (m, 12 H) 1.64 - 1.80 (m, 7 H) 1.87 - 1.98 (m, 1 H) 2.13 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.35 (dd, $J=12.51$, 8.24 Hz, 1 H) 2.47 - 2.59 (m, 2 H) 3.23 - 3.30 (m, 2 H) 3.37 (s, 3 H) 3.58 (td, $J=10.38$, 4.88 Hz, 1 H) 3.70 - 4.03 (m, 6 H) 4.72 (s, 1 H) 4.78 (d, $J=1.53$ Hz, 1 H) 5.29 (dd, $J=6.10$, 1.53 Hz, 1 H) 7.20 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.24$ Hz, 2 H).

Example 54

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-methylpiperazine-1-carboxamido)-1-(prop-1-en-2-yl)-
 5 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.



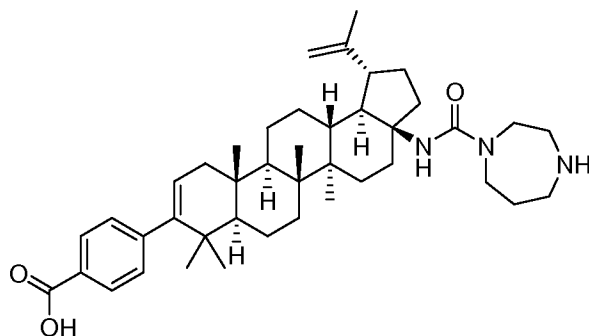
The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using 1-methylpiperazine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (49 mg, 75% yield) mono-TFA salt.
 LCMS: m/z 656 ($M+H^+$), retention time 2.44 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H)
 15 1.00 (s, 3 H) 1.03 (s, 3 H) 1.05 - 1.19 (m, 5 H) 1.23 - 1.28 (m, 1 H) 1.31 - 1.42 (m, 4 H) 1.44 - 1.59 (m, 7 H) 1.64 - 1.81 (m, 7 H) 1.86 - 1.98 (m, 1 H) 2.12 (dd, $J=17.24$, 6.26 Hz, 1 H) 2.42 (dd, $J=12.36$, 8.39 Hz, 1 H) 2.51 - 2.65 (m, 2 H) 2.90 (s, 3 H) 3.34 (br. s., 4 H) 3.96 (br. s., 2 H) 4.64 (br. s., 1 H) 4.75 (d, $J=1.22$ Hz, 1 H) 5.29 (dd, $J=6.26$, 1.68 Hz, 1 H) 7.20 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.55$ Hz, 2 H).

20

Example 55

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1,4-diazepane-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 5 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.

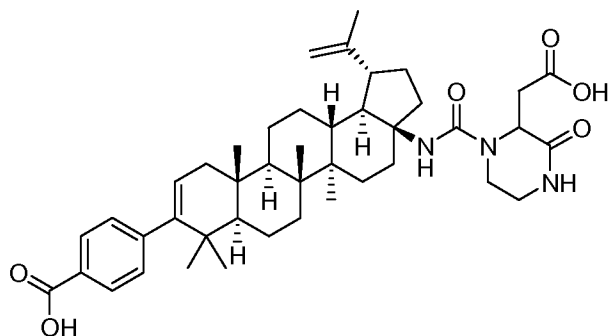


- The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using
 homopiperazine as the reactant amine. The product was isolated after reverse phase
 preparative HPLC purification as a white solid (33 mg, 53% yield) mono-TFA salt.
 LCMS: m/z 656 ($M+H^+$), retention time 2.43 min (method 11). ^1H NMR (400 MHz,
 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 6 H) 1.00 (s, 3 H) 1.04
 15 (s, 3 H) 1.09 (s, 3 H) 1.10 - 1.22 (m, 2 H) 1.24 - 1.30 (m, 1 H) 1.34 - 1.59 (m, 11 H)
 1.64 - 1.82 (m, 7 H) 1.86 - 2.01 (m, 1 H) 2.12 (dd, $J=17.07$, 6.27 Hz, 1 H) 2.18 - 2.29
 (m, 2 H) 2.42 - 2.53 (m, 2 H) 2.59 (d, $J=13.30$ Hz, 1 H) 3.20 - 3.31 (m, 4 H) 3.48 -
 3.62 (m, 2 H) 3.76 (t, $J=4.27$ Hz, 2 H) 4.47 (s, 1 H) 4.64 (s, 1 H) 4.75 (s, 1 H) 5.29 (d,
 $J=4.77$ Hz, 1 H) 7.20 (m, $J=8.03$ Hz, 2 H) 7.92 (m, $J=8.03$ Hz, 2 H).

20

Example 56

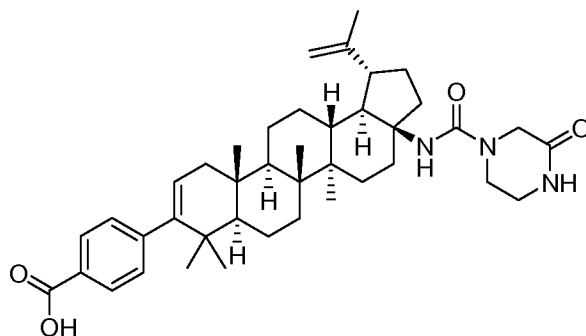
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-
 (carboxymethyl)-3-oxopiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-
 5 (prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-
 1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using ethyl 2-(3-
 oxopiperazin-2-yl)acetate as the reactant amine. The product was isolated after
 reverse phase preparative HPLC purification as a white solid (38 mg, 64% yield).
 LCMS: m/z 714 ($M+H^+$), retention time 2.66 min (method 11). This material is a
 diastereomeric mixture in a ratio of approximately 1:1. ^1H NMR (400 MHz, 1:1
 15 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.91 - 0.97 (m, 6 H) 0.97 - 1.04
 (m, 6 H) 1.05 - 1.17 (m, 5 H) 1.19 - 1.64 (m, 13 H) 1.65 - 1.80 (m, 7 H) 1.80 - 2.08
 (m, 3 H) 2.12 (dt, $J=17.07$, 6.02 Hz, 1 H) 2.23 (dd, $J=12.30$, 8.28 Hz, 0.5 H) 2.34 -
 2.44 (m, 0.5 H) 2.58 (d, $J=13.30$ Hz, 0.5 H) 2.65 - 2.76 (m, 1 H) 2.80 - 2.96 (m, 2 H)
 2.97 - 3.13 (m, 2 H) 3.14 - 3.24 (m, 1 H) 3.50 - 3.64 (m, 1.5 H) 3.94 - 4.03 (m, 0.5 H)
 20 4.07 (dd, $J=13.80$, 2.76 Hz, 0.5 H) 4.70 - 4.80 (m, 2 H) 5.25 - 5.32 (m, 1 H) 7.19 (d,
 $J=8.03$ Hz, 2 H) 7.92 (d, 2 H).

Example 57

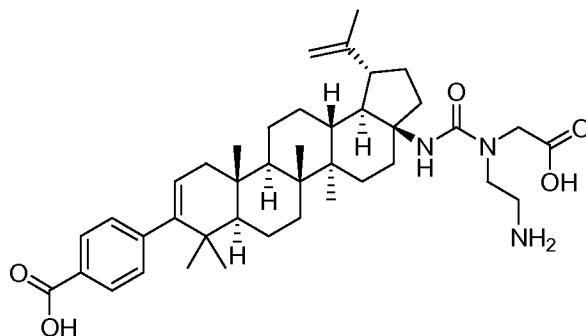
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-oxopiperazine-1-carboxamido)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using piperazin-2-one as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (7 mg, 12% yield). LCMS: m/z 656 ($M+H^+$), retention time 2.71 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.03 (s, 3 H) 1.10
 15 (s, 3 H) 1.10 - 1.20 (m, 2 H) 1.25 (d, $J=10.07$ Hz, 1 H) 1.29 - 1.44 (m, 4 H) 1.44 - 1.63 (m, 7 H) 1.65 - 1.80 (m, 7 H) 1.89 - 2.00 (m, 1 H) 2.13 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.46 (dd, $J=12.51$, 8.24 Hz, 1 H) 2.49 - 2.61 (m, 2 H) 3.36 - 3.45 (m, 2 H) 3.54 - 3.67 (m, 2 H) 3.91 - 4.02 (m, 1 H) 4.02 - 4.13 (m, 1 H) 4.64 (d, $J=1.22$ Hz, 1 H) 4.76 (d, $J=1.22$ Hz, 1 H) 5.29 (dd, $J=6.26$, 1.68 Hz, 1 H) 7.20 (d, $J=8.24$ Hz, 2 H) 7.92 (d,
 20 $J=8.55$ Hz, 2 H).

Example 58

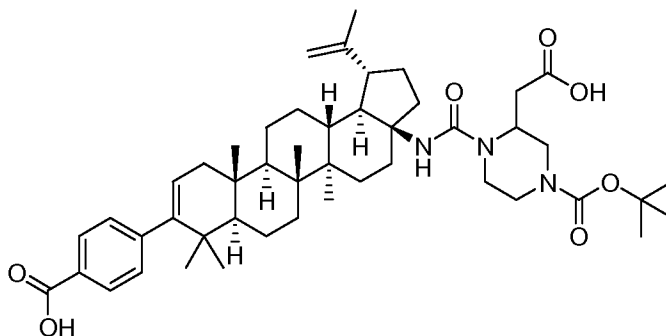
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoethyl)-3-(carboxymethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was formed as a byproduct during the ester hydrolysis step
 10 in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-oxopiperazine-1-carboxamido)-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. Purification by reverse phase preparative HPLC gave a white solid (22 mg, 33% yield) mono-TFA salt. LCMS: m/z 674
 15 (M+H⁺), retention time 2.41 min (method 11). ¹H NMR (400 MHz, 1:1 mixture of CDCl₃ and MeOD, MeOD lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.07 - 1.18 (m, 5 H) 1.20 - 1.59 (m, 12 H) 1.60 - 1.79 (m, 8 H) 1.86 - 2.01 (m, 1 H) 2.12 (dd, J=17.07, 6.27 Hz, 1 H) 2.37 - 2.51 (m, 2 H) 2.51 - 2.60 (m, 1 H) 3.05 - 3.18 (m, 2 H) 3.47 (ddd, J=15.37, 5.46, 5.27 Hz, 1 H) 3.70 - 3.82 (m, 1 H) 3.93 - 4.06
 20 (m, 2 H) 4.62 (s, 1 H) 4.75 (d, J=1.51 Hz, 1 H) 5.29 (dd, J=6.02, 1.51 Hz, 1 H) 7.20 (m, J=8.28 Hz, 2 H) 7.92 (m, J=8.28 Hz, 2 H).

Example 59

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(*tert*-
butoxycarbonyl)-2-(carboxymethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-
5 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.

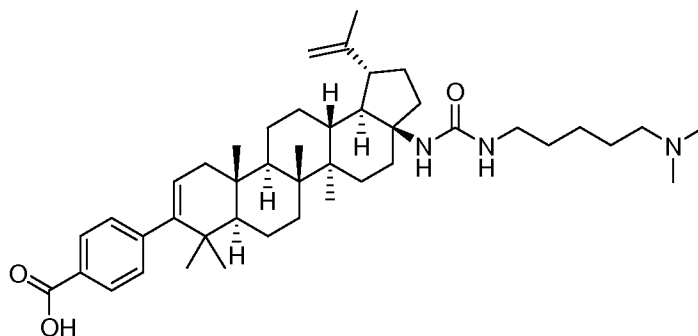


The title compound was prepared following the general procedures described
10 above for the C-17 urea formation and subsequent ester hydrolysis using *tert*-butyl 3-
(2-methoxy-2-oxoethyl)piperazine-1-carboxylate as the reactant amine. The product
was isolated after reverse phase preparative HPLC purification as a white solid (39
mg, 63% yield). LCMS: m/z 800 ($M+H^+$), retention time 2.94 min (method 11). This
material is a diastereomeric mixture in a ratio of approximately 2:1. ^1H NMR (500
15 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm ^1H NMR (500 MHz,
 $MeOD$) δ ppm 0.89 - 0.97 (m, 6 H) 0.97 - 1.05 (m, 6 H) 1.05 - 1.18 (m, 5 H) 1.25 (d,
 $J=3.36$ Hz, 1 H) 1.29 - 1.44 (m, 5 H) 1.48 (d, $J=5.80$ Hz, 13 H) 1.51 - 1.62 (m, 3 H)
1.65 - 1.80 (m, 7 H) 1.81 - 2.00 (m, 2 H) 2.12 (ddd, $J=17.09$, 6.10, 3.66 Hz, 1 H) 2.27
- 2.42 (m, 1 H) 2.57 (dd, $J=17.24$, 4.12 Hz, 1 H) 2.63 (dd, $J=12.82$, 9.77 Hz, 2 H)
20 2.75 (br. s., 0.5 H) 2.88 (d, $J=7.02$ Hz, 1.5 H) 2.95 - 3.04 (m, 1 H) 3.09 (br. s., 0.5 H)
3.80 (d, $J=11.60$ Hz, 0.5 H) 3.91 (d, $J=12.21$ Hz, 0.5 H) 4.03 (d, $J=10.38$ Hz, 1 H)
5.29 (dd, $J=4.27$, 2.14 Hz, 1 H) 7.20 (dd, $J=8.24$, 2.44 Hz, 2 H) 7.92 (d, $J=7.32$ Hz, 2
H).

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Example 60

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(5-(dimethylamino)pentyl)ureido)-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.

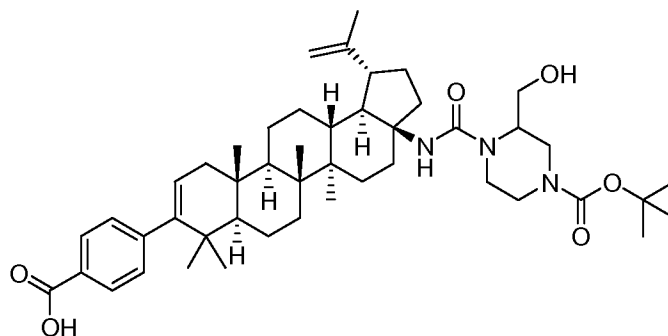


The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N,N*-dimethylpentane-1,5-diamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (21 mg, 57% yield). LCMS: m/z 686 ($M+H^+$), retention time 2.44 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (br. s., 3 H) 1.01 (br. s., 3 H) 1.04 - 1.16 (m, 5 H) 1.23 - 1.26 (m, 1 H) 1.28 - 1.44 (m, 7 H) 1.44 - 1.59 (m, 7 H) 1.59 - 1.67 (m, 2 H) 1.67 - 1.84 (m, 8 H) 1.86 - 1.98 (m, 1 H) 2.12 (dd, $J=17.40$, 6.41 Hz, 1 H) 2.34 (dd, $J=12.21$, 8.24 Hz, 1 H) 2.50 - 2.63 (m, 2 H) 2.86 (s, 6 H) 3.03 - 3.17 (m, 4 H) 4.61 (s, 1 H) 4.72 (d, $J=1.53$ Hz, 1 H) 5.24 - 5.32 (m, 1 H) 7.20 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.24$ Hz, 2 H).

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Example 61

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(*tert*-
butoxycarbonyl)-2-(hydroxymethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-
5 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.



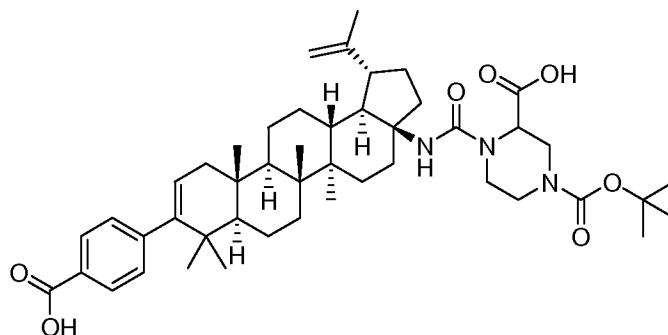
The title compound was prepared following the general procedures described
10 above for the C-17 urea formation and subsequent ester hydrolysis using *tert*-butyl 3-
(hydroxymethyl)piperazine-1-carboxylate as the reactant amine. The product was
isolated as a mixture of two diastereomers after reverse phase preparative HPLC
purification as a white solid (68 mg, 60% yield). LCMS: m/z 772 ($M+H^+$), retention
time 2.91 and 2.99 min (method 11). This material is a diastereomeric mixture in a
15 ratio of approximately 5:4. ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$,
 $MeOD$ lock) δ ppm 0.89 - 0.98 (m, 6 H) 0.98 - 1.04 (m, 6 H) 1.05 - 1.18 (m, 5 H) 1.20
- 1.44 (m, 6 H) 1.47 (d, $J=2.26$ Hz, 9 H) 1.48 - 1.61 (m, 6 H) 1.62 - 1.77 (m, 7 H) 1.80
- 2.01 (m, 2 H) 2.12 (dd, $J=16.81, 6.02$ Hz, 1 H) 2.32 - 2.42 (m, 1 H) 2.46 - 2.56 (m, 1
H) 2.60 (dd, $J=13.30, 2.51$ Hz, 1 H) 2.98 - 3.15 (m, 2 H) 3.21 (ddd, $J=18.63, 13.87,$
20 4.64 Hz, 1 H) 3.61 - 3.69 (m, 1 H) 3.71 - 3.91 (m, 4 H) 3.94 - 4.06 (m, 1 H) 4.61 (d,
 $J=8.78$ Hz, 1 H) 4.74 (dd, $J=10.79, 1.25$ Hz, 1 H) 5.24 - 5.33 (m, 1 H) 7.20 (dd,
 $J=8.41, 1.88$ Hz, 2 H) 7.86 - 7.92 (m, 1 H) 7.93 (s, 1 H).

Example 62

Preparation of 4-(*tert*-butoxycarbonyl)-1-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-

5 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-ylcarbamoyl)piperazine-2-carboxylic acid.

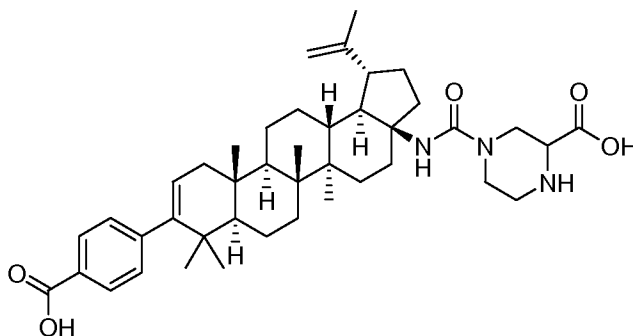


10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-*tert*-butyl 3-methyl piperazine-1,3-dicarboxylate as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC purification as a white solid (76 mg, 62% yield). LCMS: m/z 786 ($M+H^+$), retention time 2.84 min (method 11). This material is a diastereomeric mixture in a ratio of approximately 1:1. ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.04 - 1.18 (m, 5 H) 1.19 - 1.43 (m, 6 H) 1.46 (d, $J=2.75$ Hz, 9 H) 1.47 - 1.61 (m, 6 H) 1.61 - 1.80 (m, 8 H) 1.91 - 2.05 (m, 1 H) 2.12 (dd, $J=17.09, 6.41$ Hz, 1 H) 2.43 (dd, $J=12.21, 8.24$ Hz, 1 H) 2.46 - 2.53 (m, 1 H) 2.53 - 2.62 (m, 1 H) 2.98 (br. s., 1 H) 3.17 (d, $J=9.77$ Hz, 1 H) 3.35 - 3.44 (m, 1 H) 3.50 (d, $J=9.77$ Hz, 1 H) 4.09 (br. s., 1 H) 4.60 (d, $J=13.73$ Hz, 1 H) 4.63 (br. s., 1 H) 4.68 (br. s., 1 H) 4.75 (br. s., 1 H) 5.29 (d, $J=4.58$ Hz, 1 H) 7.20 (d, $J=8.24$ Hz, 2 H) 7.92 (d, $J=8.24$ Hz, 2 H).

25

Example 63

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



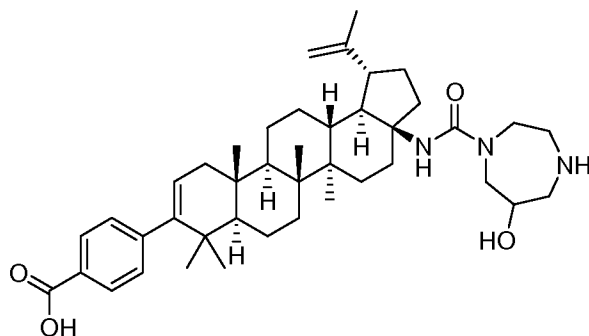
The title compound was prepared following the general procedures described
 10 above for the C-17 urea formation and subsequent ester hydrolysis using methyl piperazine-2-carboxylate as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC purification as a white solid (75 mg, 41% yield) mono-TFA salt. LCMS: m/z 686 ($M+H^+$), retention time 2.46 min (method 11). This material is a diastereomeric mixture in a ratio of
 15 approximately 1:1. ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H) 0.93 (br. s., 3 H) 0.99 (s, 3 H) 1.02 (s, 3 H) 1.05 - 1.18 (m, 5 H) 1.25 (d, $J=7.63$ Hz, 1 H) 1.28 - 1.42 (m, 4 H) 1.42 - 1.52 (m, 5 H) 1.52 - 1.64 (m, 2 H) 1.65 - 1.84 (m, 7 H) 1.87 - 1.99 (m, 1 H) 2.11 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.41 (td, $J=11.90$, 8.85 Hz, 1 H) 2.55 (dd, $J=13.43$, 2.75 Hz, 1 H) 2.63 (tt, $J=10.72$,
 20 5.46 Hz, 1 H) 3.07 - 3.18 (m, 0.5 H) 3.19 - 3.27 (m, 0.5 H) 3.34 - 3.51 (m, 2 H) 3.57 - 3.71 (m, 1 H) 3.71 - 3.83 (m, 1 H) 3.98 - 4.05 (m, 0.5 H) 4.07 - 4.16 (m, 1 H) 4.16 - 4.25 (m, 0.5 H) 4.63 (s, 1 H) 4.76 (br. s., 1 H) 5.28 (d, $J=4.88$ Hz, 1 H) 7.19 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.24$ Hz, 2 H).

25

Example 64

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(6-hydroxy-1,4-

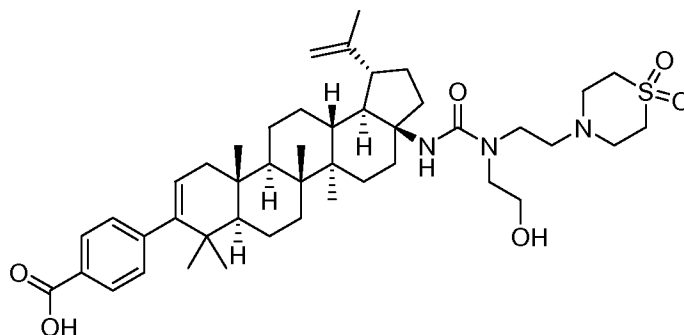
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- The title compound was prepared following the general procedures described
- 10 above for the C-17 urea formation and subsequent ester hydrolysis using 1,4-diazepan-6-ol dihydrobromide as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC purification as a white solid (30 mg, 35% yield) mono-TFA salt. LCMS: m/z 672 ($M+H^+$), retention time 2.42 min (method 11). This material is a diastereomeric mixture in a ratio of
- 15 approximately 1:1. ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.89 - 0.96 (m, 6 H) 0.97 - 1.05 (m, 6 H) 1.05 - 1.17 (m, 5 H) 1.22 - 1.42 (m, 6 H) 1.42 - 1.60 (m, 7 H) 1.64 - 1.80 (m, 7 H) 1.82 - 2.02 (m, 2 H) 2.12 (dd, $J=17.09$, 6.10 Hz, 1 H) 2.49 - 2.65 (m, 2 H) 3.12 - 3.32 (m, 4 H) 3.36 - 3.44 (m, 1 H) 3.45 - 3.53 (m, 1 H) 3.78 (d, $J=15.56$ Hz, 0.5 H) 3.95 (d, $J=15.56$ Hz, 0.5 H) 4.25 -
- 20 4.44 (m, 2 H) 4.62 (d, $J=8.85$ Hz, 1 H) 4.71 (br. s., 0.5 H) 4.75 (br. s., 0.5 H) 5.29 (d, $J=6.10$ Hz, 1 H) 5.69 (s, 0.5 H) 5.74 (s, 0.5 H) 7.20 (dd, $J=8.24$, 1.53 Hz, 2 H) 7.92 (d, $J=7.93$ Hz, 2 H).

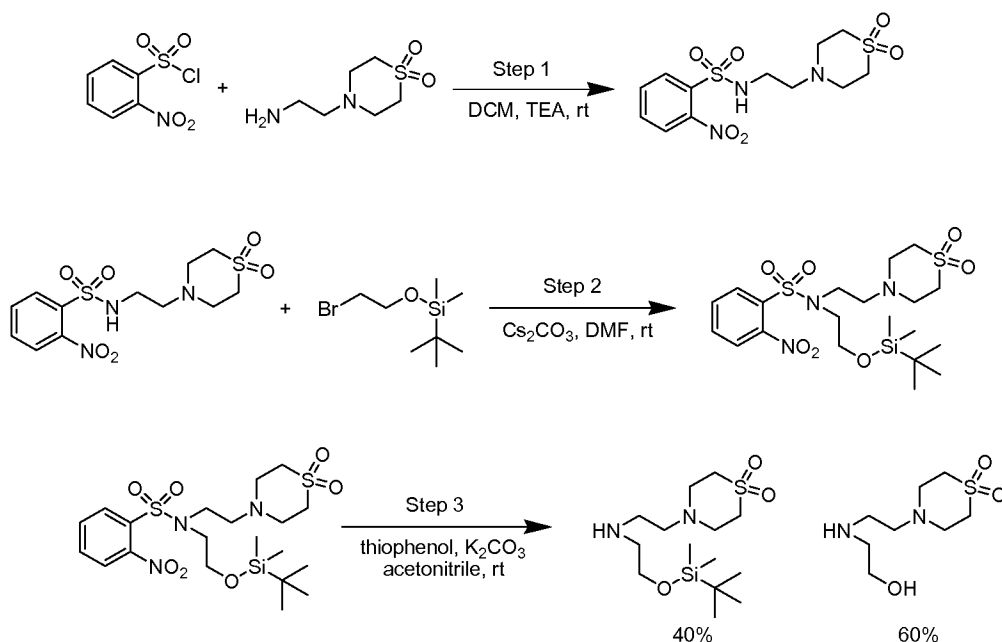
Example 65

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(2-hydroxyethyl)carbamoyl)amino)-1-isopropenyl-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)benzoic acid.



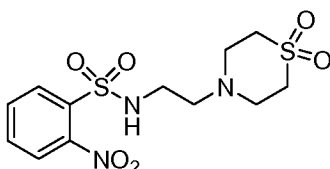
- 10 The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using the mixture of 2-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine and 2-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)ethanol acquired in Step 3 below as the reactant amine.
- 15 The urea formation step gave the desilylated material directly as the major product of the reaction, so no desilylation step was necessary. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (96 mg, 57% yield). LCMS: m/z 778 ($M+H^+$), retention time 2.43 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ
- 20 ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.01 (br. s., 3 H) 1.02 (s, 3 H) 1.06 - 1.16 (m, 5 H) 1.20 - 1.45 (m, 6 H) 1.45 - 1.64 (m, 6 H) 1.64 - 1.79 (m, 6 H) 1.81 - 2.00 (m, 2 H) 2.12 (dd, $J=17.07$, 6.27 Hz, 1 H) 2.38 (dd, $J=11.80$, 8.03 Hz, 1 H) 2.48 - 2.63 (m, 2 H) 3.16 (br. s., 2 H) 3.30 (br. s., 1 H) 3.37 (br. s., 4 H) 3.43 - 3.58 (m, 3 H) 3.60 (br. s., 4 H) 3.76 (br. s., 2 H) 4.61 (d, $J=1.51$ Hz, 1 H) 4.73 (d, $J=1.25$ Hz, 1 H) 5.29 (d,
- 25 $J=4.77$ Hz, 1 H) 7.20 (m, $J=8.28$ Hz, 2 H) 7.92 (m, $J=8.28$ Hz, 2 H).

- Synthesis of amine used in preparation of 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-
 5 thiomorpholinyl)ethyl)(2-hydroxyethyl)carbamoyl)amino)-1-isopropenyl-
 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)benzoic acid:



10

Step 1. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.



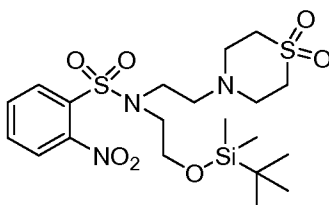
- 15 A mixture of 4-(2-aminoethyl)thiomorpholine 1,1-dioxide (2.00 g, 11.2 mmol) and triethylamine (1.42 g, 14.0 mmol) in DCM (100 mL) was cooled in an ice bath and treated slowly with 2-nitrobenzene-1-sulfonyl chloride (2.49 g, 11.2 mmol). The mixture was removed from the ice bath and stirred at rt for 18 h. The resulting mixture was washed with water (2 x 50 mL) and the combined aqueous washes were

extracted with DCM (50 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a yellow solid.

Purification by silica gel chromatography (linear gradient 100% DCM to 100:1 DCM:MeOH) gave the title compound as a pale yellow solid (3.47 g, 85% yield).

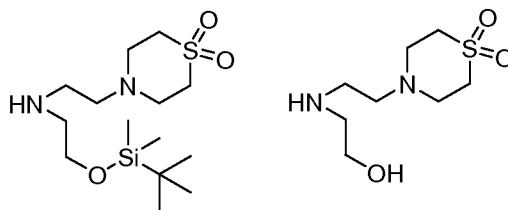
- 5 LCMS: m/z 364 ($M+H^+$), retention time 0.98 min (method 11). ^1H NMR (500 MHz, CHLOROFORM- d) δ ppm 2.71 (t, $J=5.49$ Hz, 2 H) 2.96 (br. s., 4 H) 3.05 (br. s., 4 H) 3.20 (q, $J=5.49$ Hz, 2 H) 5.93 (br. s., 1 H) 7.73 - 7.84 (m, 2 H) 7.84 - 7.93 (m, 1 H) 8.11 - 8.23 (m, 1 H).

- 10 Step 2. Preparation of *N*-(2-((*tert*-butyl(dimethyl)silyl)oxy)ethyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.



- N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added (2-bromoethoxy)(*tert*-butyl)dimethylsilane (0.527 g, 2.20 mmol). The resulting mixture was stirred at rt for 18 h. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 100:1 DCM:MeOH) gave the title compound as a yellow solid (0.560 g, 98% yield). LCMS: m/z 522 ($M+H^+$), retention time 2.22 min (method 11). ^1H NMR (500 MHz, CHLOROFORM- d) δ ppm 0.01 (s, 6 H) 0.86 (s, 9 H) 2.75 (t, $J=5.95$ Hz, 2 H) 3.05 (s, 8 H) 3.44 (t, $J=5.49$ Hz, 2 H) 3.57 (t, $J=6.41$ Hz, 2 H) 3.70 (t, $J=5.49$ Hz, 2 H) 7.63 - 7.78 (m, 3 H) 8.02 - 8.11 (m, 1 H).

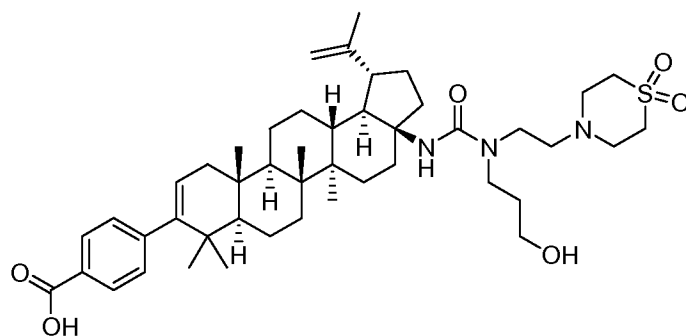
- Step 3. Preparation of a mixture of 2-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine and 2-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)ethanol



- N*-(2-((*tert*-butyl(dimethyl)silyl)oxy)ethyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.550 g, 1.05 mmol) and thiophenol (0.348 g, 3.16 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.583 g, 4.22 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave a yellow oil (0.300 g, 85% yield). ¹H NMR revealed that the material collected was a roughly 2:3 mixture of desired product and desilylated desired material. No further purification was performed and the mixture was carried forward to the next step.

Example 66

- Preparation of 4-((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,11*aS*,11*bR*,13*aR*,13*bR*)-3*a*-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-hydroxypropyl)carbamoyl)amino)-1-isopropenyl-5*a*,5*b*,8,8,11*a*-pentamethyl-2,3,3*a*,4,5,5*a*,5*b*,6,7,7*a*,8,11,11*a*,11*b*,12,13,13*a*,13*b*-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl)benzoic acid.

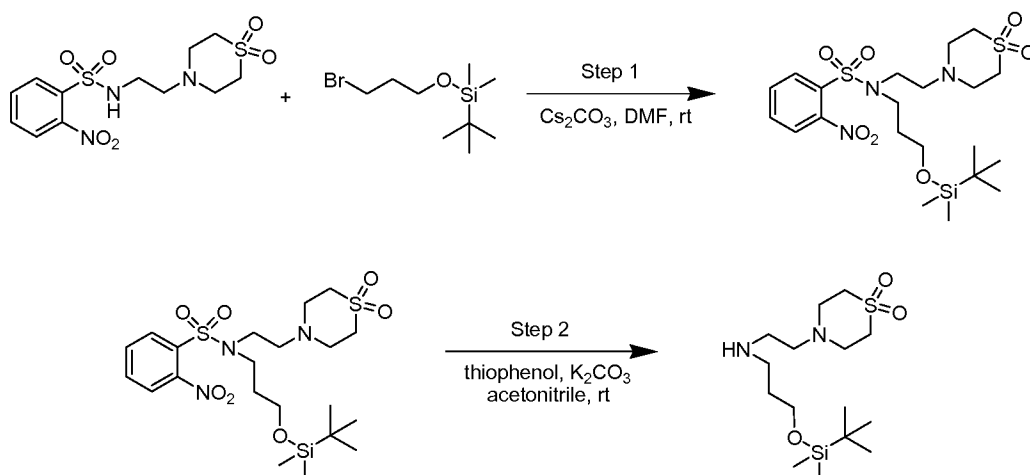


The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using 3-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-1-propanamine as the reactant amine (prepared as described below). The urea formation step gave the desilylated material directly as the major product of the reaction, so no desilylation step was necessary. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (86 mg, 53% yield). LCMS: m/z 792 ($M+H^+$), retention time 2.45 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.00 (s, 3 H) 1.02 (s, 3 H) 1.07 - 1.17 (m, 5 H) 1.25 (d, $J=7.02$ Hz, 1 H) 1.28 - 1.45 (m, 5 H) 1.45 - 1.65 (m, 7 H) 1.65 - 1.75 (m, 6 H) 1.75 - 1.85 (m, 2 H) 1.85 - 1.99 (m, 2 H) 2.12 (dd, $J=17.09, 6.41$ Hz, 1 H) 2.41 (dd, $J=12.05, 8.09$ Hz, 1 H) 2.58 (d, $J=13.43$ Hz, 1 H) 2.66 (td, $J=10.91, 4.73$ Hz, 1 H) 3.09 (br. s., 2 H) 3.39 - 3.52 (m, 2 H) 3.54 (br. s., 4 H) 3.55 - 3.63 (m, 2 H) 3.67 (ddd, $J=10.76, 5.26, 5.04$ Hz, 1 H) 4.62 (s, 1 H) 4.75 (s, 1 H) 5.29 (d, $J=4.58$ Hz, 1 H) 7.20 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.24$ Hz, 2 H).

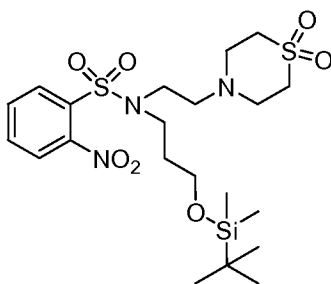
20

Synthesis of amine used in preparation of 4-((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,11*aS*,11*bR*,13*aR*,13*bR*)-3*a*-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-hydroxypropyl)carbamoyl)amino)-1-isopropenyl-5*a*,5*b*,8,8,11*a*-pentamethyl-2,3,3*a*,4,5,5*a*,5*b*,6,7,7*a*,8,11,11*a*,11*b*,12,13,13*a*,13*b*-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl)benzoic acid:

25



Step 1. Preparation of *N*-(3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.

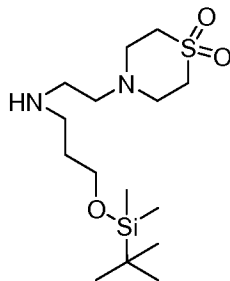


5

- N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added (3-bromopropoxy)(*tert*-butyl)dimethylsilane (0.558 g, 2.20 mmol). The resulting mixture was stirred at rt for 18 h. LCMS indicated incomplete conversion, so additional (3-bromopropoxy)(*tert*-butyl)dimethylsilane (0.558 g, 2.20 mmol) and cesium carbonate (0.538 g, 1.65 mmol) were added and the mixture was heated to 70 °C for 1 h. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 100:1 DCM:MeOH) gave the title compound as a sticky yellow material, partially crystalline (0.548 g, 93% yield).
- LCMS: m/z 536 ($M+H^+$), retention time 2.26 min (method 11). ^1H NMR (400 MHz,

CHLOROFORM-*d*) δ ppm 0.02 (s, 6 H) 0.87 (s, 9 H) 1.63 - 1.75 (m, 2 H) 2.72 (t, $J=6.40$ Hz, 2 H) 3.07 (s, 8 H) 3.32 - 3.40 (m, 2 H) 3.47 (t, $J=6.40$ Hz, 2 H) 3.56 (t, $J=5.90$ Hz, 2 H) 7.63 - 7.76 (m, 3 H) 8.08 (dd, $J=7.53$, 1.76 Hz, 1 H).

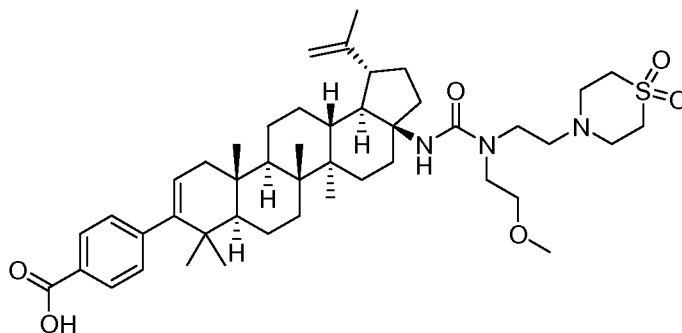
- 5 Step 2. Preparation of 3-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-1-propanamine.



- N*-(3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.540 g, 1.01 mmol) and thiophenol (0.333 g, 3.02 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.557 g, 4.03 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave the title compound as a yellow oil (0.294 g, 83% yield). No further purification was performed and the mixture was carried forward to the next step. LCMS: m/z 351 ($M+H^+$), ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.06 (s, 6 H) 0.90 (s, 9 H) 1.75 (quin, $J=6.46$ Hz, 2 H) 2.69 - 2.72 (m, 2 H) 2.72 - 2.80 (m, 4 H) 3.00 - 3.11 (m, 8 H) 3.70 (t, $J=6.02$ Hz, 2 H).

Example 67

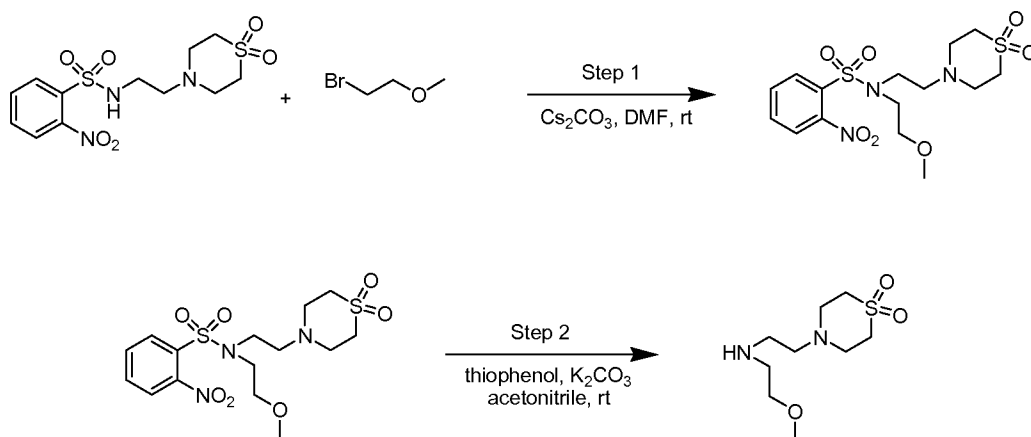
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(2-methoxyethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



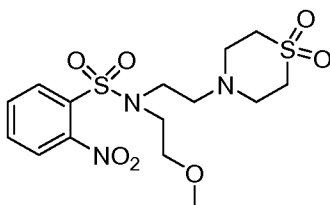
- 10 The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,1-dioxido-4-thiomorpholinyl)-N-(2-methoxyethyl)ethanamine (prepared as described below) as the reactant amine. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (89 mg, 57% yield).
- 15 LCMS: m/z 792 ($M+H^+$), retention time 2.48 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H) 0.95 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.06 - 1.17 (m, 5 H) 1.24 - 1.29 (m, 1 H) 1.30 - 1.42 (m, 4 H) 1.44 - 1.55 (m, 6 H) 1.55 - 1.65 (m, 2 H) 1.65 - 1.77 (m, 6 H) 1.82 (td, $J=12.13$, 3.20 Hz, 1 H) 1.86 - 1.98 (m, 1 H) 2.13 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.38 (dd, $J=12.36$, 8.09 Hz, 1 H) 2.47 (td, $J=10.99$, 5.19 Hz, 1 H) 2.51 - 2.61 (m, 1 H) 3.03 - 3.19 (m, 2 H) 3.34 - 3.44 (m, 5 H) 3.51 (s, 3 H) 3.52 - 3.69 (m, 8 H) 4.64 (s, 1 H) 4.73 (s, 1 H) 5.29 (d, $J=4.58$ Hz, 1 H) 7.20 (m, $J=8.24$ Hz, 2 H) 7.92 (m, $J=8.24$ Hz, 2 H).
- 20

Synthesis of amine used in preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(2-methoxyethyl)carbamoyl)amino)-1-isopropenyl-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)benzoic acid:

25



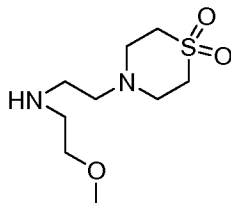
Step 1. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(2-methoxyethyl)-2-nitrobenzenesulfonamide.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added 1-bromo-2-methoxyethane (0.306 g, 2.20 mmol). The resulting mixture was stirred at rt for 72 h. LCMS indicated incomplete conversion, so additional 1-bromo-2-methoxyethane (0.306 g, 2.20 mmol) and cesium carbonate (0.538 g, 1.65 mmol) were added and the mixture was heated to 70°C for 1 h. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 60:1 DCM:MeOH) gave the title compound as a yellow oil (0.486 g, 105% yield). LCMS: m/z 422 ($M+H^+$), retention time 1.35 min (method 11). ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 2.72 (t, $J=6.41$ Hz, 2 H) 3.01 (s, 8 H) 3.21 (s, 3 H) 3.39 - 3.52 (m, 6 H) 7.62 - 7.66 (m, 1 H)

7.66 - 7.74 (m, $J=7.48$, 7.32, 7.32, 7.32, 1.68 Hz, 2 H) 8.01 (dd, $J=7.78$, 1.68 Hz, 1 H).

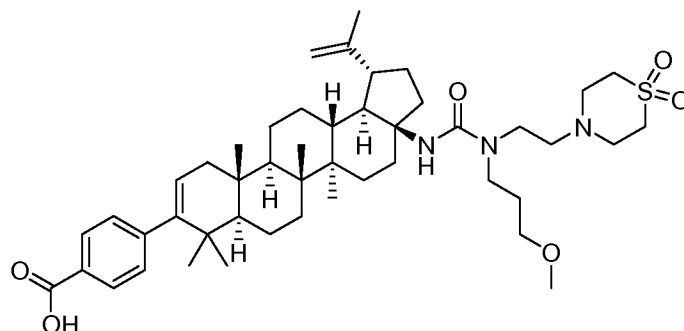
Step 2. Preparation of 2-(1,1-dioxido-4-thiomorpholinyl)-*N*-(2-methoxyethyl)ethanamine.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(2-methoxyethyl)-2-nitrobenzenesulfonamide (0.470 g, 1.12 mmol) and thiophenol (0.369 g, 3.35 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.616 g, 4.46 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave the title compound as a yellow solid (0.222 g, 84% yield). No further purification was performed and the mixture was carried forward to the next step. LCMS: m/z 237 ($M+H^+$), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 2.15 (br. s., 1 H) 2.66 - 2.71 (m, 2 H) 2.71 - 2.77 (m, 2 H) 2.82 (t, $J=5.04$ Hz, 2 H) 2.97 - 3.05 (m, 4 H) 3.05 - 3.10 (m, 4 H) 3.37 (s, 3 H) 3.51 (t, $J=5.04$ Hz, 2 H).

Example 68

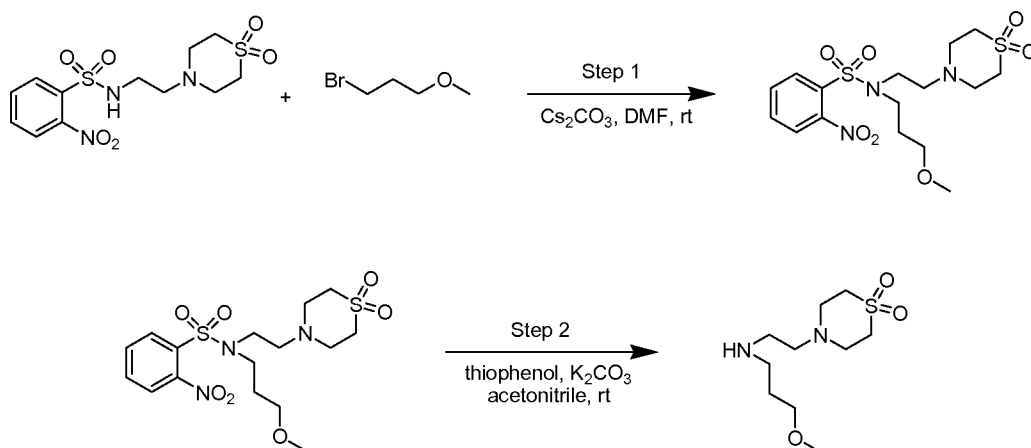
Preparation of 4-(((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,11*aS*,11*bR*,13*aR*,13*bR*)-3*a*-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-methoxypropyl)carbamoyl)amino)-1-isopropenyl-5*a*,5*b*,8,8,11*a*-pentamethyl-2,3,3*a*,4,5,5*a*,5*b*,6,7,7*a*,8,11,11*a*,11*b*,12,13,13*a*,13*b*-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl)benzoic acid.



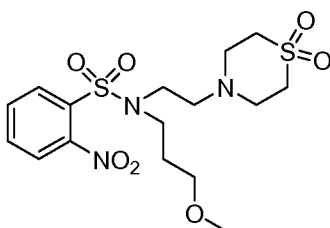
- The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-3-methoxy-1-propanamine (prepared as described below) as the reactant amine. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (132 mg, 82% yield). LCMS: m/z 806 ($M+H^+$), retention time 2.52 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (br. s., 3 H) 0.95 (s, 3 H) 1.01 (s, 3 H) 1.03 (s, 3 H) 1.10 (s, 3 H) 1.11 - 1.21 (m, 2 H) 1.21 - 1.42 (m, 5 H) 1.43 - 1.65 (m, 8 H) 1.65 - 1.77 (m, 6 H) 1.77 - 1.98 (m, 5 H) 2.12 (dd, $J=17.07$, 6.27 Hz, 1 H) 2.40 (dd, $J=12.17$, 8.16 Hz, 1 H) 2.55 - 2.67 (m, 2 H) 3.01 (t, $J=6.15$ Hz, 2 H) 3.29 (d, $J=5.02$ Hz, 4 H) 3.34 - 3.42 (m, 1 H) 3.42 - 3.59 (m, 11 H) 4.74 (d, $J=1.51$ Hz, 1 H) 5.24 - 5.34 (m, 1 H) 7.20 (m, $J=8.28$ Hz, 2 H) 7.92 (m, $J=8.28$ Hz, 2 H).

Synthesis of amine used in preparation of 4-

- ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-methoxypropyl)carbamoyl)amino)-1-isopropenyl-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)benzoic acid:



Step 1. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(3-methoxypropyl)-2-nitrobenzenesulfonamide.

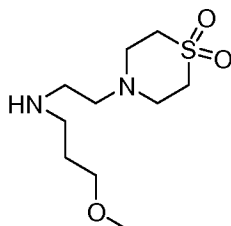


5

N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added 1-bromo-3-methoxypropane (0.337 g, 2.20 mmol). The resulting mixture was stirred at rt for 72 h. LCMS indicated incomplete conversion, so additional 1-bromo-3-methoxypropane (0.337 g, 2.20 mmol) and cesium carbonate (0.538 g, 1.65 mmol) were added and the mixture was heated to 70 °C for 1 hour. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 60:1 DCM:MeOH) gave the title compound as a yellow oil (0.522 g, 109% yield). LCMS: m/z 436 ($M+H^+$), retention time 1.50 min (method 11). ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.68 - 1.77 (m, 2 H) 2.67 (t, $J=6.26$ Hz, 2 H) 3.02 (br. s., 8 H) 3.16 (s, 3 H) 3.27 (t, $J=5.80$ Hz, 2 H) 3.31 - 3.37 (m, 2 H) 3.41 (t, $J=6.26$ Hz, 2 H) 7.61 - 7.65 (m, 1 H) 7.66 - 7.74 (m, 2 H) 7.99 - 8.03 (m, 1 H).

20

Step 2. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-3-methoxy-1-propanamine.



5

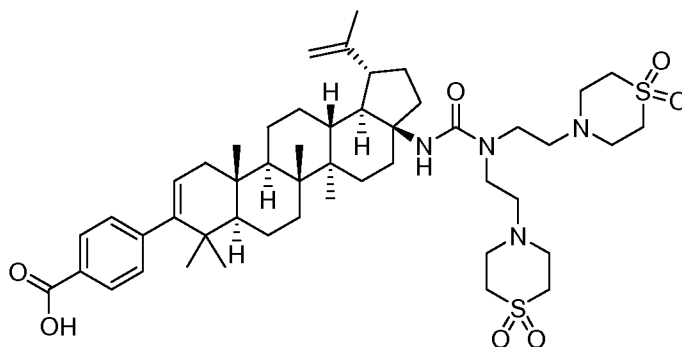
N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(3-methoxypropyl)-2-nitrobenzenesulfonamide (0.510 g, 1.17 mmol) and thiophenol (0.387 g, 3.51 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.647 g, 4.68 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave a yellow oil (0.255 g, 87% yield). No further purification was performed and the mixture was carried forward to the next step. LCMS: m/z 251 ($M+H^+$), ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.77 (quin, $J=6.53$ Hz, 2 H) 2.13 (br. s., 2 H) 2.62 - 2.68 (m, 2 H) 2.68 - 2.75 (m, 4 H) 2.93 - 3.11 (m, 8 H) 3.32 (s, 3 H) 3.44 (t, $J=6.15$ Hz, 2 H).

20

Example 69

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)carbamoyl)amino)-1-isopropenyl-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)benzoic acid.

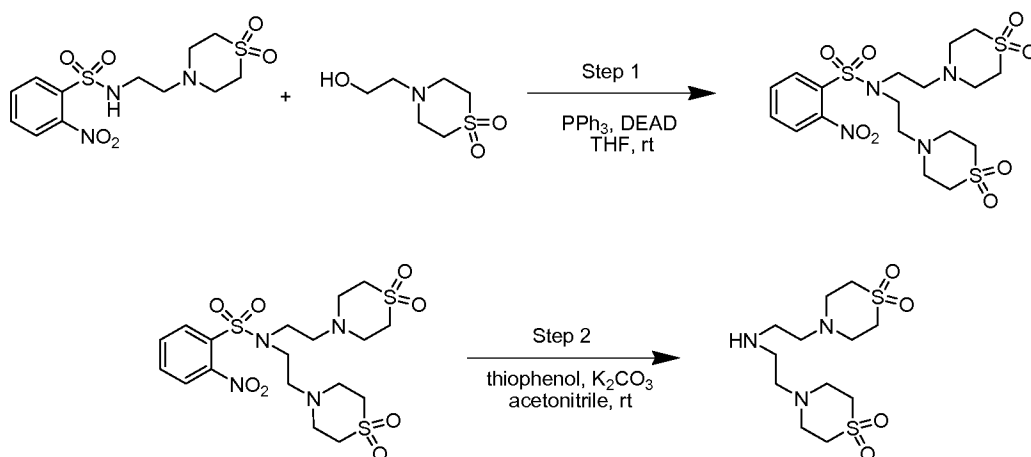
25



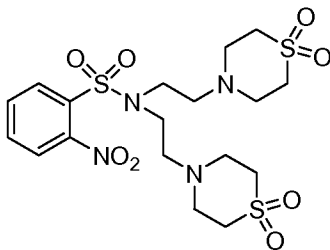
The title compound was prepared following the general procedures described
 5 for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,1-dioxido-4-
 thiomorpholinyl)-N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine (prepared as
 described below) as the reactant amine. After ester hydrolysis, the bis-TFA salt
 product was isolated by reverse phase preparative HPLC purification as a slightly
 yellow solid (109 mg, 64% yield). LCMS: m/z 895 ($M+H^+$), retention time 2.42 min
 10 (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ
 ppm 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 1.01 (s, 3 H) 1.04 (s, 3 H) 1.12 (s, 3 H) 1.13 -
 1.22 (m, 2 H) 1.23 - 1.32 (m, 2 H) 1.33 - 1.43 (m, 2 H) 1.43 - 1.63 (m, 8 H) 1.64 -
 1.81 (m, 7 H) 1.84 - 1.96 (m, 1 H) 2.13 (dd, $J=17.24, 6.26$ Hz, 1 H) 2.38 (td, $J=10.61,$
 5.04 Hz, 1 H) 2.47 (dd, $J=12.51, 8.24$ Hz, 1 H) 2.50 - 2.59 (m, 1 H) 3.01 (br. s., 4 H)
 15 3.26 (br. s., 8 H) 3.35 - 3.50 (m, 10 H) 3.50 - 3.62 (m, 2 H) 4.67 (s, 1 H) 4.80 (s, 1 H)
 5.29 (dd, $J=6.10, 1.53$ Hz, 1 H) 7.20 (d, $J=8.24$ Hz, 2 H) 7.92 (d, $J=8.55$ Hz, 2 H).

Synthesis of amine used in preparation of 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((bis(2-(1,1-dioxido-4-
 20 thiomorpholinyl)ethyl)carbamoyl)amino)-1-isopropenyl-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)benzoic acid:



Step 1. Preparation of *N,N*-bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.

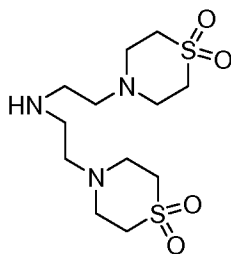


5

N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.500 g, 1.38 mmol) was combined with 4-(2-hydroxyethyl)thiomorpholine 1,1-dioxide (0.296 g, 1.65 mmol) in THF (10 mL). To this mixture was added triphenylphosphine (0.541 g, 2.06 mmol) and diethyl azodicarboxylate (0.359 g, 2.06 mmol). The resulting mixture was stirred at rt for 72 h. The mixture was concentrated in vacuo, then redissolved in acetonitrile. Purification by reverse phase preparative HPLC gave the title compound as a pale yellow solid (0.863 g, 83% yield) bis-TFA salt. LCMS: m/z 525 ($M+H^+$), retention time 1.25 min (method 11). ^1H NMR (500 MHz, MeOD) δ ppm 2.85 (t, $J=6.71$ Hz, 4 H) 3.14 (d, $J=5.49$ Hz, 8 H) 3.18 (d, $J=5.80$ Hz, 8 H) 3.51 (t, $J=6.71$ Hz, 4 H) 7.71 - 7.75 (m, 1 H) 7.75 - 7.84 (m, 2 H) 8.05 (d, $J=7.63$ Hz, 1 H).

15

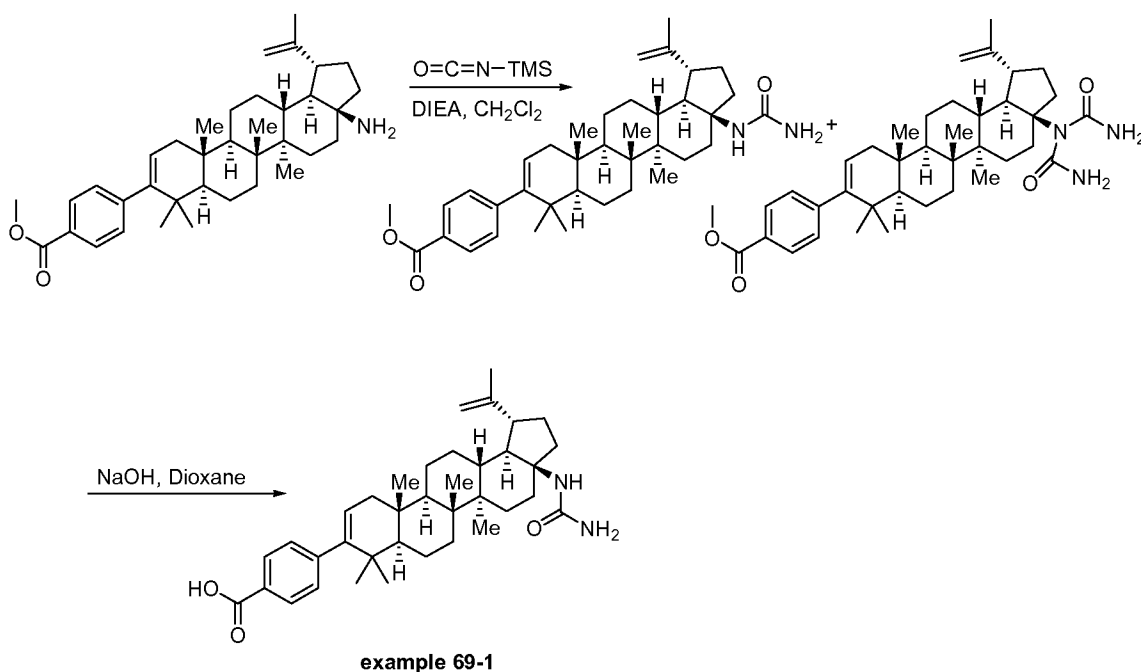
Step 2. Preparation of 2-(1,1-dioxido-4-thiomorpholinyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine.



5 *N,N*-bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide
 (0.85 g, 1.13 mmol) and thiophenol (0.373 g, 3.39 mmol) were combined in dry
 acetonitrile (10 mL). Potassium carbonate (0.936 g, 6.78 mmol) was added and the
 mixture was stirred at rt for 18h. The mixture was diluted with ethyl acetate and
 filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo,
 redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to
 capture the desired product. Undesired materials were eluted from the cartridge with
 10 methanol, and then the desired material was released from the resin by elution with
 2M ammonia in methanol. Concentration in vacuo gave a sticky yellow oil (0.381 g,
 100% yield). No further purification was performed and the mixture was carried
 forward to the next step.

15 **Example 69-1**

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
pentamethyl-1-(prop-1-en-2-yl)-3a-ureido-
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 and 4-
 20 **((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-carbamoylureido)-**
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. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, 0.092 mmol) in DCM (1 mL) was added diisopropylethylamine (0.016 mL, 0.092 mmol) and isocyanatotrimethylsilane (15.89 mg, 0.138 mmol). The resulting mixture was stirred at rt for 48 hours. LC-MS showed desired product at $M+1=587.48$ (2.87 min, method 13) and a side product $M+1=630.48$ (2.97 min, method 13). The volatiles were removed in vacuo. The crude products were obtained as yellow oil and were used in next step as is.
- Step 2. 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-ureido-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 was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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 2. The product was isolated as white solid (15 mg, 28%). **Example 69-1:** LCMS: m/e 573.45 ($M+H$)⁺, 2.67 min (method 13). ¹H NMR (400MHz, METHANOL-d₄) δ 7.94 (d, $J=8.5$ Hz, 2H), 7.24 (d, $J=8.5$

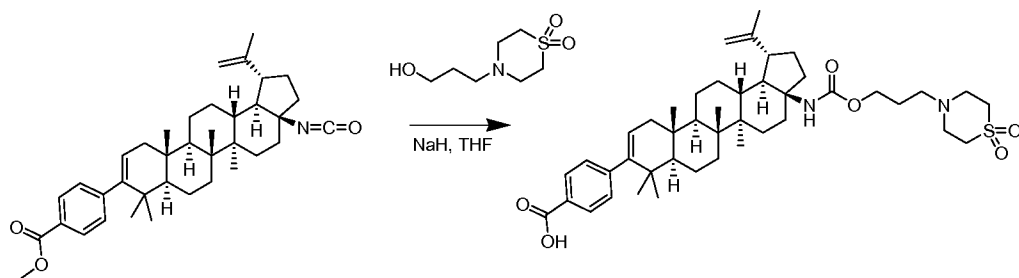
Hz, 2H), 5.32 (dd, $J=6.1, 1.6$ Hz, 1H), 4.78 (d, $J=1.8$ Hz, 1H), 4.67 - 4.63 (m, 1H),
 2.69 - 2.59 (m, 2H), 2.40 (dd, $J=12.2, 8.2$ Hz, 1H), 2.17 (dd, $J=17.2, 6.4$ Hz, 1H),
 2.04 - 1.84 (m, 2H), 1.74 (s, 3H), 1.82 - 1.67 (m, 3H), 1.63 - 1.48 (m, 6H), 1.46 - 1.26
 (m, 6H), 1.16 (s, 3H), 1.22 - 1.08 (m, 2H), 1.06 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H),
 5 0.97 (s, 3H).

Section 2. Carbamates

10

Example 70

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 [[[(3-(1,1-dioxido-4-thiomorpholinyl)propoxy)carbonyl]amino]-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-
 15 pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



To a cloudy solution of 4-(3-hydroxypropyl)thiomorpholine 1,1-dioxide (407
 20 mg, 2.106 mmol) in tetrahydrofuran (5 mL) was added sodium hydride (84 mg, 2.106
 mmol). The resulting white slurry was stirred at rt. After 40 min, the resulting paste
 was diluted with tetrahydrofuran (5 mL) and was treated with methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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-
 25 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (200 mg, 0.351 mmol) in one
 portion. The resulting white slurry was stirred at rt overnight. After 16 h, the reaction
 was poured into 0.1N HCl (20 mL) and extracted with 2 x 50 mL EtOAc. The
 combined organic layer was washed with brine, dried over MgSO₄, filtered and
 concentrated to give a white foam product. The crude material was dissolved in 2

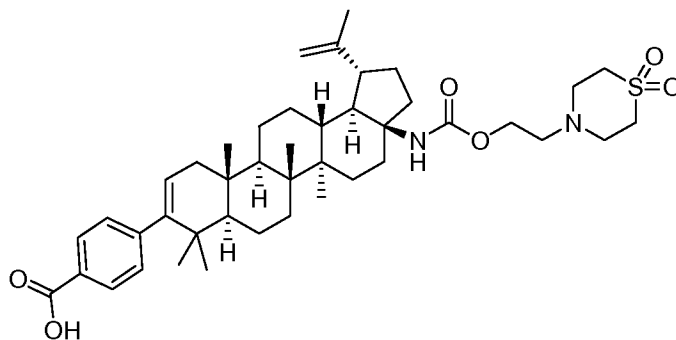
mL THF, filtered and purified by reverse phase preparative HPLC using HPLC method 1 to give the mono-TFA salt of the title compound (123.1 mg, 0.143 mmol, 40.6% yield) as white solid. LCMS: m/e 749.5 ($M+H$)⁺, 2.10 min (method 6). ¹H NMR (500MHz, 1:1 MeOD:CDCl₃) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 5.29 (dd, J = 1.8, 6.1 Hz, 1 H), 4.75 (d, J = 1.5 Hz, 1 H), 4.63 (d, J = 1.2 Hz, 1 H), 4.09 (t, J = 5.8 Hz, 2 H), 3.42 (br. s., 3 H), 2.98 (t, J = 7.0 Hz, 2 H), 2.57 (dt, J = 5.3, 10.9 Hz, 1 H), 2.51 (d, J = 12.8 Hz, 1 H), 2.35 - 2.28 (m, 1 H), 2.12 (dd, J = 6.4, 17.1 Hz, 1 H), 2.02 - 1.88 (m, 3 H), 1.82 - 1.65 (m, 7 H), 1.65 - 1.45 (m, 6 H), 1.45 - 1.19 (m, 6 H), 1.15 - 1.10 (m, 2 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ¹³C NMR (1:1 MeOD:CDCl₃) δ ppm 15.2, 16.5, 17.2, 19.9, 20.7, 21.8, 22.3, 26.2, 26.5, 28.2, 29.9, 30.2, 30.5, 34.5, 37.2, 38.4, 38.6, 41.6, 42.7, 43.0, 48.2, 50.1, 50.5, 50.6, 51.9, 53.9, 54.6, 62.4, 64.9, 78.8, 111.0, 124.9, 129.3, 129.7, 131.0, 147.4, 149.8, 150.4, 156.3, 170.1.

15

Example 71

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[2-(1,1-dioxido-4-thiomorpholinyl)ethoxy]carbonyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].

20



The title compound was prepared in 24% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 following the same procedure as described for the preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-

25

thiomorpholinyl)propoxy]carbonyl]amino]-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl], except 4-(2-hydroxyethyl)thiomorpholine 1,1-dioxide was used instead of 4-(3-

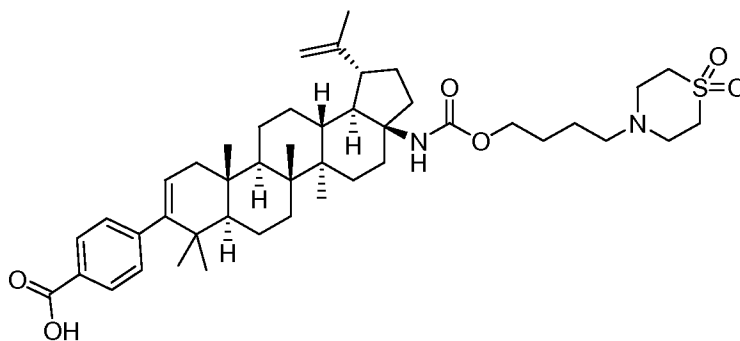
- 5 hydroxypropyl)thiomorpholine 1,1-dioxide. LCMS: m/e 735.3 (M+H)⁺, 2.63 min (method 6). ¹H NMR (500MHz, *METHANOL-d₄*) δ = 7.95 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H), 5.33 (dd, J = 1.7, 6.3 Hz, 1 H), 4.79 (d, J = 1.8 Hz, 1 H), 4.66 (s, 1 H), 4.38 - 4.28 (m, 1 H), 4.27 - 4.19 (m, 1 H), 3.56 - 3.43 (m, 3 H), 3.31 (br. s., 2 H), 3.17 (br. s., 2 H), 2.71 (dt, J = 5.3, 11.1 Hz, 1 H), 2.57 (d, J = 13.4 Hz, 1 H), 2.33 (dd, J = 8.4, 12.1 Hz, 1 H), 2.18 (dd, J = 6.4, 17.1 Hz, 1 H), 2.00 - 1.89 (m, 2 H), 1.84 - 1.76 (m, 2 H), 1.75 (s, 3 H), 1.73 (d, J = 4.3 Hz, 1 H), 1.71 - 1.64 (m, 1 H), 1.62 - 1.56 (m, 2 H), 1.56 - 1.48 (m, 4 H), 1.47 - 1.35 (m, 4 H), 1.31 (dt, J = 4.0, 9.3 Hz, 2 H), 1.15 (s, 3 H), 1.12 (d, J = 3.1 Hz, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

15

Example 72

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[4-(1,1-dioxido-4-thiomorpholinyl)butoxy]carbonyl]amino]-

- 20 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



- The title compound was prepared in 55% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 following the same procedure as described for the preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-

thiomorpholinyl)propoxy]carbonyl]amino]-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl], except 4-(3-hydroxybutyl)thiomorpholine 1,1-dioxide was used instead of 4-(3-

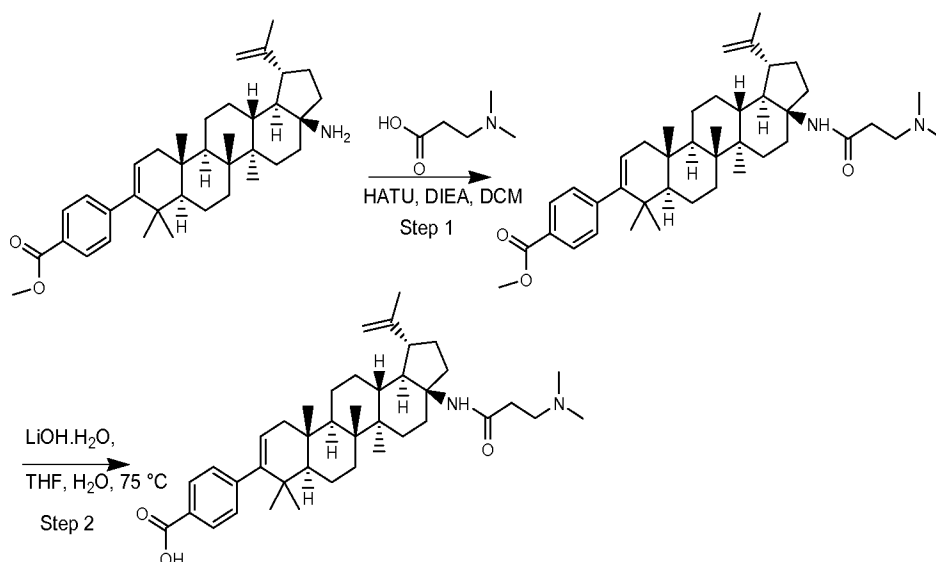
- 5 hydroxypropyl)thiomorpholine 1,1-dioxide. LCMS: m/e 763.5 (M+H)⁺, 2.14 min (method 6). ¹H NMR (500MHz, *METHANOL-d₄*) δ = 7.95 (d, J = 8.2 Hz, 2 H), 7.24 (d, J = 8.2 Hz, 2 H), 5.32 (dd, J = 1.5, 6.1 Hz, 1 H), 4.78 (d, J = 1.5 Hz, 1 H), 4.65 (s, 1 H), 4.14 - 4.04 (m, 2 H), 3.87 - 3.79 (m, 4 H), 3.62 - 3.51 (m, 4 H), 2.69 (dt, J = 5.0, 11.1 Hz, 1 H), 2.56 (d, J = 13.4 Hz, 1 H), 2.32 (dd, J = 8.9, 11.3 Hz, 1 H), 2.18 (dd, J = 6.3, 17.2 Hz, 1 H), 2.00 - 1.91 (m, 2 H), 1.91 - 1.82 (m, 2 H), 1.82 - 1.75 (m, 3 H), 1.74 (s, 4 H), 1.70 - 1.56 (m, 3 H), 1.51 (d, J = 11.0 Hz, 4 H), 1.46 - 1.34 (m, 4 H), 1.33 - 1.26 (m, 2 H), 1.14 (s, 3 H), 1.13 - 1.09 (m, 2 H), 1.08 - 1.06 (m, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).
- 10

15 Section 3. Amides

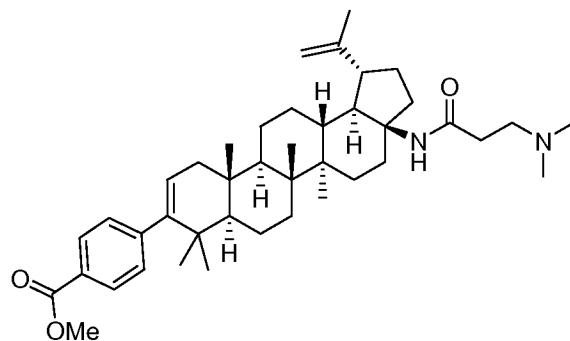
Example 73

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-

- 20 (dimethylamino)propanamido)-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.



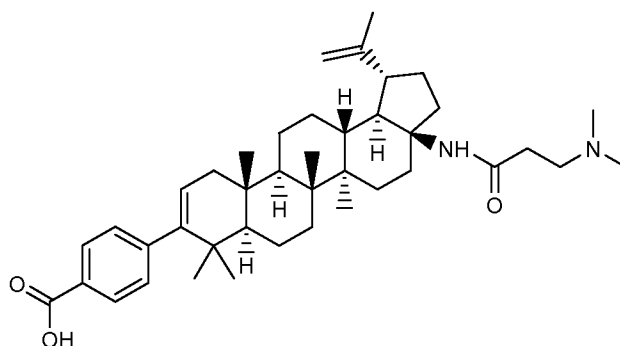
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 (3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 5 cyclopenta[a]chrysen-9-yl)benzoate.



To a cloudy solution mixture of methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-
 10 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 (0.240 g, 0.441 mmol) in THF
 (5 mL) was added *N,N*-diisopropylethylamine (0.461 mL, 2.65 mmol), 2-(3H-
 [1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium
 hexafluorophosphate(V) (0.369 g, 0.971 mmol) and 3-(dimethylamino)propionic acid
 15 hydrochloride (0.136 g, 0.883 mmol). The reaction mixture was stirred at rt. After
 16 h, the reaction mixture was diluted with EtOAc (50 mL), washed with 1N HCl (5
 mL), 5% NaHCO₃, brine, dried over MgSO₄, filtered and concentrated to a viscous oil
 product. The crude material was dissolved in THF (1 mL) and MeOH (1.5 mL),
 filtered and purified by reverse phase preparative HPLC using HPLC method 4 to
 20 give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-
 (dimethylamino)propanamido)-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, TFA (93.8 mg, 0.116 mmol, 26.4% yield) as a
 white solid. LCMS: *m/e* 643.3 (M+H)⁺, 4.17 min (method 8). ¹H NMR (500MHz ,
 25 1:1 MeOD:CDCl₃) δ = 7.97 - 7.85 (m, 2 H), 7.29 - 7.23 (m, 2 H), 7.21 (br. s., 1 H),
 5.32 (d, *J* = 4.0 Hz, 1 H), 4.80 (br. s., 1 H), 4.67 (br. s., 1 H), 3.97 - 3.88 (m, 3 H),
 3.43 - 3.37 (m, 2 H), 2.92 (br. s., 6 H), 2.84 - 2.77 (m, 2 H), 2.77 - 2.68 (m, 2 H), 2.46
 - 2.38 (m, 1 H), 2.22 - 2.13 (m, 1 H), 2.05 - 1.88 (m, 2 H), 1.83 (d, *J* = 13.4 Hz, 1 H),

1.75 (br. s., 5 H), 1.66 - 1.49 (m, 7 H), 1.48 - 1.34 (m, 4 H), 1.32 (br. s., 1 H), 1.16 (br. s., 4 H), 1.07 (br. s., 6 H), 0.98 (br. s., 3 H), 0.96 (br. s., 3 H). ^{13}C NMR (1:1 *MeOD*:*CDCl*₃) δ ppm 13.8, 15.4, 16.0, 18.4, 19.9, 20.6, 21.4, 25.6, 27.5, 28.7, 29.0, 29.5, 29.7, 33.8, 34.8, 36.4, 37.5, 37.5, 40.8, 41.8, 42.1, 47.0, 49.5, 49.8, 51.5, 53.3, 54.5, 65.8, 102.7, 109.7, 124.3, 128.2, 128.5, 130.3, 146.7, 149.2, 150.1, 167.6, 170.3.

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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.



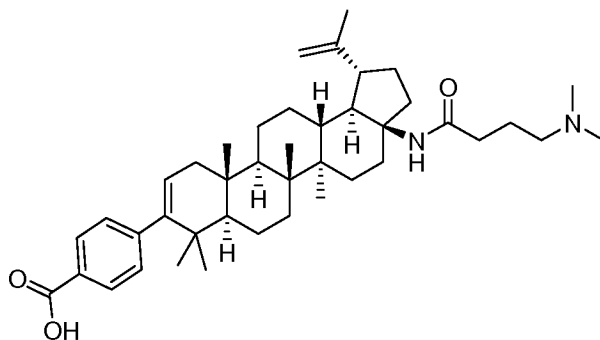
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, TFA (87.9 mg, 0.116 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (19.49 mg, 0.464 mmol) in water (1.00 mL). The reaction was stirred at 75 °C. After 8 h, the reaction was concentrated to dryness. The crude material was dissolved in THF (1 mL) and MeOH (1.5 mL), filtered and purified by reverse phase preparative HPLC using HPLC method 1 to give the title compound (59.5 mg, 0.078 mmol, 67.6% yield) as a white solid. LCMS: m/e 629.4 ($\text{M}+\text{H}$)⁺, 4.17 min (method 8). ^1H NMR (500MHz, *METHANOL-d*₄) δ = 7.95 (d, J = 8.2 Hz, 2 H), 7.24 (d, J = 8.2 Hz, 3 H), 5.33 (dd, J = 1.5, 6.1 Hz, 1 H), 4.80 (d, J = 1.5 Hz, 1 H), 4.67 (s, 1 H), 3.40 (t, J = 6.6 Hz, 2 H), 2.92 (s, 6 H), 2.88 - 2.69 (m, 4 H), 2.42 (dd, J = 8.4, 12.4 Hz, 1 H), 2.18 (dd, J = 6.4, 17.1 Hz, 1 H), 2.05 - 1.89 (m, 2 H), 1.83 (d, J = 11.3 Hz, 1 H), 1.79 - 1.76 (m, 1 H), 1.75 (s, 3 H), 1.74 - 1.71 (m, 1 H), 1.66 - 1.56 (m, 3 H), 1.56 - 1.49 (m, 4 H), 1.47 - 1.28 (m, 5 H), 1.22 -

1.17 (m, 1 H), 1.16 (s, 3 H), 1.15 - 1.10 (m, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H). ^{13}C NMR (*MeOD*) δ ppm 14.5, 16.1, 16.8, 19.1, 20.6, 21.3, 22.1, 26.2, 28.2, 29.4, 29.7, 30.4, 34.5, 35.5, 37.1, 38.1, 38.2, 41.5, 42.5, 42.8, 43.2, 47.6, 49.3, 50.1, 50.5, 54.0, 55.1, 66.4, 110.4, 124.9, 129.5, 130.9, 147.4, 149.6, 150.8, 169.6, 171.0.

5

Example 74

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(dimethylamino)butanamido)-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.



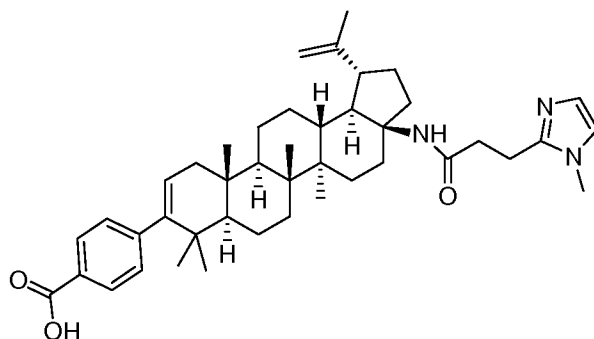
The title compound was prepared in 26% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 4-(dimethylamino)butyric acid hydrochloride was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 643.4 ($M+H$)⁺, 4.19 min (method 8). ^1H NMR (500MHz, *METHANOL-d*₄) δ = 7.95 (d, J = 8.2 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H), 5.33 (dd, J = 1.7, 6.3 Hz, 1 H), 4.80 (d, J = 1.5 Hz, 1 H), 4.67 (s, 1 H), 3.21 - 3.14 (m, 2 H), 2.93 (s, 6 H), 2.82 - 2.67 (m, 2 H), 2.49 (t, J = 6.9 Hz, 2 H), 2.41 (dd, J = 8.2, 12.2 Hz, 1 H), 2.18 (dd, J = 6.4, 17.1 Hz, 1 H), 2.06 - 1.96 (m, 3 H), 1.96 - 1.86 (m, 1 H), 1.85 - 1.79 (m, 1 H), 1.77 (br. s., 1 H), 1.75 (s, 3 H), 1.73 - 1.69 (m, 1 H), 1.64 - 1.56 (m, 3 H),

1.55 - 1.48 (m, 4 H), 1.47 - 1.38 (m, 3 H), 1.35 (d, $J = 12.2$ Hz, 1 H), 1.33 - 1.27 (m, 1 H), 1.21 - 1.17 (m, 1 H), 1.15 (s, 3 H), 1.12 (d, $J = 3.4$ Hz, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

5

Example 75

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(1-methyl-1H-imidazol-2-yl)propanamido)-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.



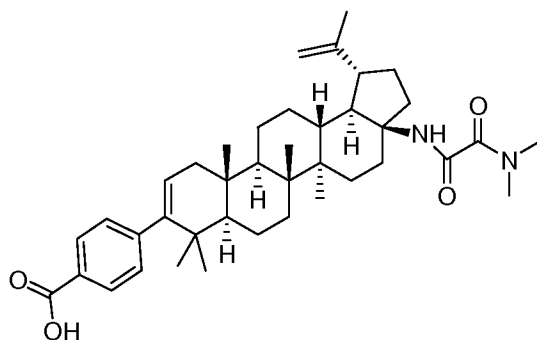
The title compound was prepared in 29% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 3-(1-methyl-1H-imidazol-2-yl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 666.4 ($M+H$)⁺, 4.15 min (method 8). ¹H NMR (500MHz, *METHANOL-d₄*) δ = 7.95 (d, $J = 8.5$ Hz, 2 H), 7.53 - 7.46 (m, 2 H), 7.25 (d, $J = 8.2$ Hz, 2 H), 5.33 (dd, $J = 1.8, 6.1$ Hz, 1 H), 4.79 (d, $J = 1.5$ Hz, 1 H), 4.66 (s, 1 H), 3.91 (s, 3 H), 3.30 - 3.18 (m, 2 H), 2.84 - 2.79 (m, 2 H), 2.73 (dt, $J = 5.2, 11.1$ Hz, 1 H), 2.64 (d, $J = 12.5$ Hz, 1 H), 2.35 (dd, $J = 8.2, 12.2$ Hz, 1 H), 2.18 (dd, $J = 6.4, 17.4$ Hz, 1 H), 1.96 (dt, $J = 3.2, 12.1$ Hz, 1 H), 1.91 - 1.78 (m, 2 H), 1.77 (s, 1 H), 1.74 (s, 3 H),

1.71 - 1.66 (m, 1 H), 1.60 (br. s., 2 H), 1.46 - 1.26 (m, 7 H), 1.22 - 1.13 (m, 1 H), 1.11 (s, 3 H), 1.07 (s, 3 H), 1.05 (s, 4 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 76

5

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoacetamido)-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.



10

The title compound was prepared in 13% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except *N,N*-dimethyloxamic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: *m/e* 627.6 (M-H)⁺, 1.91 min (method 5). ¹H NMR (500MHz, 2:1 MeOD:CDCl₃) δ = 7.93 (d, *J* = 8.2 Hz, 2 H), 7.55 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 5.30 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.77 (d, *J* = 1.2 Hz, 1 H), 4.65 (s, 1 H), 3.22 (s, 3 H), 3.01 (s, 3 H), 2.71 - 2.59 (m, 2 H), 2.46 (dd, *J* = 8.2, 11.9 Hz, 1 H), 2.14 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.02 - 1.93 (m, 1 H), 1.89 (dt, *J* = 3.4, 12.2 Hz, 1 H), 1.79 (d, *J* = 13.1 Hz, 1 H), 1.75 (d, *J* = 3.7 Hz, 1 H), 1.71 (br. s., 1 H), 1.66 (dt, *J* = 3.5, 13.5 Hz, 1 H), 1.61 - 1.54 (m, 2 H), 1.54 - 1.48 (m, 4 H), 1.46 (br. s., 1 H), 1.45 - 1.40 (m, 3 H), 1.40 - 1.34 (m, 1 H), 1.28

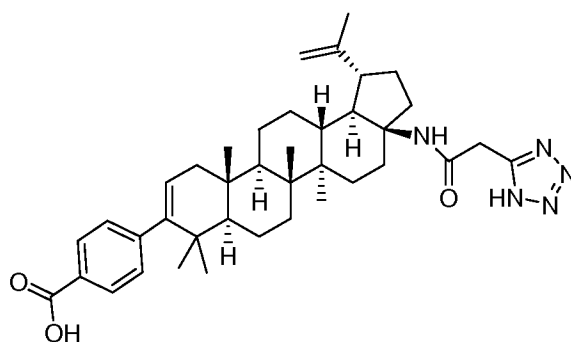
25

(br. s., 2 H), 1.20 - 1.14 (m, 2 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H) .

Example 77

5

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-tetrazol-5-yl)acetamido)-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.



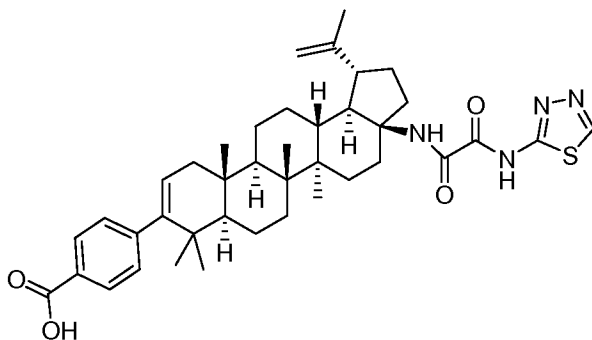
10

The title compound was prepared in 8% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except (1H-tetrazol-5-yl)-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 640.5 (M+H)⁺, 1.58 min (method 6). ¹H NMR (500MHz, METHANOL-d₄) δ = 7.95 (d, J = 8.2 Hz, 2 H), 7.48 (s, 1 H), 7.25 (d, J = 8.2 Hz, 2 H), 5.33 (dd, J = 1.5, 6.1 Hz, 1 H), 4.82 (d, J = 1.8 Hz, 1 H), 4.68 (s, 1 H), 4.12 - 4.00 (m, 2 H), 2.79 (dt, J = 5.0, 11.2 Hz, 1 H), 2.72 - 2.62 (m, 1 H), 2.45 - 2.35 (m, 1 H), 2.19 (dd, J = 6.4, 17.1 Hz, 1 H), 2.07 - 1.92 (m, 2 H), 1.84 (d, J = 11.6 Hz, 1 H), 1.77 (br. s., 1 H), 1.76 (s, 3 H), 1.73 (d, J = 7.3 Hz, 1 H), 1.66 - 1.56 (m, 3 H), 1.56 - 1.49 (m, 4 H), 1.48 - 1.27 (m, 6 H), 1.23 - 1.15 (m, 1 H), 1.12 (s, 3 H), 1.08 (s, 3 H), 1.07 (s, 3 H), 1.00 (s, 3 H), 0.97 (s, 3 H).

25

Example 78

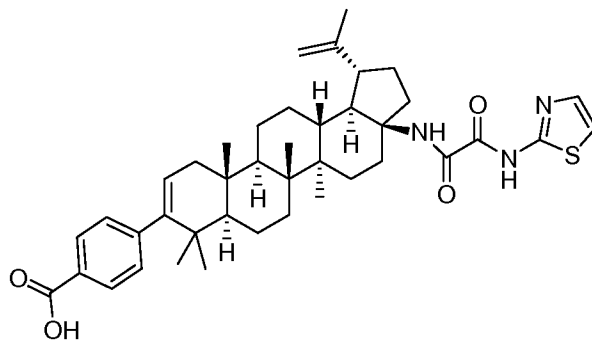
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,3,4-
 5 thiadiazol-2-ylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared in 21% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 15 3a-(3-(dimethylamino)propanamido)-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, except 2-(1,3,4-thiadiazol-2-ylamino)-2-oxoacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 683.6 (M-H)⁻, 1.77 min (method 9). ¹H NMR (500MHz, 2:1
 20 *MeOD:CDCl₃*) δ = 9.13 (s, 1 H), 7.92 (d, J = 8.5 Hz, 2 H), 7.45 (s, 1 H), 7.21 (d, J = 8.2 Hz, 2 H), 5.37 - 5.24 (m, 1 H), 4.81 - 4.78 (m, 1 H), 4.67 (s, 1 H), 2.67 - 2.56 (m, 2 H), 2.55 - 2.47 (m, 1 H), 2.15 (dd, J = 6.4, 17.1 Hz, 1 H), 1.99 - 1.90 (m, 1 H), 1.82 (dd, J = 10.5, 16.3 Hz, 3 H), 1.74 (s, 3 H), 1.71 (br. s., 1 H), 1.59 - 1.44 (m, 9 H), 1.44 - 1.39 (m, 1 H), 1.30 - 1.24 (m, 1 H), 1.22 - 1.14 (m, 2 H), 1.10 (s, 3 H), 1.07 (s, 3 H),
 25 1.03 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 79

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-oxo-2-(thiazol-2-ylamino)acetamido)-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

The title compound was prepared in 23% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-oxo-2-(thiazol-2-ylamino)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1.

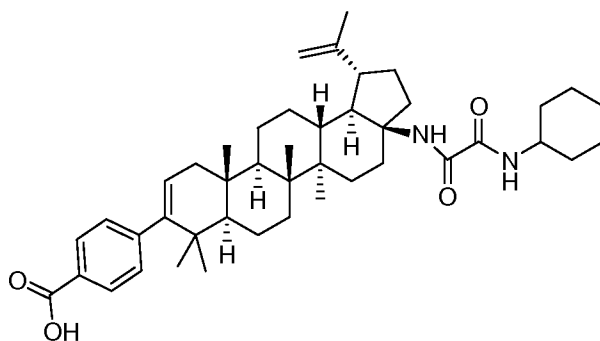
LCMS: m/e 684.5 ($M+H$)⁺, 2.04 min (method 9). ¹H NMR (500MHz, 1:1 MeOD:CDCl₃) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.54 (d, J = 3.7 Hz, 1 H), 7.49 (s, 1 H), 7.22 - 7.19 (m, 3 H), 5.30 (dd, J = 1.8, 6.1 Hz, 1 H), 4.79 (d, J = 1.2 Hz, 1 H), 2.65 - 2.55 (m, 2 H), 2.53 - 2.46 (m, 1 H), 2.14 (dd, J = 6.4, 17.1 Hz, 1 H), 1.98 - 1.89 (m, 1 H), 1.88 - 1.76 (m, 3 H), 1.73 (s, 3 H), 1.70 (s, 1 H), 1.61 - 1.36 (m, 11 H), 1.29 - 1.22 (m, 1 H), 1.21 - 1.14 (m, 2 H), 1.09 (s, 3 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.95 - 0.94 (m, 3 H), 0.93 (s, 3 H).

25

Example 80

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(cyclohexylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

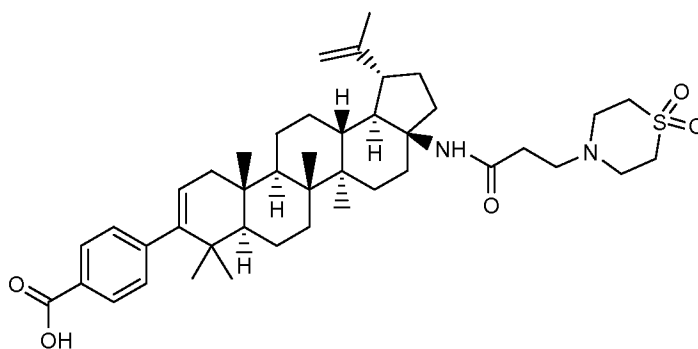
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 5 The title compound was prepared in 40% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(cyclohexylamino)-2-oxoacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1.
- LCMS: m/e 681.7 (M-H)⁻, 2.42 min (method 9). ¹H NMR (500MHz, *CHLOROFORM-d*) δ = 8.03 (d, J = 8.5 Hz, 2 H), 7.61 (s, 1 H), 7.52 (d, J = 8.5 Hz, 1 H), 7.25 (d, J = 8.2 Hz, 2 H), 6.51 (br. s., 1 H), 5.33 (d, J = 4.6 Hz, 1 H), 4.79 (d, J = 1.2 Hz, 1 H), 4.67 (s, 1 H), 3.83 - 3.72 (m, 1 H), 2.62 - 2.54 (m, 2 H), 2.50 (dd, J = 8.5, 11.6 Hz, 1 H), 2.14 (dd, J = 6.3, 17.2 Hz, 1 H), 2.00 - 1.89 (m, 3 H), 1.86 - 1.75 (m, 4 H), 1.71 - 1.62 (m, 2 H), 1.61 - 1.36 (m, 13 H), 1.35 - 1.20 (m, 5 H), 1.18 - 1.11 (m, 2 H), 1.08 (s, 3 H), 1.05 - 1.02 (m, 3 H), 1.00 (s, 3 H), 0.96 (s, 6 H).

Example 81

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



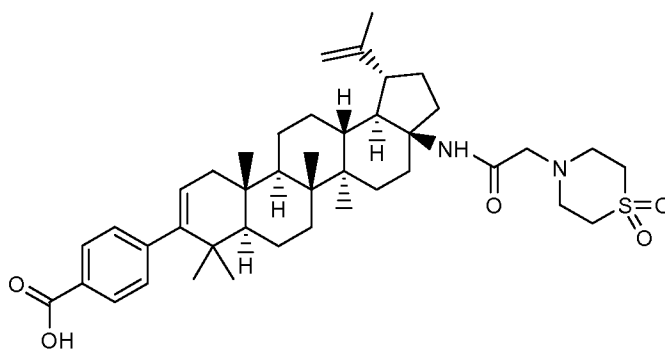
The title compound was prepared in 70% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 3-(1,1-dioxo-1,4-thiazinan-4-yl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 719.5 ($M+H$)⁺, 1.88 min (method 6). ¹H NMR (500MHz, 2:1 MeOD:CDCl₃) δ = 7.93 (d, J = 7.9 Hz, 2 H), 7.25 (br. s., 1 H), 7.21 (d, J = 7.9 Hz, 2 H), 5.30 (d, J = 6.1 Hz, 1 H), 4.78 (s, 1 H), 4.66 (s, 1 H), 3.47 (br. s., 4 H), 3.36 (br. s., 4 H), 3.19 (br. s., 2 H), 2.72 - 2.59 (m, 4 H), 2.40 (dd, J = 8.9, 11.9 Hz, 1 H), 2.15 (dd, J = 6.3, 17.2 Hz, 1 H), 1.98 - 1.86 (m, 2 H), 1.80 (d, J = 13.1 Hz, 1 H), 1.73 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.63 - 1.43 (m, 8 H), 1.42 - 1.23 (m, 5 H), 1.22 - 1.13 (m, 2 H), 1.12 (s, 3 H), 1.05 (br. s., 3 H), 1.04 (br. s., 3 H), 0.97 (br. s., 3 H), 0.95 (br. s., 3 H).

20

Example 82

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[1,1-dioxido-4-thiomorpholinyl]acetyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].

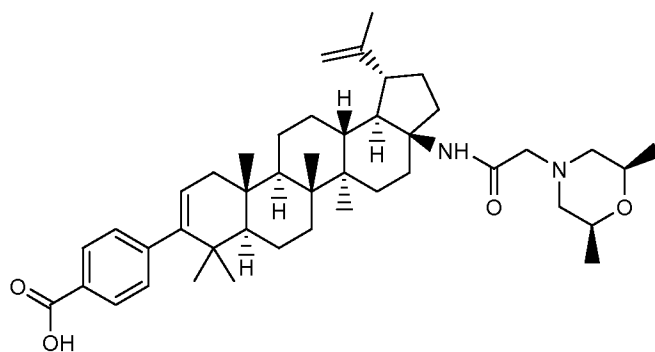
25



The title compound was prepared in 61% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 4-thiomorpholineacetic acid 1,1-dioxide was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 704.5 ($M+H$)⁺, 1.90 min (method 6). ¹H NMR (500MHz, 2:1 MeOD:CDCl₃) δ = 7.93 (d, J = 8.2 Hz, 2 H), 7.23 (br. s., 1 H), 7.21 (s, 2 H), 5.31 (dd, J = 1.7, 6.0 Hz, 1 H), 4.78 (d, J = 1.2 Hz, 1 H), 4.67 (s, 1 H), 3.29 (d, J = 5.2 Hz, 4 H), 3.24 (d, J = 5.2 Hz, 4 H), 2.67 - 2.60 (m, 1 H), 2.53 (dt, J = 5.5, 10.8 Hz, 1 H), 2.47 (dd, J = 8.1, 12.7 Hz, 1 H), 2.16 (dd, J = 6.3, 17.2 Hz, 1 H), 1.94 - 1.78 (m, 3 H), 1.76 (d, J = 2.1 Hz, 1 H), 1.74 (s, 3 H), 1.62 - 1.49 (m, 7 H), 1.47 - 1.33 (m, 4 H), 1.31 - 1.25 (m, 1 H), 1.21 - 1.13 (m, 2 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 1.05 (s, 3 H), 0.97 (s, 3 H), 0.96 (s, 3 H).

Example 83

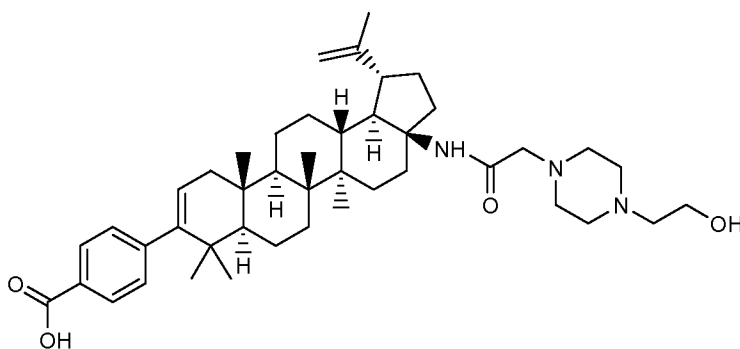
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2S,6R)-2,6-dimethylmorpholino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 43% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except [(2R,6S)-2,6-dimethylmorpholin-4-yl]acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 685.6 ($M+H$)⁺, 2.48 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeOD) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 5.29 (dd, J = 1.5, 6.1 Hz, 1 H), 4.75 (d, J = 1.2 Hz, 1 H), 3.89 (dd, J = 6.3, 9.0 Hz, 2 H), 3.64 (br. s., 1 H), 3.24 (br. s., 2 H), 2.69 - 2.49 (m, 4 H), 2.39 (dd, J = 8.1, 12.4 Hz, 1 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 1.93 - 1.76 (m, 3 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.66 (m, 1 H), 1.60 - 1.42 (m, 8 H), 1.42 - 1.30 (m, 3 H), 1.25 (d, J = 3.1 Hz, 3 H), 1.24 (d, J = 2.7 Hz, 3 H), 1.18 - 1.11 (m, 2 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 84

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(2-hydroxyethyl)piperazin-1-yl)acetamido)-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.



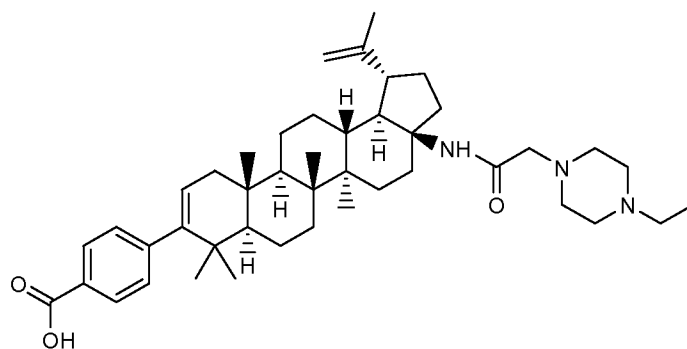
The title compound was prepared in 23% yield from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure
 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 3a-(3-(dimethylamino)propanamido)-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, except [4-(2-hydroxy-ethyl)-piperazine-1-
 yl]-acetic acid dihydrochloride was used instead of 3-(dimethylamino)propionic acid
 hydrochloride in Step 1. LCMS: m/e 700.6 ($M+H$)⁺, 2.03 min (method 6). ¹H NMR
 (500MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H),
 6.96 (s, 1 H), 5.30 (dd, J = 1.7, 6.0 Hz, 1 H), 4.76 (s, 1 H), 4.66 (s, 1 H), 3.93 - 3.89
 (m, 2 H), 3.42 (br. s., 2 H), 3.30 - 3.25 (m, 2 H), 3.22 (d, J = 4.6 Hz, 2 H), 2.97 (br. s.,
 3 H), 2.68 - 2.60 (m, 1 H), 2.55 - 2.47 (m, 1 H), 2.44 (dd, J = 8.2, 12.5 Hz, 1 H), 2.13
 (dd, J = 6.4, 17.1 Hz, 1 H), 1.91 - 1.77 (m, 2 H), 1.75 (br. s., 1 H), 1.72 (s, 3 H), 1.72 -
 1.68 (m, 1 H), 1.62 - 1.31 (m, 11 H), 1.30 - 1.24 (m, 1 H), 1.15 (d, J = 13.1 Hz, 2 H),
 1.08 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

20

Example 85

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-
 ethylpiperazin-1-yl)acetamido)-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.

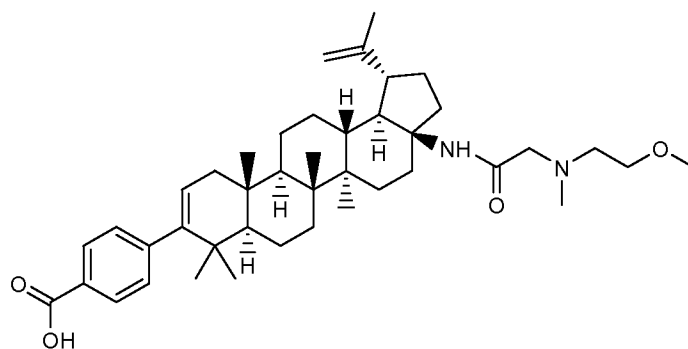
25



The title compound was prepared in 34% yield from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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-
 5 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure
 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 3a-(3-(dimethylamino)propanamido)-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-
 10 cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(4-ethylpiperazin-1-yl)acetic acid
 was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1.
 LCMS: m/e 684.6 ($M+H$)⁺, 2.35 min (method 6). ¹H NMR (500MHz, 1:1
CDCl₃:MeOD) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 6.90 (s, 1 H),
 5.29 (d, J = 6.1 Hz, 1 H), 4.75 (d, J = 1.2 Hz, 1 H), 3.27 - 3.14 (m, 5 H), 2.96 (br. s., 3
 15 H), 2.64 (d, J = 13.4 Hz, 1 H), 2.55 - 2.38 (m, 2 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H),
 1.92 - 1.76 (m, 2 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.67 (m, 1 H), 1.61 - 1.41
 (m, 9 H), 1.37 (t, J = 7.3 Hz, 4 H), 1.35 - 1.31 (m, 1 H), 1.29 - 1.23 (m, 1 H), 1.18 -
 1.12 (m, 2 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 2 H), 0.94 (s, 3 H), 0.94 (s, 3 H).

20 Example 86

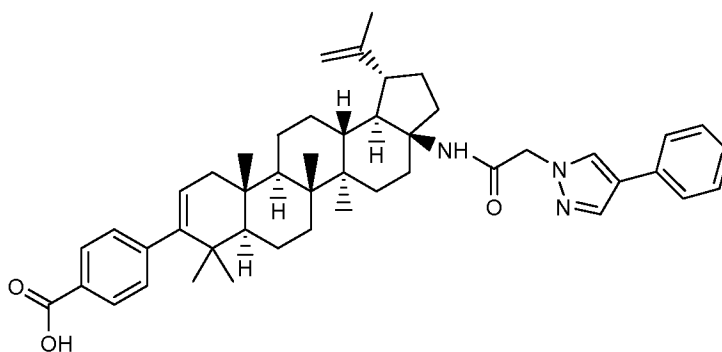
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-
 methoxyethyl)(methyl)amino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-
 yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 25 cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 38% yield from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure
 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 3a-(3-(dimethylamino)propanamido)-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, except *N*-(2-methoxyethyl)-*N*-methylglycine
 was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1.
 LCMS: m/e 659.6 ($M+H$)⁺, 2.41 min (method 6). ¹H NMR (500MHz, 1:1
*CDCl*₃:*MeOD*) δ = 7.92 (d, J = 7.9 Hz, 2 H), 7.43 (s, 1 H), 7.20 (d, J = 8.2 Hz, 2 H),
 5.29 (d, J = 5.8 Hz, 1 H), 4.75 (s, 1 H), 3.96 (br. s., 2 H), 3.73 (t, J = 4.7 Hz, 2 H),
 3.42 (s, 3 H), 3.40 (br. s., 2 H), 2.94 (s, 3 H), 2.73 - 2.61 (m, 2 H), 2.36 (dd, J = 8.4,
 12.1 Hz, 1 H), 2.12 (dd, J = 6.1, 17.1 Hz, 1 H), 1.88 (t, J = 11.6 Hz, 2 H), 1.77 (d, J =
 11.6 Hz, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70 - 1.65 (m, 1 H), 1.58 - 1.30 (m, 11
 H), 1.25 (d, J = 6.1 Hz, 1 H), 1.18 - 1.10 (m, 2 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.01 (s,
 3 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 87

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-3a-(2-(4-phenyl-1H-pyrazol-1-yl)acetamido)-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.



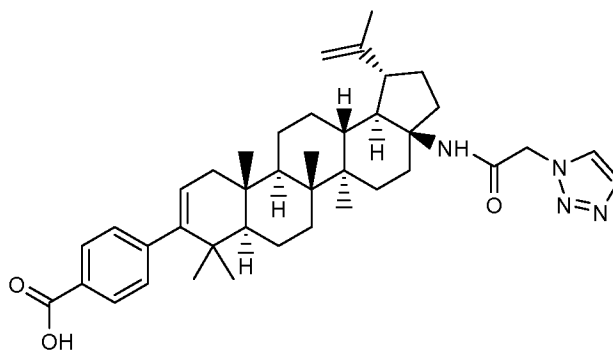
The title compound was prepared in 22% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(3-phenyl-1H-pyrazol-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 714.6 ($M+H$)⁺, 2.59 min (method 6). ¹H NMR (500MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.91 (d, J = 8.2 Hz, 4 H), 7.67 (d, J = 2.1 Hz, 1 H), 7.42 (d, J = 7.3 Hz, 2 H), 7.40 (s, 1 H), 7.37 - 7.31 (m, 1 H), 7.18 (d, J = 7.9 Hz, 2 H), 5.24 (d, J = 4.6 Hz, 1 H), 4.86 - 4.75 (m, 2 H), 4.59 (s, 1 H), 3.37 (s, 3 H), 2.50 (dd, J = 2.4, 9.2 Hz, 1 H), 2.47 - 2.38 (m, 2 H), 1.97 (dd, J = 6.4, 17.1 Hz, 1 H), 1.93 - 1.83 (m, 1 H), 1.64 (s, 3 H), 1.60 - 1.52 (m, 2 H), 1.50 - 1.37 (m, 4 H), 1.37 - 1.27 (m, 7 H), 1.26 - 1.19 (m, 1 H), 1.16 - 1.11 (m, 1 H), 1.00 (dd, J = 2.4, 9.2 Hz, 1 H), 0.90 (s, 3 H), 0.89 (s, 6 H), 0.79 (s, 3 H), 0.61 (s, 3 H), 0.49 (dd, J = 4.3, 13.1 Hz, 1 H).

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Example 88

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-1,2,3-triazol-1-yl)acetamido)-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.

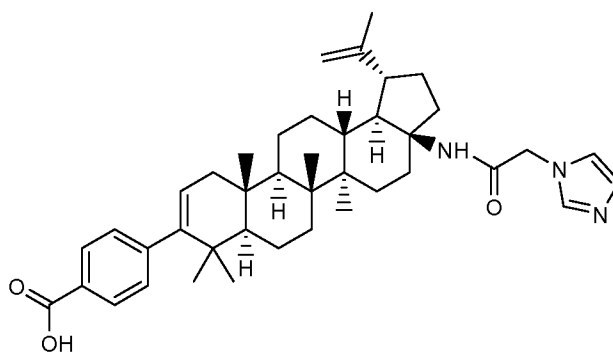
25



The title compound was prepared in 36% yield from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure
 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 3a-(3-(dimethylamino)propanamido)-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, except 1H-1,2,3-triazole-1-acetic acid
 hydrochloride was used instead of 3-(dimethylamino)propionic acid hydrochloride in
 Step 1. LCMS: m/e 639.5 ($M+H$)⁺, 2.04 min (method 6). ¹H NMR (500MHz, 1:1
CDCl₃:MeOD) δ = 7.94 (d, J = 0.9 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 2 H), 7.77 (d, J = 0.9
 Hz, 1 H), 7.20 (d, J = 8.5 Hz, 2 H), 6.93 (s, 1 H), 5.29 (dd, J = 1.7, 6.3 Hz, 1 H), 5.15
 (s, 2 H), 4.75 (d, J = 1.5 Hz, 1 H), 4.64 (br. s., 1 H), 2.63 - 2.57 (m, 1 H), 2.57 - 2.50
 (m, 1 H), 2.37 (dd, J = 8.1, 12.7 Hz, 1 H), 2.12 (dd, J = 6.4, 17.1 Hz, 1 H), 1.94 - 1.83
 (m, 1 H), 1.78 - 1.72 (m, 3 H), 1.70 (s, 3 H), 1.69 - 1.64 (m, 1 H), 1.58 - 1.39 (m, 8
 H), 1.38 - 1.29 (m, 3 H), 1.24 (dd, J = 3.7, 10.4 Hz, 1 H), 1.15 - 1.06 (m, 2 H), 1.02 (s,
 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Example 89

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-imidazol-
 1-yl)acetamido)-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.



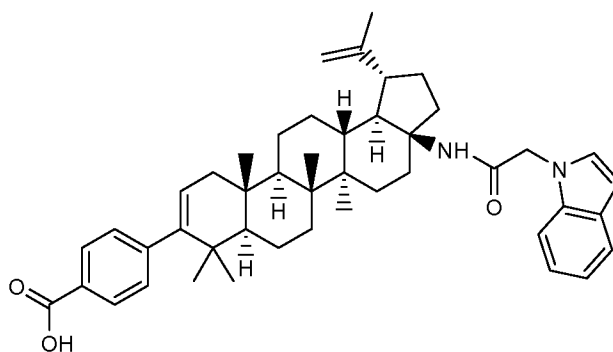
The title compound was prepared in 60% yield from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure
 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 3a-(3-(dimethylamino)propanamido)-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, except imidazol-1-ylacetic acid was used
 instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e
 638.5 (M+H)⁺, 2.05 min (method 6). ¹H NMR (400MHz, 1:1 CDCl₃:MeOD) δ =
 8.88 (s, 1 H), 7.92 (d, J = 8.3 Hz, 2 H), 7.47 (ddd, J = 1.6, 1.8, 9.7 Hz, 2 H), 7.42 (s, 1
 H), 7.20 (d, J = 8.5 Hz, 2 H), 5.33 - 5.25 (m, 1 H), 5.02 (d, J = 5.0 Hz, 2 H), 4.78 (d, J
 = 1.3 Hz, 1 H), 4.65 (d, J = 1.8 Hz, 2 H), 2.72 (dt, J = 5.3, 11.0 Hz, 1 H), 2.66 - 2.57
 (m, 1 H), 2.33 (dd, J = 8.2, 12.7 Hz, 1 H), 2.13 (dd, J = 6.3, 17.1 Hz, 1 H), 2.00 - 1.88
 (m, 2 H), 1.80 (d, J = 14.6 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.67 (m, 1
 H), 1.60 - 1.32 (m, 11 H), 1.30 - 1.22 (m, 1 H), 1.19 - 1.13 (m, 1 H), 1.12 (s, 3 H),
 1.03 (s, 3 H), 1.02 (s, 2 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

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Example 90

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-indol-1-
 yl)acetamido)-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.

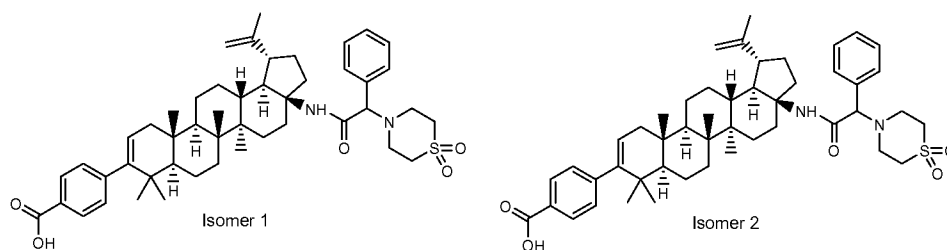
25



The title compound was prepared in 31% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(1H-indol-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 687.6 ($M+H$)⁺, 2.60 min (method 6). ¹H NMR (400MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.72 (d, J = 7.8 Hz, 1 H), 7.40 - 7.35 (m, 1 H), 7.32 - 7.25 (m, 1 H), 7.24 - 7.16 (m, 4 H), 6.71 (dd, J = 0.8, 3.3 Hz, 1 H), 5.27 (dd, J = 1.6, 6.1 Hz, 1 H), 4.90 (s, 1 H), 4.83 (s, 2 H), 4.44 (s, 1 H), 4.33 (d, J = 1.8 Hz, 1 H), 2.48 (d, J = 12.5 Hz, 1 H), 2.39 - 2.31 (m, 1 H), 2.08 (dd, J = 6.4, 17.2 Hz, 1 H), 1.64 (d, J = 16.6 Hz, 1 H), 1.54 (d, J = 8.0 Hz, 2 H), 1.50 (s, 3 H), 1.39 (br. s., 3 H), 1.37 - 1.23 (m, 6 H), 1.23 - 1.13 (m, 4 H), 1.04 (br. s., 1 H), 1.00 (s, 4 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 3 H), 0.82 (s, 3 H).

Example 91 (Isomer 1) and Example 92 (Isomer 2)

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[1,1-dioxido-4-thiomorpholinyl]phenylacetyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



The title compounds were prepared in 21% and 11% yield, respectively, from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(1,1-dioxo-1-lambda-6-4-thiazinan-4-yl)-2-phenylacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. The two isomers formed in the reaction were separated by reverse phase preparative HPLC.

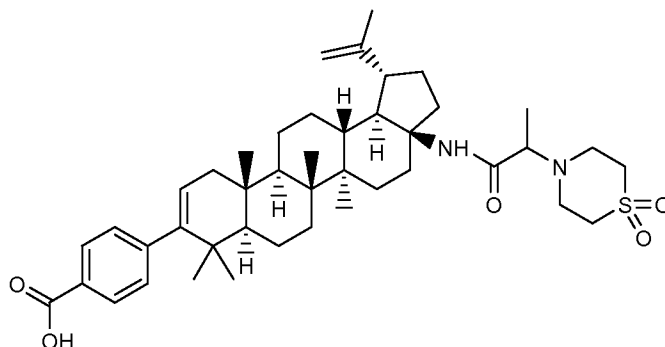
Isomer 1: LCMS: m/e 781.6 ($M+H$)⁺, 2.21 min (method 6). ¹H NMR (400MHz, 1:1 $CDCl_3:MeOD$) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.49 - 7.44 (m, 2 H), 7.43 - 7.36 (m, 3 H), 7.20 (d, J = 8.3 Hz, 2 H), 6.62 (s, 1 H), 5.29 (dd, J = 1.6, 6.1 Hz, 1 H), 4.76 (d, J = 1.3 Hz, 1 H), 4.64 (br. s., 1 H), 4.26 (s, 1 H), 3.19 - 3.13 (m, 4 H), 3.12 - 3.01 (m, 4 H), 2.57 - 2.48 (m, 2 H), 2.40 (dd, J = 8.0, 11.8 Hz, 1 H), 2.12 (dd, J = 6.3, 17.1 Hz, 1 H), 1.76 (d, J = 14.6 Hz, 1 H), 1.71 (br. s., 1 H), 1.70 (s, 3 H), 1.66 (d, J = 11.0 Hz, 3 H), 1.50 (d, J = 16.3 Hz, 3 H), 1.46 - 1.38 (m, 3 H), 1.38 - 1.09 (m, 9 H), 1.00 (s, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.92 (s, 3 H), 0.84 (s, 3 H).

Isomer 2: LCMS: m/e 781.6 ($M+H$)⁺, 2.22 min (method 6). ¹H NMR (400MHz, 1:1 $CDCl_3:MeOD$) δ = 7.92 (d, J = 8.3 Hz, 2 H), 7.49 - 7.44 (m, 2 H), 7.43 - 7.34 (m, 3 H), 7.21 (d, J = 8.3 Hz, 2 H), 6.64 (s, 1 H), 5.30 (dd, J = 1.6, 6.1 Hz, 1 H), 4.75 (s, 1 H), 4.65 (s, 1 H), 4.16 (s, 1 H), 3.25 - 2.99 (m, 8 H), 2.65 - 2.57 (m, 1 H), 2.42 (dt, J = 5.6, 10.9 Hz, 1 H), 2.32 (dd, J = 8.3, 12.5 Hz, 1 H), 2.15 (dd, J = 6.4, 16.9 Hz, 1 H), 1.85 - 1.72 (m, 3 H), 1.70 (s, 3 H), 1.61 - 1.23 (m, 14 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H).

Example 93

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-

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



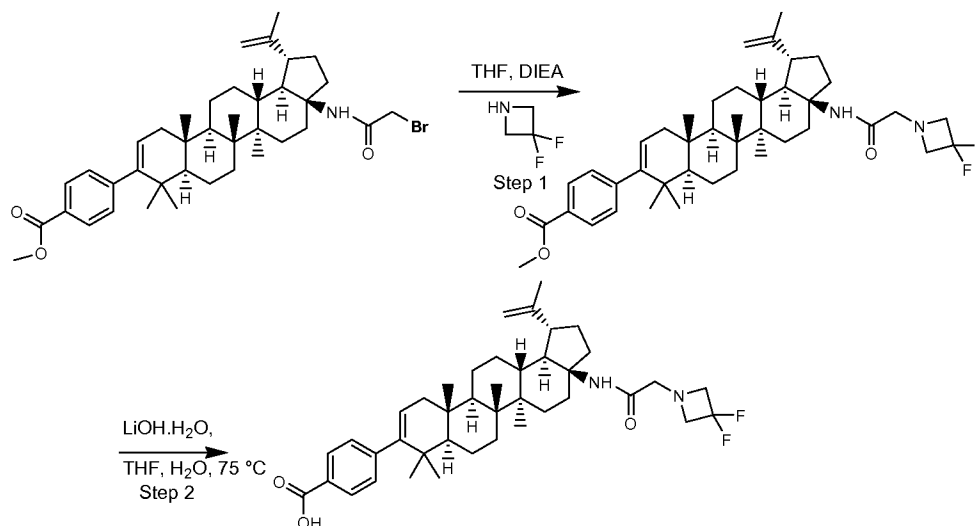
- The title compound was prepared in 44% yield from methyl 4-
- 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 15 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, except 2-(1,1-dioxidothiomorpholin-4-yl)-propionic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 719.5 ($M+H$)⁺, 2.03 min (method 6). ¹H NMR (500MHz, 1:1 $CDCl_3$: $MeOD$) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.20 (d, J = 7.9 Hz, 2 H), 5.29 (d, J = 5.2 Hz, 1 H), 4.75 (d, J = 10.4 Hz, 1 H), 4.66 (br. s., 1 H), 3.48 - 3.39 (m, 1 H), 3.28 - 3.11 (m, 8 H), 2.69 - 2.55 (m, 1 H), 2.50 - 2.34 (m, 2 H), 2.13 (dd, J = 6.1, 17.1 Hz, 1 H), 1.80 (d, J = 11.6 Hz, 2 H), 1.72 (s, 6 H), 1.59 - 1.44 (m, 8 H), 1.43 - 1.36 (m, 2 H), 1.33 (dd, J = 6.9, 14.8 Hz, 4 H), 1.25 (d, J = 6.7 Hz, 1 H), 1.15 (d, J = 11.0 Hz, 2 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 6 H).
- 20

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Example 94

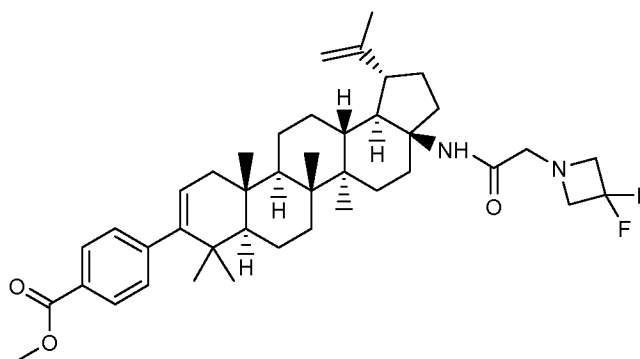
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

5



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-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.

10



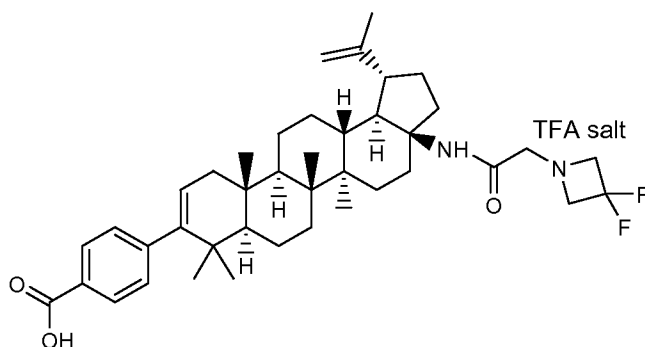
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (129 mg, 0.194 mmol) in THF (3 mL) was added *N,N*-diisopropylethylamine (0.338 mL, 1.941 mmol) and 3,3-difluoroazetidine, HCl

15

(126 mg, 0.970 mmol). The reaction mixture was stirred at 160 °C for 5 h. The mixture was concentrated and the crude residue was dissolved in THF (1.5 mL), filtered and purified by reverse phase preparative HPLC using Prep HPLC method 3 to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-

5 difluoroazetidin-1-yl)acetamido)-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 (28.8 mg, 0.043 mmol, 21.9 % yield) as brown solid. LC/MS: m/e 677.5 (M+H)⁺, 2.93 min (method 6).

10 Step 2. Preparation of give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-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, TFA.



15

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-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 (28.8 mg, 0.043 mmol) in THF (Volume: 3 mL)

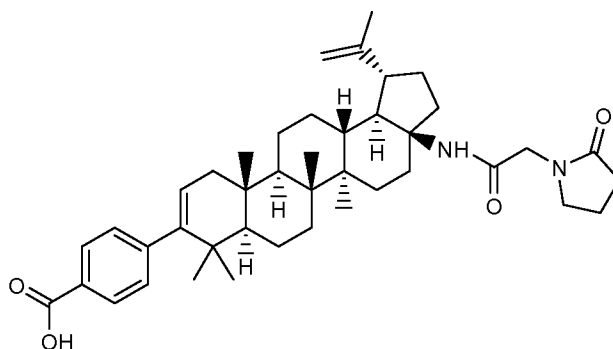
20 was added a 0.753 molar solution of Li . H O . H₂O (0.340 mL, 0.170 mmol) in H₂O. The reaction was heated to 75 °C for 6 h and was then concentrated to a brown viscous oil. The crude residue was dissolved in THF (1.3 mL) and 0.2 mL 1N HCl, filtered and purified by reverse phase preparative HPLC using prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-

25 1-yl)acetamido)-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, TFA (17.6 mg, 0.022 mmol, 52.7 % yield) as a light yellow solid. LCMS: m/e 663.7 (M+H)⁺, 2.22 min (method 2). ¹H NMR

(500MHz, 1:1 $CDCl_3$: $METHANOL-d_4$) δ 7.90 (d, $J=8.2$ Hz, 2H), 7.18 (d, $J=8.2$ Hz, 2H), 5.27 (d, $J=4.6$ Hz, 1H), 4.73 (s, 1H), 3.88 (t, $J=12.5$ Hz, 2H), 3.69 - 3.59 (m, 1H), 3.55 - 3.39 (m, 3H), 2.64 - 2.53 (m, 2H), 2.39 (dd, $J=12.2, 8.2$ Hz, 1H), 2.10 (dd, $J=17.1, 6.4$ Hz, 1H), 1.93 - 1.73 (m, 3H), 1.69 (s, 3H), 1.67 (d, $J=4.6$ Hz, 1H), 1.58 - 1.39 (m, 8H), 1.39 - 1.29 (m, 3H), 1.23 (d, $J=10.1$ Hz, 1H), 1.11 (d, $J=13.7$ Hz, 2H), 1.06 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.92 (br. s., 3H), 0.91 (br. s., 3H).

Example 95

10 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)acetamido)-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.



15

The title compound was prepared in 14% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(2-oxopyrrolidin-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1.

20 LCMS: m/e 655.5 ($M+H$)⁺, 1.99 min (method 6). ¹H NMR (500MHz, 1:1 $CDCl_3$: $MeOD$) δ = 7.92 (d, $J = 7.9$ Hz, 2 H), 7.20 (d, $J = 7.9$ Hz, 2 H), 6.77 (s, 1 H), 5.29 (d, $J = 4.7$ Hz, 1 H), 4.75 (d, $J = 1.3$ Hz, 1 H), 4.63 (s, 1 H), 3.97 - 3.85 (m, 2 H),

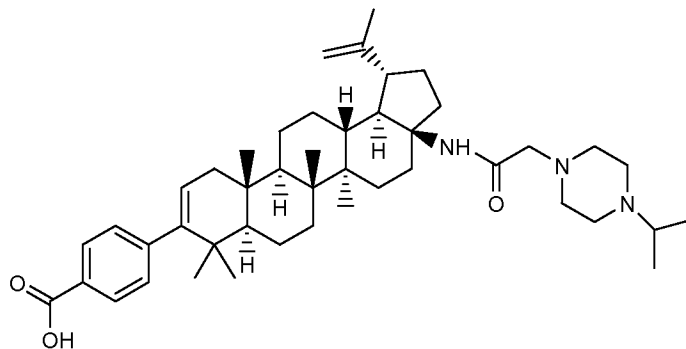
25

3.58 - 3.51 (m, 2 H), 2.65 - 2.54 (m, 2 H), 2.47 (t, $J = 8.0$ Hz, 2 H), 2.38 (dd, $J = 8.4$, 12.5 Hz, 1 H), 2.17 - 2.07 (m, 3 H), 1.95 - 1.85 (m, 1 H), 1.83 - 1.74 (m, 2 H), 1.73 (br. s., 1 H), 1.70 (s, 3 H), 1.68 - 1.62 (m, 1 H), 1.60 - 1.43 (m, 8 H), 1.42 - 1.22 (m, 6 H), 1.13 (br. s., 1 H), 1.09 (s, 3 H), 1.01 (s, 6 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

5

Example 96

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-isopropylpiperazin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
10 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.



The title compound was prepared in 22% yield from methyl 4-
15 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
20 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, except (4-isopropyl-piperazin-1-yl)-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 698.6 ($M+H$)⁺, 2.64 min (method 6). ¹H NMR (500MHz, 1:1 $CDCl_3$: $MeOD$) δ = 7.92 (d, $J = 8.2$ Hz, 2 H), 7.37 (br. s., 1 H), 7.20 (d, $J = 8.2$ Hz, 2 H), 6.34 - 6.03 (m, 1 H), 5.29 (d, $J = 4.6$ Hz, 1 H), 4.76 (br. s., 1 H), 4.70 (br. s., 1 H), 3.95 (br. s., 1 H), 3.84 - 3.55 (m, 8 H), 3.17 (q, $J = 7.2$ Hz, 2 H), 2.64 (d, $J = 13.1$ Hz, 2 H), 2.39 (dd, $J = 8.1$, 11.4 Hz, 1 H), 2.12 (dd, $J = 6.3$, 17.2 Hz, 1 H), 1.96 - 1.84 (m,

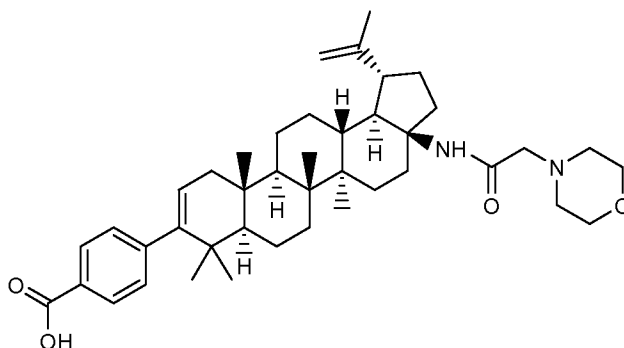
2 H), 1.79 (d, $J = 12.5$ Hz, 1 H), 1.76 - 1.65 (m, 5 H), 1.59 - 1.40 (m, 14 H), 1.35 (t, $J = 7.2$ Hz, 4 H), 1.29 - 1.21 (m, 1 H), 1.15 (d, $J = 6.1$ Hz, 1 H), 1.10 (br. s., 3 H), 1.02 (s, 3 H), 1.01 (br. s., 2 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

5

Example 97

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoacetamido)-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.

10



The title compound was prepared in 40% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except morpholin-4-yl-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 657.6 ($M+H$)⁺, 2.20 min (method 6). ¹H NMR (500MHz, 1:1 $CDCl_3:MeOD$) δ = 7.91 (d, $J = 7.9$ Hz, 2 H), 7.48 (br. s., 1 H), 7.19 (d, $J = 8.2$ Hz, 2 H), 5.28 (d, $J = 4.9$ Hz, 1 H), 4.77 (br. s., 1 H), 4.12 - 3.79 (m, 6 H), 3.57 - 3.40 (m, 2 H), 3.22 - 3.11 (m, 1 H), 2.74 (br. s., 1 H), 2.65 (d, $J = 12.8$ Hz, 1 H), 2.42 - 2.29 (m, 1 H), 2.12 (dd, $J = 6.1, 17.1$ Hz, 1 H), 2.03 - 1.85 (m, 2 H), 1.79 (d, $J = 12.8$ Hz, 1 H), 1.72 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (br. s., 1 H), 1.60 - 1.30 (m, 12 H), 1.24 (d, $J = 5.8$ Hz, 1 H), 1.14

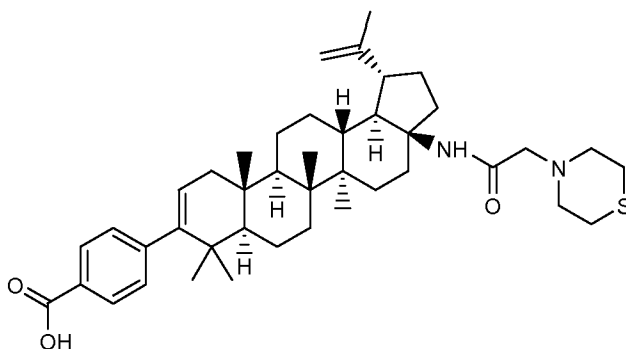
25

(br. s., 1 H), 1.10 (br. s., 4 H), 1.02 (br. s., 3 H), 1.00 (br. s., 3 H), 0.93 (br. s., 3 H), 0.92 (br. s., 3 H).

Example 98

5

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-thiomorpholinoacetamido)-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.



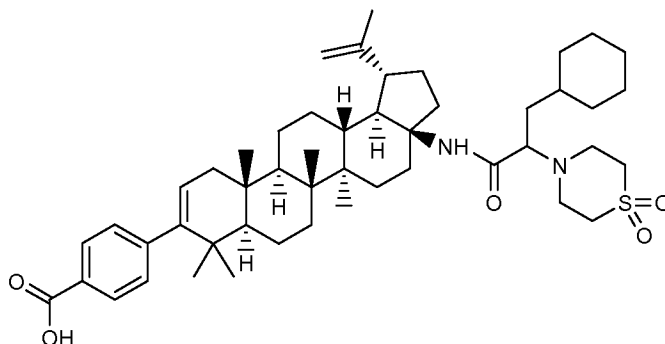
10

The title compound was prepared in 44% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-thiomorpholinoacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 671.8 (M-H)⁺, 2.37 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeOD) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.47 (s, 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 5.29 (d, J = 4.3 Hz, 1 H), 4.75 (s, 1 H), 3.79 - 3.63 (m, 2 H), 3.58 (td, J = 6.5, 12.9 Hz, 1 H), 3.47 - 3.35 (m, 3 H), 2.95 (br. s., 4 H), 2.68 - 2.57 (m, 2 H), 2.37 (dd, J = 8.4, 12.4 Hz, 1 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 1.92 - 1.82 (m, 2 H), 1.81 - 1.76 (m, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.69 - 1.64 (m, 1 H), 1.60 - 1.31 (m, 12 H), 1.30 - 1.22 (m, 1 H), 1.19 - 1.11 (m, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

25

Example 99

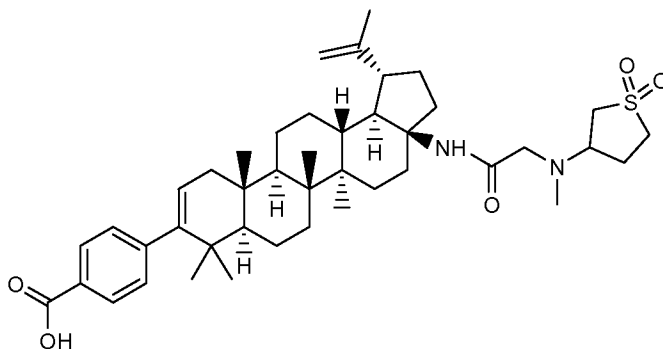
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-cyclohexyl-2-(1,1-dioxido-4-thiomorpholinyl)-1-oxopropyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



The title compound was prepared in 23% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 3-cyclohexyl-2-(1,1-dioxo-11lambda6,-4,thiazinan-4-yl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 801.6 ($M+H$)⁺, 2.43 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeOD) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 6.56 (s, 1 H), 5.29 (d, J = 4.6 Hz, 1 H), 4.76 (s, 1 H), 3.58 (td, J = 6.6, 13.4 Hz, 1 H), 3.44 (dd, J = 5.0, 9.6 Hz, 1 H), 3.30 - 3.25 (m, 3 H), 3.24 - 3.15 (m, 2 H), 3.14 - 3.06 (m, 2 H), 2.68 (d, J = 13.4 Hz, 1 H), 2.56 (dt, J = 5.6, 11.1 Hz, 1 H), 2.41 (dd, J = 8.4, 12.7 Hz, 1 H), 2.13 (dd, J = 6.3, 17.2 Hz, 1 H), 1.92 - 1.75 (m, 5 H), 1.73 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.64 (m, 4 H), 1.61 - 1.40 (m, 10 H), 1.40 - 1.29 (m, 3 H), 1.28 - 1.11 (m, 7 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.97 (d, J = 3.1 Hz, 1 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 100

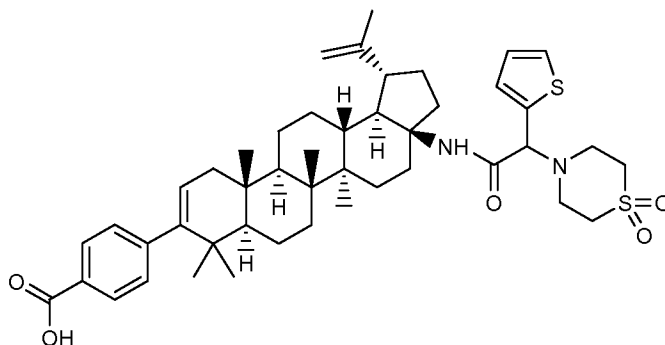
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-
 pentamethyl-1-(1-methylethenyl)-3a-[[[methyl(tetrahydro-1,1-dioxido-3-
 thienyl)amino]acetyl]amino]-1H-cyclopenta[a]chrysen-9-yl].



10 The title compound was prepared in 17% yield from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure
 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 15 3a-(3-(dimethylamino)propanamido)-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, except *N*-(1,1-dioxidotetrahydro-3-thienyl)-
N-methylglycine was used instead of 3-(dimethylamino)propionic acid hydrochloride
 in Step 1. LCMS: m/e 719.5 ($M+H$)⁺, 2.00 min (method 6). ¹H NMR (500MHz,
 20 $CDCl_3:MeOD$) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.20 (d, J = 8.2
 Hz, 2 H), 5.29 (d, J = 4.9 Hz, 1 H), 3.80 (br. s., 1 H), 3.40 (dd, J = 7.6, 13.4 Hz, 1 H),
 3.30 - 3.05 (m, 4 H), 2.60 (br. s., 1 H), 2.57 (d, J = 1.5 Hz, 3 H), 2.55 - 2.41 (m, 3 H),
 2.23 (quin, J = 10.6 Hz, 1 H), 2.13 (dd, J = 6.1, 17.1 Hz, 1 H), 1.91 - 1.76 (m, 2 H),
 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70 (br. s., 1 H), 1.60 - 1.29 (m, 12 H), 1.25 (d, J =
 25 7.0 Hz, 1 H), 1.21 - 1.11 (m, 3 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (s, 3
 H), 0.93 (br. s., 3 H).

Example 101

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)-1-oxo-3-(2-thienyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].

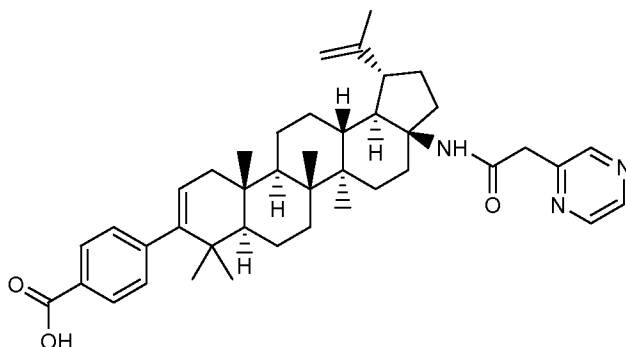


The title compound was prepared in 39% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 3-(1,1-dioxo-1λ⁶,4-thiazinan-4-yl)-3-(2-thienyl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 801.6 (M+H)⁺, 2.16 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeOD) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.36 - 7.28 (m, 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 7.05 - 6.91 (m, 2 H), 6.59 (s, 1 H), 5.29 (d, J = 4.9 Hz, 1 H), 4.74 (d, J = 7.6 Hz, 1 H), 4.60 - 4.52 (m, 2 H), 3.18 - 3.05 (m, 6 H), 3.04 - 2.93 (m, 2 H), 2.91 - 2.72 (m, 2 H), 2.68 - 2.49 (m, 2 H), 2.48 - 2.40 (m, 1 H), 2.27 (dd, J = 8.5, 11.9 Hz, 1 H), 2.12 (dd, J = 4.9, 17.1 Hz, 1 H), 1.93 - 1.72 (m, 3 H), 1.69 (d, J = 7.9 Hz, 3 H), 1.64 (d, J = 11.6 Hz, 1 H), 1.61 - 1.38 (m, 8 H), 1.37 - 1.19 (m, 5 H), 1.13 (br. s., 1 H), 1.11 (br. s., 15 H), 1.10 (br. s., 2 H), 1.02 (br. s., 1 H), 1.01 (br. s., 2 H), 1.01 (br. s., 1 H), 1.00 (br. s., 2 H), 0.95 (br. s., 1 H), 0.95 (br. s., 2 H), 0.93 (s, 3 H).

Example 102

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyrazin-2-yl)acetamido)-

- 5 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.

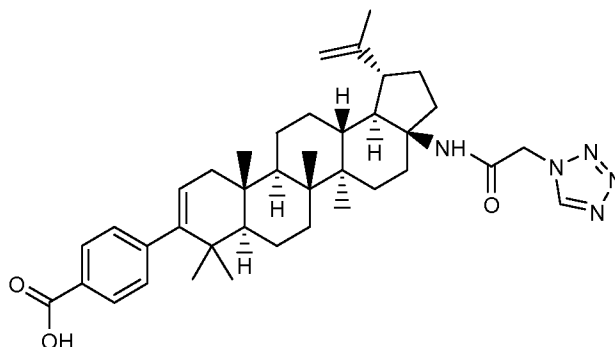


- The title compound was prepared in 14% yield from methyl 4-
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 15 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, except 2-pyrazine acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 650.6 (M+H)⁺, 2.12 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeOD) δ = 8.68 - 8.50 (m, 3 H), 7.92 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 3 H), 5.29 (dd, J = 8.68 - 8.50 Hz, 1 H), 4.76 (s, 1 H), 3.79 (q, J = 14.3 Hz, 2 H), 2.66 - 2.53 (m, 2 H), 2.42 - 2.31 (m, 1 H), 2.12 (dd, J = 6.4, 17.1 Hz, 1 H), 1.91 - 1.74 (m, 3 H), 1.72 (br. s., 1 H), 1.71 (s, 2 H), 1.67 (d, J = 11.9 Hz, 2 H), 1.57 - 1.18 (m, 13 H), 1.17 - 1.02 (m, 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 0.94 (s, 3 H), 0.92 (br. s., 3 H), 0.92 (br. s., 3 H).

Example 103

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-tetrazol-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

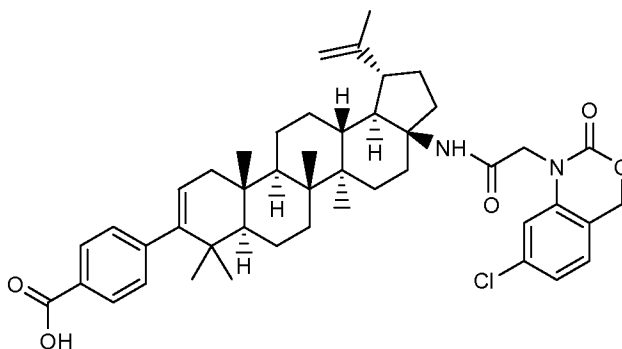
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- The title compound was prepared in 33% yield from methyl 4-
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 15 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, except 1-H-tetrazole-1-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 638.7 (M-H)⁻, 1.98 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeOD) δ = 9.10 (s, 1 H), 7.93 (d, J = 8.2 Hz, 2 H), 7.39 (s, 1 H), 7.21 (d, J = 8.2 Hz, 2 H), 5.30 (dd, J = 1.5, 6.1 Hz, 1 H), 5.27 (d, J = 1.5 Hz, 2 H), 4.78 (d, J = 1.2 Hz, 1 H), 4.65 (s, 1 H), 2.71 (dt, J = 5.2, 11.1 Hz, 1 H), 2.64 - 2.56 (m, 1 H), 2.34 (dd, J = 8.1, 12.7 Hz, 1 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 2.00 - 1.86 (m, 2 H), 1.80 (d, J = 11.0 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.62 - 1.30 (m, 11 H), 1.29 - 1.22 (m, 1 H), 1.20 - 1.14 (m, 1 H), 1.12 (s, 3 H), 1.10 (d, J = 4.3 Hz, 1 H), 1.03 (s, 6 H), 0.95
 20 (s, 3 H), 0.94 (s, 3 H).

Example 104

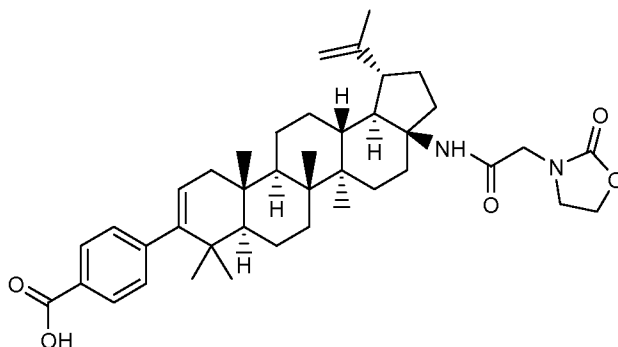
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(7-chloro-2-oxo-2,4-dihydro-1H-benzo[d][1,3]oxazin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 36% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(6-chloro-3-oxo-2H-benzo[b][1,4]oxazin-4(3H)-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 653.5 ($M+H$)⁺, 2.29 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeOD) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.5 Hz, 2 H), 7.05 - 7.01 (m, 1 H), 7.01 - 6.97 (m, 2 H), 6.83 (s, 1 H), 5.29 (dd, J = 1.7, 6.3 Hz, 1 H), 4.73 (d, J = 1.8 Hz, 1 H), 4.70 (d, J = 1.2 Hz, 2 H), 4.66 (br. s., 1 H), 4.63 (s, 1 H), 4.57 - 4.50 (m, 1 H), 2.65 - 2.57 (m, 1 H), 2.51 - 2.34 (m, 2 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 1.96 - 1.85 (m, 1 H), 1.83 - 1.72 (m, 3 H), 1.70 (s, 3 H), 1.69 - 1.64 (m, 1 H), 1.63 - 1.55 (m, 2 H), 1.54 - 1.45 (m, 4 H), 1.45 - 1.30 (m, 5 H), 1.30 - 1.23 (m, 1 H), 1.18 - 1.12 (m, 2 H), 1.10 (s, 3 H), 1.02 (s, 6 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 105

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxooxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-
 5 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.

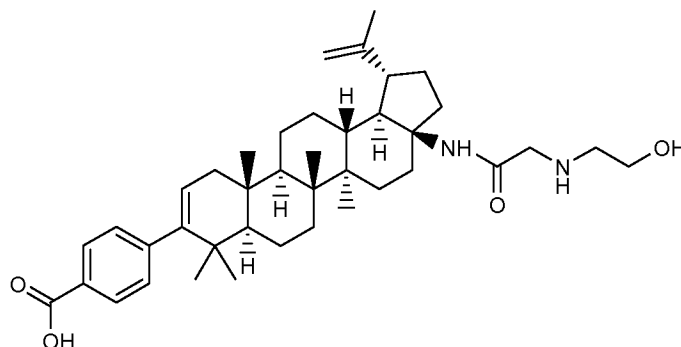


The title compound was prepared in 29% yield from methyl 4-
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 15 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, except 2-(2-oxooxazolidin-3-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1.

LCMS: m/e 657.5 ($M+H$)⁺, 1.97 min (method 6). ¹H NMR (500MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 6.82 (s, 1 H),
 20 5.29 (dd, J = 1.7, 6.3 Hz, 1 H), 4.76 (d, J = 1.5 Hz, 1 H), 4.64 (s, 2 H), 4.43 (dt, J = 1.7, 8.2 Hz, 2 H), 3.98 - 3.84 (m, 2 H), 3.74 (t, J = 8.1 Hz, 2 H), 2.69 - 2.56 (m, 2 H), 2.40 (dd, J = 8.1, 12.4 Hz, 1 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 1.98 - 1.81 (m, 2 H), 1.81 - 1.75 (m, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70 - 1.65 (m, 1 H), 1.61 - 1.43 (m, 7 H), 1.42 - 1.29 (m, 4 H), 1.29 - 1.21 (m, 2 H), 1.16 - 1.12 (m, 1 H), 1.10 (s, 3
 25 H), 1.02 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 106

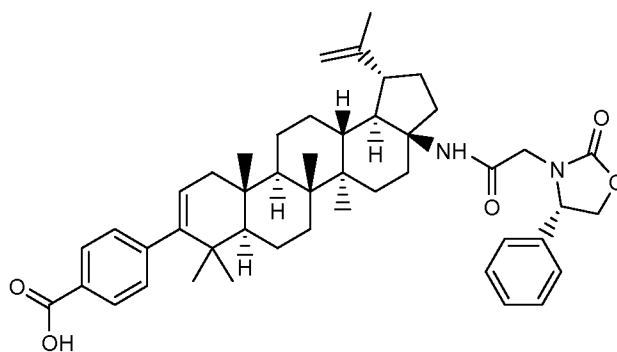
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylamino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 14% yield as a by-product during the
 10 above described preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxooxazolidin-3-yl)acetamido)-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. LCMS: m/e 631.5 ($M+H$)⁺, 1.94 min (method 6). ¹H NMR (500MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.92 (d, J = 8.2 Hz, 2 H),
 15 7.20 (d, J = 8.2 Hz, 2 H), 5.29 (d, J = 4.6 Hz, 1 H), 4.76 (s, 1 H), 4.65 (s, 1 H), 3.87 - 3.75 (m, 4 H), 3.17 - 3.12 (m, 2 H), 2.73 - 2.62 (m, 2 H), 2.37 (dd, J = 8.4, 12.1 Hz, 1 H), 2.13 (dd, J = 6.3, 17.2 Hz, 1 H), 2.16 - 2.09 (m, 1 H), 1.95 - 1.85 (m, 2 H), 1.79 (d, J = 11.0 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.58 - 1.47 (m, 6 H), 1.47 - 1.32 (m, 5 H), 1.30 - 1.23 (m, 1 H), 1.16 - 1.11 (m, 2 H), 1.10 (s, 3
 20 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Example 107

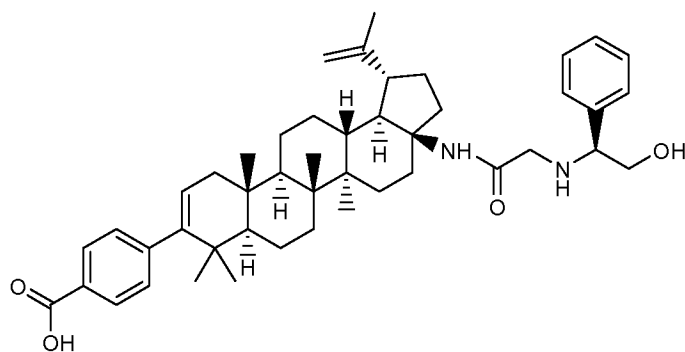
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-((S)-2-oxo-4-phenyloxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 30% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except (S)-(+)-2-oxo-4-phenyl-3-oxazolidineacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 733.5 ($M+H$)⁺, 2.25 min (method 6). ¹H NMR (400MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.92 (d, J = 8.3 Hz, 2 H), 7.47 - 7.39 (m, 3 H), 7.37 - 7.32 (m, 2 H), 7.20 (d, J = 8.3 Hz, 2 H), 6.60 (s, 1 H), 5.28 (d, J = 4.5 Hz, 1 H), 5.04 (t, J = 8.3 Hz, 1 H), 4.75 (t, J = 8.9 Hz, 1 H), 4.71 (s, 1 H), 4.61 (br. s., 1 H), 4.25 - 4.19 (m, 1 H), 4.04 (d, J = 16.3 Hz, 1 H), 3.40 (d, J = 16.3 Hz, 1 H), 2.65 - 2.59 (m, 1 H), 2.47 (dt, J = 4.8, 11.0 Hz, 1 H), 2.37 (dd, J = 8.2, 11.7 Hz, 1 H), 2.11 (dd, J = 6.3, 17.1 Hz, 1 H), 1.84 - 1.70 (m, 4 H), 1.69 (s, 3 H), 1.66 - 1.59 (m, 1 H), 1.58 - 1.40 (m, 7 H), 1.39 - 1.22 (m, 6 H), 1.09 (br. s., 1 H), 1.07 (s, 3 H), 1.00 (s, 6 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Example 108

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((S)-2-hydroxy-1-phenylethylamino)acetamido)-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.



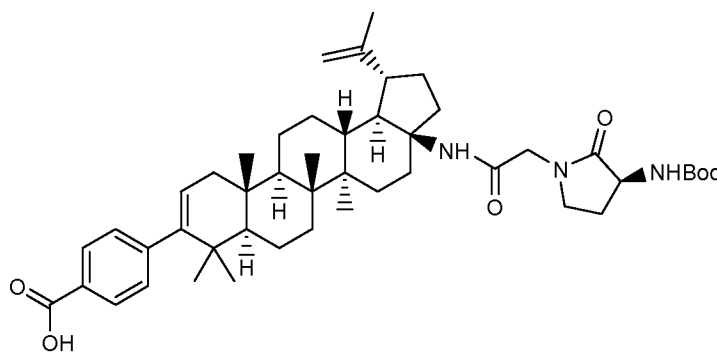
The title compound was prepared in 8% yield as a by-product during the above described preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-((S)-2-oxo-4-phenyloxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. LCMS: m/e 707.5 ($M+H$)⁺, 2.18 min (method 6). ¹H NMR (400MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.92 (d, J = 8.3 Hz, 2 H), 7.49 - 7.45 (m, 3 H), 7.45 - 7.40 (m, 2 H), 7.19 (d, J = 8.3 Hz, 2 H), 5.28 (d, J = 4.8 Hz, 1 H), 4.71 (s, 1 H), 4.62 (br. s., 2 H), 4.35 (dd, J = 4.9, 7.7 Hz, 1 H), 4.04 - 3.90 (m, 2 H), 3.72 - 3.55 (m, 2 H), 2.60 - 2.50 (m, 2 H), 2.36 (dd, J = 8.5, 12.0 Hz, 1 H), 2.10 (dd, J = 6.4, 17.2 Hz, 1 H), 1.91 - 1.75 (m, 2 H), 1.73 (d, J = 7.3 Hz, 2 H), 1.69 (s, 3 H), 1.65 - 1.60 (m, 1 H), 1.50 - 1.37 (m, 6 H), 1.37 - 1.19 (m, 7 H), 1.07 (d, J = 18.6 Hz, 3 H), 0.99 (s, 6 H), 0.97 (s, 3 H), 0.94 (br. s., 3 H), 0.94 (br. s., 3 H).

15

Example 109

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((S)-3-(tert-butoxycarbonylamino)-2-oxopyrrolidin-1-yl)acetamido)-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



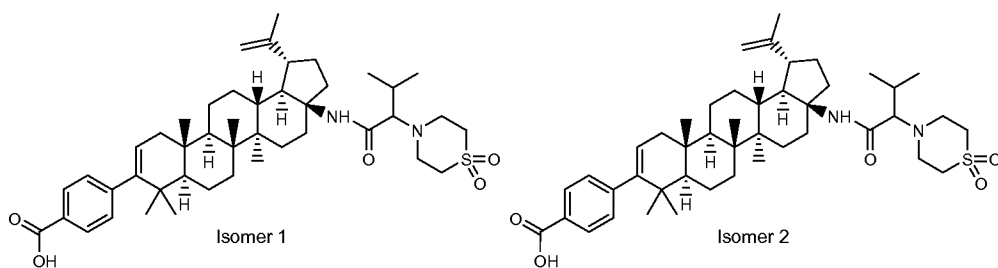
The title compound was prepared in 34% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except (S)-2-(3-(*tert*-butoxycarbonylamino)-2-oxopyrrolidin-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 770.6 (M+H)⁺, 2.07 min (method 6). ¹H NMR (400MHz, 1:1 CDCl₃:MeOD) δ = 7.92 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 6.83 - 6.60 (m, 1 H), 5.29 (d, J = 4.8 Hz, 1 H), 4.76 (s, 1 H), 4.63 (br. s., 1 H), 4.32 - 4.16 (m, 1 H), 4.07 - 3.84 (m, 2 H), 3.44 (d, J = 7.0 Hz, 2 H), 2.70 - 2.56 (m, 2 H), 2.55 - 2.44 (m, 1 H), 2.43 - 2.31 (m, 1 H), 2.13 (dd, J = 6.3, 17.1 Hz, 1 H), 2.08 - 1.95 (m, 1 H), 1.94 - 1.82 (m, 2 H), 1.81 - 1.73 (m, 2 H), 1.71 (s, 3 H), 1.68 - 1.62 (m, 1 H), 1.61 - 1.48 (m, 6 H), 1.46 (s, 9 H), 1.43 - 1.22 (m, 6 H), 1.13 (br. s., 1 H), 1.10 (d, J = 3.8 Hz, 3 H), 1.02 (s, 6 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

20

Example 110 (Isomer 1) and Example 111 (Isomer 2)

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

25



The title compounds were prepared in 9% yield each from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(1,1-dioxo-1-lambda-6,4-thiazinan-4-yl)3-methylbutanoic acid (91 mg, 0.388 mmol) was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. The two isomers formed in the reaction were separated by reverse phase preparative HPLC.

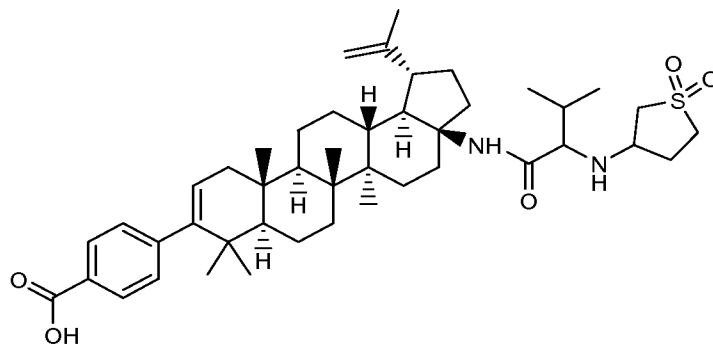
Isomer 1: LCMS: m/e 747.5 ($M+H$)⁺, 2.23 min (method 6). ¹H NMR (500MHz, 1:1 $CDCl_3:MeOD$) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 6.42 (s, 1 H), 5.29 (dd, J = 1.5, 6.1 Hz, 1 H), 4.75 (d, J = 1.5 Hz, 1 H), 4.64 (br. s., 1 H), 3.31 - 3.23 (m, 2 H), 3.16 - 3.07 (m, 4 H), 3.06 - 2.97 (m, 2 H), 2.84 (d, J = 10.4 Hz, 1 H), 2.77 - 2.71 (m, 1 H), 2.63 (dt, J = 5.5, 11.1 Hz, 1 H), 2.42 (dd, J = 8.2, 12.5 Hz, 1 H), 2.12 (dd, J = 6.4, 17.1 Hz, 1 H), 2.03 (qd, J = 6.5, 16.9 Hz, 1 H), 1.91 - 1.81 (m, 2 H), 1.78 (d, J = 12.2 Hz, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.68 (d, J = 11.3 Hz, 1 H), 1.62 (dd, J = 3.4, 13.4 Hz, 1 H), 1.57 (d, J = 4.9 Hz, 1 H), 1.51 (br. s., 3 H), 1.47 (d, J = 12.5 Hz, 1 H), 1.44 - 1.28 (m, 5 H), 1.28 - 1.23 (m, 2 H), 1.18 (d, J = 13.7 Hz, 1 H), 1.11 (dd, J = 4.0, 12.8 Hz, 1 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 4 H), 0.99 (s, 2 H), 0.94 (s, 3 H), 0.94 (br. s., 3 H), 0.90 (d, J = 6.4 Hz, 3 H).

Isomer 2: LCMS: m/e 747.5 ($M+H$)⁺, 2.29 min (method 6). ¹H NMR (500MHz, 1:1 $CDCl_3:MeOD$) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 6.40 (s, 1 H), 5.29 (dd, J = 1.5, 6.1 Hz, 1 H), 4.76 (d, J = 1.5 Hz, 1 H), 4.64 (s, 1 H), 3.77 - 3.72 (m, 1 H), 3.23 - 3.14 (m, 2 H), 3.13 - 3.06 (m, 4 H), 3.05 - 2.99 (m, 2 H), 2.80 (d, J = 10.4 Hz, 1 H), 2.74 - 2.67 (m, 1 H), 2.61 (dt, J = 5.3, 11.1 Hz, 1 H), 2.49 (dd, J = 8.4, 12.7

Hz, 1 H), 2.12 (dd, $J = 6.4, 17.1$ Hz, 1 H), 2.08 - 2.01 (m, 1 H), 1.99 - 1.91 (m, 1 H), 1.88 (ddd, $J = 3.1, 3.3, 6.8$ Hz, 1 H), 1.86 - 1.82 (m, 1 H), 1.78 (d, $J = 11.0$ Hz, 1 H), 1.72 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (d, $J = 4.6$ Hz, 1 H), 1.67 - 1.63 (m, 1 H), 1.61 - 1.53 (m, 2 H), 1.51 (br. s., 1 H), 1.48 (br. s., 2 H), 1.47 - 1.41 (m, 2 H), 1.12 (dd, $J =$
 5 3.4, 13.4 Hz, 2 H), 1.07 (s, 3 H), 1.01 (br. s., 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.97 (d, $J = 6.7$ Hz, 3 H), 0.93 (s, 3 H), 0.93 (s, 3 H).

Example 112

- 10 Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[[3-methyl-1-oxo-2-[(tetrahydro-1,1-dioxido-3-thienyl)amino]butyl]amino]-1H-cyclopenta[a]chrysen-9-yl].



15

- The title compound was prepared in 30% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure
 20 as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(1,1-dioxo-tetrahydro-1λ6-thiophene-3-yl-amino)-3-methylbutyric acid was used instead of 3-
 25 (dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 747.5 ($M+H$)⁺, 2.09 min (method 6). ¹H NMR (500MHz, 1:1 *CDCl*₃:*MeOD*) δ = 7.92 (d, $J = 8.2$ Hz, 2 H), 7.25 (br. s., 1 H), 7.19 (d, $J = 8.2$ Hz, 2 H), 5.28 (d, $J = 4.9$ Hz, 1 H), 4.78 (s, 1

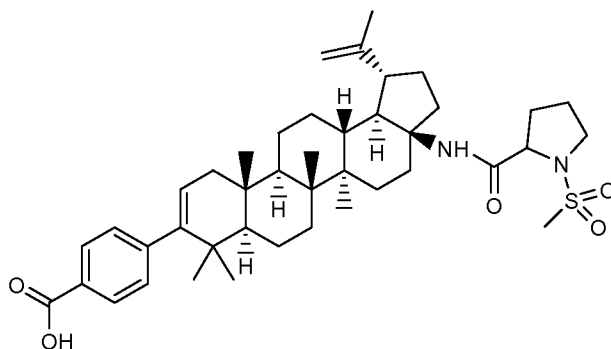
H), 4.65 (br. s., 1 H), 3.73 (ddd, $J = 6.6, 6.7, 9.3$ Hz, 1 H), 3.47 (dd, $J = 7.2, 13.3$ Hz, 1 H), 3.41 (dt, $J = 4.1, 8.6$ Hz, 1 H), 3.27 (br. s., 1 H), 3.17 - 3.07 (m, 1 H), 2.75 - 2.63 (m, 2 H), 2.59 (dd, $J = 7.2, 13.0$ Hz, 1 H), 2.43 (dd, $J = 8.5, 12.2$ Hz, 1 H), 2.35 (dd, $J = 8.9, 12.8$ Hz, 1 H), 2.25 - 2.16 (m, 1 H), 2.12 (dd, $J = 6.3, 17.2$ Hz, 1 H), 1.91 - 1.76 (m, 3 H), 1.74 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (br. s., 1 H), 1.58 - 1.47 (m, 6 H), 1.46 - 1.35 (m, 4 H), 1.35 - 1.28 (m, 1 H), 1.25 (d, $J = 9.8$ Hz, 1 H), 1.18 - 1.12 (m, 2 H), 1.10 (d, $J = 6.7$ Hz, 3 H), 1.08 (s, 3 H), 1.06 (d, $J = 7.3$ Hz, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.93 (s, 3 H), 0.93 (br. s., 3 H).

10

Example 113

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(1-(methylsulfonyl)pyrrolidine-2-carboxamido)-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.

15



The title compound was prepared in 17% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 1-(methylsulfonyl)pyrrolidine-2-carboxylic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 705.5 ($M+H$)⁺, 2.04 min (method 6). ¹H NMR (500MHz, 1:1

25

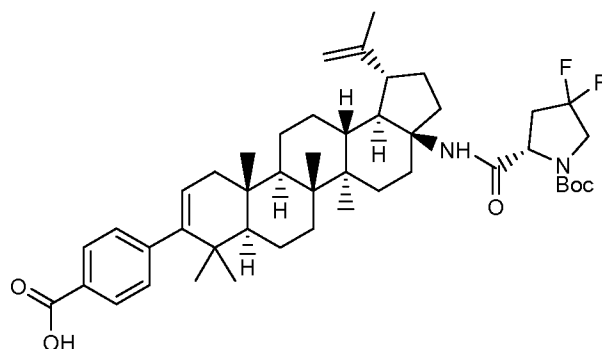
$CDCl_3:MeOD$) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 6.88 (s, 1 H), 5.29 (dd, J = 1.5, 6.1 Hz, 1 H), 4.76 (d, J = 1.5 Hz, 1 H), 4.10 (dd, J = 3.1, 8.8 Hz, 1 H), 3.60 (ddd, J = 3.5, 7.0, 10.2 Hz, 1 H), 3.40 (dt, J = 6.4, 9.6 Hz, 1 H), 2.96 (s, 3 H), 2.62 - 2.52 (m, 2 H), 2.42 (dd, J = 8.2, 11.6 Hz, 1 H), 2.31 (dddd, J = 3.2, 3.4, 6.4, 9.7 Hz, 1 H), 2.21 - 2.16 (m, 1 H), 2.16 - 2.10 (m, 1 H), 2.03 (tdd, J = 3.2, 6.6, 13.0 Hz, 1 H), 1.99 - 1.89 (m, 2 H), 1.82 - 1.75 (m, 1 H), 1.75 - 1.72 (m, 1 H), 1.70 (s, 3 H), 1.69 - 1.66 (m, 1 H), 1.58 - 1.46 (m, 6 H), 1.46 - 1.29 (m, 5 H), 1.28 - 1.22 (m, 1 H), 1.14 (d, J = 13.1 Hz, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.93 (s, 6 H).

10

Example 114

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxamido)-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.

15



The title compound was prepared in 29% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 763.5 ($M+H$)⁺,

25

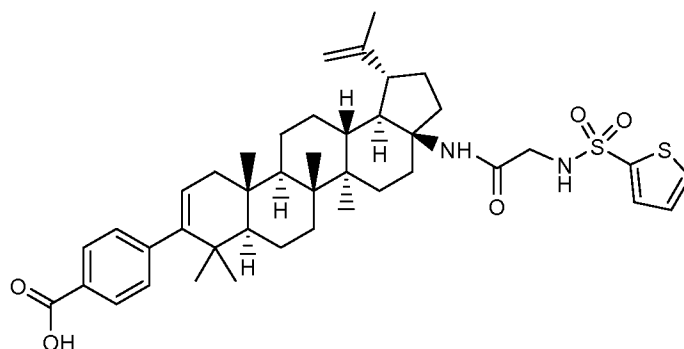
2.55 min (method 6). ^1H NMR (500MHz, 1:1 $\text{CDCl}_3:\text{MeOD}$) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 6.46 (br. s., 1 H), 5.29 (dd, J = 1.7, 6.3 Hz, 1 H), 4.72 (s, 1 H), 4.63 (br. s., 1 H), 4.50 (d, J = 9.2 Hz, 1 H), 3.84 (br. s., 1 H), 3.72 (td, J = 6.7, 13.4 Hz, 1 H), 2.84 (br. s., 1 H), 2.55 (d, J = 13.4 Hz, 1 H), 2.51 - 2.37 (m, 2 H), 2.12 (dd, J = 6.4, 17.1 Hz, 1 H), 1.96 (br. s., 1 H), 1.73 (br. s., 1 H), 1.70 (s, 4 H), 1.61 (br. s., 2 H), 1.56 (br. s., 9 H), 1.53 - 1.45 (m, 5 H), 1.45 - 1.37 (m, 3 H), 1.36 - 1.29 (m, 2 H), 1.28 - 1.23 (m, 1 H), 1.17 - 1.09 (m, 2 H), 1.08 (s, 3 H), 1.02 (s, 6 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

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Example 115

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(thiophene-2-sulfonamido)acetamido)-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.

15



The title compound was prepared in 31% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(thiophene-2-sulfonamido)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 733.6 ($\text{M}+\text{H}$) $^+$, 2.06 min (method 6). ^1H NMR (500MHz, 1:1

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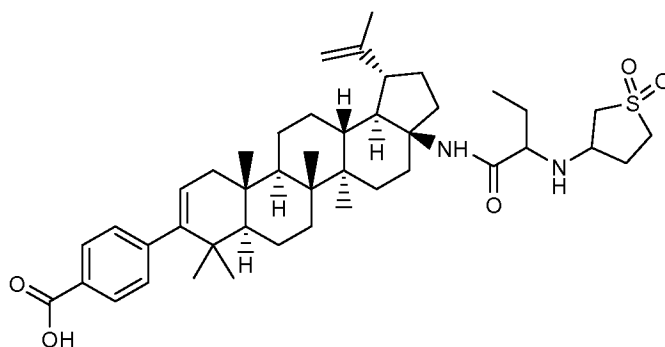
$CDCl_3:MeOD$) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.73 (dd, J = 1.4, 5.0 Hz, 1 H), 7.66 (dd, J = 1.2, 3.7 Hz, 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 7.16 (dd, J = 3.8, 5.0 Hz, 1 H), 6.88 (s, 1 H), 5.32 - 5.26 (m, 1 H), 4.78 (d, J = 1.5 Hz, 1 H), 3.58 - 3.45 (m, 2 H), 2.63 - 2.57 (m, 1 H), 2.56 - 2.50 (m, 1 H), 2.42 (dd, J = 8.2, 12.2 Hz, 1 H), 2.13 (dd, J = 6.3, 17.2 Hz, 1 H), 1.98 - 1.88 (m, 1 H), 1.87 - 1.76 (m, 2 H), 1.73 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.66 (m, 1 H), 1.63 - 1.53 (m, 3 H), 1.53 - 1.46 (m, 4 H), 1.45 - 1.37 (m, 3 H), 1.37 - 1.30 (m, 2 H), 1.28 - 1.22 (m, 1 H), 1.14 (s, 3 H), 1.10 (d, J = 3.1 Hz, 1 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.94 (br. s., 3 H).

10

Example 116

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[[[1-oxo-2-[(tetrahydro-1,1-dioxido-3-thienyl)amino]butyl]amino]-1H-cyclopenta[a]chrysen-9-yl].

15



The title compound was prepared in 19% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except 2-(1,1-dioxo-tetrahydro-1 λ 6-thiophene-3-yl-amino)-butyric acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 733.6 ($M+H$)⁺, 2.00 min (method 6). ¹H

25

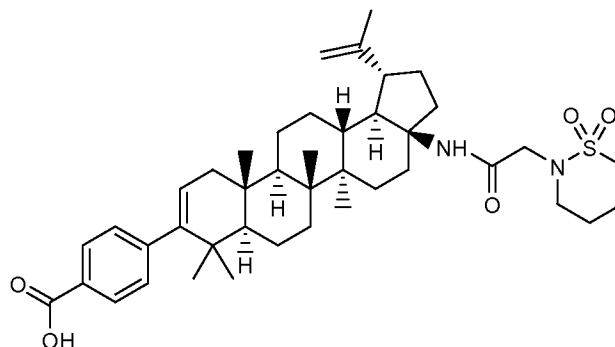
NMR (500MHz, 1:1 $CDCl_3$:MeOD) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.38 (br. s., 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 5.29 (d, J = 4.6 Hz, 1 H), 4.77 (d, J = 8.5 Hz, 1 H), 3.77 (br. s., 1 H), 3.51 - 3.36 (m, 2 H), 3.22 - 3.09 (m, 2 H), 2.65 (d, J = 15.9 Hz, 3 H), 2.37 (br. s., 2 H), 2.13 (dd, J = 6.4, 17.4 Hz, 1 H), 1.96 - 1.77 (m, 5 H), 1.73 (br. s., 1 H), 1.73 (s, 3 H), 1.72 - 1.67 (m, 1 H), 1.61 - 1.52 (m, 2 H), 1.50 (d, J = 2.1 Hz, 3 H), 1.48 - 1.30 (m, 6 H), 1.29 - 1.23 (m, 1 H), 1.22 - 1.14 (m, 2 H), 1.12 (s, 2 H), 1.09 (d, J = 1.8 Hz, 2 H), 1.08 - 1.05 (m, 1 H), 1.04 (d, J = 1.8 Hz, 4 H), 1.03 (d, J = 4.0 Hz, 4 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

10

Example 117

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[[[(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)acetyl]amino]-1H-cyclopenta[a]chrysen-9-yl].

15



The title compound was prepared in 13% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-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, except (1,1-dioxo-1,6-[1,2]thiazinan-2-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 705.5 ($M+H$)⁺, 2.01 min (method 6). ¹H NMR (500MHz,

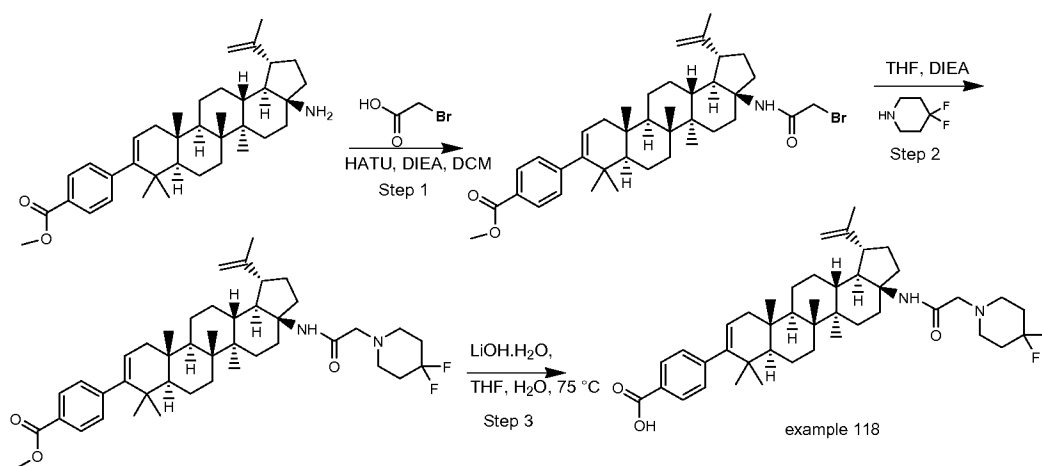
25

METHANOL- d_4) δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 6.83 (s, 1 H), 5.32 - 5.26 (m, 1 H), 4.77 (d, J = 1.5 Hz, 1 H), 4.64 (s, 1 H), 3.83 - 3.72 (m, 2 H), 3.63 - 3.46 (m, 2 H), 3.37 (s, 2 H), 3.21 - 3.11 (m, 2 H), 2.62 - 2.54 (m, 1 H), 2.53 - 2.50 (m, 1 H), 2.49 - 2.41 (m, 1 H), 2.32 - 2.23 (m, 2 H), 2.13 (dd, J = 6.6, 17.2 Hz, 1 H), 1.99 - 1.87 (m, 1 H), 1.78 (br. s., 1 H), 1.77 - 1.73 (m, 3 H), 1.72 (s, 3 H), 1.71 - 1.67 (m, 1 H), 1.62 - 1.51 (m, 3 H), 1.48 (d, J = 5.2 Hz, 3 H), 1.46 - 1.31 (m, 5 H), 1.28 - 1.23 (m, 1 H), 1.14 (d, J = 13.4 Hz, 2 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.94 (s, 3 H).

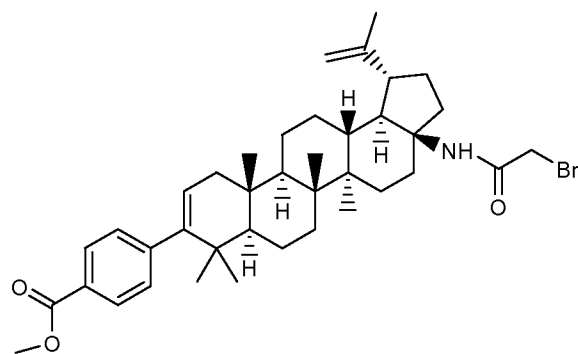
10

Example 118

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-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.

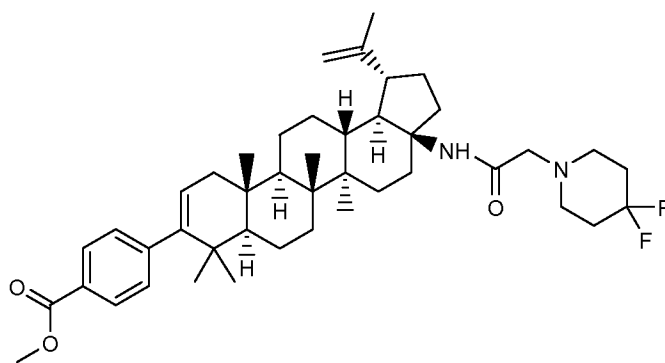


Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



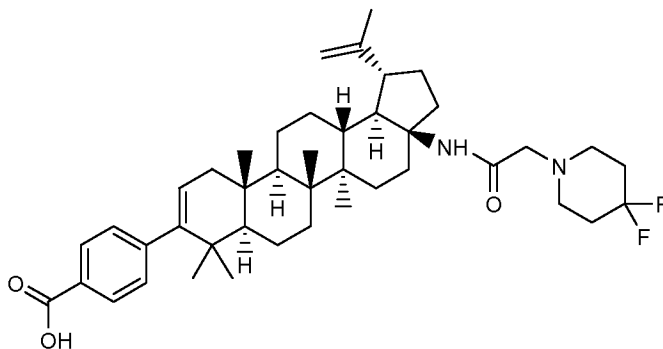
- To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (403 mg, 0.694 mmol) in DCM (10 mL) was added *N,N*-diisopropylethylamine (0.484 mL, 2.78 mmol), bromoacetic acid (106 mg, 0.764 mmol) and 2-(3H-[1,2,3]triazolo[4,5- β]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (317 mg, 0.833 mmol). The reaction
- 10 mixture was stirred at rt for 15 h. Then, the reaction was concentrated and the crude residue was dissolved in THF (3.0 mL) filtered and purified by reverse phase preparative HPLC using HPLC method 3 to give methyl 4-
- ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 15 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 (148.9 mg, 0.224 mmol, 32.3% yield) as white solid. LCMS: m/e 664.6 ($M+H$)⁺, 2.41 min (method 6).

- Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
- 20 (2-(4,4-difluoropiperidin-1-yl)acetamido)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 5 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 (30 mg, 0.045 mmol) in THF (3 mL) was added *N,N*-diisopropylethylamine (0.039 mL, 0.226 mmol) and 4,4-difluoropiperidine, HCl (21.34 mg, 0.135 mmol). The reaction mixture was stirred at 80 °C for 18 h. Additional *N,N*-diisopropylethylamine (0.078 mL, 0.452 mmol) and 4,4-
- 10 difluoropiperidine, HCl (40 mg, 0.354 mmol) were added, and the mixture was heated to 150 °C in a microwave for 7.5 h. The mixture was concentrated to brown viscous oil. The crude residue was dissolved in THF (1.5 mL), filtered and purified by reverse phase preparative HPLC using HPLC method 3 to give methyl 4-
- 15 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-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, TFA (13.1 mg, 0.016 mmol, 35.4% yield) as white solid. LCMS: m/e 705.6 (M+H)⁺, 2.95 min (method 6). ¹H NMR (500MHz, CHLOROFORM-*d*) δ = 7.94 (d, J = 8.5 Hz, 2 H), 7.90 - 7.80 (m, 1 H), 7.21 (d, J = 8.2 Hz, 2 H), 6.32 (s, 1 H), 5.31 (dd, J = 1.4, 6.0 Hz, 1 H), 4.77 (s, 1 H), 4.67 (s, 1 H), 3.93 (s, 3 H), 3.72 - 3.61 (m, 3 H), 3.51 - 3.41 (m, 5 H), 2.83 (d, J = 2.7 Hz, 2 H), 2.63 (d, J = 13.1 Hz, 1 H), 2.56 (dt, J = 5.3, 10.9 Hz, 1 H), 2.39 (dd, J = 8.2, 12.8 Hz, 1 H), 2.12 (dd, J = 6.4, 17.1 Hz, 1 H), 1.91 - 1.81 (m, 1 H), 1.79 - 1.73 (m, 2 H), 1.72 (s, 3 H), 1.70 - 1.64 (m, 1 H), 1.54 - 1.40 (m, 7 H), 1.39 - 1.26 (m, 3 H), 1.26 - 1.21 (m, 1 H), 1.18 - 1.09 (m, 2 H), 1.04 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).
- 20
- 25

Step 3. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-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

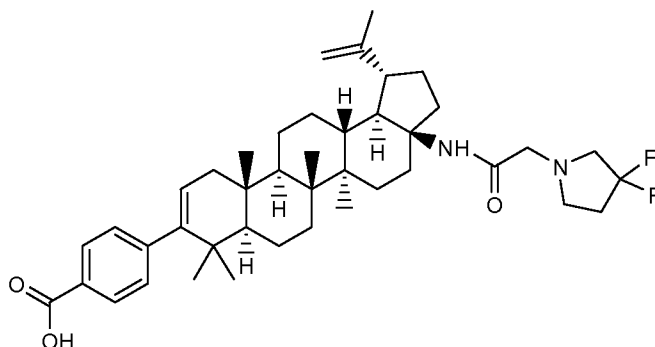
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (13.1 mg, 0.019 mmol) in THF (3 mL) was added a 0.753 molar aqueous solution of LiOH · H₂O (0.149 mL, 0.074 mmol). The reaction was heated to 75 °C for 6h. The reaction was concentrated to brown viscous oil, and the crude material was purified by reverse phase preparative HPLC using HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-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, TFA (9.4 mg, 0.012 mmol, 62.8% yield) as white solid. LCMS: m/e 691.6 (M+H)⁺, 2.34 min (method 6). ¹H NMR (500MHz, METHANOL-d₄) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.43 (s, 1 H), 7.20 (d, J = 8.5 Hz, 2 H), 5.30 (dd, J = 1.7, 6.3 Hz, 1 H), 4.75 (d, J = 1.2 Hz, 1 H), 4.66 (d, J = 1.5 Hz, 1 H), 3.71 - 3.58 (m, 2 H), 3.24 (br. s., 3 H), 2.67 - 2.61 (m, 1 H), 2.57 (dt, J = 5.3, 11.1 Hz, 1 H), 2.41 (dd, J = 8.2, 12.5 Hz, 1 H), 2.33 - 2.22 (m, 4 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 1.95 - 1.83 (m, 1 H), 1.81 (d, J = 9.2 Hz, 2 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.67 (m, 1 H), 1.59 - 1.43 (m, 8 H), 1.42 - 1.31 (m, 3 H), 1.29 - 1.23 (m, 1 H), 1.18 - 1.12 (m, 2 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

20

25

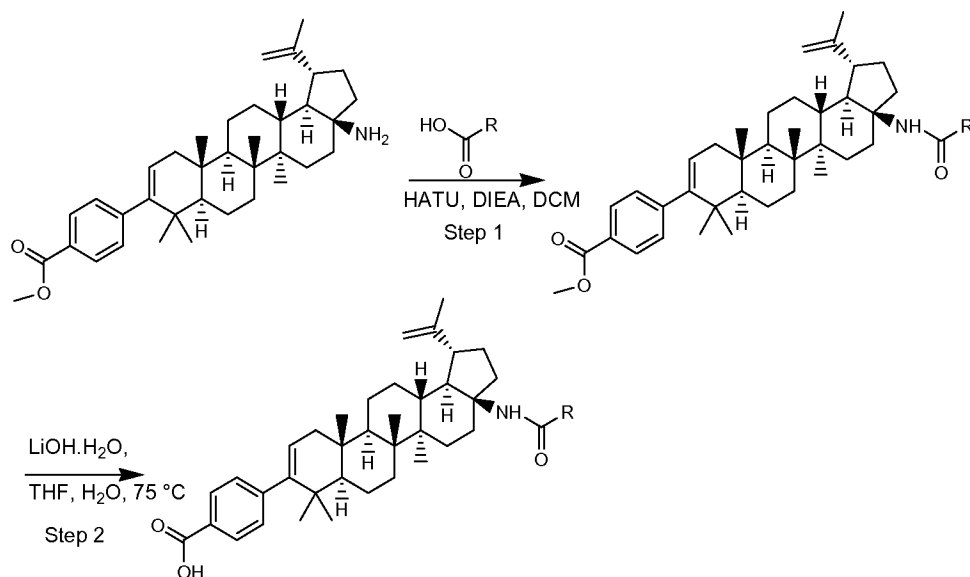
Example 119

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoropyrrolidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 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.



The title compound was prepared in 38% yield from methyl 4-
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-
 15 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, except and 3,3-difluoropyrrolidine, HCl was used instead of 4,4-difluoropiperidine, HCl in Step 2. LCMS: m/e 677.5 (M+H)⁺, 2.26 min (method 6). ¹H NMR (500MHz, 1:1 CDCl₃:MeO D) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.40 (s, 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 5.29 (dd, J = 1.7, 6.3 Hz, 1 H),
 20 4.75 (d, J = 1.2 Hz, 1 H), 4.65 (s, 1 H), 3.59 - 3.44 (m, 2 H), 3.43 - 3.36 (m, 1 H), 3.31 - 3.20 (m, 2 H), 2.63 - 2.55 (m, 1 H), 2.55 - 2.47 (m, 3 H), 2.47 - 2.39 (m, 1 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 1.94 - 1.83 (m, 1 H), 1.81 - 1.76 (m, 2 H), 1.76 - 1.73 (m, 1 H), 1.72 (s, 3 H), 1.70 - 1.65 (m, 1 H), 1.57 - 1.46 (m, 6 H), 1.46 - 1.40 (m, 2 H), 1.39 - 1.31 (m, 2 H), 1.26 (dd, J = 2.7, 10.7 Hz, 1 H), 1.19 - 1.10 (m, 2 H), 1.09 (s, 3
 25 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

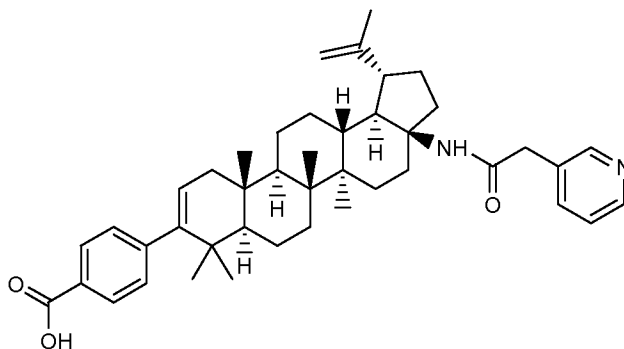
General procedure for parallel synthesis of C-17 amides:



A stock solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 5 3a-amino-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, HCl (0.990 g, 1.7 mmol) and DIPEA (1.10 g,
 8.52 mmol) in DCE (13 mL) was prepared. A stock solution of the HATU (1.94 g,
 5.11 mmol) in DCE (13 mL) was prepared. To each of the carboxylic acids (0.393
 10 mmol) weighed into 16x100 mm Wheaton vials was added 1 mL of the stock HATU
 solution. The vials were capped and shaken at rt for 10 min before adding 1 mL of
 the stock methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-
 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-
 15 cyclopenta[a]chrysen-9-yl)benzoate, HCl /DIPEA solution to each vial. The vials
 were capped and shaken at rt for 18 h. Samples were concentrated. A stock solution
 of lithium hydroxide monohydrate (0.286 g, 6.81 mmol) in water (6.50 mL) was
 prepared. To each of the reaction vials was added 2.5 mL of THF and 0.5 mL of the
 stock lithium hydroxide solution. The vials were capped and the reactions were
 20 stirred at 75°C for 18 h. Added an additional 0.5 mL of the stock lithium hydroxide
 solution and stirred at 75°C for an additional 48 h. Samples were concentrated,
 redissolved in a small quantity of a mixture of THF and methanol, filtered and
 purified by reverse phase preparative HPLC.

Example 120

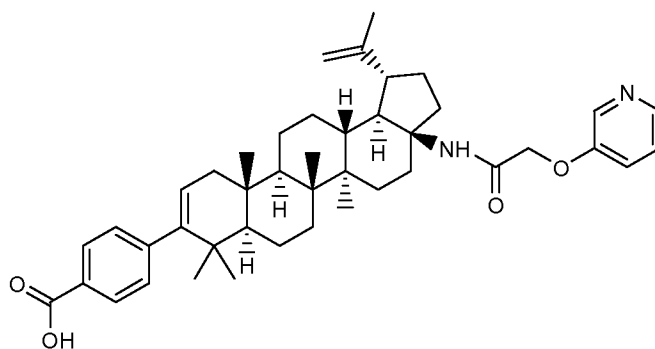
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-
 pentamethyl-1-(1-methylethenyl)-3a-[(3-pyridinylacetyl)amino]-1H-
 cyclopenta[a]chrysen-9-yl].



10 The title compound was prepared from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the general
 procedure described for the parallel synthesis of C-17 amides above, using
 15 pyridylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 649.6
 (M+H)⁺, 4.09 min (method 3).

Example 121

20 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-yloxy)acetamido)-
 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.

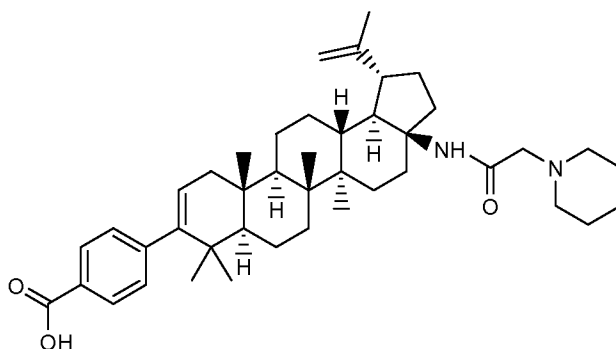


The title compound was prepared from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
 5 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general
 procedure described for the parallel synthesis of C-17 amides above, using 3-
 pyridyloxyacetic acid as the reacting carboxylic acid. LCMS: m/e 665.6 (M+H)⁺,
 4.37 min (method 3).

10

Example 122

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-3a-(2-(piperidin-1-yl)acetamido)-1-(prop-1-en-2-yl)-
 15 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.



The title compound was prepared from methyl 4-
 20 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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-

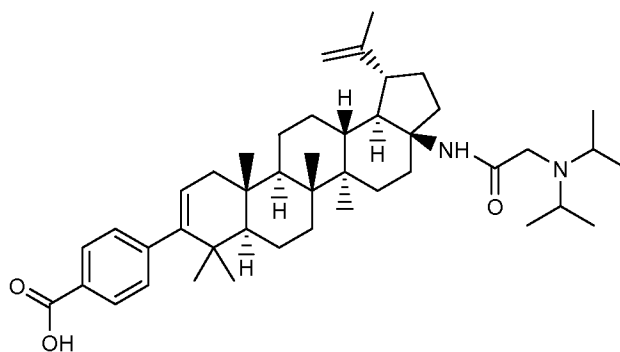
octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using piperidin-1-ylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 655.7 (M+H)⁺, 4.68 min (method 3).

5

Example 123

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(diisopropylamino)acetamido)-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.

10



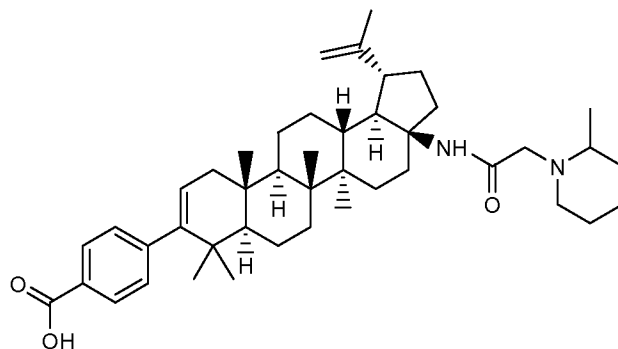
The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using diisopropylamino-acetic acid as the reacting carboxylic acid. LCMS: m/e 671.7 (M+H)⁺, 4.99 min (method 3). ¹H NMR (599MHz, <DMSO-CDCl₃>) δ = 8.45 - 8.37 (m, 1 H), 7.89 (d, J = 8.2 Hz, 2 H), 7.69 - 7.65 (m, 1 H), 7.24 - 7.20 (m, 2 H), 5.31 - 5.24 (m, 1 H), 4.79 - 4.73 (m, 1 H), 4.67 - 4.62 (m, 1 H), 3.95 (br. s., 2 H), 3.66 (d, J = 5.9 Hz, 3 H), 2.94 (s, 1 H), 2.78 (s, 1 H), 2.74 (br. s., 1 H), 2.63 (d, J = 13.5 Hz, 1 H), 2.30 (t, J = 9.1 Hz, 1 H), 2.13 (dd, J = 6.2, 16.7 Hz, 1 H), 2.07 - 1.98 (m, 1 H), 1.75 (br. s., 1 H), 1.72 (s, 4 H), 1.69 - 1.61 (m, 1 H), 1.52 - 1.41 (m, 8 H), 1.36 - 1.33 (m, 3 H), 1.33 - 1.31 (m, 2 H), 1.30 - 1.28 (m, 3 H), 1.28 - 1.25 (m, 3 H), 1.09 (s, 6 H), 1.01 (s, 6 H), 0.93 (br. s., 6 H).

20

25

Example 124

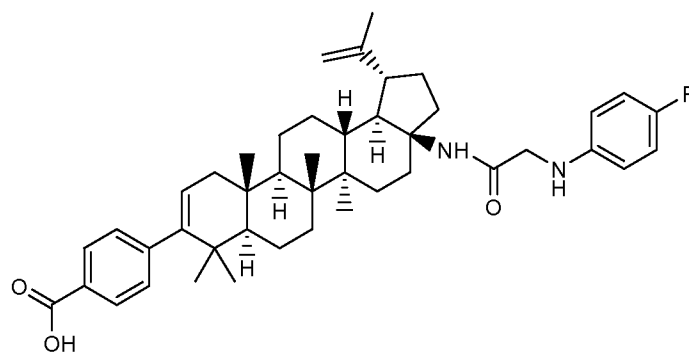
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-methylpiperidin-1-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the general procedure described for the parallel synthesis of C-17 amides above, using (2-methylpiperidin-1-yl)acetic acid as the reacting carboxylic acid. LCMS: m/e 669.7 (M+H)⁺, 4.73 min (method 3).

Example 125

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-fluorophenylamino)acetamido)-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.

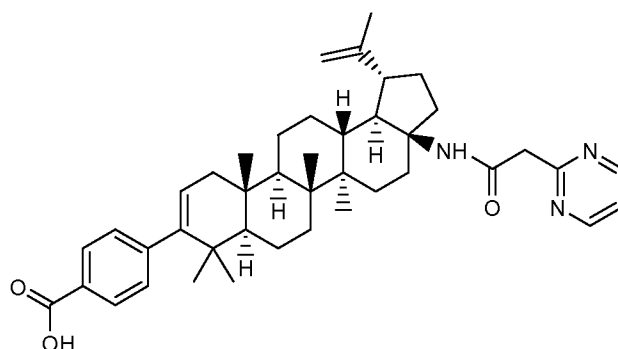


The title compound was prepared from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general
 procedure described for the parallel synthesis of C-17 amides above, using (4-
 fluorophenylamino)acetic acid as the reacting carboxylic acid. LCMS: m/e 681.7
 (M+H)⁺, 6.62 min (method 3).

10

Example 126

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyrimidin-2-yl)acetamido)-
 15 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.

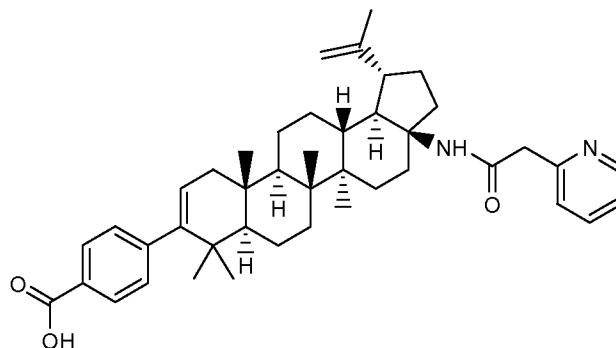


The title compound was prepared from methyl 4-
 20 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using 2-pyrimidine acetic acid as the reacting carboxylic acid. LCMS: m/e 650.6 ($M+H$)⁺, 5.57 min (method 3). ¹H NMR (599MHz, $<DMSO_CDCl_3>$) δ = 8.78 (d, J = 4.7 Hz, 2 H), 7.88 (d, J = 8.2 Hz, 2 H), 7.29 (s, 1 H), 7.22 (d, J = 7.6 Hz, 2 H), 5.28 (d, J = 5.3 Hz, 1 H), 4.75 (s, 1 H), 4.62 (br. s., 1 H), 3.93 (s, 1 H), 3.82 (d, J = 14.6 Hz, 1 H), 2.77 - 2.72 (m, 1 H), 2.63 (d, J = 12.9 Hz, 1 H), 2.40 - 2.32 (m, 1 H), 2.16 - 2.04 (m, 1 H), 2.00 - 1.81 (m, 2 H), 1.73 (br. s., 2 H), 1.71 (s, 3 H), 1.67 - 1.52 (m, 4 H), 1.50 - 1.39 (m, 7 H), 1.36 - 1.20 (m, 7 H), 0.99 (br. s., 6 H), 0.98 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 127

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-2-yl)acetamido)-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.

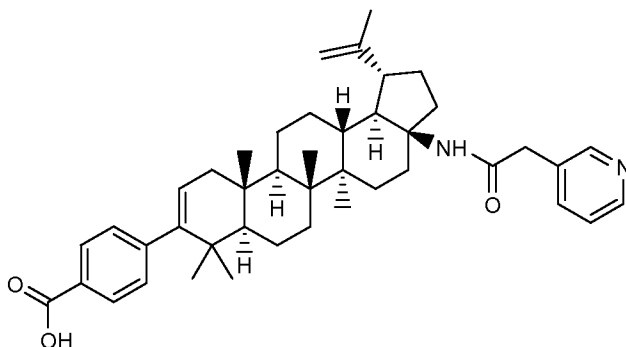


The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using 2-pyridylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 649.6 ($M+H$)⁺, 4.23 min (method 3).

Example 128

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-yl)acetamido)-

- 5 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.



The title compound was prepared from methyl 4-

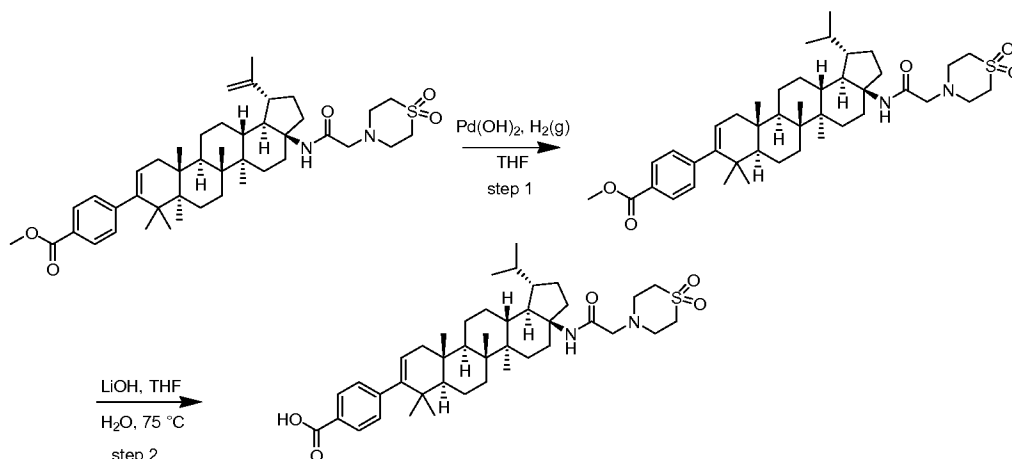
- 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using 3-pyridylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 649.6
- 15 (M+H)⁺, 4.07 min (method 3). ¹H NMR (599MHz, <DMSO-CDCl₃>) δ = 8.49 (d, J = 5.3 Hz, 2 H), 7.88 (s, 2 H), 7.33 (d, J = 5.3 Hz, 2 H), 7.22 (d, J = 8.2 Hz, 2 H), 7.17 (s, 1 H), 5.28 (d, J = 5.3 Hz, 1 H), 4.86 - 4.81 (m, 1 H), 4.76 (s, 1 H), 4.63 (br. s., 1 H), 3.66 (d, J = 12.9 Hz, 1 H), 3.49 (d, J = 12.9 Hz, 1 H), 2.85 - 2.79 (m, 1 H), 2.60 - 2.56 (m, 1 H), 2.35 - 2.28 (m, 1 H), 2.12 (dd, J = 6.4, 17.0 Hz, 1 H), 2.06 (t, J = 11.1
- 20 Hz, 1 H), 1.87 - 1.79 (m, 1 H), 1.73 (br. s., 2 H), 1.71 (s, 3 H), 1.61 - 1.50 (m, 2 H), 1.50 - 1.35 (m, 6 H), 1.37 - 1.27 (m, 3 H), 1.24 (d, J = 9.4 Hz, 3 H), 1.13 - 1.05 (m, J = 12.9 Hz, 1 H), 1.03 - 1.00 (m, 6 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Example 129

25

Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-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)benzoic acid



5

Step 1. Preparation of methyl 4-[(1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,11,11b,12,13,13a,13b-tetradecahydrocyclopenta[a]chrysen-9-yl]benzoate.

- 10 A solution of methyl 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (152 mg, 0.211 mmol) in THF (10 mL) was flushed with $\text{N}_2(\text{g})$ and palladium hydroxide (44.5 mg, 0.063 mmol) was added. The
- 15 reaction mixture was purged with $\text{H}_2(\text{g})$ then stirred under $\text{H}_2(\text{g})$ atmosphere. After 68 h, the reaction was purged with $\text{N}_2(\text{g})$, the catalyst was removed by filtering through celite and washed with DCM. The resulting liquid filtrate was concentrated to a viscous oil which was dissolved in THF (2.0 mL) filtered and injected into reverse phase HPLC for purification using HPLC method 5 to give the title compound
- 20 (28.8 mg, 0.040 mmol, 18.89% yield; 62.8% yield based on recovered starting material). LCMS: m/z 721.6 ($\text{M}+\text{H}^+$), retention time 2.655 min (method 6). ^1H NMR (500MHz, *CHLOROFORM-d*) δ = 8.47 (br. s., 2 H), 7.95 (d, J = 8.2 Hz, 2 H), 7.22 (d, J = 8.5 Hz, 2 H), 6.98 (s, 1 H), 5.32 (dd, J = 1.5, 6.1 Hz, 1 H), 3.94 (s, 3 H), 3.69 - 3.61 (m, 1 H), 3.58 - 3.52 (m, 4 H), 3.31 - 3.27 (m, 3 H), 2.65 (d, J = 11.6 Hz, 1 H),
- 25 2.37 (dd, J = 7.5, 12.7 Hz, 1 H), 2.20 - 2.11 (m, 1 H), 1.98 - 1.86 (m, 1 H), 1.72 (d, J

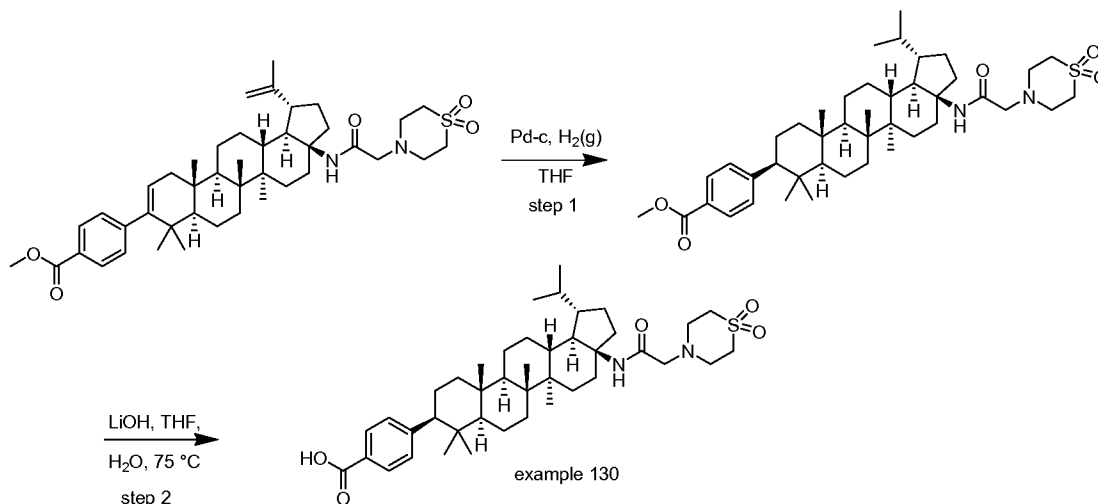
= 15.9 Hz, 3 H), 1.62 - 1.52 (m, 3 H), 1.52 - 1.36 (m, 9 H), 1.34 - 1.23 (m, 3 H), 1.21 - 1.14 (m, 2 H), 1.03 (s, 3 H), 1.02 (br. s., 3 H), 1.01 (br. s., 3 H), 0.95 (s, 6 H), 0.91 (d, $J = 7.0$ Hz, 3 H), 0.81 (d, $J = 6.7$ Hz, 3 H).

- 5 Step 2. Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-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)benzoic acid.

To a solution of methyl 4-[(1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 10 [[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,11,11b,12,13,13a,13b-tetradecahydrocyclopenta[a]chrysen-9-yl]benzoate, TFA (33 mg, 0.040 mmol) in THF (Volume: 3 mL) was added a 0.753 molar solution of lithium hydroxide monohydrate (0.316 mL, 0.158 mmol) in H₂O. The reaction mixture was heated to
 15 75 °C. After 5.5 h, the reaction was concentrated to dryness. The crude residue was dissolved in THF (1.2 mL), MeOH (0.3 mL) and 1N HCl (0.2 mL). The solution was filtered and injected into reverse phase HPLC for purification using HPLC method 3 to give 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-
 20 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, TFA (17.9 mg, 0.021 mmol, 54.1% yield) as a white solid. LCMS: m/z 707.6 ($M+H^+$), retention time 2.030 min (method 6). ¹H NMR (500MHz, *METHANOL-d*₄) δ = 7.93 (d, $J = 8.5$ Hz, 2 H), 7.21 (d, $J = 8.5$ Hz, 2 H), 7.13 (s, 1 H), 5.31 (dd, $J = 1.5, 6.1$ Hz, 1 H), 3.26 - 3.22 (m, 5 H), 3.21 - 3.15 (m, 4 H), 2.66 - 2.59 (m, 1 H), 2.37 (dd, $J = 6.7, 12.5$ Hz, 1 H), 2.17 (dd, $J = 6.4, 17.1$ Hz, 1 H), 1.99 - 1.91 (m, 1 H), 1.80 - 1.70 (m, 4 H), 1.67 - 1.57 (m, 2 H), 1.57 - 1.45 (m, 9 H), 1.44 - 1.39 (m, 1 H), 1.39 - 1.26 (m, 3 H), 1.18 - 1.11 (m, 2 H), 1.09 (s, 3 H), 1.04 (s, 6 H), 0.96 (s, 3 H), 0.95 (s, 3 H), 0.91 (d, $J = 7.0$ Hz, 3 H), 0.82 (d, $J = 6.7$ Hz, 3 H).
 25
 30

Example 130

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (51 mg, 0.071 mmol) in THF (3 mL) was added palladium on activated charcoal (10% Pd content) (18 mg, 0.017 mmol). The reaction mixture was purged by bubbling H₂ (g) slowly into the mixture over 30 mins. and then the mixture was stirred under H₂ (g) atmosphere. After 24 h, the reaction mixture was purged with N₂ (g) and more catalyst (36 mg, 0.034 mmol) was added. The reaction mixture was stirred under H₂ (g) for an additional 24 h. The mixture was then purged with N₂ (g), and the catalyst was filtered and washed with THF. The liquid filtrate was concentrated. The crude residue was purified by preparative HPLC using HPLC method 5 to give methyl 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysen-9-yl]benzoate, TFA (24.4 mg, 0.029 mmol, 41.1% yield) as a white solid. LCMS: m/z 723.6 (M+H⁺),

retention time 2.648 min (method 6). ^1H NMR (500MHz, *CHLOROFORM-d*) δ = 7.94 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.13 (br. s., 2 H), 7.05 (s, 1 H), 3.56 - 3.49 (m, 1 H), 3.48 - 3.39 (m, 5 H), 3.27 - 3.19 (m, 4 H), 2.66 (d, J = 12.5 Hz, 1 H), 2.42 (dd, J = 3.2, 13.3 Hz, 1 H), 2.40 - 2.34 (m, 1 H), 2.16 - 2.07 (m, 1 H), 1.96 - 1.90 (m, 1 H), 1.74 - 1.60 (m, 6 H), 1.59 - 1.51 (m, 2 H), 1.51 - 1.38 (m, 9 H), 1.37 - 1.31 (m, 2 H), 1.30 - 1.26 (m, 1 H), 1.21 - 1.10 (m, 2 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 1 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.78 (s, 3 H), 0.72 (s, 3 H). ^{13}C NMR (*CHLOROFORM-d*) δ ppm 167.7, 167.2, 149.5, 129.8, 129.4, 128.4, 128.3, 127.5, 65.9, 58.8, 57.3, 55.7, 51.8, 51.3, 49.9, 49.9, 48.2, 44.7, 41.9, 40.4, 40.3, 37.9, 37.4, 37.3, 34.5, 34.0, 29.4, 29.2, 28.1, 26.8, 26.2, 24.6, 22.6, 21.8, 20.4, 18.5, 17.4, 16.1, 15.6, 14.5, 14.1.

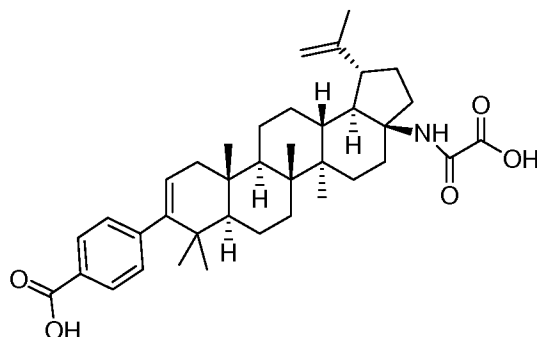
Step 2. Preparation 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysen-9-yl]benzoate, TFA (24.3 mg, 0.029 mmol) in THF (3 mL) was added a 0.753 molar aqueous solution of lithium hydroxide monohydrate (0.232 mL, 0.116 mmol). The reaction mixture was heated to 75 °C. After 5.5 h, the reaction mixture was concentrated to dryness. The crude residue was dissolved in THF (1.2 mL), MeOH (0.3 mL) and 1N HCl (0.2 mL). The resulting solution was filtered and purified using prep HPLC method 3 to give 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (16.5 mg, 0.020 mmol, 69.1% yield) as a white solid. LCMS: m/z 709.6 ($\text{M}+\text{H}^+$), retention time 2.072 min (method 6). ^1H NMR (500MHz, *METHANOL-d*₄) δ = 7.91 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 8.2 Hz, 2 H), 7.11 (s, 1 H), 3.25 - 3.20 (m, 6 H), 3.17 (d, J = 5.5 Hz, 4 H), 2.65 - 2.59 (m, 1 H), 2.44 (dd, J = 2.7, 13.1 Hz, 1 H), 2.37 (dd, J = 7.0, 12.5 Hz, 1 H), 2.19 - 2.04 (m, 1 H), 1.98 - 1.89 (m, 1 H), 1.85 (d, J = 13.1 Hz, 1 H), 1.74 (dd, J = 3.7, 7.9 Hz, 2 H), 1.71 - 1.60 (m, 3 H), 1.56 - 1.45 (m, 8 H), 1.44 - 1.37 (m, 4 H), 1.36 - 1.25 (m, 2 H), 1.16 - 1.09 (m, 2 H), 1.05 (s, 3 H), 1.04 (s, 3 H), 1.00 (s, 3 H),

0.95 (d, $J = 2.1$ Hz, 1 H), 0.91 (d, $J = 6.7$ Hz, 3 H), 0.81 (d, $J = 6.7$ Hz, 3 H), 0.78 (s, 3 H), 0.72 (s, 3 H).

Example 130-1

- 5 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(carboxyformamido)-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.



10

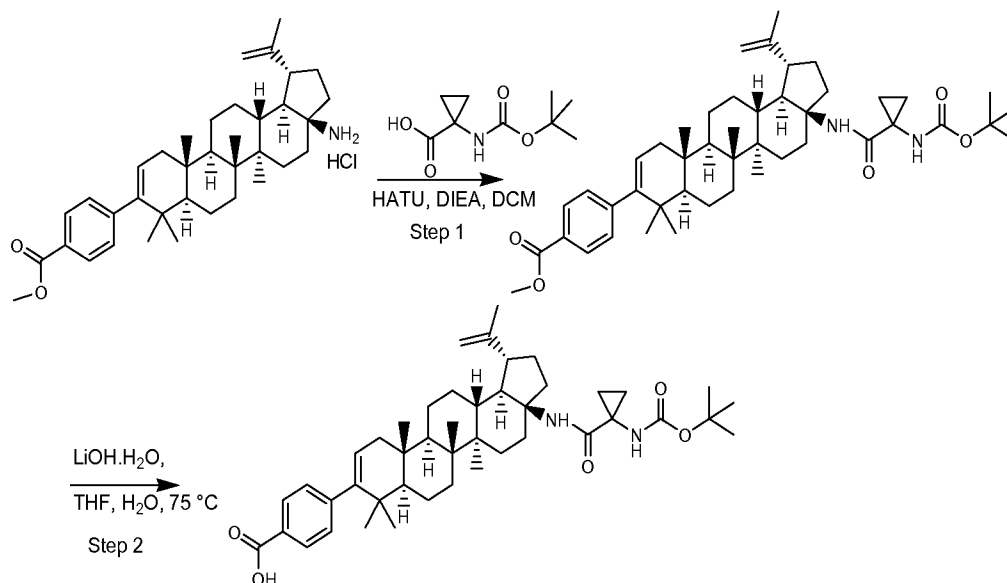
- The title compounds was obtained in 25% yield as a by-product during the ester hydrolysis in Step 2 of the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. LCMS: m/e 600.5 (M-H)⁺, 1.33 min (method 5). ¹H NMR (500MHz, *CHLOROFORM-d*) δ = 8.02 (d, $J = 8.2$ Hz, 2 H), 7.26 (d, $J = 8.2$ Hz, 3 H), 5.33 (d, $J = 4.9$ Hz, 1 H), 4.80 (s, 1 H), 4.70 (s, 1 H), 3.84 - 3.80 (m, 1 H), 2.59 (d, $J = 10.1$ Hz, 1 H), 2.54 (d, $J = 5.2$ Hz, 1 H), 2.46 (dd, $J = 8.4, 11.7$ Hz, 1 H), 2.18 - 2.11 (m, 1 H), 1.91 (ddd, $J = 3.1, 3.3, 6.8$ Hz, 2 H), 1.83 - 1.75 (m, 2 H), 1.74 (s, 3 H), 1.62 - 1.34 (m, 12 H), 1.28 (s, 1 H), 1.27 - 1.12 (m, 3 H), 1.07 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.97 (br. s., 3 H), 0.96 (br. s., 3 H).
- 15
- 20

Example 130-2

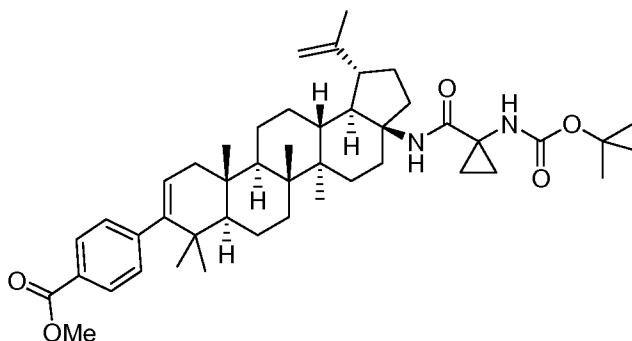
25

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-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.



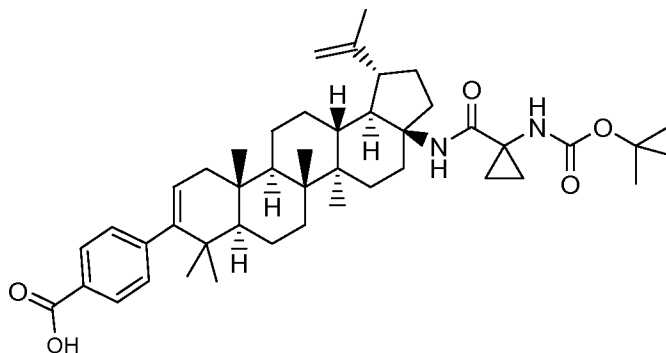
- 5 Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



10

- To a solution mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (0.302 g, 0.555 mmol) and
- 15 *N,N*-diisopropylethylamine (0.580 mL, 3.33 mmol) in DCM (5 mL) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.465 g, 1.222 mmol) and 1-(tert-

- butoxycarbonylamino)cyclopropanecarboxylic acid (0.223 g, 1.111 mmol). The reaction mixture was stirred at rt. After 18 h, the reaction was diluted with DCM (20 mL) and silica gel (4g) was added. The mixture was concentrated to dryness and dried *in vacuo* to a free flowing powder. The material was loaded onto a silica gel column (25g cartridge) gradient 100% hexanes to 25% EtOAc in hexanes over 240 mL, hold 25% EtOAc in hexanes to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-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 (234 mg, 0.309 mmol, 55.6 % yield) as a white solid. LCMS: m/e 727.4 (M+H)⁺, 5.17 min (method 2). ¹H NMR (500MHz, CHLOROFORM-*d*) δ 7.97 - 7.89 (m, 2H), 7.20 (d, $J=8.5$ Hz, 2H), 6.47 (br. s., 1H), 5.30 (dd, $J=6.3, 1.7$ Hz, 1H), 5.16 - 5.06 (m, 1H), 4.72 (d, $J=1.8$ Hz, 1H), 4.62 (s, 1H), 4.19 - 4.09 (m, 1H), 3.92 (s, 3H), 2.66 - 2.60 (m, 1H), 2.49 (d, $J=4.6$ Hz, 2H), 2.11 (dd, $J=17.1, 6.4$ Hz, 1H), 2.07 - 1.96 (m, 1H), 1.53 (s, 9H), 1.46 (s, 3H), 1.43 (d, $J=2.7$ Hz, 1H), 1.37 (d, $J=3.4$ Hz, 1H), 1.34 (d, $J=3.7$ Hz, 1H), 1.26 (dd, $J=7.0, 3.1$ Hz, 1H), 1.19 - 1.16 (m, 1H), 1.12 (br. s., 3H), 1.10 - 1.07 (m, 1H), 1.01 (s, 3H), 1.01 - 0.99 (m, 3H), 0.94 (s, 3H), 0.94 (s, 3H).
- Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-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.



25

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-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 (101 mg, 0.139 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (17.49 mg, 0.417 mmol) in water (1.000 mL). The resulting mixture was stirred at 75°C. After 18 h, the reaction mixture was concentrated. The residue was redissolved in THF/MeOH, silica gel (2g) was added and the mixture was concentrated to dryness. The absorbed material was loaded onto a silica gel column (25g cartridge) and eluted with 0%B (solvent B = (90:10 DCM:MeOH, A = 100% DCM) to 50% B for 180 mL, then hold at 50 % B for 900 mL. Thus was obtained 4-

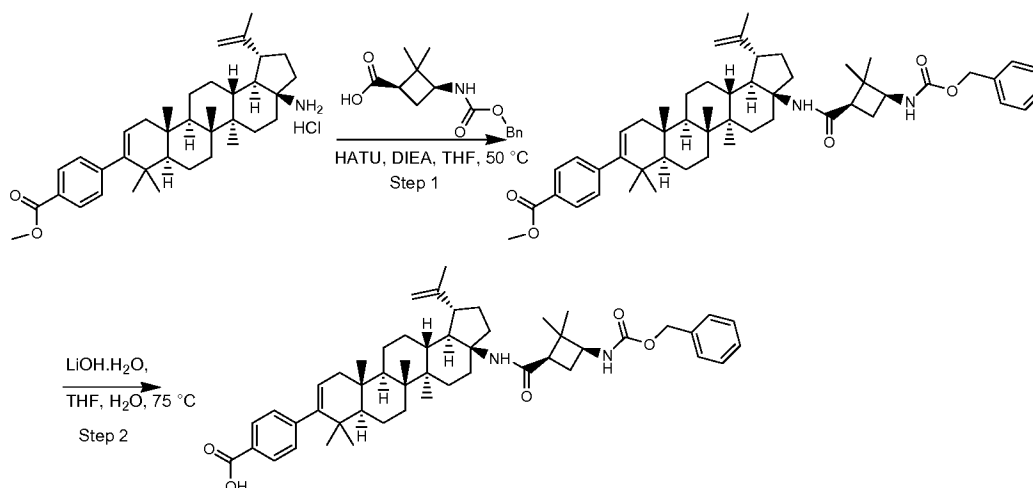
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (39 mg, 0.054 mmol, 38.6 % yield) as white solid. LCMS: m/e 713.6 (M+H)⁺, 2.32 min (method 1). ¹H NMR (500MHz, 1:1 CDCl₃:METHANOL-d₄) δ 7.92 (d, J=8.2 Hz, 2H), 7.20 (d, J=8.2 Hz, 3H), 6.62 (br. s., 1H), 5.33 - 5.24 (m, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 2.61 - 2.36 (m, 3H), 2.13 (dd, J=17.2, 6.3 Hz, 1H), 2.04 - 1.95 (m, 1H), 1.73 (br. s., 1H), 1.71 (s, 3H), 1.41 (d, J=6.1 Hz, 2H), 1.26 (br. s., 9H), 1.15 (s, 3H), 1.10 (br. s., 1H), 1.03 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.88 (d, J=6.7 Hz, 2H), 0.86 - 0.83 (m, 2H).

20

Example 130-3

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-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.

25



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-
 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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 amino-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, HCl (265 mg, 0.457 mmol) in tetrahydrofuran
 (5 mL) was added *N,N*-di-iso-propylethylamine (0.278 mL, 1.598 mmol), (1R,3S)-3-
 (((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxylic acid (152 mg,
 0.548 mmol) (for preparation see: J. Aguilera et al. *Tetrahedron Asymmetry* **2008**, *19*,
 302) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium
 hexafluorophosphate (226 mg, 0.594 mmol). The reaction mixture was heated to 50
 °C. After 6h, the mixture was dilute with EtOAc (30 mL) and washed with 1N HCl
 (5 mL). The aqueous layer was extracted with EtOAc (25 mL). The combined
 organic layer was washed with 5% NaHCO₃, brine, dried over MgSO₄, filtered and
 concentrated to afford a light brown viscous oil. The material was dissolved in
 DCM, loaded onto a silicagel column and eluted with 97:3 DCM:MeOH to give
 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-
 (((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-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 (335 mg, 0.355 mmol, 78 %

yield) as brown foam. LC/MS: m/e 802.4 (M+H)⁺, 4.23 min (method 8). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.95 (d, *J*=8.3 Hz, 2H), 7.40 - 7.37 (m, 5H), 7.21 (d, *J*=8.3 Hz, 2H), 5.31 (d, *J*=4.6 Hz, 1H), 5.18 - 5.12 (m, 2H), 5.10 - 5.06 (m, 1H), 4.97 (s, 1H), 4.76 (s, 1H), 4.66 (s, 1H), 3.93 (s, 3H), 2.85 (s, 6H), 2.69 - 2.55 (m, 2H), 2.44 - 2.29 (m, 3H), 2.17 - 2.09 (m, 2H), 1.94 - 1.81 (m, 3H), 1.72 (s, 3H), 1.70 - 1.66 (m, 1H), 1.62 - 1.52 (m, 4H), 1.46 (d, *J*=7.3 Hz, 1H), 1.42 (d, *J*=2.7 Hz, 1H), 1.37 (s, 3H), 1.32 - 1.22 (m, 3H), 1.15 (d, *J*=11.7 Hz, 2H), 1.09 (s, 2H), 1.02 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.95 (s, 6H).

10 Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-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.

15 To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-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 (135 mg, 0.168 mmol) in THF (5 mL), MeOH (2 mL) was added a solution of lithium hydroxide monohydrate (0.014 mL, 0.504 mmol) in water (1 mL). The reaction mixture was stirred at 75 °C. After 4h, the mixture was concentrated to a white paste. The crude material was dissolved in THF (1.75 mL), MeOH (1 mL) and 1N HCl (0.25 mL) and injected into a reverse phase prep-HPLC using HPLC method 11 and dried in a vacuum oven to give the title compound

20 (30.4 mg, 0.035 mmol, 21.09 % yield) as white solid. LCMS: m/e 789.4 (M+H)⁺, 3.14 min (method 8). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.02 (d, *J*=8.3 Hz, 2H), 7.41 - 7.37 (m, 4H), 7.36 (d, *J*=3.4 Hz, 1H), 7.25 (d, *J*=8.3 Hz, 2H), 5.33 (d, *J*=4.6 Hz, 1H), 5.19 - 5.07 (m, 3H), 4.99 (br. s., 1H), 4.77 (s, 1H), 4.66 (s, 1H), 3.98 - 3.88 (m, 1H), 2.70 - 2.55 (m, 3H), 2.47 - 2.28 (m, 3H), 2.19 - 2.09 (m, 2H), 1.99 - 1.87 (m, 1H), 1.76 (d, *J*=7.8 Hz, 1H), 1.72 (s, 3H), 1.71 - 1.63 (m, 2H), 1.58 (d, *J*=8.1 Hz, 3H), 1.50 (br. s., 3H), 1.43 (br. s., 1H), 1.37 (br. s., 3H), 1.33 (d, *J*=12.2 Hz, 2H), 1.28 (s, 3H), 1.24 (d, *J*=7.1 Hz, 1H), 1.16 (d, *J*=12.2 Hz, 2H), 1.09 (s, 3H), 1.02 (s, 6H), 1.01 (br. s., 3H), 0.96 (s, 6H).

30

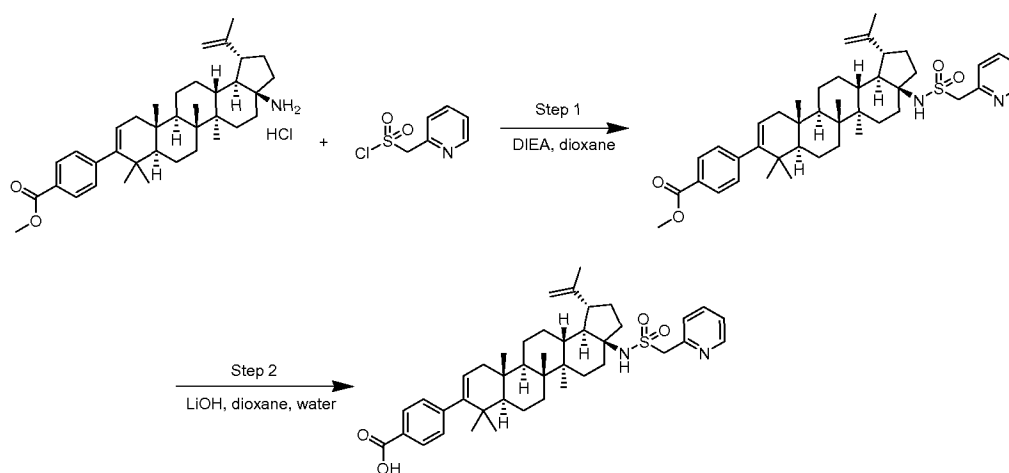
Section 4. Sulfonyl amides

Example 131

5

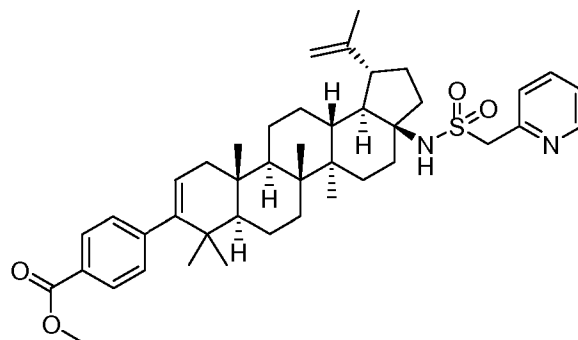
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

10



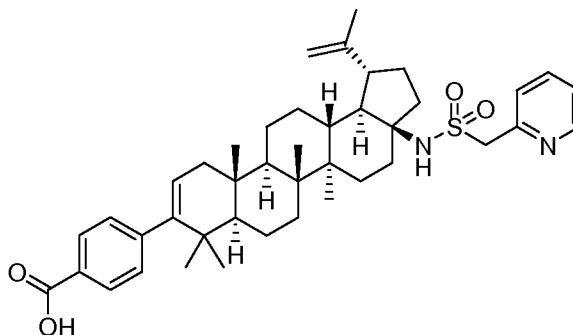
Step 1: Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

15



Methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (0.100 g, 0.184 mmol) was combined with
 5 pyridin-2-ylmethanesulfonyl chloride, triflic acid salt (0.189 g, 0.552 mmol). To the mixture was added dry 1,4-dioxane (1.5 mL) followed by addition of DIPEA (0.095 g, 0.736 mmol). The mixture was shaken at rt for 3 h. The crude reaction mixture was concentrated, redissolved in a mixture of MeOH and THF, and purified by reverse phase preparative HPLC. The title compound was isolated as a mono-TFA
 10 salt white solid (66 mg, 44% yield). LCMS: m/z 699 ($M+H^+$), retention time 3.03 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.93 (s, 3 H) 0.94 (s, 3 H) 1.01 (d, $J=1.76$ Hz, 6 H) 1.07 - 1.20 (m, 5 H) 1.21 - 1.28 (m, 1 H) 1.34 - 1.57 (m, 11 H) 1.63 - 1.78 (m, 6 H) 1.78 - 1.95 (m, 2 H) 1.95 - 2.05 (m, 1 H) 2.12 (dd, $J=17.19, 6.40$ Hz, 1 H) 2.31 - 2.41 (m, 1 H) 2.41 - 2.51
 15 (m, 1 H) 2.61 (td, $J=10.98, 4.64$ Hz, 1 H) 3.90 (s, 3 H) 4.56 - 4.59 (m, 1 H) 4.64 (br. s., 1 H) 4.75 (d, $J=1.51$ Hz, 1 H) 5.28 (dd, $J=6.02, 1.51$ Hz, 1 H) 7.20 (m, $J=8.28$ Hz, 2 H) 7.53 (br. s., 1 H) 7.70 (d, $J=6.27$ Hz, 1 H) 7.90 (m, $J=8.28$ Hz, 2 H) 7.98 (t, $J=7.78$ Hz, 1 H) 8.67 (br. s., 1 H).

20 Step 2: Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-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.



25

In a 1 dram vial with PTFE lined screw cap were combined methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-

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 (0.060 g, 0.086 mmol), lithium hydroxide monohydrate (0.022 g, 0.515 mmol), 1,4-dioxane (0.8 mL) and water (0.4 mL). The vial was sealed and heated with stirring to 75 °C for 7 min. Small quantities of

5 MeOH and THF were added to completely dissolve all solids, and the mixture was filtered and purified by reverse phase preparative HPLC. The mono-TFA salt product was isolated after purification as a white solid (56 mg, 96% yield). LCMS: m/z 685 ($M+H^+$), retention time 2.62 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of $CDCl_3$ and $MeOD$, $MeOD$ lock) δ ppm 0.94 (s, 3 H) 0.95 (s, 3 H) 1.02 (d, $J=2.14$ Hz,

10 6 H) 1.09 - 1.20 (m, 5 H) 1.22 - 1.29 (m, 1 H) 1.29 - 1.40 (m, 1 H) 1.40 - 1.60 (m, 9 H) 1.65 - 1.80 (m, 6 H) 1.82 - 2.02 (m, 3 H) 2.13 (dd, $J=17.09$, 6.41 Hz, 1 H) 2.33 - 2.41 (m, 1 H) 2.41 - 2.49 (m, 1 H) 2.64 (td, $J=11.06$, 4.73 Hz, 1 H) 4.64 (s, 3 H) 4.77 (d, $J=1.53$ Hz, 1 H) 5.29 (dd, $J=6.26$, 1.68 Hz, 1 H) 7.20 (d, $J=8.54$ Hz, 2 H) 7.61 - 7.67 (m, 1 H) 7.80 (d, $J=7.93$ Hz, 1 H) 7.92 (d, $J=8.24$ Hz, 2 H) 8.11 (td, $J=7.78$, 1.53

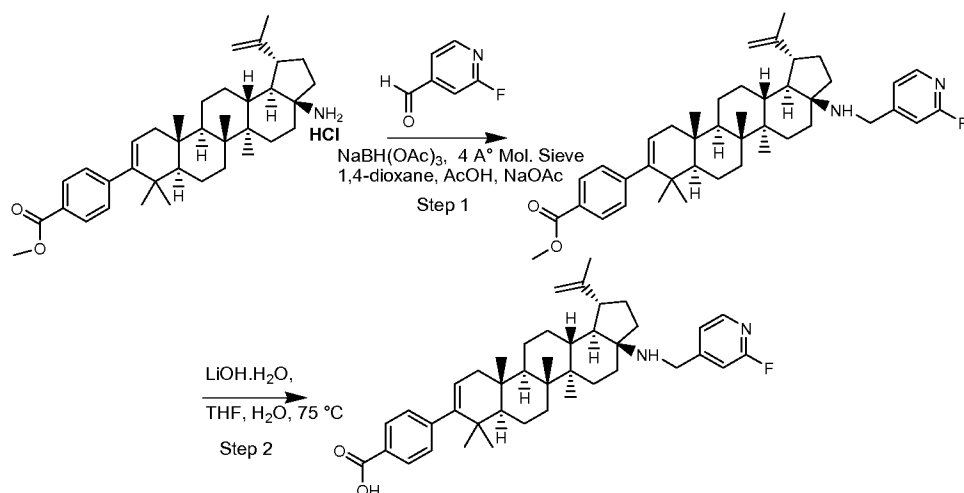
15 Hz, 1 H) 8.69 (d, $J=3.97$ Hz, 1 H).

Section 5. Amines

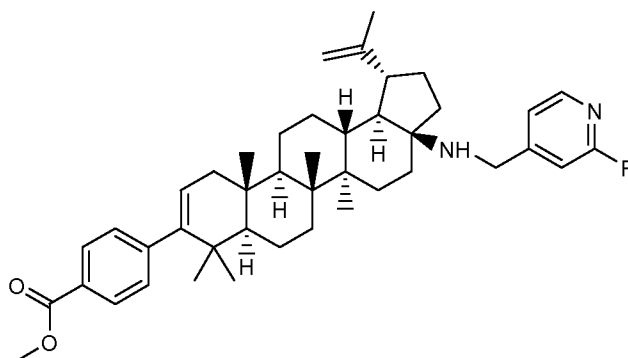
Example 132

20 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-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.

25



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((2-fluoropyridin-4-yl)methylamino)-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.

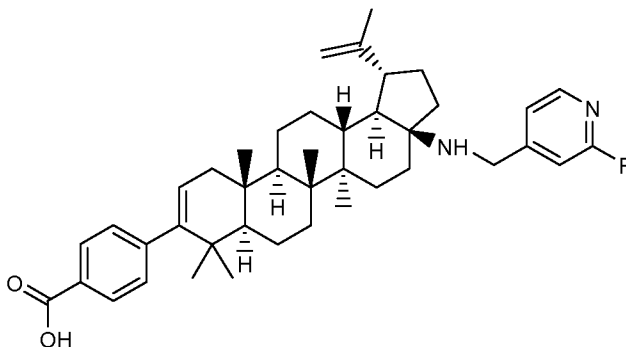


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoate, HCl (318 mg, 0.548 mmol) in DCE (10 mL) was
 added glacial acetic acid (0.314 mL, 5.48 mmol), sodium acetate (67.4 mg, 0.822
 mmol), 2-fluoropyridine-4-carboxaldehyde (206 mg, 1.644 mmol) and 4A molecular
 sieves. The reaction mixture was heated to 65 °C for 18 h. To the reaction mixture
 was added sodium triacetoxyhydroborate (581 mg, 2.74 mmol) and the resulting
 mixture was heated to 65 °C for 7.5 h, then the mixture was left at rt for 48 h. The
 reaction was diluted with DCM (50 mL) and washed with saturated NaHCO_3 (20

mL). The aqueous layer was extracted with DCM (2 x 25 mL). The combined organic layer was dried over MgSO_4 , filtered and concentrated. The resulting dark brown residue was dissolved in THF (3 mL) and MeOH (0.6 mL), filtered and purified by reverse phase preparative HPLC using HPLC method 3 to give methyl 4-
 5 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-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, TFA (218.4 mg, 0.285 mmol, 52.0% yield) as a white solid. LCMS: m/e 653.4 ($\text{M}+\text{H}$)⁺, 2.69 min (method 6).

10

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-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.



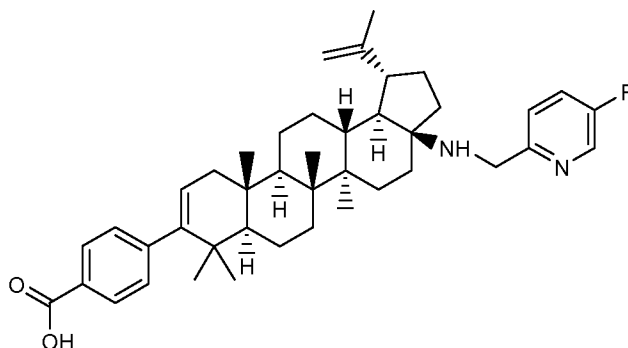
15

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-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, TFA (77.7 mg, 0.101 mmol) in THF (3 mL) was
 20 added a 0.753 molar aqueous solution of $\text{LiOH} \cdot \text{H}_2\text{O}$ (0.539 mL, 0.405 mmol). The reaction mixture was heated to 75 °C. After 4 h, the reaction mixture was concentrated. The crude residue was dissolved in THF (1.5 mL) and MeOH (200 μL), filtered and purified by reverse phase preparative HPLC using HPLC method 3
 25 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-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, TFA (30.6 mg, 0.037 mmol, 36.1% yield) as a white solid. LCMS: m/e 637.7 ($M-H$), 3.12 min (method 6). ^1H NMR (500MHz, 1:1 $CDCl_3:MeOD$) δ = 8.24 (d, J = 5.2 Hz, 1 H), 7.92 (d, J = 8.2 Hz, 2 H), 7.43 (d, J = 5.2 Hz, 1 H), 7.24 (s, 1 H), 7.20 (d, J = 8.5 Hz, 2 H), 5.29 (dd, J = 1.7, 6.3 Hz, 1 H), 4.78 (s, 1 H), 4.17 (br. s., 2 H), 2.78 - 2.69 (m, 1 H), 2.18 - 2.10 (m, 2 H), 2.09 - 2.01 (m, 2 H), 1.98 (dd, J = 3.1, 11.9 Hz, 1 H), 1.96 - 1.88 (m, 1 H), 1.83 - 1.76 (m, 1 H), 1.72 (s, 3 H), 1.70 - 1.64 (m, 1 H), 1.63 - 1.40 (m, 10 H), 1.39 - 1.31 (m, 1 H), 1.31 - 1.23 (m, 2 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (1:1 $CDCl_3:MeOD$) δ ppm 15.3, 16.6, 17.4, 19.5, 20.6, 21.8, 22.2, 26.1, 27.6, 29.0, 29.5, 30.2, 33.9, 34.6, 37.2, 38.2, 38.4, 41.8, 42.8, 43.1, 45.7, 47.2, 49.7, 49.9, 50.3, 50.5, 53.9, 78.8, 123.1, 123.2, 124.9, 129.3, 129.7, 131.0, 147.4, 149.7, 164.0, 166.0, 170.1.

Example 133

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((5-fluoropyridin-2-yl)methylamino)-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.

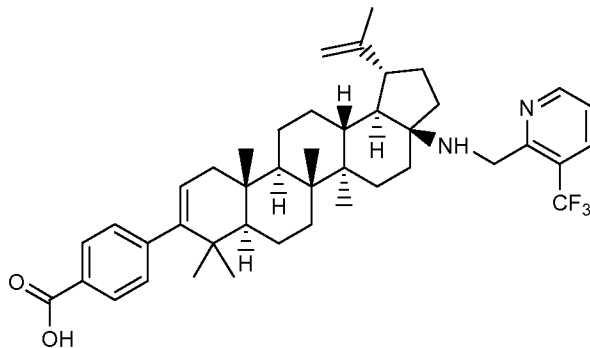


The title compound was prepared in 47% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-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, except 5-fluoro-2-formylpyridine was used instead of 2-fluoropyridine-4-carboxaldehyde in Step 1. LCMS: m/e 639.5 ($M+H$)⁺, 3.33 min (method 6). ¹H NMR (500MHz, 1:1 *CDCl*₃:*MeOD*) δ = 8.46 (d, J = 2.7 Hz, 1 H), 7.93 (d, J = 8.2 Hz, 2 H), 7.68 (dt, J = 2.7, 8.2 Hz, 1 H), 7.53 (dd, J = 4.1, 8.7 Hz, 1 H), 7.21 (d, J = 8.5 Hz, 2 H), 5.31 (dd, J = 1.7, 6.3 Hz, 1 H), 4.83 (s, 1 H), 4.74 (s, 1 H), 4.49 (d, J = 15.3 Hz, 1 H), 4.32 (d, J = 15.0 Hz, 1 H), 2.78 (dt, J = 5.3, 10.9 Hz, 1 H), 2.22 - 2.06 (m, 5 H), 1.96 (dt, J = 3.4, 12.2 Hz, 1 H), 1.89 - 1.82 (m, 1 H), 1.80 (d, J = 10.7 Hz, 2 H), 1.76 (s, 3 H), 1.74 - 1.66 (m, 2 H), 1.64 - 1.54 (m, 4 H), 1.53 - 1.47 (m, 2 H), 1.46 - 1.42 (m, 1 H), 1.41 - 1.37 (m, 1 H), 1.33 (s, 3 H), 1.29 (dd, J = 3.8, 9.9 Hz, 1 H), 1.24 (dd, J = 4.1, 13.0 Hz, 1 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

Example 134

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3-(trifluoromethyl)pyridin-2-yl)methylamino)-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

The title compound was prepared in 42% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-

25

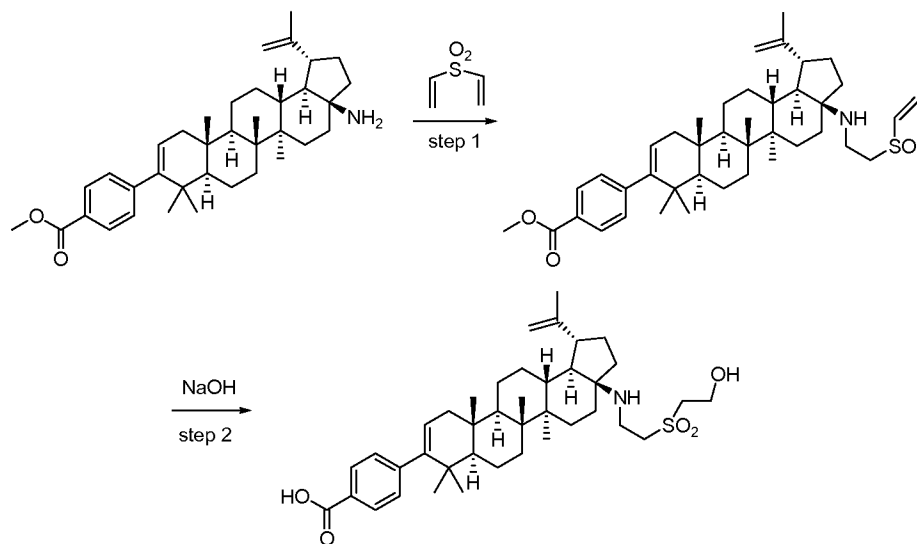
yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-trifluoromethylpyridine-2-carbaldehyde was used instead of 2-fluoropyridine-4-carboxaldehyde in Step 1.

LCMS: m/e 689.6 (M+H)⁺, 4.12 min (method 6). ¹H NMR (500MHz, 1:1

- 5 $CDCl_3:MeOD$) δ = 8.83 (d, J = 4.3 Hz, 1 H), 8.28 (d, J = 7.9 Hz, 1 H), 7.93 (d, J = 8.5 Hz, 2 H), 7.72 (dd, J = 5.0, 7.8 Hz, 1 H), 7.21 (d, J = 8.5 Hz, 2 H), 5.31 (dd, J = 1.5, 6.1 Hz, 1 H), 4.85 (s, 1 H), 4.76 (s, 1 H), 4.44 (d, J = 16.2 Hz, 1 H), 2.80 (dt, J = 5.5, 11.0 Hz, 1 H), 2.25 - 2.10 (m, 5 H), 2.02 (dt, J = 3.5, 12.1 Hz, 1 H), 1.92 - 1.79 (m, 2 H), 1.78 (s, 3 H), 1.76 - 1.68 (m, 3 H), 1.64 - 1.54 (m, 4 H), 1.52 - 1.43 (m, 3 H), 1.40
- 10 (br. s., 1 H), 1.36 (s, 3 H), 1.32 - 1.22 (m, 2 H), 1.16 - 1.13 (m, 3 H), 1.08 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

Example 135

- 15 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-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

Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(vinylsulfonyl)ethylamino)-

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 mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 5 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 (30 mg, 0.055 mmol), TEA (0.023 mL, 0.165 mmol) and vinylsulfonyl ethene (19.5 mg, 0.165 mmol) in EtOH (1 mL) was heated for 3 h at 100 °C. The reaction mixture was quenched with water, extracted with DCM (3 x 2 mL). The organic phases were combined, dried over sodium sulfate,
10 filtered and concentrated under reduced pressure to provide the title compound as a brown oil (25 mg, 68%). LCMS: m/e 662.42 (M+H)⁺, 3.45 min (method 10).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
15 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.

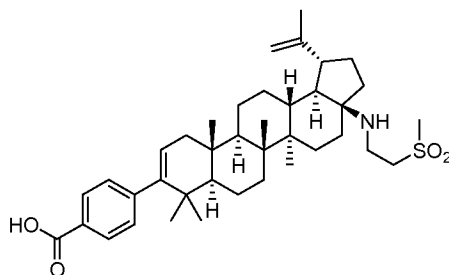
- A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(vinylsulfonyl)ethylamino)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
20 cyclopenta[a]chrysen-9-yl)benzoate (25 mg, 0.038 mmol) and sodium hydroxide (0.189 mL, 0.189 mmol) in dioxane (1 mL) was heated at 78 °C for 3 h. The reaction mixture was filtered and the clear solution was purified by prep HPLC to provide the title compound as a white solid (14 mg, 53%). LCMS: m/e 666.39 (M+H)⁺, 2.48 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.03 (d, *J*=8.24 Hz, 2 H),
25 7.30 (d, *J*=8.24 Hz, 2 H), 5.37 (d, *J*=4.27 Hz, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 4.31 - 4.01 (m, 3 H), 3.93 - 3.74 (m, 3 H), 3.68 - 3.41 (m, 2 H), 3.06 - 2.73 (m, 1 H), 2.48 - 1.26 (m, 22 H), 1.76 (s, 3 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

30

Example 136

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(methylsulfonyl)ethylamino)-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.



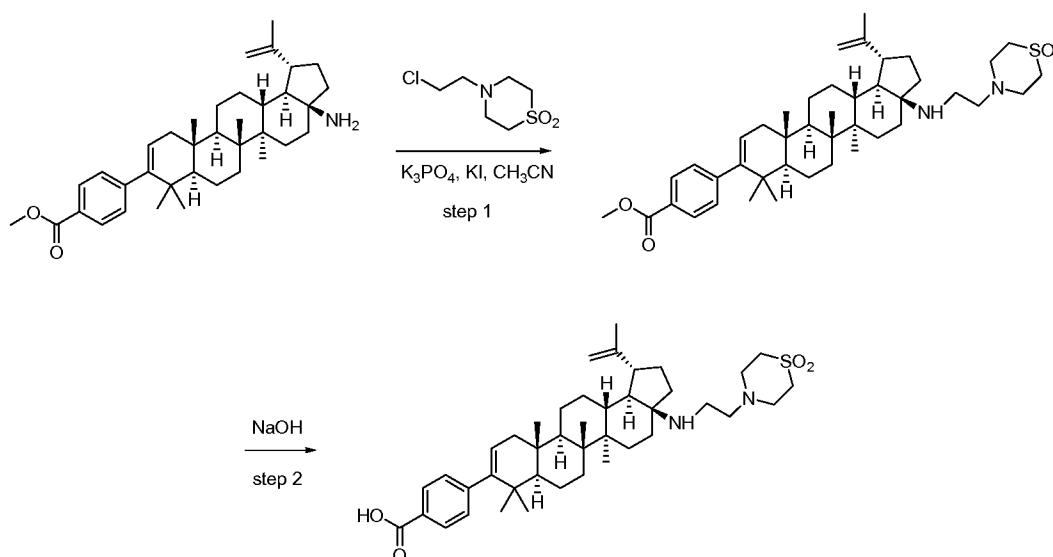
5

The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-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 methylsulfonyl ethene instead of vinylsulfonyl ethene in Step 1. The product was isolated as a white solid (6 mg, 39%). LCMS: m/e 636.37 ($M+H$)⁺, 2.53 min (method 10). ¹H NMR (500 MHz, *Acetic acid* *d*₄) δ ppm 8.04 (d, $J=8.24$ Hz, 2 H), 7.30 (d, $J=8.24$ Hz, 2 H), 5.44 - 5.33 (m, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 4.17 - 4.00 (m, 1 H), 3.93 - 3.69 (m, 3 H), 3.22 (s, 3 H), 3.00 - 2.85 (m, 1 H), 2.40 - 1.26 (m, 22 H), 1.77 (s, 3 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

15

Example 137

20 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 5 ((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoate.

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 amino-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-
 10 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 (600 mg, 1.10 mmol), 4-(2-
 chloroethyl)thiomorpholine 1,1-dioxide (600 mg, 2.56 mmol) (prepared as described
 in WO2002045652), anhydrous potassium phosphate (3.00 g, 14.1 mmol) and
 potassium iodide (10 mg, 0.060 mmol) in acetonitrile (50 mL) was placed in 150 mL
 15 AceGlass resealable pressure vessel. The white suspension was blanketed with
 nitrogen. The vessel was sealed and warmed to 115-125°C for 48 h. The crude
 reaction was filtered through a short bed of silica gel and washed with ethyl acetate.
 The filtrate was concentrated *in vacuo* and purified by silica gel chromatography
 eluted with ethyl acetate and hexanes (0-50%) to afford the title compound as a
 20 colorless foam (566 mg, 73%). ^1H NMR (500MHz, CHLOROFORM-d) δ 7.95 (d,
 J=8.2 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 5.31 (d, J=4.6 Hz, 1H), 4.74 (d, J=1.8 Hz, 1H),
 4.62 (s, 1H), 3.93 (s, 3H), 3.22 - 2.99 (m, 9H), 2.79 - 2.55 (m, 4H), 2.52 - 2.42 (m,
 1H), 2.18 - 2.09 (m, 1H), 1.99-1.02 (m, 20H), 1.72 (s, 3H), 1.11 (s, 3H), 1.01 (s, 3H),

1.10 (s, 3H), 0.95 (s, 3H), 0.95 (s, 3H). LCMS: m/e 705.51 (M+H)⁺, 3.01 min (method 10).

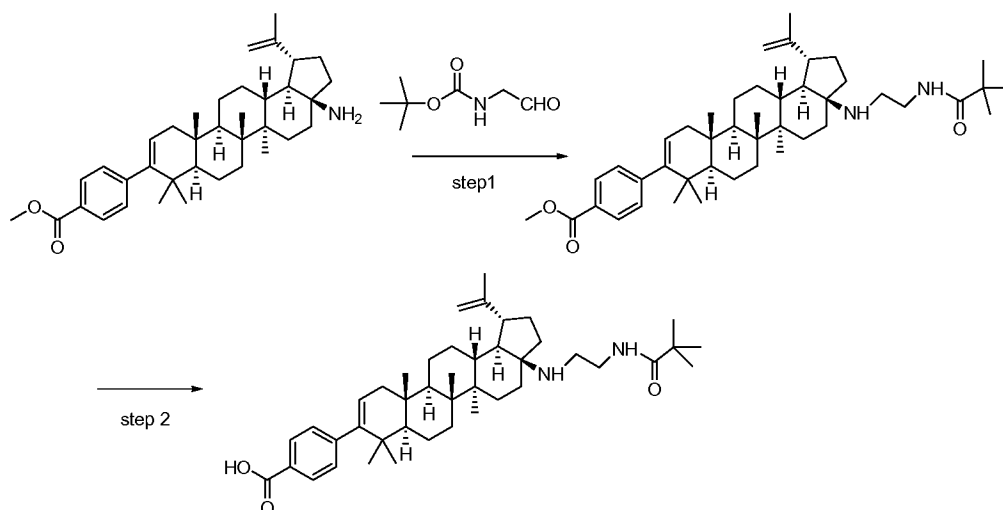
Step 2. Preparation of 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]- benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-
 10 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)benzoate (500 mg, 0.709 mmol) and aqueous sodium hydroxide 10N (1.42 mL, 14.2 mmol) in dioxane (10 mL) was heated at 78 °C for 3 h. The reaction was filtered and the resulting clear solution was purified by prep HPLC to provide the title compound as white solid (200 mg, 39%). LCMS: m/e 691.59
 15 (M+H)⁺, 2.53 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, $J=8.24$ Hz, 2 H), 7.30 (d, $J=8.24$ Hz, 2 H), 5.45 - 5.34 (m, 1 H), 4.85 (s, 1 H), 4.74 (s, 1 H), 3.55 - 3.40 (m, 1 H), 3.39 - 3.22 (m, 6 H), 3.22 - 3.11 (m, 4 H), 3.11 - 3.03 (m, 1 H), 3.04 - 2.94 (m, 1 H), 2.36 - 1.18 (m, 22 H), 1.76 (s, 3 H), 1.30 (s, 3 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

20

Example 138

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 25 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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-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.

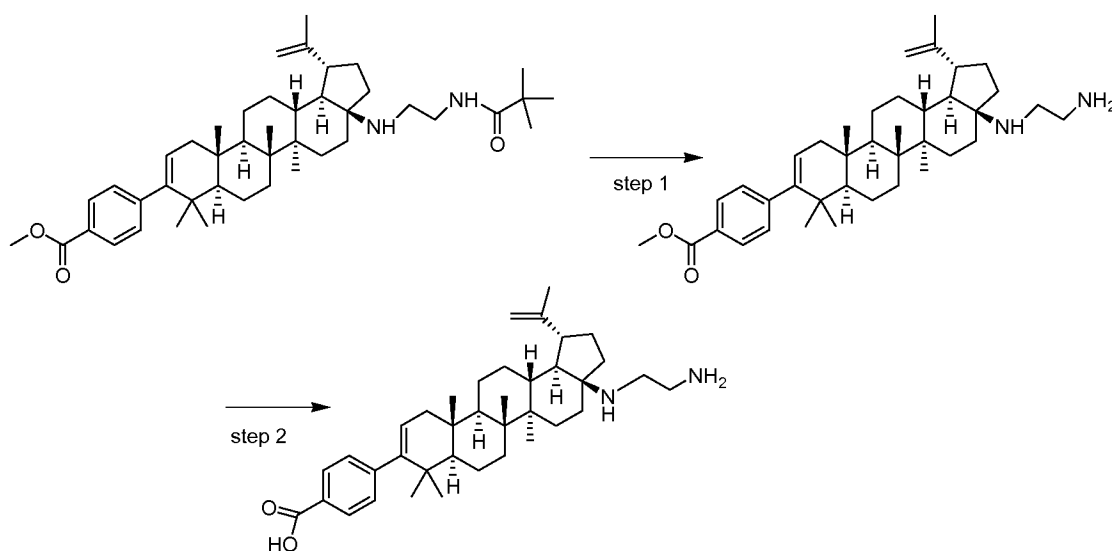
To methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (1.00 g, 1.84 mmol) in DCE (5 mL) was added *tert*-butyl 2-oxoethylcarbamate (1.17 g, 7.36 mmol) and tetraisopropoxytitanium (0.700 mL, 2.39 mmol). The reaction mixture was stirred for 1 h, then sodium triacetoxyborohydride (1.17 g, 5.52 mmol) was added. The reaction mixture was stirred for 18 h. The reaction mixture was quenched with sodium bicarbonate and was extracted with DCM (3 x 40 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using ethyl acetate and hexanes (20-100%) as the eluent to provide the title compound as a pale yellow oil. (900 mg, 71%). LCMS: m/e 688.24 ($M+H$)⁺, 2.51 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-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.

The title compound was prepared following the hydrolysis method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-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 (10 mg, 0.015 mmol) as starting material. The title compound was isolated as a white solid (4 mg, 39%). LCMS: m/e 673.45 $(M+H)^+$, 2.65 min (method 10). ^1H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, $J=8.24$ Hz, 2 H), 7.30 (d, $J=8.55$ Hz, 2 H), 5.51 - 5.32 (m, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 3.82 - 3.53 (m, 1 H), 3.53 - 3.24 (m, 3 H), 3.04 - 2.83 (m, 1 H), 2.37 - 1.15 (m, 22 H), 1.77 (s, 3 H), 1.53 - 1.49 (m, 9 H), 1.27 (s, 3 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 139

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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.

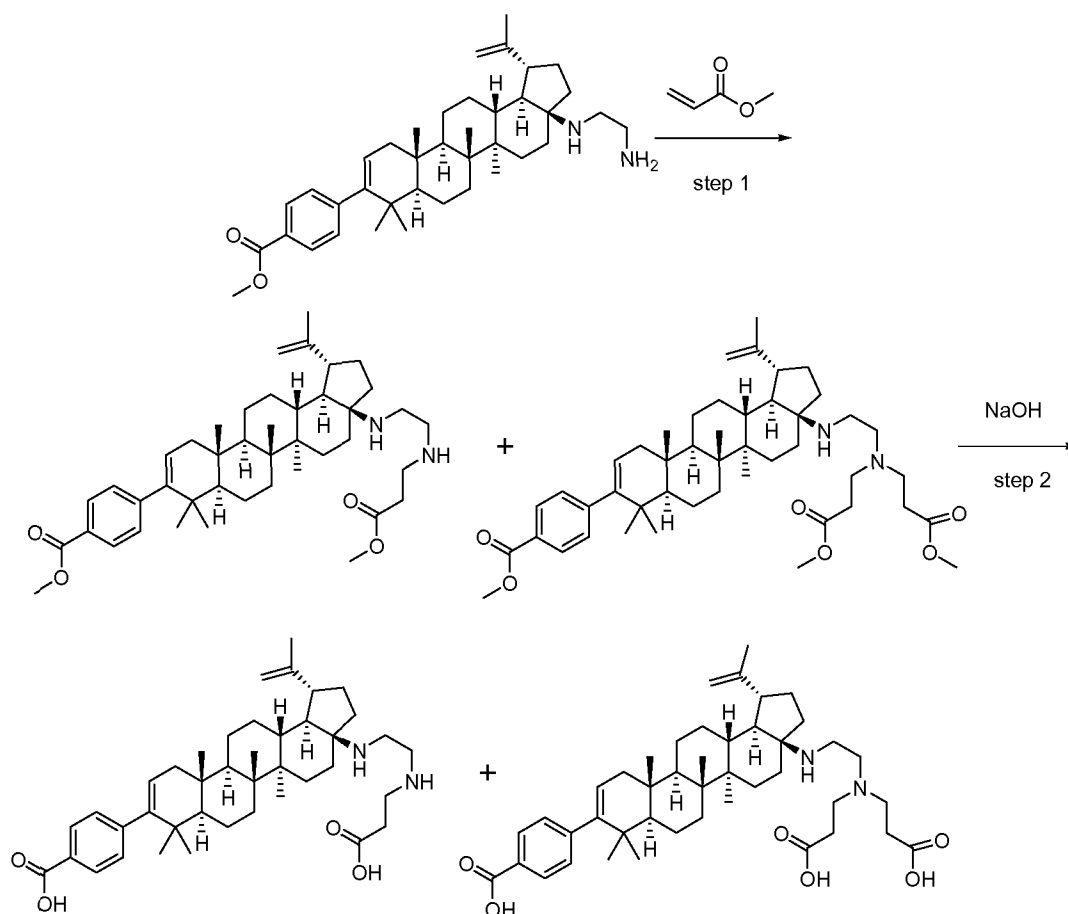
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(tert-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (900 mg, 1.310 mmol) in dioxane (1 mL) was added HCl (4M in dioxane) (4.26 mL, 17.03 mmol) and the reaction mixture was stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure to provide the title compound as a brown solid (769 mg, 100%). LCMS: m/e 588.08 (M+H)⁺, 2.44 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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.

The title compound was prepared following the hydrolysis method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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 (4 mg, 0.006 mmol) as starting material. The title compound was isolated as a white solid (2.4 mg, 67%). LCMS: m/e 573.2 (M+H)⁺, 2.39 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.03 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.37 (d, *J*=4.27 Hz, 1 H), 4.87 (s, 1 H), 4.76 (s, 1 H), 3.80 - 3.68 (m, 3 H), 3.68 - 3.59 (m, 1 H), 2.97 - 2.80 (m, 1 H), 2.38 - 1.21 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H).

Examples 140 and 141

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-
 5 carboxyethylamino)ethylamino)-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 and 3,3'-(2-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-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-
 10 octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)ethylazanediy)diopropanoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-
 15 (3-methoxy-3-oxopropylamino)ethylamino)-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 and dimethyl 3,3'-(2-

((1R,3aS,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-ylamino)ethylazanediyldipropanoate.

- 5 Methyl acrylate (9.97 mg, 0.116 mmol) was added to a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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 (34 mg, 0.058 mmol) in MeOH (2 mL) and the
- 10 mixture was stirred for 16 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide a mixture of the two title compounds as a brown oil (20 mg, 51%). LCMS: m/e 673.47 (M+H)⁺, 2.96 min and 759.51 (M+H)⁺, 3.43 min (method 10). The mixture was taken to the next step without further purification.

15

Step 2. Ester hydrolysis.

The mixture of esters from above (20 mg) in dioxane (1 mL) was treated with sodium hydroxide (0.297 mL, 0.297 mmol) at 78 °C for 3 hours. The reaction mixture was filtered and purified by prep. HPLC to provide the following two compounds:

20

Example 140

- 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-carboxyethylamino)ethylamino)-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.
- 25

- White solid (16 mg, 43% over 2 steps). LCMS: m/e 645.44 (M+H)⁺, 2.37 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.2 Hz, 2 H), 7.30 (d, *J*=8.5 Hz, 2 H), 5.37 (d, *J*=4.6 Hz, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 3.78 (s, 2 H), 3.77 - 3.59 (m, 2 H), 3.45 (t, *J*=6.4 Hz, 2 H), 2.90 (t, *J*=6.4 Hz, 2 H), 2.87 - 2.72 (m, 1 H), 2.42 - 1.22 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).
- 30

Example 141

3,3'-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-
5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

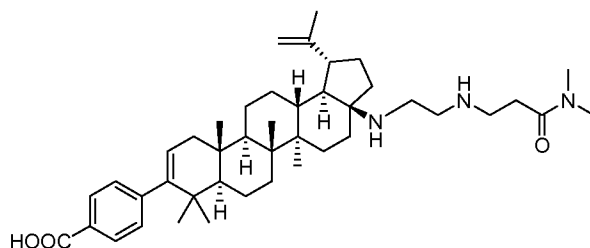
5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-3a-ylamino)ethylazanediyldipropionic acid

White solid (5.7 mg, 57% over 2 steps). LCMS: m/e 717.51 ($M+H$)⁺, 2.25
min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.03 (d, $J=8.2$ Hz, 2 H),
10 7.29 (d, $J=8.2$ Hz, 2 H), 5.36 (d, $J=4.9$ Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 3.83 -
3.66 (m, 4 H), 3.51 (t, $J=6.3$ Hz, 4 H), 2.93 (t, $J=6.9$ Hz, 4 H), 2.88 - 2.74 (m, 1 H),
2.42 - 1.22 (m, 22 H), 1.78 (s, 3 H), 1.19 (s, 3 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.01 (s,
3 H), 0.99 (s, 3 H).

15

Example 142

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3-
(dimethylamino)-3-oxopropylamino)ethylamino)-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-
20 cyclopenta[a]chrysen-9-yl)benzoic acid.



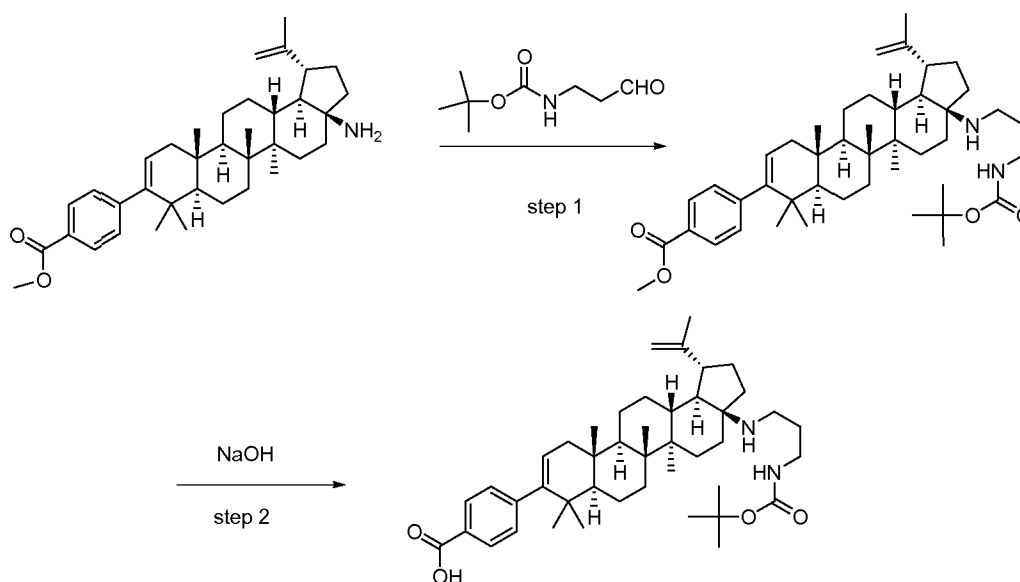
The title compound was prepared following the method described above for
25 the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-
carboxyethylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)benzoic acid using *N,N*-dimethylacrylamide as the Michael
acceptor reagent in the first step. The product was isolated as a white solid (9 mg,
30 50%). LCMS: m/e 672.47 ($M+H$)⁺, 2.33 min (method 2). ¹H NMR (500 MHz, *Acetic*

acid d4) δ ppm 8.04 (d, $J=8.2$ Hz, 2 H), 7.30 (d, $J=8.2$ Hz, 2 H), 5.37 (d, $J=4.6$ Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 3.86 - 3.59 (m, 4 H), 3.51 - 3.37 (m, 2 H), 3.07 (s, 3 H), 2.99 (s, 3 H), 2.95 (t, $J=5.6$ Hz, 2 H), 2.90 - 2.76 (m, 1 H), 2.37 - 1.22 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

5

Example 142

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-
butoxycarbonylamino)propylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
10 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.



15 Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
(3-(*tert*-butoxycarbonylamino)propylamino)-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.

Acetic acid (0.013 mL, 0.221 mmol) and *tert*-butyl 3-oxopropylcarbamate
20 (38.2 mg, 0.221 mmol) were added to a solution of methyl 4-
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, 0.074 mmol) in EtOH

(1 mL) and dioxane (1.0 mL) and the mixture was stirred for 2 h at rt. Sodium triacetoxyborohydride (78 mg, 0.368 mmol) was added and the reaction mixture was stirred at 20 °C for two hours. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate (3 mL), washed with 0.1N HCl (5 mL) and brine (5 mL) and extracted with DCM (3 x 5 mL). All the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as pale yellow oil (28 mg, 54%). LCMS: m/e 701.51 (M+H)⁺, 4.0 min (method 10).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-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.

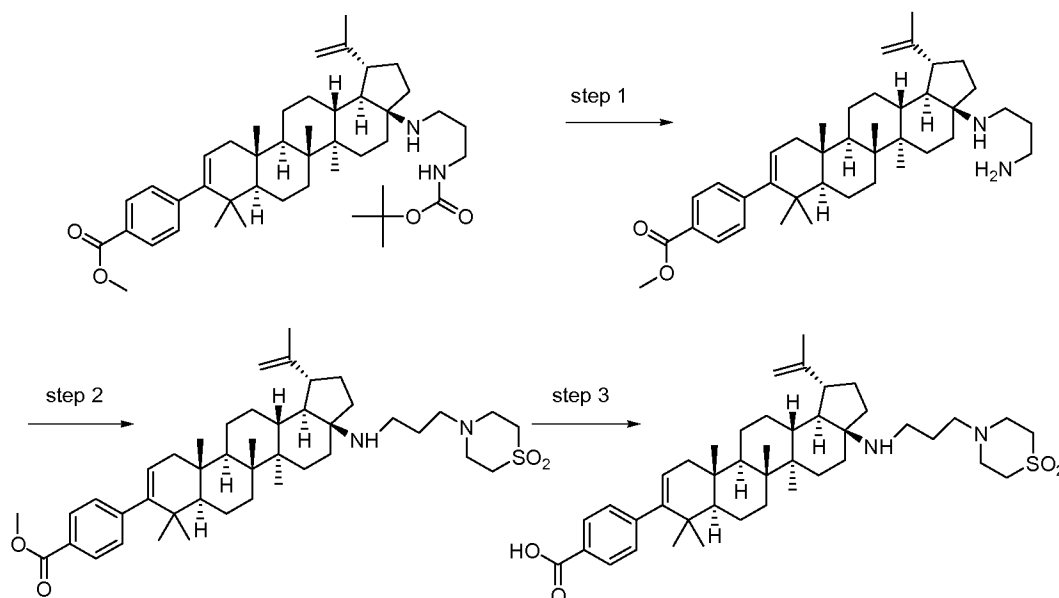
The title compound was prepared following the hydrolysis method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-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 (5 mg, 0.007 mmol) as starting material. The title compound was isolated as a white solid (3 mg, 58%). LCMS: m/e 687.54 (M+H)⁺, 2.69 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.37 (d, *J*=4.58 Hz, 1 H), 4.87 (s, 1 H), 4.74 (s, 1 H), 3.38 - 3.17 (m, 4 H), 3.04 - 2.86 (m, 1 H), 2.36 - 1.17 (m, 24 H), 1.77 (s, 3 H), 1.50 (s, 9 H), 1.25 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

30

Example 144

Preparation of 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl)- benzoic acid.



5

Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-aminopropylamino)-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.

4.0M HCl in dioxane (32.8 μ l, 0.131 mmol) was added to a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-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 (23 mg, 0.033 mmol) in dioxane (1 mL) and the mixture was stirred for 6 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide the title compound as a brown oil (15 mg, 76%). LCMS: m/e 601.48 ($M+H$)⁺, 2.88 min (method 10).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-(1,1-dioxido-4-thiomorpholinyl)propyl)amino)-1-isopropenyl-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)benzoic acid.

Vinylsulfonylethene (5.90 mg, 0.050 mmol) and triethylamine (6.96 μ l, 0.050 mmol) were added to a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-aminopropylamino)-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, 0.025 mmol) in EtOH (1 mL). The reaction mixture was heated to 100 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to provide the desired product as a brown solid (15 mg, 76%). LCMS: m/e 719.46 (M+H)⁺, 3.68 min (method 10).

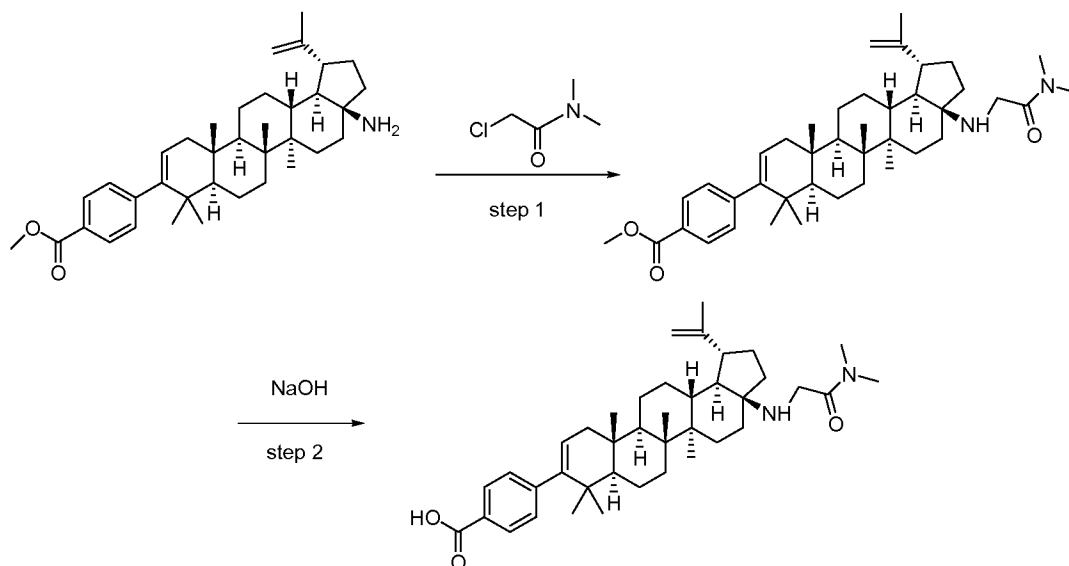
Step 3. Preparation of, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-(1,1-dioxido-4-thiomorpholinyl)propyl)amino)-1-isopropenyl-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)benzoic acid (15 mg, 0.021 mmol) and 1N sodium hydroxide (0.104 mL, 0.104 mmol) in dioxane (1 mL) was heated at 78 °C for 3 hours. The reaction mixture was purified by prep HPLC to provide the title compound as a white solid (9 mg, 58%). LCMS: m/e 705.49 (M+H)⁺, 2.60 min (method 10). ¹H NMR (400 MHz, *Acetic acid d4*) δ ppm 7.99 (d, *J*=8.28 Hz, 2 H), 7.25 (d, *J*=8.28 Hz, 2 H), 5.33 (d, *J*=4.77 Hz, 1 H), 4.82 (s, 1 H), 4.71 (s, 1 H), 3.87 (br. s., 4 H), 3.56 (d, *J*=4.27 Hz, 4 H), 3.51 - 3.40 (m, 2 H), 3.39 - 3.22 (m, 2 H), 2.86 - 2.69 (m, 1 H), 2.57 - 2.34 (m, 2 H), 2.27 - 1.18 (m, 22 H), 1.72 (s, 3 H), 1.16 (s, 3 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 0.98 (s, 3 H), 0.96 (s, 3 H).

Example 145

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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

Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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 mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, 0.092 mmol), 2-chloro-*N,N*-dimethylacetamide (33.5 mg, 0.276 mmol), potassium phosphate (78 mg, 0.368 mmol) and potassium iodide (36.6 mg, 0.221 mmol) in acetonitrile (1 mL) was heated at 120 °C for 33 h in a sealed tube. The reaction mixture was quenched with distilled water (5 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as a pale yellow solid (30 mg, 52%). LCMS: m/e 629.51 ($M+H$)⁺, 3.03 min (method 10). The product was used in the next step without further purification.

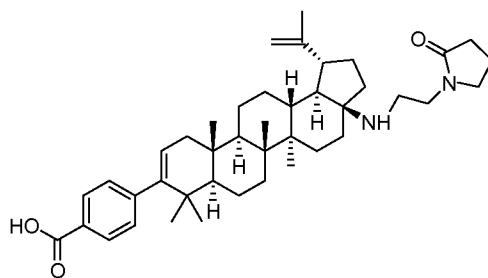
20

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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 A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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 (30 mg, 0.048 mmol) and aqueous 1N sodium hydroxide (0.048 mL, 0.048 mmol) in dioxane (1 mL) was heated up at 78 °C for 3 h.
- 10 The reaction mixture was filtered and the clear solution was purified by prep HPLC to provide the title compound as a white solid (9.5 mg, 31%). LCMS: m/e 615.56 (M+H)⁺, 2.52 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.38 (d, *J*=4.58 Hz, 1 H), 4.89 (s, 1 H), 4.76 (s, 1 H), 4.52 (d, *J*=16.17 Hz, 1 H), 4.04 (d, *J*=16.17 Hz, 1 H), 3.08 (d, *J*=10.99
- 15 Hz, 6 H), 3.01 – 2.86 (m, 1 H), 2.37 – 1.22 (m, 22 H), 1.79 (s, 3 H), 1.30 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Example 146

- 20 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-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.



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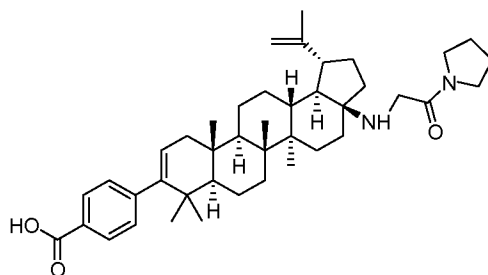
The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)pyrrolidin-2-one as the alkylating reagent in Step 1. The product was isolated as a white solid (19 mg, 62%).

LCMS: m/e 641.57 ($M+H$)⁺, 2.58 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, $J=8.24$ Hz, 2 H), 7.30 (d, $J=8.55$ Hz, 2 H), 5.37 (d, $J=4.88$ Hz, 1 H), 4.91 (s, 1 H), 4.76 (s, 1 H), 3.89 - 3.73 (m, 2 H), 3.72 - 3.56 (m, 3 H), 3.55 - 3.45 (m, 1 H), 2.93 - 2.80 (m, 1 H), 2.57 (td, $J=8.24$, 3.97 Hz, 2 H), 2.34 - 1.19 (m, 24 H), 1.78 (s, 3 H), 1.23 (s, 3 H), 1.13 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 147

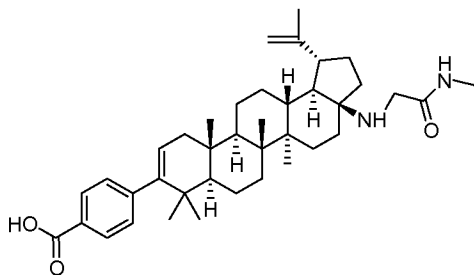
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-oxo-2-(pyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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 2-chloro-1-(pyrrolidin-1-yl)ethanone as the alkylating reagent in Step 1. The product was isolated as a white solid (19 mg, 46%). LCMS: m/e 641.46 ($M+H$)⁺, 2.55 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, $J=8.24$ Hz, 2 H), 7.30 (d, $J=8.24$ Hz, 2 H), 5.38 (d, $J=4.58$ Hz, 1 H), 4.89 (s, 1 H), 4.76 (s, 1 H), 4.43 (d, $J=16.48$ Hz, 1 H), 3.99 (d, $J=16.17$ Hz, 1 H), 3.73 - 3.42 (m, 4 H), 3.15 - 2.86 (m, 1 H), 2.41 - 1.19 (m, 26 H), 1.79 (s, 3 H), 1.28 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Example 148

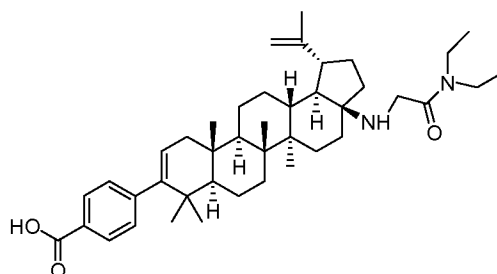
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(methylamino)-2-oxoethylamino)-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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 2-chloro-N-methylacetamide as the
 15 alkylating reagent in Step 1. The product was isolated as a white solid (41 mg, 80%). LCMS: m/e 601.45 (M+H)⁺, 2.31 min (method 11). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.38 (d, *J*=4.58 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 4.24 (d, *J*=15.56 Hz, 1 H), 3.92 (d, *J*=15.26 Hz, 1 H), 2.88 (s, 3 H), 3.08 – 2.74 (m, 1 H), 2.31 – 1.30 (m, 22 H), 1.78 (s, 3 H), 1.29 (s, 3 H),
 20 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H).

Example 149

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(diethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 25 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.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-

5 (dimethylamino)-2-oxoethylamino)-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 2-chloro-*N,N*-diethylacetamide as alkylating reagent in Step 1. The product was isolated as a white solid (20 mg, 39%). LCMS: m/e 643.50 ($M+H$)⁺, 2.35 min (method 11). ¹H NMR (400 MHz,

10 *CHLOROFORM-d*) δ ppm 7.99 (d, $J=8.28$ Hz, 2 H), 7.24 (d, $J=8.28$ Hz, 2 H), 5.31 (d, $J=4.52$ Hz, 1 H), 4.74 (d, $J=1.76$ Hz, 1 H), 4.60 (s, 1 H), 3.58 - 3.21 (m, 6 H), 2.82 - 2.69 (m, 1 H), 2.22 - 1.02 (m, 28 H), 1.72 (s, 3 H), 1.18 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.95 (s, 6 H).

15

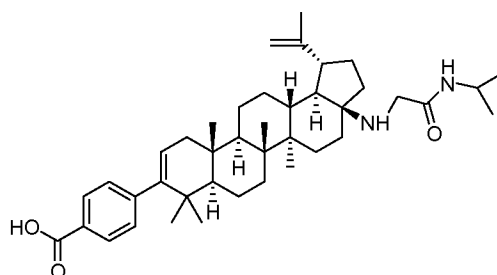
Example 150

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-

(isopropylamino)-2-oxoethylamino)-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-

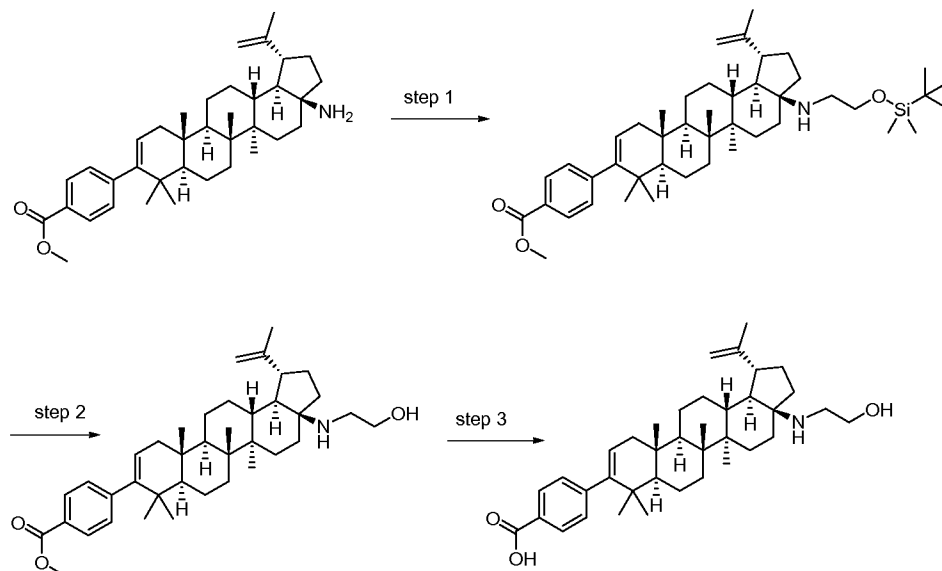
20 cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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 2-chloro-*N*-isopropylacetamide as the alkylating reagent in Step 1. The product was isolated as a white solid (50 mg, 81%). LCMS: m/e 629.46 ($M+H$)⁺, 2.60 min (method 10). ¹H NMR (400 MHz, *Acetic acid d4*) δ ppm 7.99 (d, $J=8.53$ Hz, 2 H), 7.26 (d, $J=8.53$ Hz, 2 H), 5.34 (d, $J=4.77$ Hz, 1 H), 4.84 (s, 1 H), 4.72 (s, 1 H), 4.15 (d, $J=15.31$ Hz, 1 H), 4.06 (dt, $J=13.11, 6.62$ Hz, 1 H), 3.85 (d, $J=15.31$ Hz, 1 H), 3.07 – 2.77 (m, 1 H), 2.41 – 1.26 (m, 22 H), 1.74 (s, 3 H), 1.24 (s, 3 H), 1.16 (d, $J=6.53$ Hz, 6 H), 1.10 (s, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 151

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butyldimethylsilyloxy)ethylamino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 5 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, 0.552 mmol) in DCE (4 mL) was added (*tert*-butyldimethylsilyloxy)acetaldehyde (131 mL, 0.690 mmol) and titanium(IV) isopropoxide (0.202 mL, 0.690 mmol). The mixture was stirred at rt for 45 minutes and sodium triacetoxyborohydride (234 mg, 1.103 mmol) was added. The mixture
- 10 was stirred at rt for 23 h and an additional 0.1 mL of (*tert*-butyldimethylsilyloxy)acetaldehyde and an additional 150 mg of sodium triacetoxyborohydride were added. The mixture was stirred at rt for an additional 22 h, then was diluted with 15 mL of sat. NaHCO₃ and was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried with Na₂SO₄,
- 15 the drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by flash chromatography using a 0-10% EtOAc in hexanes gradient. The fractions containing the expected product were combined and were concentrated under reduced pressure to give the title compound (0.211 g, 0.301 mmol, 54.5% yield) as a clear yellow film.
- 20 The product was used in the next step with no additional purification. LCMS: m/e 702.7 (M+H)⁺, 2.35 min (method 2).

- Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 25 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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butyldimethylsilyloxy)ethylamino)-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-
- 30 cyclopenta[a]chrysen-9-yl)benzoate (0.211 g, 0.301 mmol) in THF (2 mL) was added TBAF (1M in THF) (0.601 mL, 0.601 mmol). The mixture was stirred at rt for 2.75 h then was diluted with water (10 mL) and was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with Na₂SO₄, the drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The

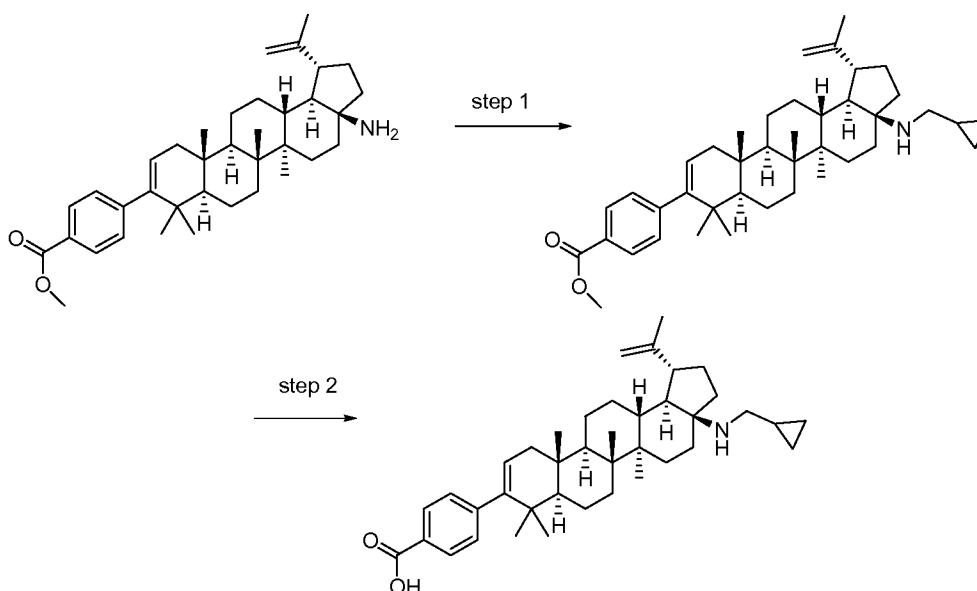
residue was adsorbed to silica gel and was purified by flash chromatography using a 0-25% EtOAc in hexanes gradient. The title compound (93.4 mg, 0.159 mmol, 52.9% yield), was isolated as a colorless film. LCMS: m/e 588.6 (M+H)⁺, 1.98 min (method 2). ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.91 (d, *J*=8.24 Hz, 2 H), 7.18 (d, *J*=8.24 Hz, 2 H), 5.27 (d, *J*=4.58 Hz, 1 H), 4.70 (d, *J*=1.83 Hz, 1 H), 4.59 (s, 1 H), 3.89 (s, 3 H), 3.54 - 3.64 (m, 2 H), 2.52 - 2.69 (m, 3 H), 2.09 (dd, *J*=17.09, 6.41 Hz, 1 H), 1.68 (s, 3 H), 1.07 (s, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.93 - 2.05 (m, 21 H), 0.91 (s, 3 H), 0.91 (s, 3 H).

10 Step 3. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-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, 0.060 mmol) in dioxane (1 mL) was added NaOH (1N) (0.298 mL, 0.298 mmol). The mixture was heated to 85 °C for 15 h then was cooled to rt. The mixture was diluted with MeOH and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give the title compound (25 mg, 0.041 mmol, 69.5% yield) as a white solid. LCMS: m/e 574.5 (M+H)⁺, 1.69 min (method 2). ¹H NMR (500 MHz, Acetic acid *d*4) δ ppm 8.04 (2 H, d, *J*=8.2 Hz), 7.30 (2 H, d, *J*=8.2 Hz), 5.37 (1 H, d, *J*=4.6 Hz), 4.86 (1 H, s), 4.75 (1 H, s), 3.95 - 4.11 (2 H, m), 3.25 - 3.43 (2 H, m), 2.90 - 2.98 (1 H, m), 1.77 (3 H, s), 1.21 (3 H, s), 1.14 (3 H, s), 1.09 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.97 - 2.32 (22 H, m).

Example 152

30 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(cyclopropylmethylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(cyclopropylmethylamino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (0.022 g, 0.040 mmol) in DCE (0.25 mL) was added cyclopropanecarbaldehyde (2.84 mg, 0.040 mmol) and titanium (IV) isopropoxide (0.015 mL, 0.051 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (0.017 g, 0.081 mmol) was added. After stirring the mixture for 16.75 h, the mixture was diluted with 3 mL of water and was filtered through a pad of celite, then was extracted with dichloromethane (3 x 4 mL). The combined organic layers were dried with Na₂SO₄. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give the title compound (0.024 g, 0.040 mmol, 99% yield) as a clear film. The crude product was used in the next step with no additional purification. LCMS: m/e 598.6 (M+H)⁺, 2.13 min (method 2).

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

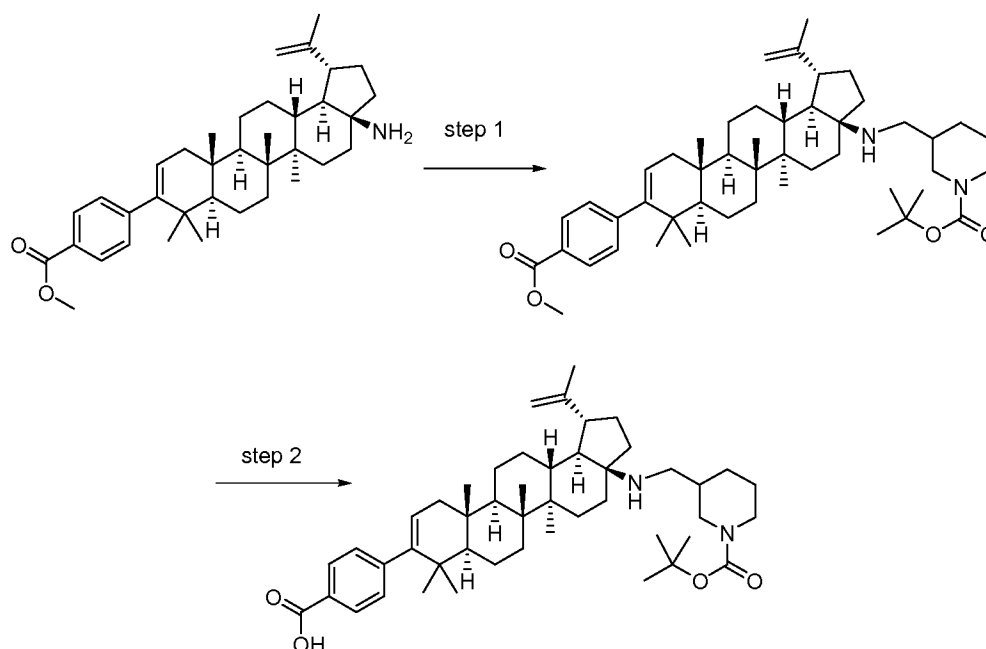
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

- To a cloudy mixture of methyl 4-
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(cyclopropylmethylamino)-
5 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 (0.024 g, 0.040 mmol) in 1,4-dioxane (1.5 mL) was added NaOH (1N) (0.5 mL, 0.5 mmol). The mixture was heated to 65 °C. After two hours, the mixture was cooled to rt and stirred at rt overnight. The mixture was
10 filtered through plug of glass wool and was purified by prep HPLC to afford the title compound (0.007 g, 10.79 µmol, 26.9% yield) as a white film. LCMS: m/e 584.6 (M+H)⁺, 1.83 min (method 2). ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.00 (2 H, d, J=8.0 Hz), 7.21 (2 H, d, J=8.0 Hz), 5.31 (1 H, d, J=5.0 Hz), 4.75 (1 H, d, J=1.5 Hz), 4.61 (1 H, s), 2.76 (1 H, td, J=10.9, 5.6 Hz), 2.62 (1 H, dd, J=11.2, 6.1
15 Hz), 2.23 (1 H, dd, J=11.5, 7.8 Hz), 1.97 - 2.16 (3 H, m), 1.82 - 1.95 (2 H, m), 1.70 (3 H, s), 1.16 (3 H, s), 1.01 (3 H, s), 1.00 (3 H, s), 0.96 (3 H, s), 0.95 (3 H, s), 0.80 - 1.77 (19 H, m), 0.48 - 0.58 (2 H, m), 0.09 - 0.24 (2 H, m).

Example 153

20

Preparation of *tert*-butyl 3-(((1R,3aS,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-ylamino)methyl)piperidine-1-carboxylate.



Step 1. Preparation of tert-butyl 3-(((1R,3aS,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-ylamino)methyl)piperidine-1-carboxylate.

To a solution of methyl 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (30 mg, 0.055 mmol) in DCE (0.5 mL) was added 3-formyl-piperidine-1-carboxylic acid *tert*-butyl ester (14.71 mg, 0.069 mmol) and titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. After stirring the mixture for 16.5 h, the mixture was diluted with 3 mL of sat. NaHCO₃ and was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried with Na₂SO₄. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by silica gel flash chromatography using a 0-10% EtOAc in hexanes gradient and a Thomson 12 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to afford the title compound (29 mg, 0.039 mmol, 70.9% yield) as an off-white film. The product was used in the

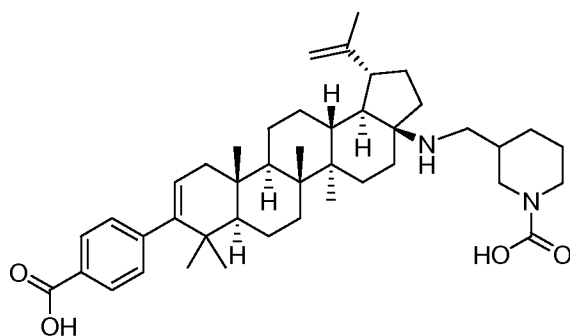
next step with no additional purification. LCMS: m/e 741.7 ($M+H$)⁺, 3.76 min (method 2).

Step 2. Preparation of *tert*-butyl 3-(((1R,3aS,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-ylamino)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 3-(((1R,3aS,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-ylamino)methyl)piperidine-1-carboxylate (0.029 g, 0.039 mmol) in dioxane (2 mL) was added NaOH (1N) (0.196 mL, 0.196 mmol). The mixture was heated to 85°C overnight. After heating the mixture for 22 h, it was cooled to rt, diluted with MeOH, and purified by prep HPLC to afford the title compound (24 mg, 0.031 mmol, 80% yield) as a clear, colorless film. LCMS: m/e 727.7 ($M+H$)⁺, 2.00 min (method 2). ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.98 (2 H, d, $J=7.9$ Hz), 7.21 (2 H, d, $J=7.9$ Hz), 5.29 (1 H, d, $J=5.5$ Hz), 4.70 (1 H, br. s.), 4.58 (1 H, br. s.), 3.83 - 4.22 (4 H, m), 2.46 - 2.85 (4 H, m), 2.29 (2 H, br. s.), 1.68 (3 H, s), 1.47 (9 H, d, $J=4.6$ Hz), 1.10 (3 H, d, $J=7.9$ Hz), 0.98 (6 H, br. s.), 0.93 (3 H, s), 0.92 (3 H, s), 0.77 - 2.15 (25 H, m).

Example 154

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidin-3-ylmethylamino)-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.

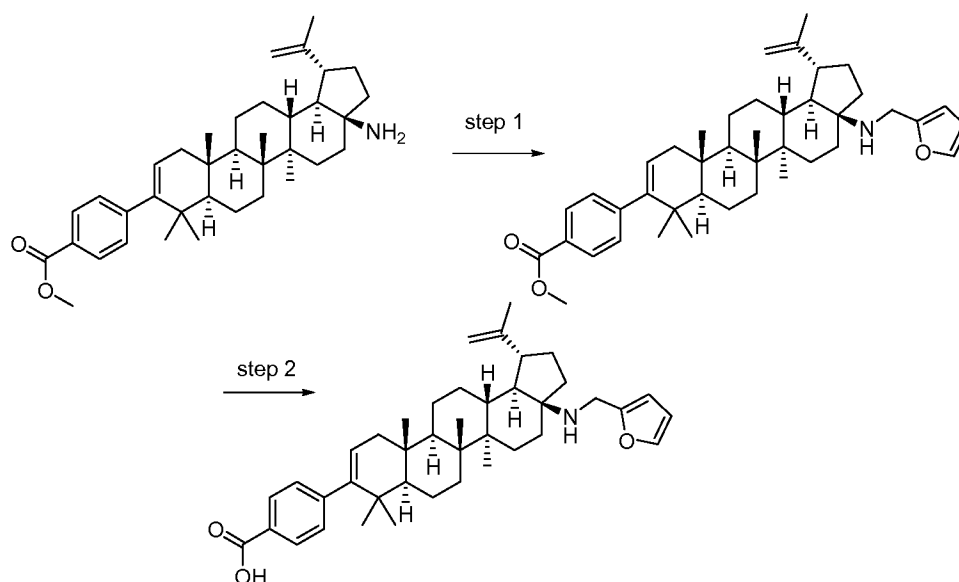


To a solution of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-
 5 butoxycarbonyl)piperidin-3-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-
 en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoic acid (0.019 g, 0.026 mmol) in DCM (1 mL) was
 added TFA (0.25 mL, 3.24 mmol). The mixture was stirred at rt for 1.75 h. Then, the
 mixture was concentrated under reduced pressure and purified by prep HPLC to give
 the title compound (14.2 mg, 0.021 mmol, 81% yield) as a white solid. LCMS: m/e
 10 627.6 (M+H)⁺, 1.50 min (method 2). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04
 (2 H, d, *J*=8.2 Hz), 7.30 (2 H, d, *J*=7.9 Hz), 5.37 (1 H, s), 4.85 (1 H, d, *J*=5.5 Hz),
 4.75 (1 H, s), 2.98 - 3.83 (6 H, m), 2.82 - 2.91 (1 H, m), 2.57 - 2.72 (1 H, m), 0.85 -
 2.33 (44 H, m).

15

Example 155

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-
 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-
 20 yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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-
 10 cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in DCE (0.5 mL) was added furfural (5.71 μ L, 0.069 mmol) and titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxborohydride (23.38 mg, 0.110 mmol) was added. After stirring the mixture for 16 h at rt an additional 5 μ L of furfural was added along with an additional 0.025 g of sodium
 15 triacetoxborohydride. After stirring the mixture overnight at rt, it was purified by passing through a plug of silica gel and washing with 0-25% EtOAc in hexanes. The fractions containing the product were combined and concentrated under reduced pressure to give the title compound (31 mg, 0.050 mmol, 90% yield) as a light-yellow film. The product was used in the next step with no additional purification. LCMS:
 20 m/e 625.6 (M+H)⁺, 3.08 min (method 2).

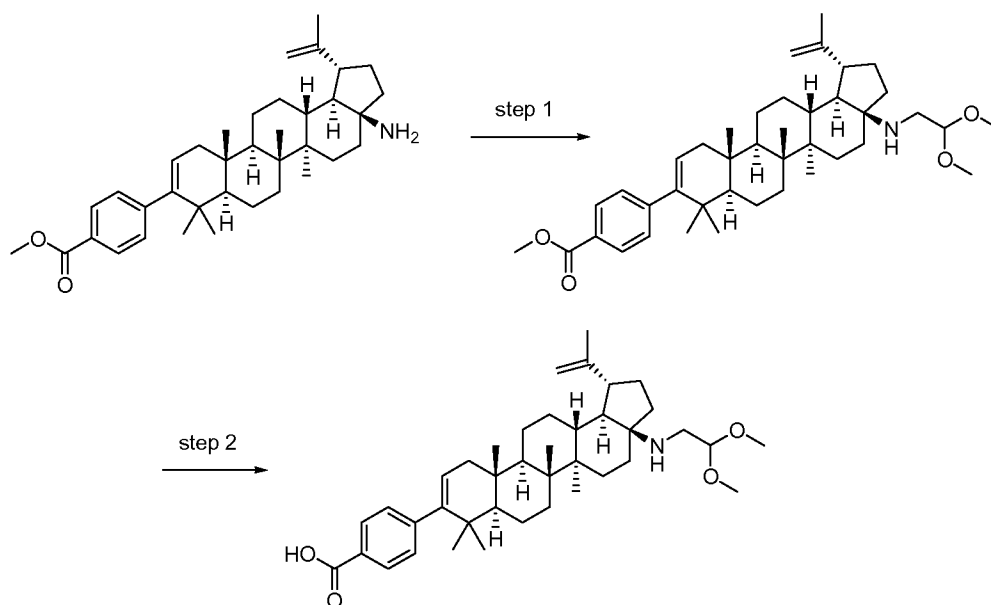
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 5 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 (31 mg, 0.050 mmol) in 1,4-dioxane (2 mL) was added 1N NaOH (0.248 mL, 0.248 mmol). The mixture was heated to 85 °C for 22 h then was cooled to rt. The crude product was purified by prep HPLC. The fractions
- 10 containing the expected product were combined and were concentrated under reduced pressure to afford the title compound (19.3 mg, 0.030 mmol, 60.5% yield) as a clear film. LCMS: m/e 610.69 (M+H)⁺, 2.35 min (method 2). ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.00 (d, J=7.78 Hz, 2 H), 7.37 (d, J=1.00 Hz, 1 H), 7.23 (d, J=7.78 Hz, 2 H), 6.33 (dd, J=3.14, 1.88 Hz, 1 H), 6.21 (d, J=2.76 Hz, 1 H), 5.53 (br. s., 1 H), 5.29 - 5.34 (m, 1 H), 4.72 (d, J=1.76 Hz, 1 H), 4.60 (s, 1 H), 3.67 (s, 2
- 15 H), 2.64 (td, J=10.85, 5.40 Hz, 1 H), 1.71 (s, 3 H), 1.10 - 1.15 (m, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.97 - 2.18 (m, 22 H), 0.96 (s, 6 H).

Example 156

- 20 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, HCl (0.9 g, 1.551 mmol) in DCM (Volume: 15 mL) was added glyoxal 1,1-dimethyl acetal solution (45% in MTBE) (0.498 mL, 1.939 mmol), acetic acid (0.178 mL, 3.10 mmol), and sodium triacetoxyborohydride (0.493 g, 2.326 mmol). The mixture was stirred at rt. After 4 h of stirring, an additional 0.5 mL of glyoxal 1,1-dimethyl acetal solution (45% in MTBE) was added along with an additional 0.5 g of sodium triacetoxyborohydride. After a total of 7 h of stirring, the mixture was diluted with 25 mL of sat. NaHCO₃ and was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with Na₂SO₄. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by flash chromatography using a 0-10% EtOAc in hexanes gradient to give the title compound (0.67 g, 1.060 mmol, 68.4% yield) as a white foam. LCMS: m/e 632.75 (M+H)⁺, 2.45 min (method 11).

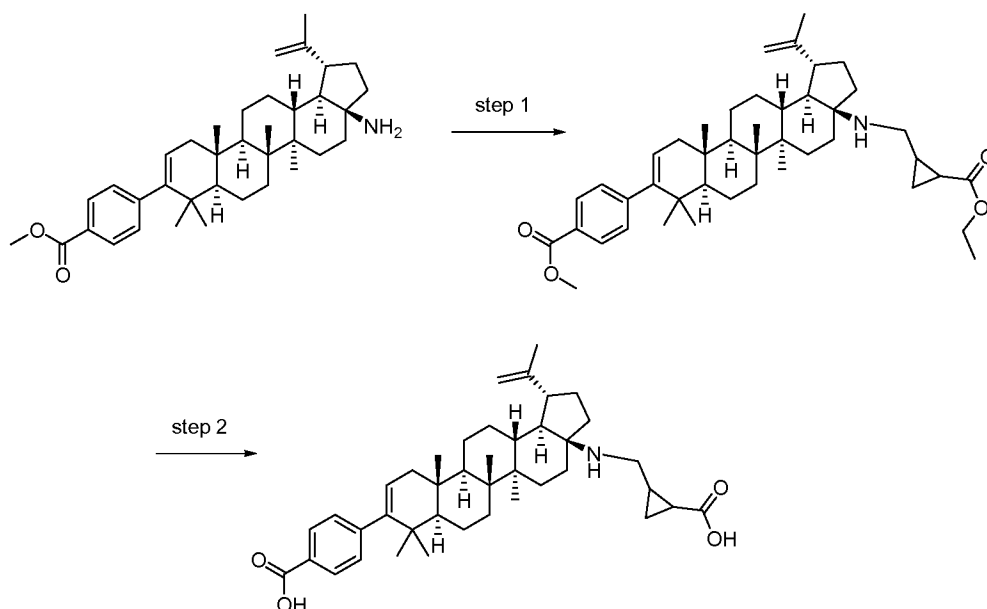
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

- 5 To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-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 (0.025 g, 0.040 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.198 mL, 0.198 mmol). The mixture was heated to 85 °C. After
10 6 h of heating, the mixture was cooled to rt, the reaction mixture was diluted with MeOH and was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give the title compound (17 mg, 0.026 mmol, 66.1% yield) as a clear film. LCMS: m/e 618.8 (M+H)⁺, 2.28 min (method 11). ¹H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.99 (d, J=7.93 Hz, 2 H), 7.20 (d, J=7.93 Hz, 2 H), 5.28 (d, J=4.88 Hz, 1 H), 5.12 (br. s., 1 H), 4.72 (s, 1 H), 4.58 (s, 1 H), 4.53 (t, J=5.49 Hz, 1 H), 3.44 (s, 3 H), 3.41 (s, 3 H), 2.64 - 2.74 (m, 2 H), 2.60 (dd, J=11.44, 6.56 Hz, 1 H), 1.97 - 2.13 (m, 2 H), 1.86 - 1.95 (m, 2 H), 1.81 (dd, J=12.51, 8.24 Hz, 1 H), 1.68 (s, 3 H), 1.11 (s, 3 H), 0.98 (s, 3 H), 0.97 (br. s., 3 H), 0.95 - 1.72 (m, 17 H), 0.93 (br. s., 6 H).

20

Example 157

- Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxycyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
25 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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((2-(ethoxycarbonyl)cyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-
 5 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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 amino-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-
 10 cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in DCE (0.5 mL) was
 added ethyl 2-formyl-1-cyclopropanecarboxylate (9.13 mL, 0.069 mmol) and
 titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for
 1 h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. After
 stirring the mixture for 16.25 h additional ethyl 2-formyl-1-cyclopropanecarboxylate
 15 (9.13 mL, 0.069 mmol) and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol)
 were added and the mixture was again stirred at rt for 24 h. The reaction mixture was
 loaded directly onto a silica gel column and was purified by flash chromatography
 using a 0-25% EtOAc in hexanes gradient. The fractions containing the expected
 product were combined and concentrated under reduced pressure to give methyl 4-
 20 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-
 (ethoxycarbonyl)cyclopropyl)methylamino)-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-

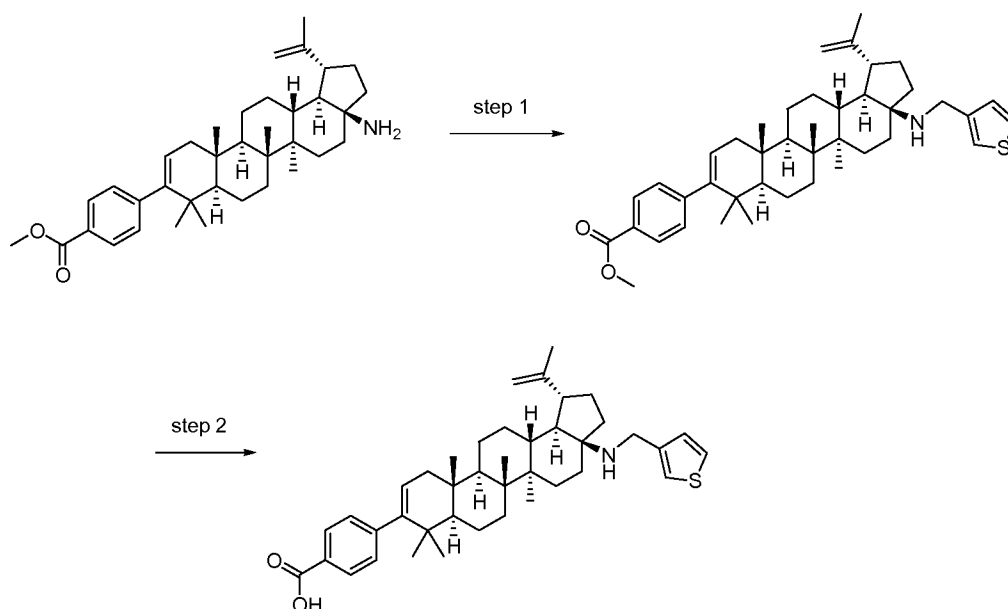
cyclopenta[a]chrysen-9-yl)benzoate (33 mg, 0.049 mmol, 89% yield). LCMS: m/e 670.8 (M+H)⁺, 2.47 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxycyclopropyl)methylamino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(ethoxycarbonyl)cyclopropyl)methylamino)-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 (33 mg, 0.049 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.246 mL, 0.246 mmol). The mixture was heated to 85 °C for 22 h then was cooled to rt. An additional 0.25 mL of 1N NaOH was added to the mixture and it was again heated to 85 °C. After stirring the mixture over the weekend, the reaction mixture was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure. ¹H NMR still showed impurities present, so the mixture was purified a second time by prep HPLC. The fractions containing the product were combined and concentrated under reduced pressure to give the title compound (8.3 mg, 0.012 mmol, 24.15% yield) as a white solid. LCMS: m/e 628.6 (M+H)⁺, 1.66 min (method 2).

Example 158

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-
 5 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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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-
 10 cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in DCE (0.5 mL) was added 3-thiophenecarboxaldehyde (7.73 mg, 0.069 mmol) and titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. The mixture was stirred for 18 h at rt. The reaction mixture was loaded directly onto a silica gel
 15 column and was purified by flash chromatography using a 0-25% EtOAc in hexanes gradient. The fractions containing the expected product were combined and were concentrated under reduced pressure to give the title compound (32 mg, 0.05 mmol, 91% yield). LCMS: m/e 640.6 (M+H)⁺, 2.13 min (method 2).

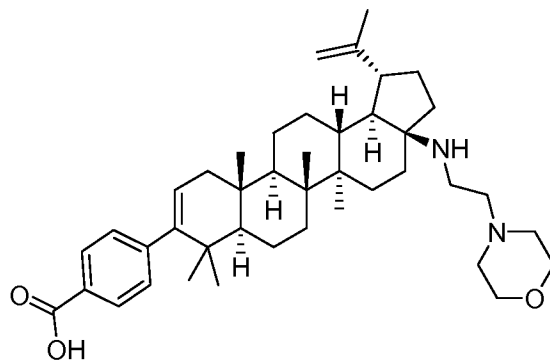
20 Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-

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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-
 5 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 (32 mg, 0.050 mmol) in dioxane (1 mL) was added NaOH (1N) (0.250 mL, 0.250 mmol). The mixture was heated to 85 °C for 15 h. The mixture was cooled to rt and was purified by prep HPLC to give the title compound (18 mg, 0.027 mmol, 53.5% yield) as a white solid. LCMS: m/e 626.5
 10 (M+H)⁺, 1.82 min (method 2). ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.00 (2 H, d, *J*=8.3 Hz), 7.30 (1 H, dd, *J*=4.8, 3.0 Hz), 7.24 (2 H, d, *J*=8.3 Hz), 7.20 (1 H, d, *J*=2.0 Hz), 7.12 (1 H, dd, *J*=5.0, 1.0 Hz), 5.30 - 5.34 (1 H, m), 4.72 (1 H, d, *J*=1.8 Hz), 4.61 (1 H, s), 2.61 (1 H, td, *J*=10.7, 5.4 Hz), 1.89 - 2.17 (5 H, m), 1.77 - 1.88 (1 H, m), 1.72 (3 H, s), 1.14 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.94 - 1.74 (18 H, m),
 15 0.96 (6 H, s).

Example 159

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-
 20 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.



25

The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-

10

Example 160

15

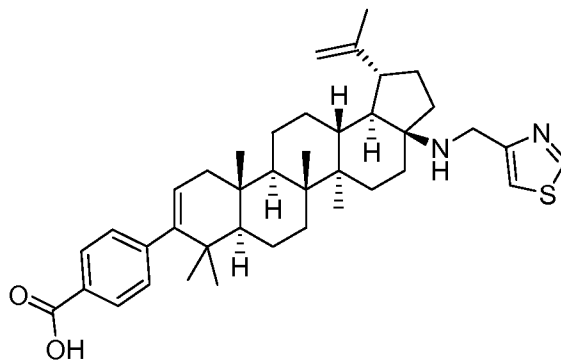


25

MeOD) δ ppm 7.95 (m, $J=8.3$ Hz, 2 H), 7.24 (m, $J=8.3$ Hz, 2 H), 5.32 (d, $J=4.8$ Hz, 1 H), 4.86 (s, 1 H), 4.73 (s, 1 H), 4.19 (t, $J=7.5$ Hz, 2 H), 4.02 - 4.14 (m, 6 H), 3.88 (t, $J=4.4$ Hz, 4 H), 3.70 - 3.84 (m, 4 H), 3.57 (br. s., 2 H), 3.42 - 3.51 (m, 2 H), 2.96 - 3.19 (m, 4 H), 2.79 (br. s., 1 H), 2.01 - 2.26 (m, 5 H), 1.87 - 1.96 (m, 1 H), 1.68 - 1.82 (m, 6 H), 1.46 - 1.68 (m, 8 H), 1.26 - 1.45 (m, 4 H), 1.17 - 1.26 (m, 4 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 161

10 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiazol-4-ylmethylamino)-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



15

The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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-(chloromethyl)thiazole as the alkylating agent in Step 1. MS: m/e 627.5 ($M+H$)⁺, 1.56 min (method 12). ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.95 (s, 3 H) 0.96 (s, 3 H) 1.01 (s, 3 H) 1.10 (s, 3 H) 1.21 (s, 3 H) 1.72 (s, 3 H) 0.89 - 1.83 (m, 16 H) 1.84 - 2.05 (m, 3 H) 2.07 - 2.22 (m, 1 H) 2.13 (dd, $J=17.07, 6.53$ Hz, 1 H) 2.22 - 2.32 (m, 1 H) 2.33 - 2.49 (m, 1 H) 4.24 (d, $J=14.05$ Hz, 1 H) 4.70 (s, 1 H) 4.72 (d, $J=13.55$ Hz, 1 H) 4.81 (s, 1 H)

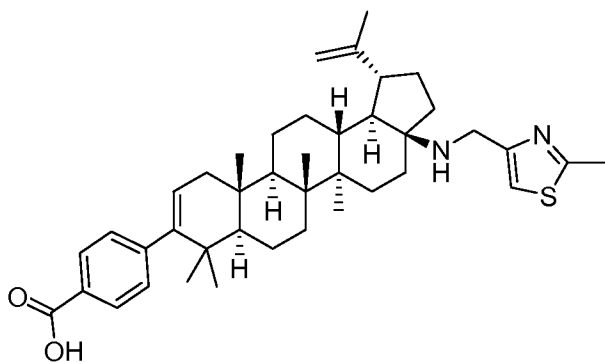
5.31 (dd, $J=6.02$, 1.51 Hz, 1 H) 7.24 (d, $J=8.28$ Hz, 2 H) 7.59 (s, 1 H) 8.00 (d, $J=8.28$ Hz, 2 H) 8.83 (s, 1 H).

Example 162

5

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-methylthiazol-4-yl)methylamino)-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.

10



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-

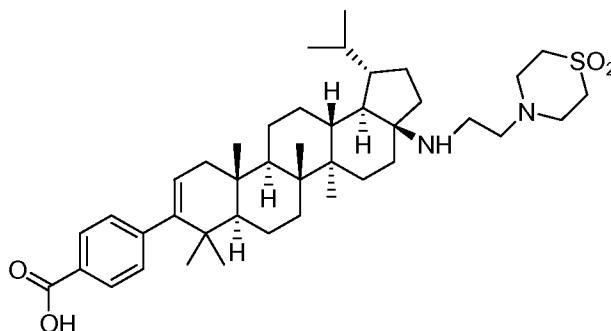
15 (dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(chloromethyl)-2-methylthiazole hydrochloride as the alkylating agent in Step 1. MS: m/e 641.5 ($M+H$)⁺, 1.56 min (method 12). ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.96 (s, 3 H) 0.97 (s, 3

20 H) 1.02 (s, 3 H) 1.10 (s, 3 H) 1.26 (s, 3 H) 1.71 (s, 3 H) 0.88 - 1.83 (m, 16 H) 1.89 - 2.04 (m, 3 H) 2.08 - 2.21 (m, 1 H) 2.14 (dd, $J=17.19$, 6.15 Hz, 1 H) 2.22 - 2.30 (m, 1 H) 2.33 - 2.45 (m, 1 H) 2.68 (s, 3 H) 4.09 (d, $J=13.05$ Hz, 1 H) 4.64 (d, $J=12.80$ Hz, 1 H) 4.69 (s, 1 H) 4.80 (s, 1 H) 5.32 (d, $J=4.52$ Hz, 1 H) 7.24 (d, $J=8.28$ Hz, 2 H) 7.28 (s, 1 H) 8.00 (d, $J=8.28$ Hz, 2 H).

25

Example 163

Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-
 5 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



10

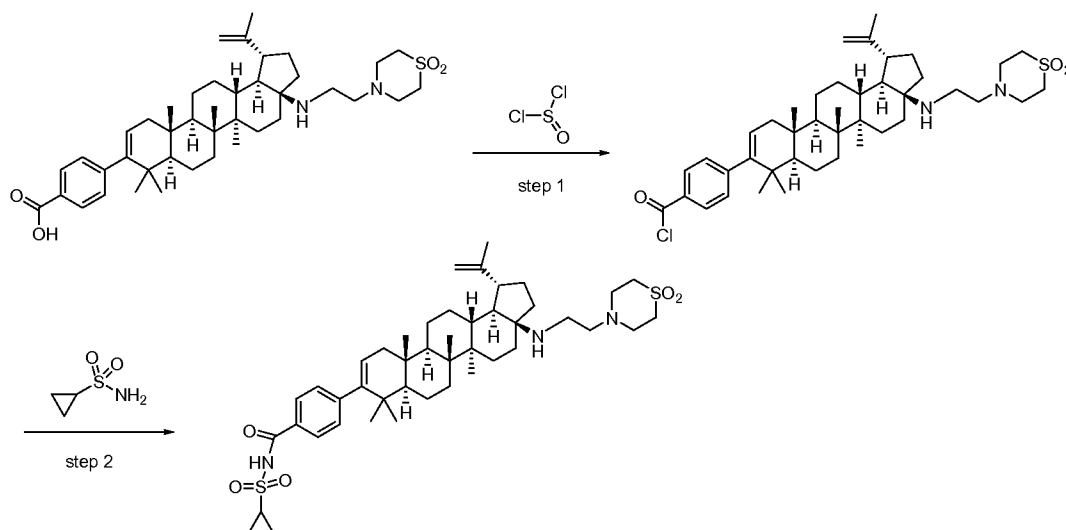
A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (100 mg, 0.145 mmol) and 10% Pd/C (90 mg,
 15 0.087 mmol) in methanol (5 mL) and ethyl acetate (5 mL) was loaded onto a PARR shaker reactor and treated with hydrogen for 25 hours under 40 psi at room temperature. The reaction mixture was filtered through a celite pad to remove the catalyst. The filtrate was purified by HPLC to provide the title compound as a white solid (5.6 mg, 28%). LCMS: m/e 693.46 (M+H)⁺, 2.46 min (method 10). ¹H NMR
 20 (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.2 Hz, 2 H), 7.31 (d, *J*=8.2 Hz, 2 H), 5.39 (d, *J*=4.6 Hz, 1 H), 3.50 - 3.36 (m, 1 H), 3.36 - 3.21 (m, 6 H), 3.21 - 2.98 (m, 5 H), 2.31 - 1.29 (m, 24 H), 1.29 (s, 3 H), 1.13 (s, 6 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (d, *J*=6.7 Hz, 3 H), 0.86 (d, *J*=6.7 Hz, 3 H).

25

Example 164

Preparation of *N*-(cyclopropylsulfonyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzamide.



5

Step 1. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoyl chloride.

A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoic acid (200 mg, 0.289 mmol) and thionyl chloride (0.211 mL, 2.89 mmol) in dichloroethane (5 mL) was refluxed for 30 h. The reaction mixture was concentrated under reduced pressure to provide the title compound as a white solid (150 mg, 73%). LCMS: m/e 705.46 ($M-Cl+OMe+H$)⁺, 3.0 min (method 10).

20

Step 2. Preparation of *N*-(cyclopropylsulfonyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzamide

25

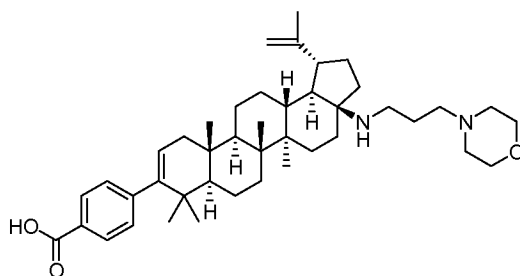
A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoyl chloride (30 mg, 0.042 mmol),
 5 cyclopropanesulfonamide (6.15 mg, 0.051 mmol), Hunig's Base (0.022 mL, 0.127 mmol) and DMAP (2.58 mg, 0.021 mmol) in dichloromethane (1 mL) was stirred for 16 h at room temperature. The crude reaction mixture was purified by prep HPLC to provide the title compound as a white solid (4 mg, 11%). LCMS: m/e 794.53 (M+H)⁺, 2.44 min (method 10). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 7.94 (d, J=8.5 Hz, 2 H), 7.32 (d, J=8.2 Hz, 2 H), 5.38 (d, J=4.6 Hz, 1 H), 4.84 (s, 1 H), 4.74 (s, 1 H), 3.56 - 3.39 (m, 1 H), 3.38 - 3.21 (m, 7 H), 3.21 - 3.11 (m, 3 H), 3.11 - 3.03 (m, 2 H), 3.01 - 2.89 (m, 1 H), 2.41 - 1.16 (m, 26 H), 1.76 (s, 3 H), 1.29 (s, 3 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

15

Example 165

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-morpholinopropylamino)-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



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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-chloropropyl)morpholine hydrochloride as the alkylating reagent in Step 1. The product was isolated as a white solid (60 mg, 48.1%). LCMS: m/e 657.55 (M+H)⁺, 2.24 min (method 13). ¹H NMR (400MHz, METHANOL-d₄) δ 7.95 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 5.33

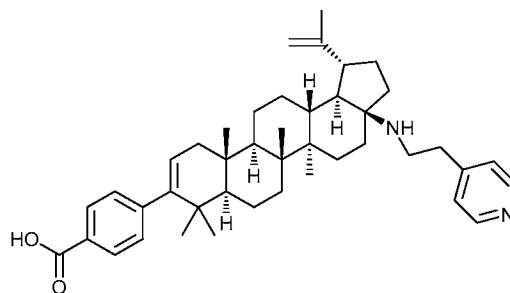
(d, $J=4.5$ Hz, 1H), 4.88 (s, 1H), 4.75 (s, 1H), 3.97 (m, 4H), 3.30 - 3.04 (m, 8H), 2.85 - 2.66 (m, 1H), 2.46 - 2.24 (m, 2H), 2.24 - 1.85 (m, 7H), 1.82 - 1.65 (m, 7H), 1.65 - 1.45 (m, 7H), 1.45 - 1.26 (m, 4H), 1.22 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

5

Example 166

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(pyridin-4-yl)ethyl)amino)-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

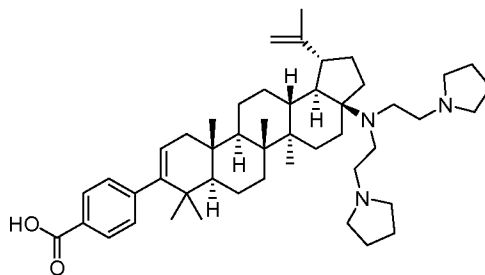
10



- 15 The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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-chloroethyl)pyridine as the
- 20 alkylating reagent in Step 1. The product was isolated as an off white solid (10 mg, 2.9%). LCMS: m/e 635.40 ($M+H$)⁺, 2.31 min (method 13). ¹H NMR (400MHz, METHANOL- d_4) δ 8.83 (d, $J=5.8$ Hz, 2H), 8.06 (d, $J=6.0$ Hz, 2H), 7.95 (d, $J=8.5$ Hz, 2H), 7.25 (d, $J=8.3$ Hz, 2H), 5.33 (d, $J=4.5$ Hz, 1H), 4.90 (s, 1H), 4.76 (s, 1H), 3.57 - 3.46 (m, 4H), 2.86 - 2.75 (m, 1H), 2.27 - 2.08 (m, 5H), 2.05 - 1.89 (m, 2H),
- 25 1.79 (s, 3H), 1.85 - 1.67 (m, 4H), 1.66 - 1.49 (m, 7H), 1.45 - 1.23 (m, 4H), 1.21 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H).

Example 167

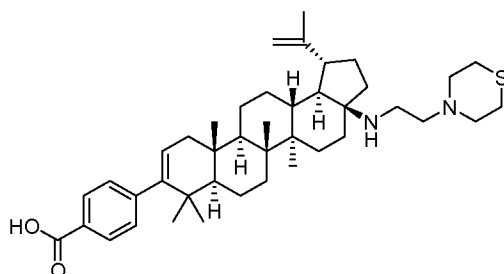
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(bis(2-
 (pyrrolidin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the
 synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-
 (dimethylamino)-2-oxoethylamino)-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 1-(2-chloroethyl)pyrrolidine
 hydrochloride as the alkylating reagent in Step 1. The product was isolated as a white
 solid (10 mg, 2.57%). LCMS: m/e 724.52 ($M+H$)⁺, 1.43 min (method 15). ¹H NMR
 (400MHz, METHANOL-d) δ 7.88 (d, $J=8.0$ Hz, 2H), 7.19 (d, $J=8.0$ Hz, 2H), 5.26 (d,
 $J=4.8$ Hz, 1H), 4.79 (s, 1H), 4.66 (s, 1H), 4.03 - 3.86 (m, 4H), 3.86 - 3.62 (m, 6H),
 3.59 - 3.29 (m, 6H), 2.81 - 2.58 (m, 1H), 2.26 (br. s., 4H), 2.21 - 1.88 (m, 9H), 1.82
 (d, $J=13.1$ Hz, 1H), 1.73 - 1.62 (m, 5H), 1.62 - 1.40 (m, 9H), 1.40 - 1.19 (m, 4H), 1.13
 (s, 4H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H),

Example 168

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-1-(prop-1-en-2-yl)-3a-(2-thiomorpholinoethylamino)-
 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

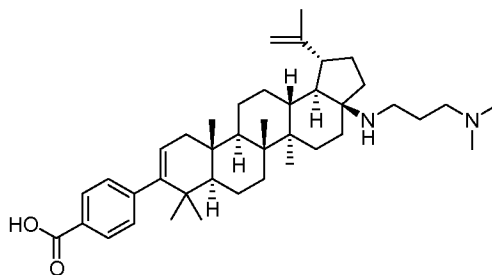


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(2-chloroethyl)thiomorpholine hydrochloride (prepared as describe in WO 2009058859) as the alkylating reagent in Step 1. The product was isolated as a white solid (3 mg, 0.85%). LCMS: m/e 659.37 ($M+H$)⁺, 2.38 min (method 13). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.00 (d, $J=8.3$ Hz, 2H), 7.21 (d, $J=8.5$ Hz, 2H), 5.32 - 5.19 (m, 1H), 4.77 (s, 1H), 4.65 (s, 1H),
 10 3.11 - 2.98 (m, 1H), 2.89 (m, 5H), 2.75 (m, 5H), 2.67 - 2.57 (m, 1H), 2.31 - 2.16 (m, 1H), 2.14 - 1.85 (m, 6H), 1.71 (s, 7H), 1.59 - 1.40 (m, 6H), 1.38 - 1.15 (m, 8H), 1.08 - 0.96 (m, 10H), 0.94 (s, 3H)

15

Example 169

**Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propylamino)-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-
 20 cyclopenta[a]chrysen-9-yl)benzoic acid**



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

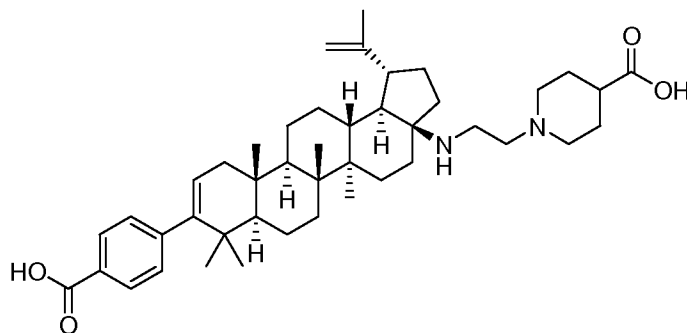
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 3-chloro-N,N-dimethylpropan-1-amine hydrochloride as the alkylating reagent in Step 1. The product was isolated as a white solid (3 mg, 0.85%). LCMS: m/e 615.75 (M+H)⁺, 2.24 min (method 13). ¹H NMR (400MHz, METHANOL-d₄) δ 7.95 (d, J=8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 5.34 (s, 1H), 4.89 (s, 1H), 4.75 (s, 1H), 3.58 - 3.36 (m, 2H), 3.26 (br. s., 8H), 2.78 (d, J=7.5 Hz, 1H), 2.51 - 2.26 (m, 3H), 2.26 - 1.97 (m, 7H), 1.92 (m, 1H), 1.78 (m, 6H), 1.63 - 1.47 (m, 6H), 1.45 - 1.36 (m, 2H), 1.32 - 1.18 (m, 5H), 1.14 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

10

Example 170

Preparation of 1-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-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)amino)ethyl)piperidine-4-carboxylic acid

15

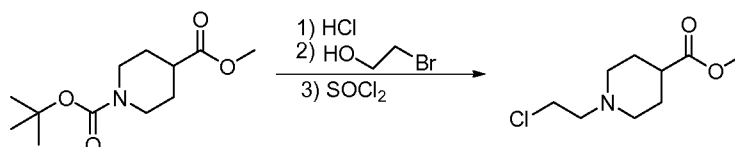


20 The title compound was prepared following the method described above for the synthesis of 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using methyl 1-(2-chloroethyl)piperidine-4-carboxylate hydrochloride (prepared as described below) as the alkylating reagent in Step 1. The product was isolated as a white solid (8 mg, 83%). LCMS: m/e 685.6 (M+H)⁺, 2.33 min (method 10). ¹H NMR (400MHz, METHANOL-d₄) δ 7.94 (d, J=8.3 Hz, 2H), 7.23 (d, J=8.3 Hz, 2H), 5.31 (d, J=4.5 Hz, 1H), 4.86 (s, 1H), 4.74 (s,

25

1H), 3.48 - 3.36 (m, 5H), 3.12 - 2.88 (m, 2H), 2.79 - 2.69 (m 1H), 2.68 - 2.60 (m, 1H), 2.24 - 2.11 (m, 4H), 2.11 - 2.00 (m, 4H), 1.97 - 1.81 (m, 3H), 1.77 (s, 3H), 1.81 - 1.71 (m, 2H), 1.70 - 1.46 (m, 10H), 1.45 - 1.27 (m, 4H), 1.21 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

5 **Preparation of methyl 1-(2-chloroethyl)piperidine-4-carboxylate**

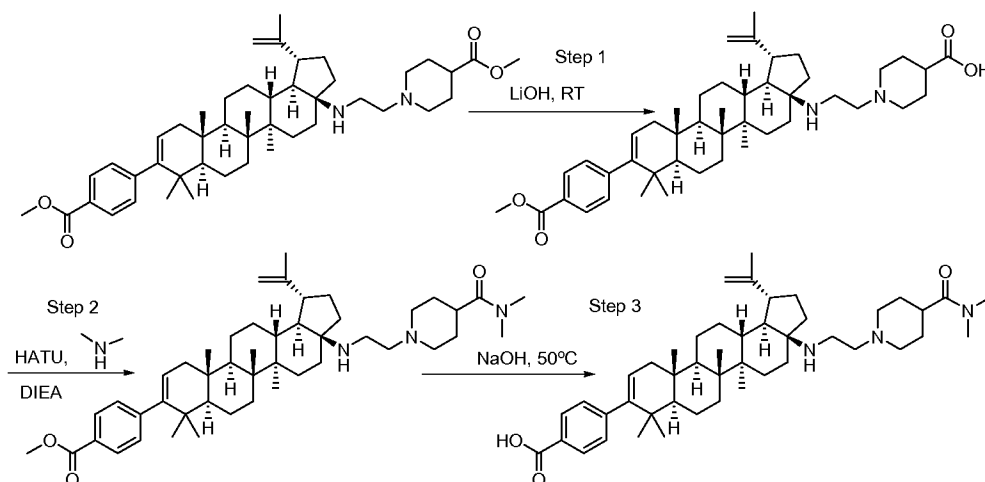


To a solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (5.4 g, 22.19
 10 mmol) in ether was added hydrogen chloride (27.7 mL, 111 mmol) in dioxane. The
 resulted clear solution was stirred for 4 hours. Bubbles and white precipitates were
 observed. Then the solvent was removed and dried in vacuo. The residue was
 suspended in acetonitrile (50 mL), and 2-bromoethanol (1.567 mL, 22.19 mmol) was
 added followed by powdered K₂CO₃ (14.72 g, 107 mmol). After the reaction mixture
 15 was refluxed for 18 hours, it was filtered and concentrated. The residue was
 redissolved in water (50.0 mL) and extracted with ethyl acetate (50.0 mL). The
 organic layer was dried over sodium sulfate. After filtration the solvent was removed
 in vacuo. The residue was dissolved in DCE (50.0 mL) before sulfurous dichloride
 (2.428 mL, 33.3 mmol) was added. The reaction mixture was reflux for 3 hours, then
 20 all volatile was removed in vacuo, the resulting solid was suspended in ether, then
 filtered and washed with ether (50.0 mL), resuspended in ethyl acetate and neutralized
 with sodium bicarbonate. The organic layer was collected and dried with sodium
 sulfate to afford methyl 1-(2-chloroethyl)piperidine-4-carboxylate (1 g, 4.86 mmol,
 21.91 % yield) as a brown oil. ¹H NMR (400MHz, CHLOROFORM-d) δ 3.70 (s,
 25 3H), 3.61 (t, *J*=7.0 Hz, 2H), 2.97 - 2.86 (m, 2H), 2.75 (t, *J*=7.2 Hz, 2H), 2.40 - 2.27
 (m, 1H), 2.19 (m, 2H), 2.01 - 1.88 (m, 2H), 1.87 - 1.72 (m, 2H).

Example 171

30 **Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(dimethylcarbamoyl)piperidin-1-yl)ethylamino)-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. To a solution of methyl 1-(2-(((1R,3aS,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-ylamino)ethyl)piperidine-4-carboxylate (40 mg) in dioxane (1 mL) was added lithium hydroxide (2.7 mg, 0.112 mmol) in water (1 mL). A white precipitate was observed. The mixture was stirred at 25°C for 3 hours. The desired product was observed at m/e 699.7 ($M+H$)⁺, 2.703 min, method 10. The reaction mixture was neutralized with 1 N HCl to pH~4 and diluted with methylene chloride (10 mL). The organic layer was then collected, dried over sodium sulfate and filtered. After removal of solvent, the crude product was obtained as an oil (40 mg, ~ 100%) which was used without further purification.

15

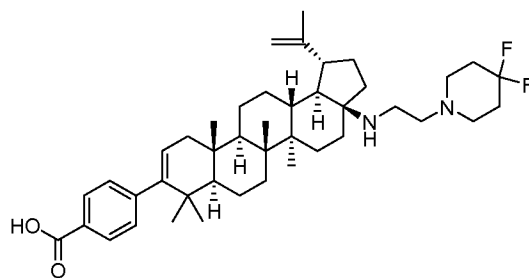
Step 2. To a solution of 1-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperidine-4-carboxylic acid (40 mg, 0.057 mmol) in CH₂Cl₂ (5 ml) at rt was added dimethylamine (7.6 mg, 0.17 mmol) and HATU (65 mg, 0.18 mmol) followed by DIEA (29 mg, 0.23 mmol). The mixture was stirred for 3 hour at rt. The resulted mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate. The crude product was obtained after removal of solvent as a white solid (40 mg, ~ 100%) which was used without further purification

25

- Step 3. 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(dimethylcarbamoyl)piperidin-1-yl)ethylamino)-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 was prepared following step 2 of the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-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. The product was isolated as a white solid (9 mg, 23.0%). LCMS: m/e 712.64 (M+H)⁺, 2.265 min (method 11). ¹H NMR (400MHz, METHANOL-d₄) δ 7.95 (d, J=8.3 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 5.33 (d, J=4.5 Hz, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 3.65 - 3.38 (m, 6H), 3.16 (s, 3H), 3.05 (m, 2H), 2.96 (s, 3H), 2.75 (m, 1H), 2.23 - 1.85 (m, 11H), 1.82 - 1.74 (m, 6H), 1.70 - 1.48 (m, 9H), 1.44 - 1.28 (m, 3H), 1.22 (m, 4H), 1.13 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H),

Example 172

- 20 **Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)ethylamino)-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**



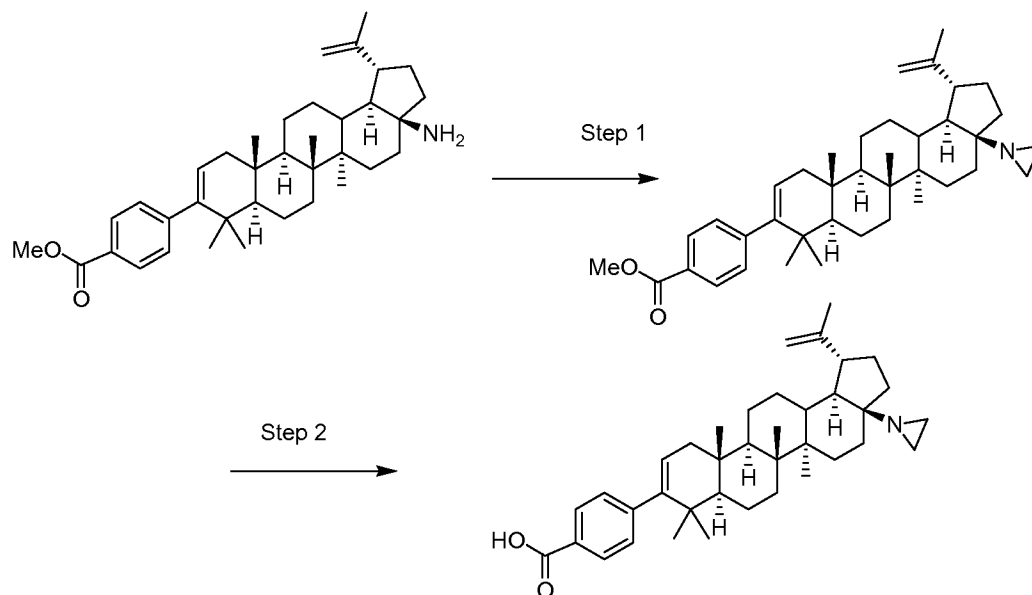
- 25 The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4,4-difluoropiperidine hydrochloride as

the alkylating reagent in Step 3. The product was isolated as a white solid (20 mg, 58.3%). LCMS: m/e 677.57 ($M+H$)⁺, 2.30 min (method 11). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.97 (d, $J=8.3$ Hz, 2H), 7.22 (d, $J=8.3$ Hz, 2H), 5.27 (d, $J=4.8$ Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.32 (m, 1H), 3.19 - 3.05 (m, 1H), 2.94 (m, 2H),
 5 2.83 - 2.68 (m, 5H), 2.36 - 2.21 (m, 2H), 2.15 - 1.90 (m, 7H), 1.74 (br. s., 7H), 1.60 - 1.45 (m, 6H), 1.44 - 1.30 (m, 4H), 1.26 (s, 2H), 1.18 (s, 3H), 1.06 (s, 4H) 0.98 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -98.39 (br. s., 2F)

Example 173

10

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-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



15

Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-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 methyl-
 20 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (0.160 g, 0.276 mmol) in a

mixture of acetonitrile (25 mL) and dichloroethane (5 mL) was added anhydrous potassium phosphate (0.25 gm, 1.18 mmol). The resulting suspension was heated to 120 °C under nitrogen in a thick-walled tube for 24 hours. The cooled reaction suspension was filtered through a short bed of silica gel (Type-H), washed with ethyl acetate (60 mL). The clear filtrate was concentrated in vacuo to give a white solid (0.150 g, 96%). LCMS: m/e 570.5 (M+H)⁺, 3.32 min (method 12, but modified to gradient over 3 minutes). ¹H NMR (400MHz, CHLOROFORM-d) δ 7.95 (d, J=8.3 Hz, 2H), 7.22 (d, J=8.5 Hz, 2H), 5.31 (dd, J=6.1, 1.6 Hz, 1H), 4.81 - 4.73 (m, 1H), 4.67 - 4.59 (m, 1H), 3.93 (s, 3H), 2.82 - 2.45 (m, 1H), 2.19 - 2.04 (m, 1H), 1.88 - 1.74 (m, 1H), 1.71 (s, 3H), 1.68 (br. s., 1H), 1.63 - 1.21 (m, 7H), 1.11 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.95 (s, 6H).

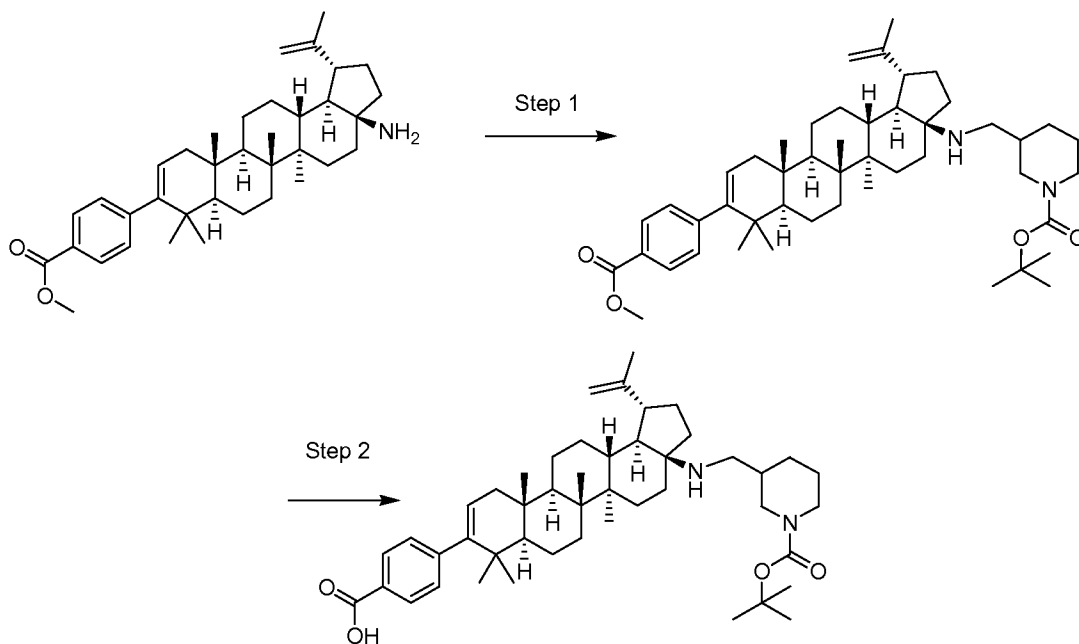
Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.150 g, 0.264 mmol) in a mixture of methanol (2 mL) and THF (6 mL) at rt was added a stock solution of lithium hydroxide (1.0 Molar, 2 mL, 2.0 mmol) forming a thick suspension. The mixture was kept at 50 °C under nitrogen for 60 hours. The reaction mixture was neutralized with HCl (0.5 Molar, 10 mL), the organic material was extracted into ethyl acetate (30 mL). While the 2-phase mixture was stirred at rt, a white precipitate slowly separated out. It was filtered to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-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 as a white solid (99 mg, 68 %). LCMS: m/e 592.5 (M+MeOH+Na)⁺, 3.03 min (method 12, but modified to gradient over 3 minutes). Selected ¹H NMR (400MHz, CHLOROFORM-d) δ 8.01 (d, J=8.3 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 5.28 (m, 1H), 4.94 (br. s, 1H), 4.73 (br. s, 1H), 1.74 (s, 3H), 1.20 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

30

Example 174

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(tert-butoxycarbonyl)piperidin-3-yl)methylamino)-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



Step 1. Preparation of tert-butyl 3-(((1R,3aS,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-ylamino)methyl)piperidine-1-carboxylate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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 (30 mg, 0.055 mmol) in dichloroethane (0.5 mL) was added 3-formyl-piperidine-1-carboxylic acid tert-butyl ester (14.71 mg, 0.069 mmol) and titanium (IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. The mixture was stirred at rt for 16.5h, then was diluted with 3 mL of sat.

NaHCO₃ and was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried with Na₂SO₄, were filtered and were concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by flash

chromatography using a 0-10% ethyl acetate in hexanes gradient and a Thomson 12g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give the title compound as an off-white foam. LCMS: m/e 741.7 (M+H)⁺, 3.76 min (method 2).

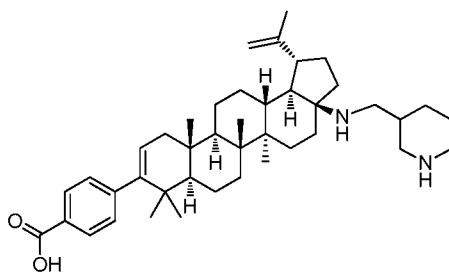
5

Step 2. To a solution of tert-butyl 3-(((1R,3aS,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-ylamino)methyl)piperidine-1-carboxylate (0.029 g, 0.039 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.196 mL, 0.196 mmol). The mixture was heated to 85°C for 22h, then was cooled to rt, was diluted with MeOH, and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(tert-butoxycarbonyl)piperidin-3-yl)methylamino)-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 (24 mg, 0.031 mmol, 56 % yield over 2 steps) as a clear, colorless film. LCMS: m/e 727.7 (M+H)⁺, 2.00 min (method 2). ¹H NMR (500 MHz, *Chloroform-d*) δppm 7.98 (d, *J*=7.93 Hz, 2 H), 7.21 (d, *J*=7.93 Hz, 2 H), 5.29 (d, *J*=5.49 Hz, 1 H), 4.70 (br. s., 1 H), 4.58 (br. s., 1 H), 3.82 - 4.51 (m, 5 H), 1.68 (s, 3 H), 1.47 (d, *J*=4.58 Hz, 9 H), 1.10 (d, *J*=7.93 Hz, 3 H), 0.98 (br. s., 6 H), 0.93 (s, 3 H), 0.92 (s, 3 H), 0.90 - 2.85 (m, 30 H).

25

Example 175

Preparation of 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidin-3-ylmethylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(tert-butoxycarbonyl)piperidin-3-yl)methylamino)-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 (0.019 g, 0.026 mmol) in dichloromethane (1 mL) was added TFA (0.25 mL, 3.24 mmol). The mixture was stirred at rt for 1.75h then was concentrated under reduced pressure. The residue was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give 4-

10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidin-3-ylmethylamino)-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 (14.2 mg, 0.021 mmol, 81 % yield) as a white solid. LCMS: m/e 627.6 (M+H)⁺, 1.50 min (method 2).

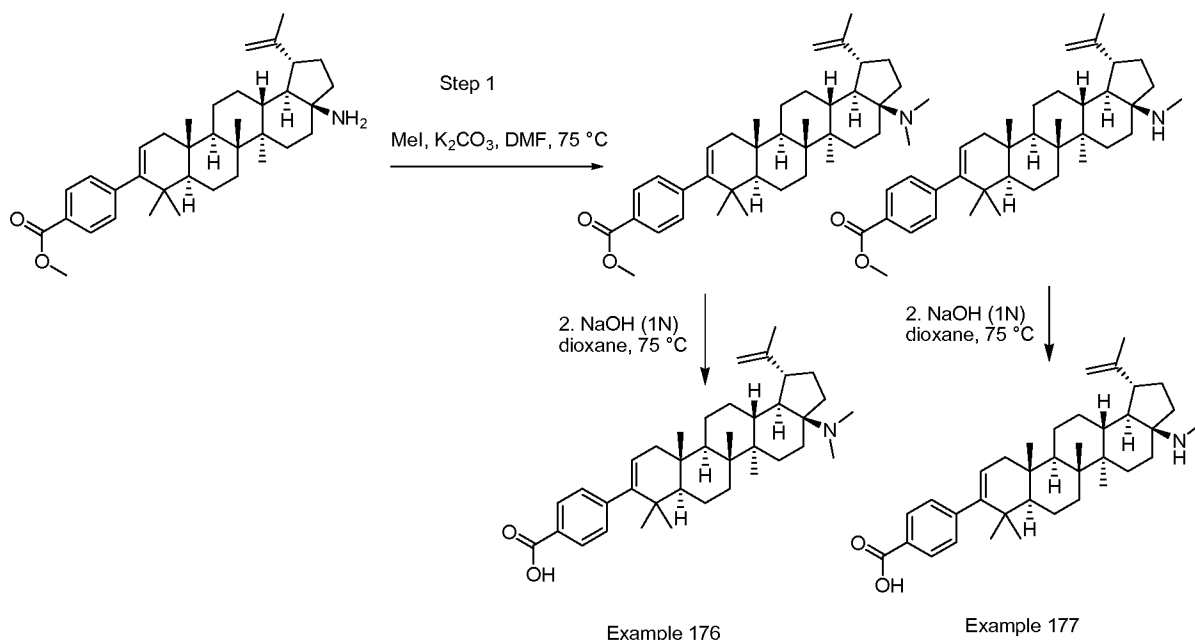
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Examples 176 and 177

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-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 and 4-

20 **((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-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**

25



- Step 1. To a sealable vial containing methyl 4-
- 5 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, HCl (1.0 g, 1.72 mmol) was added potassium carbonate (0.48 g, 3.45 mmol). The mixture was diluted with DMF (15 mL) and methyl iodide (323 mL, 3.45 mmol) was added. The vial was sealed and
- 10 the mixture was heated to 75 °C for 4 h then was cooled to rt. The vial was opened to the air and was stirred at rt overnight. The mixture was diluted with 20 mL of saturated aqueous sodium thiosulfate. Solids formed and were collected by filtration and were washed with water. The residue was purified by flash chromatography in silica gel using a 0-25% ethyl acetate in hexanes gradient with 0.1% ammonium
- 15 hydroxide added to the mixture. Two main isolates were recovered from the column. The less polar product, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-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 (0.247 g, 0.405 mmol, 23.5 % yield) was
- 20 recovered as a white foam. The more polar isolate, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-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 (0.5 g, 0.807 mmol, 46.8 % yield), was recovered as a white solid. LCMS of the less polar isolate: m/e 572.6 (M+H)⁺, 2.03 min (method 2). ¹H NMR (400MHz, *Chloroform-d*) δ = 7.96 - 7.92 (m, 2H), 7.23 - 7.19 (m, 2H), 5.31 - 5.29 (m, 1H), 4.71 (d, *J*=2.0 Hz, 1H), 4.61 (dd, *J*=2.3, 1.3 Hz, 1H), 3.92 (s, 3H), 2.86 (td, *J*=11.2, 6.1 Hz, 1H), 2.34 - 2.24 (m, 7H), 2.12 (dd, *J*=17.1, 6.5 Hz, 1H), 2.04 - 1.80 (m, 5H), 1.70 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 1.74 - 0.85 (m, 15H). LCMS of the more polar isolate: m/e 558.6 (M+H)⁺, 2.04 min (method 2). ¹H NMR (400MHz, *Chloroform-d*) δ = 7.93 (d, *J*=8.0 Hz, 2H), 7.20 (d, *J*=8.3 Hz, 2H), 5.30 (dd, *J*=6.1, 1.6 Hz, 1H), 4.72 (d, *J*=2.0 Hz, 1H), 4.59 (s, 1H), 3.92 (s, 3H), 2.60 (td, *J*=10.9, 5.8 Hz, 1H), 2.24 (s, 3H), 2.11 (dd, *J*=17.2, 6.1 Hz, 1H), 2.03 - 1.91 (m, 2H), 1.88 - 1.79 (m, 2H), 1.09 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 1.69 - 0.91 (m, 20H).

Step 2. The saponification of the isolates were carried out independently:

Example 176: Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-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, HCl. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-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 (88 mg, 0.158 mmol) in 1,4-dioxane (3 mL) was added NaOH (1M) (1 mL, 1.000 mmol). The mixture was heated to 75 °C for 17h then was cooled to rt and was acidified with 3 mL of 1N HCl. Solids formed upon standing and were collected by filtration and were washed with water. The solids were dissolved and were purified by flash chromatography using a 0-40% methanol in ethyl acetate gradient and a Thomson 25g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure then were redissolved in dichloromethane and methanol and were filtered through a plug of celite. The filtrate was concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-

(methylamino)-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, HCl (40 mg, 0.065 mmol, 41% yield) as a white solid. LCMS: m/e 544.5 (M+H)⁺, 1.79 min (method 2). ¹H NMR (500MHz,

5 *Acetic acid d₄*) δ = 8.01 (d, J=8.2 Hz, 2H), 7.27 (d, J=8.2 Hz, 2H), 5.34 (d, J=4.6 Hz, 1H), 4.84 (s, 1H), 4.71 (s, 1H), 2.85 - 2.77 (m, 1H), 2.74 (s, 3H), 1.75 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.24 - 0.95 (m, 22H).

Example 177: Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-

10 **3a-(dimethylamino)-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 suspension of methyl 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-5a,5b,8,8,11a-

15 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (100 mg, 0.164 mmol)

in 1,4-dioxane (3 mL) was added 1N NaOH (1 mL, 1.000 mmol) and the mixture was heated to 70 °C. After 3.75h the mixture was cooled to rt and was diluted with 2 mL of MeOH and then 1N HCl (6 mL) was added. The solids that formed were collected by filtration and were washed with water. The solids were dissolved in dioxane and

20 methanol and were purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-5a,5b,8,8,11a-

octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (45 mg, 0.077 mmol, 46.6

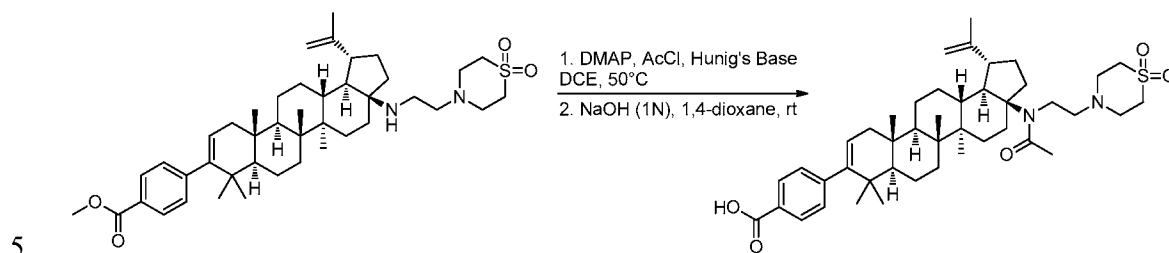
25 % yield) as a white solid. LCMS: m/e 558.3 (M+H)⁺, 2.28 min (method 11). ¹H

NMR (500 MHz, *Acetic acid d₄*) δ ppm 8.04 (2 H, d, J=8.2 Hz), 7.30 (2 H, d, J=8.2 Hz), 5.37 (1 H, d, J=4.9 Hz), 4.92 (1 H, s), 4.77 (1 H, s), 3.08 (7 H, br. s.), 1.80 (3 H, s), 1.22 (3 H, s), 1.18 (3 H, s), 1.09 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.98 - 2.46 (22 H, m).

30

Example 178

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropenyl-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)benzoate (0.05 g, 0.071 mmol) in dichloroethane (1 mL) and Hunig's base (0.062 mL, 0.355 mmol) was added acetyl chloride (0.020 mL, 0.284 mmol). The mixture was heated to 50 °C. After heating the mixture for 71.25h, the mixture was cooled to rt and was directly loaded onto a 12g Thomson silica gel column and was purified by Biotage flash chromatography using a 0-5% MeOH in dichloromethane gradient. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoate (40 mg, 0.054 mmol, 75%) as a clear, colorless film. LCMS: m/e 747.5 (M+H)⁺, 2.26 min (method 2).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoate (40 mg, 0.054 mmol) in 1,4-dioxane (1 mL) was

added NaOH (1N) (0.27 mL, 0.27 mmol). The mixture was stirred at rt for 16.5h then was purified directly by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-

thiomorpholinyl)ethyl)amino)-1-isopropenyl-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)benzoic acid (14 mg, 0.018 mmol, 33%) as a white solid.

LCMS: m/e 733.5 (M+H)⁺, 1.96 min (method 2). ¹H NMR (400MHz, *Chloroform-d*)

δ = 7.99 (d, J =7.8 Hz, 2H), 7.22 (d, J =7.8 Hz, 2H), 5.23 (d, J =4.0 Hz, 1H), 4.85 (br.

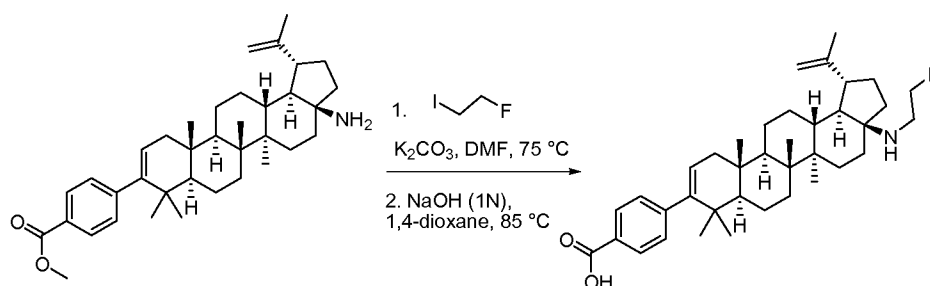
s., 1H), 4.68 (br. s., 1H), 3.65 (br. s., 2H), 3.40 - 3.04 (m, 8H), 2.97 - 2.46 (m, 4H),

1.74 (s, 3H), 1.27 (s, 3H), 1.03 - 0.98 (m, 9H), 0.95 (br. s., 3H), 0.89 (br. s., 3H), 2.20

- 0.71 (m, 21H).

Example 179

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-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 sealable vial containing methyl 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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-

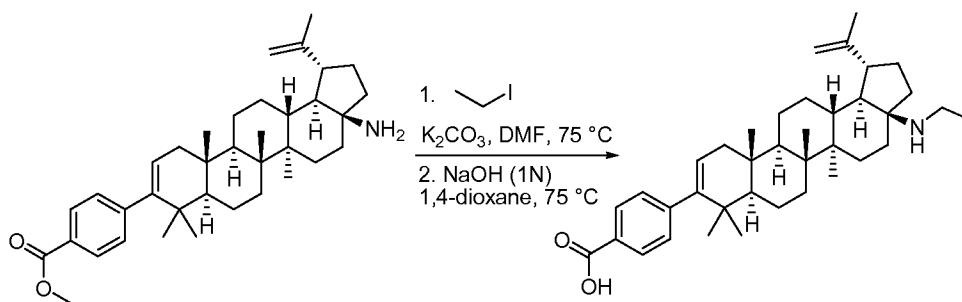
octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with DMF (1 mL) and 1-fluoro-2-iodoethane (0.032 mL, 0.388 mmol) was added. The vial was sealed and the mixture was heated to 75 °C for 26h then was cooled to rt. The mixture was diluted with 3 mL of sat. aq. sodium thiosulfate and was extracted with dichloromethane (3 x 4 mL). The combined organic layers were dried with sodium sulfate, the drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in toluene and was loaded onto a Thomson 12g silica gel column and was purified by Biotage flash chromatography using a 0-15% ethyl acetate in hexanes gradient with 0.1% ammonium hydroxide added to the mixture. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-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 (0.062 g, 0.103 mmol, 80 % yield) as a white foam. LCMS: m/e 590.6 (M+H)⁺, 2.05 min (method 2). ¹H NMR (400 MHz, *chloroform-d*) 7.94 (d, *J*=8.53 Hz, 2H), 7.21 (d, *J*=8.28 Hz, 2H), 5.30 (dd, *J*=2.01, 6.27 Hz, 1H), 4.73 (d, *J*=2.01 Hz, 1H), 4.58-4.64 (m, 2H), 4.50 (t, *J*=4.89 Hz, 1H), 3.92 (s, 3H), 2.57-2.85 (m, 3H), 2.11 (dd, *J*=6.40, 17.19 Hz, 1H), 1.71 (s, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 0.86-2.05 (m, 21H).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-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 (0.059 g, 0.100 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.5 mL, 0.500 mmol). The mixture was heated to 85 °C for 15.25h, was cooled to rt, then was diluted with methanol and 1,4-dioxane and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-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 (29.2 mg, 0.048 mmol, 48.2 % yield) as a

white solid. LCMS: m/e 576.6 (M+H)⁺, 1.74 min (method 2). ¹H NMR (400 MHz, *Acetic acid d*₄) δ 7.99 (d, $J=8.53$ Hz, 2H), 7.26 (d, $J=8.28$ Hz, 2H), 5.33 (d, $J=4.77$ Hz, 1H), 4.73-4.99 (m, 3H), 4.70 (s, 1H), 3.41-3.73 (m, 2H), 2.83-2.94 (m, 1H), 1.73 (s, 3H), 1.19 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.82-2.27 (m, 22H).

Example 180

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-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.

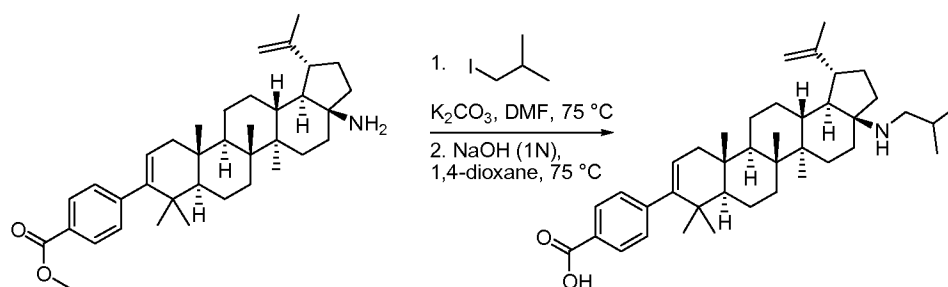
To a sealable vial containing methyl 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with DMF (1 mL) and iodoethane (0.031 mL, 0.388 mmol) was added. The mixture was heated to 75 °C for 23h then was cooled to rt. The mixture was diluted with 1mL of DMF and additional iodoethane (0.031 mL, 0.388 mmol) was added to the mixture. The vial was sealed and heated to 75 °C for 24h, then was concentrated under reduced pressure and was adsorbed to silica gel. The mixture was purified by flash

- chromatography using a 0-25% EtOAc in hexanes gradient with 0.1% ammonium hydroxide added and a Thomson 12g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-
- 5 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 (0.039 g, 0.065 mmol, 50.1 % yield) as a white foam. LCMS: m/e 572.7 (M+H)⁺, 2.16 min (method 2). ¹H NMR (400 MHz, *chloroform-d*) δ 7.94 (d, $J=8.28$ Hz, 2H), 7.21 (d, $J=8.53$ Hz, 2H), 5.30 (dd, $J=1.76$, 6.27 Hz, 1H), 4.73 (d, $J=2.51$ Hz, 1H), 4.59 (dd, $J=1.38$, 2.38 Hz, 1H), 3.92 (s, 3H), 2.62 (dt, $J=5.40$, 10.98 Hz, 1H), 2.38-2.53 (m, 2H), 2.11 (dd, $J=6.40$, 17.19 Hz, 1H), 1.88-2.03 (m, 3H), 1.83 (dd, $J=7.78$, 12.55 Hz, 1H), 1.70 (s, 3H), 1.10 (s, 3H), 1.11 (t, $J=7.03$ Hz, 3H), 0.99 (s, 6H), 0.94 (s, 3H), 0.94 (s, 3H), 0.91-1.74 (m, 17H).
- 15 Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-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 (0.037 g, 0.065 mmol) in 1,4-dioxane (1.5 mL) was added NaOH (1N) (0.3 mL, 0.300 mmol). The mixture was heated to 75 °C for
- 20 18.5h then was cooled to rt, was diluted with methanol and 1,4-dioxane, was filtered through a plug of glass wool and was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 25 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 (0.023 g, 0.040 mmol, 61.2 % yield) as a white solid. LCMS: m/e 558.6 (M+H)⁺, 1.77 min (method 2). ¹H NMR (400 MHz, *Acetic acid d4*) δ 7.99 (d, $J=8.53$ Hz, 2H), 7.26 (d, $J=8.28$ Hz, 2H), 5.33 (d, $J=4.52$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 3.23 (q, $J=7.11$ Hz, 2H), 2.81-2.92 (m, 1H), 1.72 (s, 3H), 1.40 (t, $J=7.15$ Hz, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H),
- 30 0.96 (s, 3H), 0.83-2.24 (m, 22H).

Example 181

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

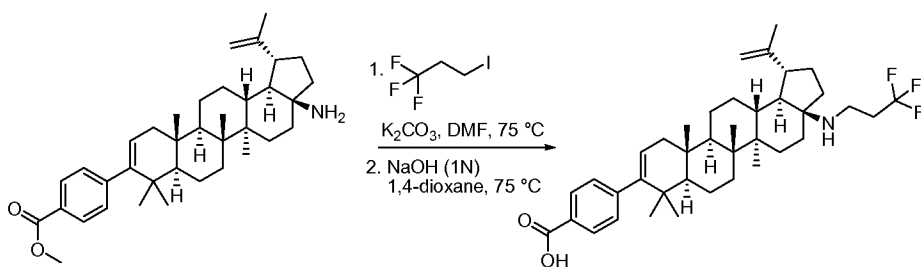
- 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate. To a sealable vial containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with DMF (1 mL) and isobutyl iodide (0.045 mL, 0.388 mmol) was added. The vial was sealed and the mixture was heated to 75 °C for 23h, then the mixture was cooled to rt. LC/MS showed formation of the expected product, but starting material still remained. To the mixture was added additional isobutyl iodide (0.045 mL, 0.388 mmol) and the vial was sealed and heated to 75 °C for 48h. The mixture was cooled to rt then was diluted with 5 mL of water. The solids that formed were collected by filtration then were washed with water to give the expected product, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-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 (53 mg, 0.075 mmol, 58.1 % yield) as a light-yellow solid. The crude product was used in the next step with no additional purification. LCMS: m/e 600.6 (M+H)⁺, 2.14 min (method 2).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-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 (52 mg, 0.087 mmol) in 1,4-dioxane (1.5 mL) was added NaOH (1N) (0.3 mL, 0.300 mmol). The mixture was heated to 75 °C for 67h then was cooled to rt. The mixture was diluted with 1,4-dioxane and methanol, was filtered through a plug of glass wool, and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-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 (25.2 mg, 0.041 mmol, 47.1 % yield) as a white solid. LCMS: m/e 586.6 (M+H)⁺, 1.85 min (method 2). ¹H NMR (400 MHz, *Acetic acid d₄*) δ 8.00 (d, *J*=8.28 Hz, 2H), 7.26 (d, *J*=8.28 Hz, 2H), 5.33 (d, *J*=4.52 Hz, 1H), 4.81 (s, 1H), 4.69 (s, 1H), 3.15 (dd, *J*=5.02, 12.05 Hz, 1H), 2.88-2.98 (m, 1H), 2.78 (dd, *J*=9.03, 11.80 Hz, 1H), 1.72 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.09 (d, *J*=6.78 Hz, 3H), 1.06 (s, 3H), 1.01 (d, *J*=6.78 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.83-2.31 (m, 23H).

20

Example 182

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-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.

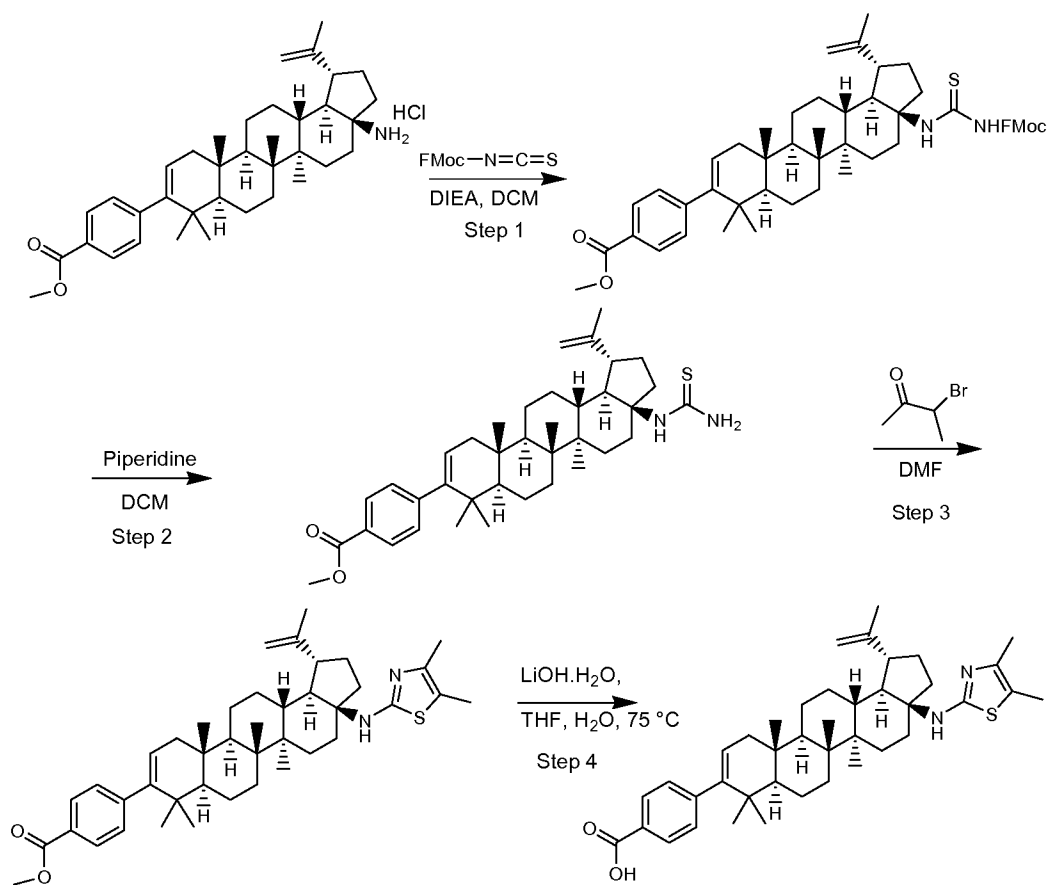
- 5 To a sealable vial containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with
- 10 DMF (1 mL) and 1-iodo-3,3,3-trifluoropropane (0.045 mL, 0.388 mmol) was added. The vial was sealed and the mixture was heated to 75 °C for 23h then was cooled to rt. LC/MS showed a mixture of starting material and product. An additional 0.045 mL of 1-Iodo-3,3,3-trifluoropropane was added and the mixture and was heated to 75 °C for 48h then was cooled to rt. LC/MS showed further progression, but the reaction
- 15 was still not complete. An additional 0.045 mL of 1-iodo-3,3,3-trifluoropropane was added and the mixture was heated to 75 °C for 71h, then was cooled to rt and was concentrated under reduced pressure. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 0-15% EtOAc in hexanes gradient with 0.1% ammonium hydroxide added to the mixture and a Thomson 12g silica gel
- 20 column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-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 (0.032 g, 0.044 mmol, 34.1 % yield) as a white
- 25 foam. LCMS: m/e 640.6 (M+H)⁺, 2.15 min (method 2). ¹H NMR (500 MHz, *chloroform-d*) δ 7.92 (d, *J*=8.24 Hz, 2H), 7.19 (d, *J*=8.24 Hz, 2H), 5.28 (dd, *J*=1.53, 6.10 Hz, 1H), 4.70 (d, *J*=1.83 Hz, 1H), 4.59 (s, 1H), 3.90 (s, 3H), 2.60-2.73 (m, 2H), 2.56 (dt, *J*=5.34, 10.91 Hz, 1H), 2.21-2.32 (m, 2H), 2.09 (dd, *J*=6.41, 17.09 Hz, 1H),
- 30 1.68 (s, 3H), 1.07 (s, 3H), 0.98 (s, 6H), 0.92 (s, 3H), 0.92 (br. s., 3H), 0.84-2.01 (m, 21H).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-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 (0.032 g, 0.050 mmol) in 1,4-dioxane (1 mL) was
5 added NaOH (1N) (0.2 mL, 0.200 mmol). The mixture was heated to 75 °C for 22.5h then was cooled to rt. The mixture was diluted with methanol, was filtered through a plug of glass wool and was purified by Prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-
10 en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-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 (0.022 g, 0.033 mmol, 66.8 % yield) as a white solid. LCMS: m/e 626.6 (M+H)⁺, 1.87 min (method 2). ¹H NMR (400 MHz, *Acetic acid d*₄) δ7.99 (d, *J*=8.28 Hz, 2H), 7.25 (d, *J*=8.28 Hz, 2H), 5.33 (d, *J*=4.77 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.36-3.51 (m, 2H), 2.81-2.97 (m, 3H), 2.12-2.28 (m, 4H), 1.72 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.82-2.11 (m, 18H).

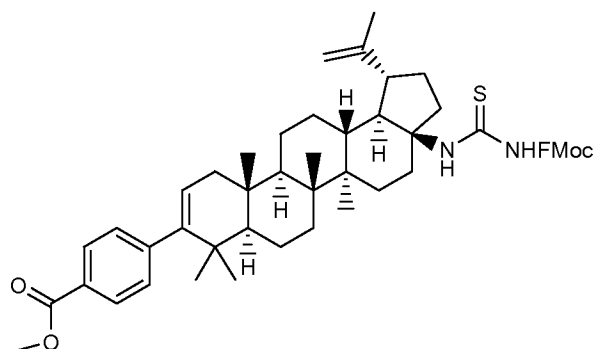
Example 183

20

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-
 5 (((9H-fluoren-9-yl)methoxy)carbonyl)thioureido)-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.



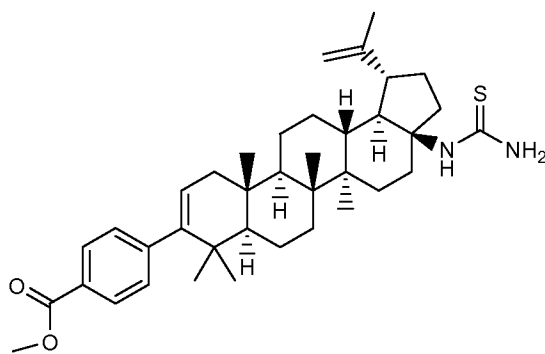
10

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 amino-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, HCl (2 g, 3.45 mmol) in DCM (50 mL) was added. *N,N*-diisopropylethylamine (3.00 mL, 17.23 mmol) and Fmoc-isothioisocyanate (1.939 g, 6.89 mmol). The reaction mixture was stirred at rt. After 5 3h, the reaction was washed with 0.1 N HCl (50 mL). The aqueous layer was extracted with DCM (50 mL). The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated to about 30 mL of DCM and treated with MeOH (100 mL). The mixture was concentrated to remove all DCM until approximately 50 mL of MeOH remained. The resulting yellow precipitate was 10 filtered and washed with MeOH. The solid product was saved and the liquid filtrate was concentrated to effect more precipitation. The resulting solid was isolated by filtration and washed with MeOH. The combined solid product was dried in a 50 °C vacuum oven to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-yl)methoxy)carbonyl)thioureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-15 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 (2.52 g, 3.05 mmol, 89 % yield) as a yellow solid. ¹H NMR (500MHz, *CHLOROFORM-d*) δ 9.84 (s, 1 H), 8.00 (s, 1 H), 7.95 (d, *J* = 8.2 Hz, 2 H), 7.82 (d, *J* = 7.6 Hz, 2 H), 7.64 (t, *J* = 8.2 Hz, 2 H), 7.49 - 7.44 (m, 2 H), 7.38 (tt, *J* = 1.5, 7.4 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 5.33 - 5.27 (m, 1 H), 4.79 20 (s, 1 H), 4.67 (s, 1 H), 4.58 - 4.53 (m, 2 H), 4.29 (t, *J* = 6.9 Hz, 1 H), 3.93 (s, 3 H), 3.39 (d, *J* = 13.7 Hz, 1 H), 3.23 (dd, *J* = 8.2, 12.8 Hz, 1 H), 2.50 (dt, *J* = 5.3, 10.8 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.98 - 1.88 (m, 1 H), 1.87 - 1.77 (m, 3 H), 1.74 (s, 3 H), 1.70 (d, *J* = 17.4 Hz, 1 H), 1.54 - 1.42 (m, 8 H), 1.41 - 1.29 (m, 3 H), 1.24 (d, *J* = 10.4 Hz, 1 H), 1.19 - 1.10 (m, 2 H), 1.05 (s, 3 H), 1.00 (s, 6 H), 0.94 (s, 6 H).

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Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-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.

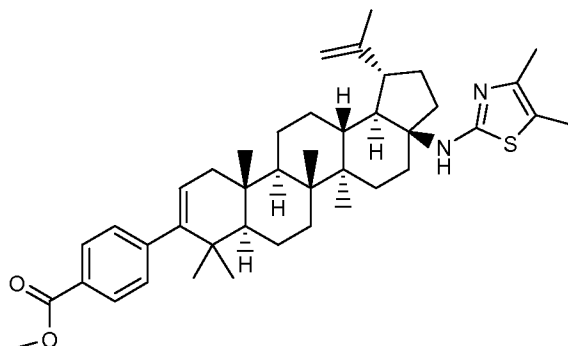


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-yl)methoxy)carbonyl)thioureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (2.51 g, 3.04 mmol) in DCM (30 mL) was added piperidine (1.502 mL, 15.21 mmol). The resulting brown reaction mixture was stirred at rt for 5 h. The reaction was concentrated and triturated with MeOH to give white solid product and fulvene adduct. This material was then re-dissolved in hot DCM and allowed to cool to rt. The resulting white precipitate was filtered and washed with cold DCM. The liquid filtrate was concentrated and more white precipitate was filtered. The combined white solid product was dried in a vacuum oven. The liquid filtrate was concentrated and loaded onto a column of SiO₂ (90 g) and eluted with DCM (1L) to remove top spot by-product then the desired product was eluted with 97:3 DCM:MeOH. After drying in a vacuum oven all solid product was combined to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-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 (1.7 g, 2.82 mmol, 93 % yield) as a white solid.

LCMS: m/e 603.5 (M+H)⁺, 2.51 min (method 1). ¹H NMR (500MHz, CHLOROFORM-*d*) δ 7.94 (d, J = 7.9 Hz, 2 H), 7.28 (s, 1 H), 7.21 (d, J = 7.9 Hz, 2 H), 6.07 (br. s., 1 H), 5.94 (br. s., 1 H), 5.34 - 5.28 (m, 2 H), 4.78 (s, 1 H), 4.68 (br. s., 1 H), 3.92 (s, 3 H), 2.64 - 2.55 (m, 1 H), 2.17 - 2.02 (m, 2 H), 1.85 - 1.74 (m, 3 H), 1.71 (s, 3 H), 1.67 (br. s., 1 H), 1.60 - 1.38 (m, 10 H), 1.35 - 1.35 (m, 1 H), 1.27 - 1.17 (m, 2 H), 1.13 (s, 4 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H), 0.91 - 0.90 (m, 1 H). ¹³C NMR (126MHz, CHLOROFORM-*d*) δ 182.0, 167.4, 148.8, 148.4, 146.4, 130.2, 128.6, 128.0, 124.0, 111.0, 66.8, 53.5, 53.0, 52.1, 50.3,

49.5, 46.8, 42.0, 41.8, 40.6, 37.9, 37.6, 36.4, 34.2, 33.5, 29.7, 29.5, 29.5, 27.6, 25.1, 21.3, 21.1, 19.8, 19.4, 16.5, 15.9, 14.6.

Step 3. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-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.



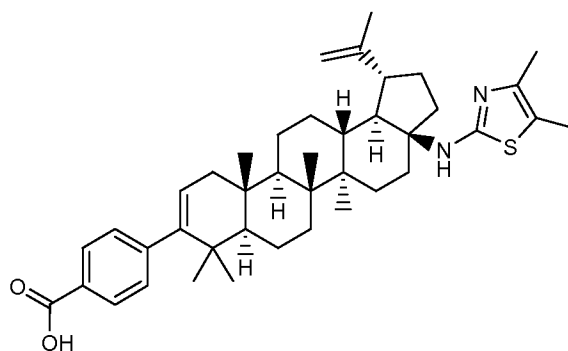
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To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (150 mg, 0.249 mmol) in DMF (5 mL) was added *N,N*-diisopropylethylamine (0.173 mL, 0.995 mmol) and 3-bromobutan-2-one (56.4 mg, 0.373 mmol). The reaction mixture was stirred at rt. After 18 h, the reaction mixture was poured into a separatory funnel containing H₂O (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated to white solid. The material was redissolved in DCM (5 mL) and MeOH was added to effect precipitation. The mixture was concentrated to remove most of DCM and the resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-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 (121 mg, 0.175 mmol, 70.5 % yield) as a white solid. LCMS: *m/e* 655.3 (M+H)⁺, 2.72 min (method 2). ¹H NMR (500MHz ,

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CHLOROFORM-d) δ 7.95 (d, $J = 8.2$ Hz, 2 H), 7.21 (d, $J = 8.2$ Hz, 2 H), 5.31 (d, $J = 4.6$ Hz, 1 H), 4.76 (br. s., 1 H), 4.65 (s, 1 H), 3.93 (s, 3 H), 2.43 (d, $J = 10.4$ Hz, 1 H), 2.21 (s, 3 H), 2.15 (s, 3 H), 2.11 (d, $J = 6.7$ Hz, 1 H), 2.07 - 1.96 (m, 1 H), 1.80 - 1.65 (m, 6 H), 1.57 - 1.36 (m, 8 H), 1.35 - 1.27 (m, 2 H), 1.23 (d, $J = 10.1$ Hz, 1 H), 1.17 - 1.11 (m, 1 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 6 H).

Step 4. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-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, TFA.



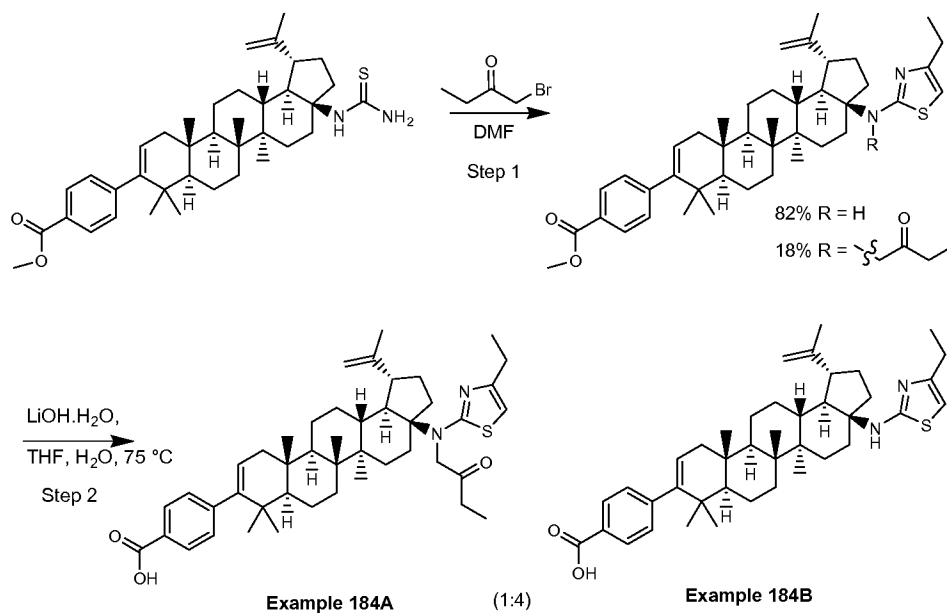
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (107 mg, 0.163 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (20.57 mg, 0.490 mmol) in water (1.000 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) into reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-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, TFA (58.3 mg, 0.073 mmol, 44.4 % yield) as a white solid. LCMS: m/e 641.3 ($M+H$)⁺, 2.51 min (method 2). ¹H NMR (500MHz, *CHLOROFORM-d*) δ 10.10 (s, 1 H), 8.02 (d, $J = 8.2$ Hz, 2 H), 7.25 (d, $J = 8.2$ Hz, 2 H), 5.33 (d, $J = 4.6$ Hz, 1 H), 4.84 (s, 1 H), 4.69 (s, 1 H), 2.97 (dt, $J = 5.2$,

11.0 Hz, 1 H), 2.48 (d, $J = 13.7$ Hz, 1 H), 2.32 - 2.25 (m, 2 H), 2.23 (s, 3 H), 2.20 (s, 3 H), 2.16 (dd, $J = 6.4, 17.1$ Hz, 1 H), 2.03 - 1.89 (m, 1 H), 1.89 - 1.79 (m, 2 H), 1.74 (s, 3 H), 1.71 (br. s., 1 H), 1.60 - 1.34 (m, 11 H), 1.26 - 1.19 (m, 1 H), 1.12 (d, $J = 13.4$ Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ 171.0, 164.9, 149.8, 148.9, 146.2, 132.4, 130.3, 129.2, 127.0, 124.4, 117.7, 111.4, 110.7, 68.1, 53.1, 50.3, 49.8, 45.4, 41.9, 40.8, 37.6, 36.5, 36.4, 33.8, 33.1, 29.6, 27.3, 25.3, 21.2, 19.9, 19.6, 16.5, 15.7, 14.5, 11.4, 10.8.

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Examples 184A and 184B

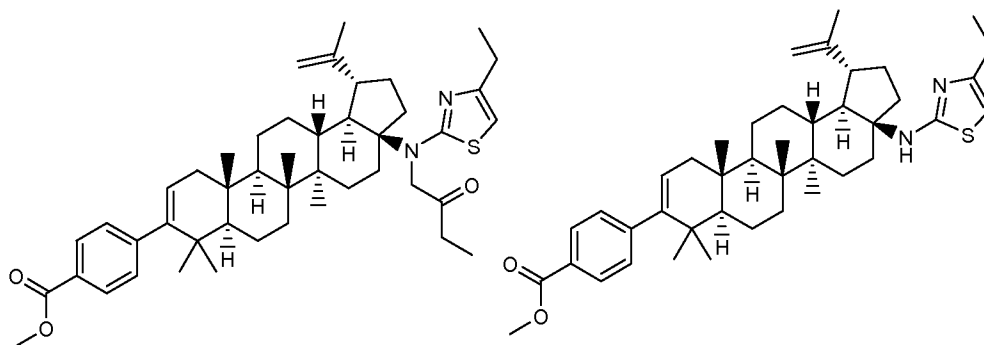
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[*a*]chrysen-9-yl)benzoic acid and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(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



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Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-

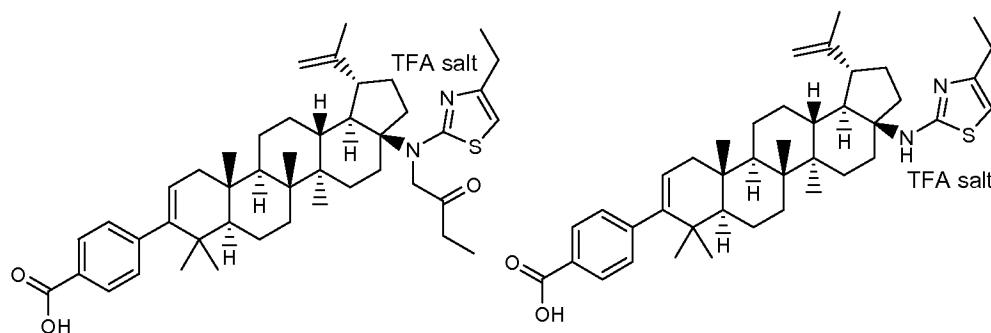
- yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



- To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
- 10 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-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 (158 mg, 0.262 mmol) in DMF (3 mL) was added *N,N*-diisopropylethylamine (0.183 mL, 1.048 mmol) and 1-bromobutan-2-one (0.042 mL, 0.393 mmol). The reaction mixture was stirred at rt. After 16 h, the reaction
- 15 mixture was poured into H₂O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated. The crude material was dissolved in DCM and treated with MeOH to effect precipitation. The mixture was concentrated to remove all DCM and the resulting white precipitate was filtered and washed with MeOH. The product was dried in a vacuum oven to give a
- 20 mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-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 and methyl 4-
- ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-
- 25 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 as a white solid in quantitative yield (173 mg, 0.264 mmol). LC/MS: *m/e* 725.4 (M+H)⁺, 2.70 min and *m/e* 655.3 (M+H)⁺, 2.95 min

(method 9), respectively. Reversed phased analytical HPLC showed ratio of major product with $rt = 23.45$ min (m/e 655.3 ($M+H$)⁺) to minor product with $rt = 26.86$ min (m/e 725.4 ($M+H$)⁺) of 82%:18% (using analytical HPLC method 1).

- 5 Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-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, TFA and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-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, TFA.



- 15 To a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-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 and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-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 in THF (3 mL) was added a solution of Li . H O . H₂O (32.7 mg, 0.779 mmol) in water (1.50 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) into reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-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, TFA.

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, TFA (22.3 mg, 0.027 mmol, 10.31 % yield) and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

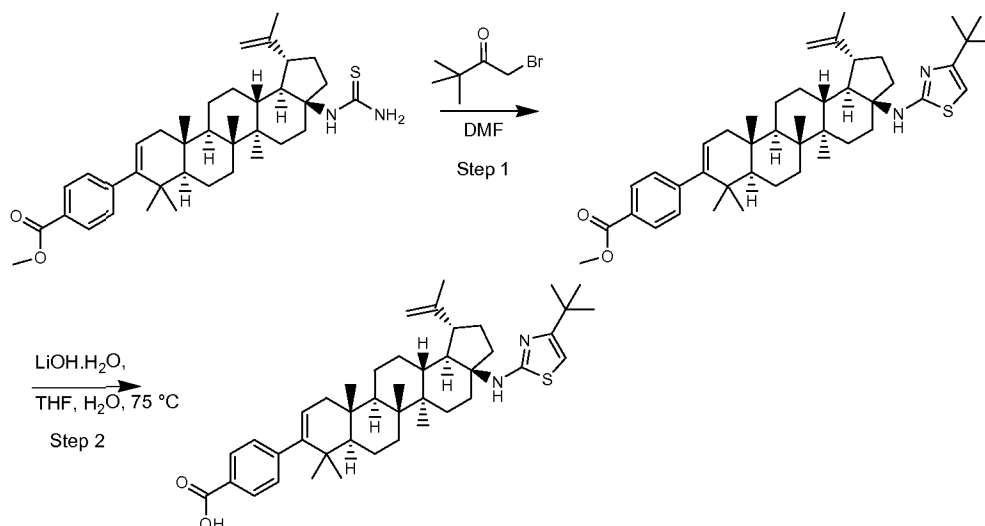
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (91.7 mg, 0.118 mmol, 45.4 % yield) both as a white solid.

Example 184A: LC/MS: m/e 711.4 (M+H)⁺, 2.45 min (method 11), ¹H NMR (500MHz, CHLOROFORM-d) δ 8.14 (br. s., 1 H), 7.97 (d, J = 7.9 Hz, 2 H), 7.21 (d, J = 8.2 Hz, 2 H), 6.56 - 6.45 (m, 1 H), 6.32 (s, 1 H), 5.26 (d, J = 5.2 Hz, 1 H), 5.16 (d, J = 19.5 Hz, 1 H), 4.84 (s, 1 H), 4.67 (br. s., 1 H), 3.11 - 2.98 (m, 1 H), 2.89 - 2.77 (m, 1 H), 2.73 - 2.61 (m, 2 H), 2.54 - 2.47 (m, 1 H), 2.43 (dd, J = 7.6, 16.2 Hz, 1 H), 2.30 - 2.22 (m, 1 H), 2.21 - 2.11 (m, 1 H), 2.11 - 1.98 (m, 2 H), 1.95 - 1.87 (m, 1 H), 1.71 (s, 3 H), 1.63 (d, J = 16.2 Hz, 2 H), 1.51 (d, J = 11.0 Hz, 2 H), 1.48 - 1.37 (m, 6 H), 1.34 - 1.25 (m, 6 H), 1.23 - 1.19 (m, 1 H), 1.16 (t, J = 7.2 Hz, 3 H), 1.11 (d, J = 10.7 Hz, 1 H), 1.00 (br. s., 3 H), 0.99 (br. s., 3 H), 0.96 (br. s., 6 H), 0.95 (br. s., 2 H). ¹³C NMR (126MHz, CHLOROFORM-d) δ 203.2, 170.6, 167.1, 149.4, 148.6, 146.3, 144.3, 130.2, 129.1, 127.8, 124.6, 110.7, 100.1, 70.7, 55.2, 53.0, 50.7, 49.4, 44.3, 42.0, 41.8, 40.7, 37.6, 36.4, 36.3, 33.6, 33.4, 32.7, 29.6, 29.4, 27.3, 27.2, 25.2, 21.5, 21.2, 20.7, 19.8, 19.7, 16.5, 15.5, 14.5, 10.8, 7.3.

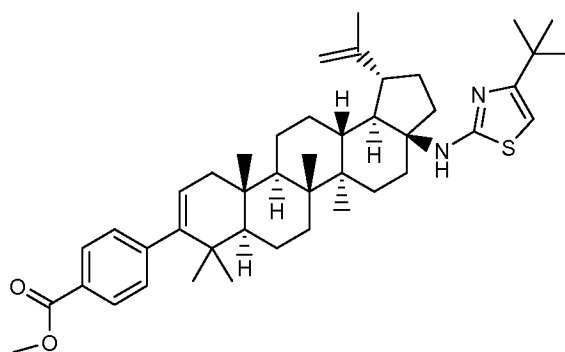
Example 184B: LC/MS: m/e 641.3 (M+H)⁺, 2.51 min (method 11), ¹H NMR (500MHz, CHLOROFORM-d) δ 10.17 (s, 1 H), 8.02 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 8.2 Hz, 2 H), 6.07 (s, 1 H), 5.33 (d, J = 4.6 Hz, 1 H), 4.85 (s, 1 H), 4.70 (s, 1 H), 2.97 (dt, J = 5.0, 11.1 Hz, 1 H), 2.71 (dq, J = 0.9, 7.5 Hz, 2 H), 2.53 - 2.45 (m, 1 H), 2.32 (dd, J = 7.8, 13.0 Hz, 1 H), 2.26 (dt, J = 2.9, 12.1 Hz, 1 H), 2.16 (dd, J = 6.3, 17.2 Hz, 1 H), 2.05 - 1.92 (m, 1 H), 1.90 - 1.79 (m, 2 H), 1.74 (s, 3 H), 1.69 (d, J = 16.8 Hz, 1 H), 1.60 - 1.35 (m, 11 H), 1.30 (t, J = 7.6 Hz, 3 H), 1.23 (dd, J = 4.1, 9.6 Hz, 1 H), 1.13 (d, J = 13.1 Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H). ¹³C NMR (126MHz, CHLOROFORM-d) δ 171.5, 167.1, 163.3, 163.0, 149.8, 148.8, 146.2, 144.6, 130.3, 129.3, 127.1, 124.4, 117.5, 115.2, 110.8, 98.3, 68.3, 53.1, 50.3, 49.7, 45.4, 41.9, 40.8, 37.6, 36.5, 36.4, 33.8, 32.8, 29.6, 27.3, 27.1, 25.3, 21.7, 21.2, 19.8, 19.6, 16.5, 15.7, 14.5, 11.8.

Example 185

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 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 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 10 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 To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-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, 0.249 mmol) in DMF (3 mL) was added

N,N-diisopropylethylamine (0.217 mL, 1.244 mmol) and 1-bromopinacolone (0.056 mL, 0.373 mmol). The reaction mixture was stirred at rt overnight. After 18 h, the reaction mixture was poured into a separatory funnel containing H₂O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over

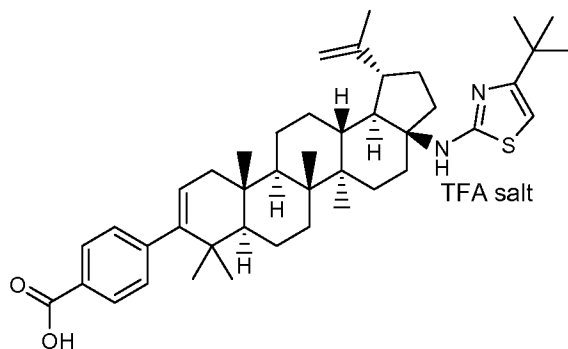
5 MgSO₄, filtered and concentrated to white solid. The material was redissolved in DCM (3 mL), MeOH wash added and concentrated to remove most of the DCM. The resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

10 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 (154.0 mg, 0.225 mmol, 91 % yield) as a white solid. LC/MS: m/e 683.4 (M+H)⁺, 2.88 min (method 11). ¹H NMR (500MHz, CHLOROFORM-*d*) δ 7.95 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 6.06 (s, 1 H), 5.31 (d, *J* = 4.6 Hz, 1 H), 4.88 (s, 1 H), 4.77 (s, 1 H), 4.66 (s, 1 H), 3.93 (s, 3 H),

15 2.72 (d, *J* = 13.7 Hz, 1 H), 2.68 - 2.62 (m, 1 H), 2.55 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.07 - 1.98 (m, 1 H), 1.92 - 1.83 (m, 1 H), 1.82 - 1.76 (m, 1 H), 1.74 (s, 3 H), 1.73 - 1.66 (m, 2 H), 1.61 (s, 1 H), 1.57 - 1.49 (m, 3 H), 1.49 - 1.40 (m, 4 H), 1.40 - 1.31 (m, 3 H), 1.29 (s, 9 H), 1.27 - 1.21 (m, 1 H), 1.18 - 1.12 (m, 1 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 6 H).

20

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-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, TFA.



25

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-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 (139 mg, 0.204 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (25.6 mg, 0.611 mmol) in water (1 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) into reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-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, TFA (49.3 mg, 0.059 mmol, 28.8 % yield) as a white solid. LC/MS: m/e 669.4 (M+H)⁺, 2.61 min (method 11). ¹H NMR (500MHz, *CHLOROFORM-d*) δ 8.02 (d, *J* = 7.9 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.05 (s, 1 H), 5.33 (d, *J* = 4.9 Hz, 1 H), 4.86 (s, 1 H), 4.70 (s, 1 H), 3.52 (s, 1 H), 3.03 (dt, *J* = 5.0, 10.9 Hz, 1 H), 2.54 (d, *J* = 14.0 Hz, 1 H), 2.34 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.31 – 2.22 (m, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.09 – 1.96 (m, 1 H), 1.92 – 1.80 (m, 2 H), 1.75 (s, 3 H), 1.69 (d, *J* = 16.8 Hz, 1 H), 1.58 (br. S., 1 H), 1.53 – 1.42 (m, 8 H), 1.39 (s, 9 H), 1.28 (s, 2 H), 1.23 (d, *J* = 9.2 Hz, 2 H), 1.13 (d, *J* = 13.7 Hz, 1 H), 1.08 (s, 4 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.95 (br. S., 3 H), 0.95 (br. S., 3 H). ¹³C NMR (126MHz, *CHLOROFORM-d*) δ 170.9, 167.4, 151.7, 149.5, 148.3, 145.6, 129.9, 128.8, 126.5, 124.0, 110.5, 96.6, 68.0, 52.7, 50.0, 49.3, 44.9, 41.5, 41.5, 40.3, 37.2, 36.1, 36.0, 33.5, 33.4, 32.3, 29.2, 29.2, 28.5, 27.0, 26.8, 24.9, 20.8, 20.7, 19.4, 19.3, 16.1, 15.4, 14.1.

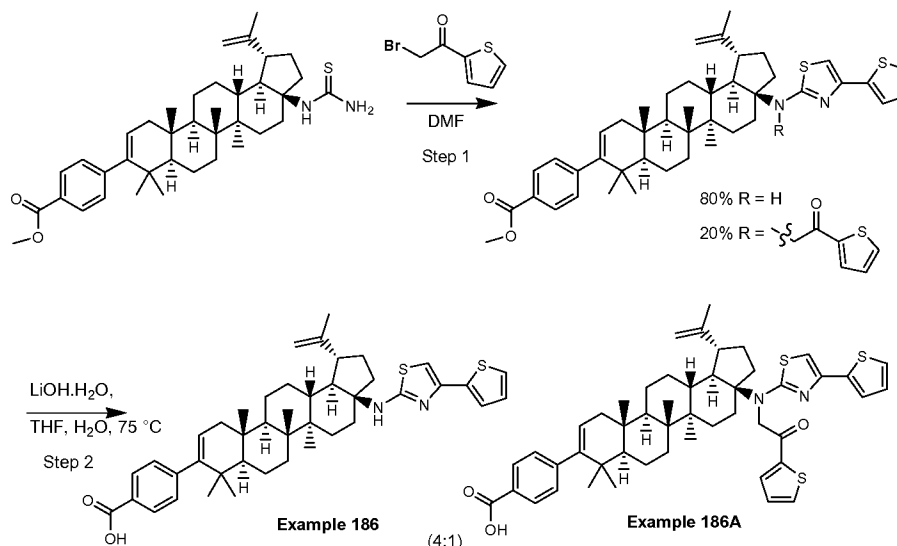
25

Example 186

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-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 and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-

30

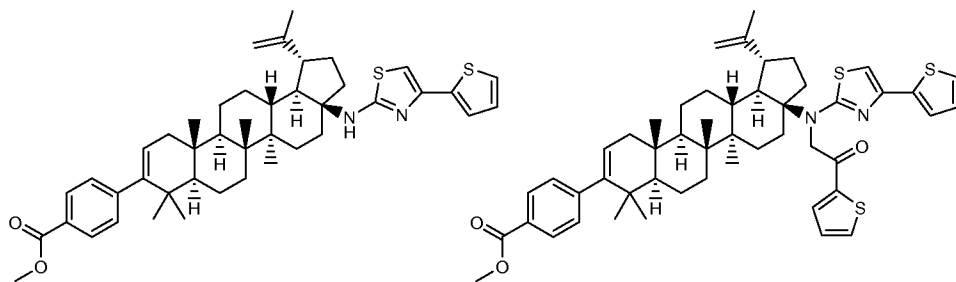
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



5

Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-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 and methyl 4-

10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-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.

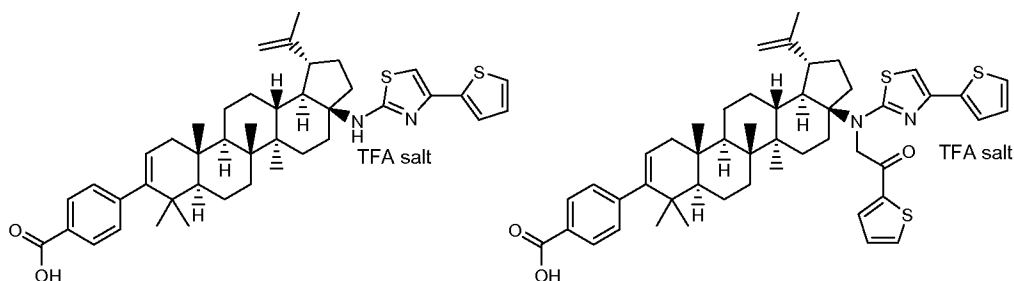


15

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-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, 0.249 mmol) in DMF (3 mL) was added

N,N-diisopropylethylamine (0.217 mL, 1.244 mmol) and 2-bromo-1-(thiophen-3-yl)ethanone (77 mg, 0.373 mmol). The reaction mixture was stirred at rt overnight. After 18 h, the reaction mixture was poured into a separatory funnel containing H₂O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine,
 5 dried over MgSO₄, filtered and concentrated to white solid. The material was redissolved in DCM (3 mL). MeOH was added and the mixture was concentrated to remove most of DCM. The resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give a 4:1 mixture of (as determined by HPLC integration) methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 10 pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-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 and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-
 15 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 (134 mg, 82 % yield) as white solid. LC/MS: m/e 709.3 (M+H)⁺, 3.62 min and m/e 833.3 (M+H)⁺, 2.63 min (method 9), respectively. Reverse phased analytical HPLC showed ratio of major product with rt = 16.04 min (m/e 709.3 (M+H)⁺) to minor product with rt = 15.42 min (m/e 833.3 (M+H)⁺) product of 80%:20% (using analytical HPLC method 2).
 20

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-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, TFA and 4-
 25 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-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, TFA.



To a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-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 (119.36 mg, 0.168 mmol) and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-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 (29.84 mg, 0.036 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (25.4 mg, 0.606 mmol) in water (1 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) onto reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-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, TFA (110.7 mg, 0.134 mmol, 80 % yield) and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-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, TFA (13.4 mg, 0.016 mmol, 9.52 % yield).

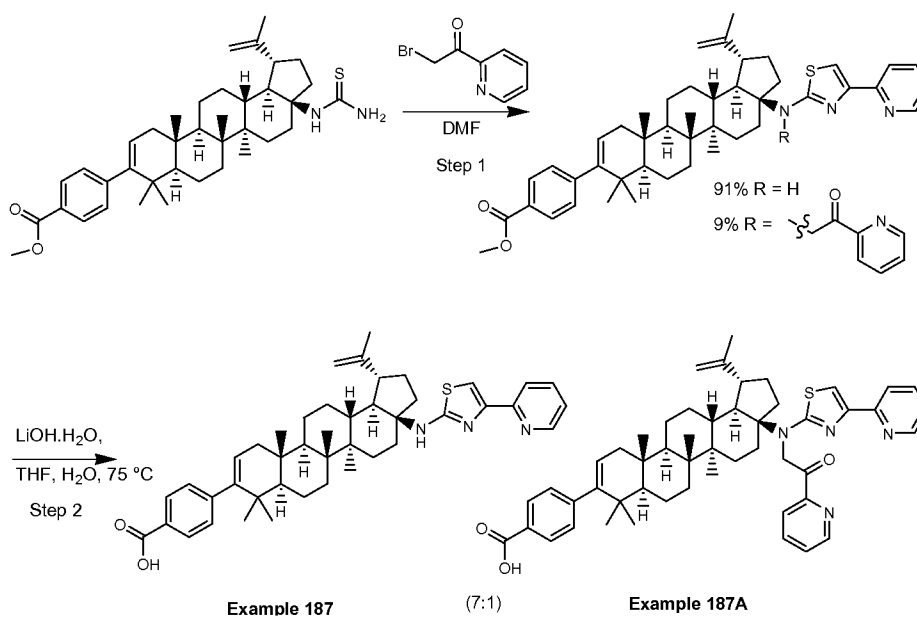
Example 186: LC/MS: m/e 695.3 ($M+H$)⁺, 2.92 min (method 11). ¹H NMR (500MHz, *CHLOROFORM-d*) δ 8.12 (br. s., 1 H), 8.03 (d, J = 8.2 Hz, 2 H), 7.42 - 7.39 (m, 1 H), 7.38 - 7.36 (m, 1 H), 7.25 (d, J = 8.2 Hz, 2 H), 6.52 (s, 1 H), 5.33 (d, J = 4.6 Hz, 1 H), 4.86 (s, 1 H), 4.71 (s, 1 H), 3.04 (dt, J = 5.0, 11.1 Hz, 1 H), 2.58 (d, J = 14.0 Hz, 1 H), 2.39 (dd, J = 7.9, 12.8 Hz, 1 H), 2.33 - 2.25 (m, 1 H), 2.15 (dd, J = 6.4, 17.1 Hz, 1 H), 2.06 - 1.98 (m, 1 H), 1.92 - 1.82 (m, 2 H), 1.76 (s, 3 H), 1.70 (d, J = 17.1 Hz, 1 H), 1.64 - 1.56 (m, 1 H), 1.55 - 1.47 (m, 5 H), 1.46 - 1.37 (m, 5 H), 1.23 (d, J = 10.1 Hz, 1 H), 1.15 (d, J = 13.1 Hz, 1 H), 1.06 (s, 3 H), 1.05 (s, 3 H), 0.99 (s, 3

H), 0.95 (s, 3 H), 0.94 (s, 3 H). ¹³C NMR (126MHz, *CHLOROFORM-d*) δ 171.2, 167.1, 163.3, 149.3, 148.5, 145.9, 129.9, 128.8, 127.0, 126.9, 124.7, 124.4, 123.9, 117.4, 115.1, 110.4, 98.1, 68.0, 52.6, 50.0, 49.3, 45.0, 41.6, 41.5, 40.4, 37.2, 36.2, 36.0, 33.4, 32.6, 29.2, 29.2, 27.0, 26.9, 24.9, 20.8, 19.5, 19.2, 16.1, 15.3, 14.1.

5 **Example 186A:** LC/MS: m/e 818.4 (M+H)⁺, 2.50 min (method 11).

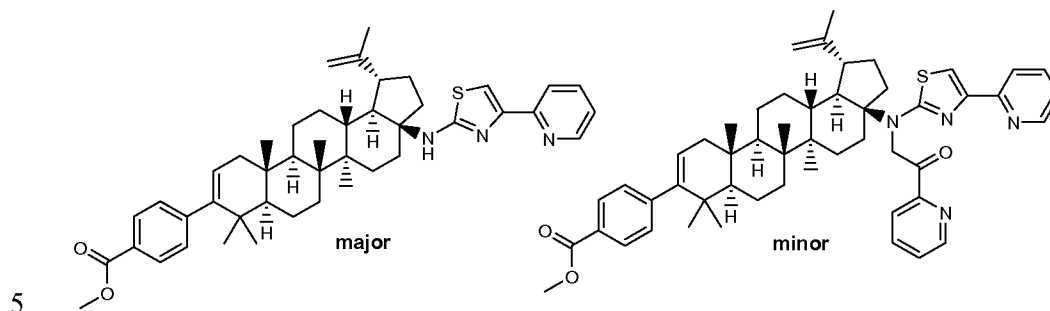
Examples 187 and 187A

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
10 pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-
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 and 4-
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-
15 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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
20 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-
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 and methyl 4-

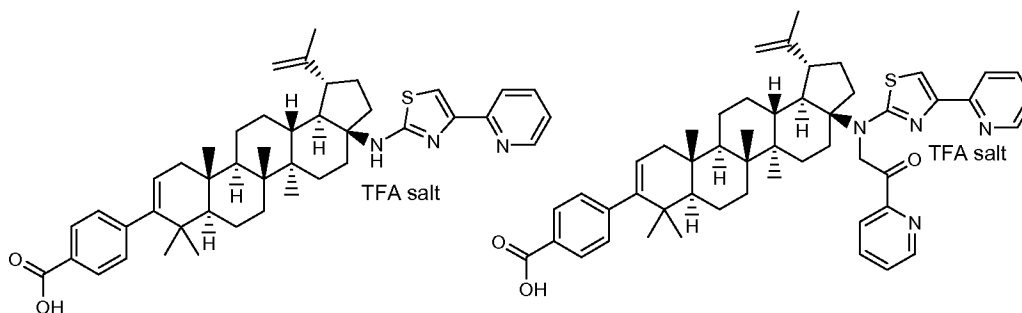
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-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, 0.249 mmol) was added *N,N*-diisopropylethylamine (0.217 mL, 1.244 mmol) and 2-bromo-1-(pyridin-2-yl)ethanone, hydrobromide (116 mg, 0.373 mmol). The reaction mixture was stirred at rt overnight. After 18 h, the reaction mixture was poured into a separatory funnel containing H₂O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated to brown solid. The material was redissolved in DCM (3 mL), MeOH was added and the resulting mixture was concentrated to remove most of DCM. The resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give a 91:9 mixture (as determined by HPLC integration) of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((4-(pyridin-2-yl)thiazol-2-yl)amino)-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 and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-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 (137 mg, 76.57 % yield) as brown solid. LC/MS: *m/e* 704.3 (M+H)⁺, 3.72 min and *m/e* 823.4 (M+H)⁺, 2.56 min (method 9),

respectively. Reversed phased analytical HPLC showed ratio of major product with $rt = 22.43$ min (m/e 704.3 ($M+H$)⁺) to minor product with $rt = 23.61$ min (m/e 823.4 ($M+H$)⁺) product of 91%:9% (using analytical HPLC method 1).

- 5 Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-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, TFA and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-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, TFA.

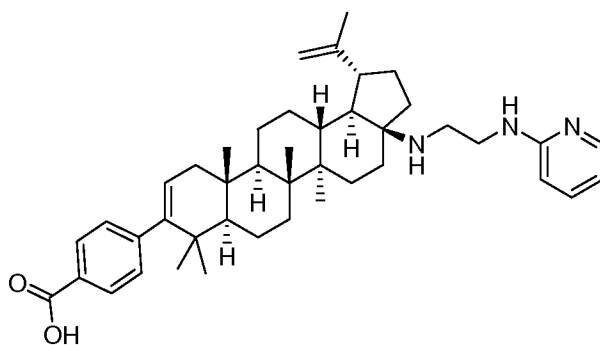


- 15 To a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (117.66 mg, 0.167 mmol) and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-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 (19.6 mg, 0.024 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (25.2 mg, 0.602 mmol) in water (1 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was injected onto reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-

- 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, TFA (70.2 mg, 0.085 mmol, 50.7 % yield) and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-
- 5 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, TFA (10.3 mg, 0.011 mmol, 6.86 % yield).
- Example 187:** LC/MS: m/e 690.3 (M+H)⁺, 2.53 min (method 11). ¹H NMR (500MHz, CHLOROFORM-d) δ 9.67 (br. s., 1 H), 8.73 (td, J = 0.9, 5.0 Hz, 1 H), 8.14 (d, J = 7.9 Hz, 1 H), 8.02 (d, J = 8.2 Hz, 2 H), 7.96 (dt, J = 1.7, 7.9 Hz, 1 H), 7.42 (s, 1 H), 7.40 (ddd, J = 0.9, 4.9, 7.6 Hz, 1 H), 7.25 (d, J = 8.5 Hz, 2 H), 5.33 (d, J = 4.6 Hz, 1 H), 4.86 (s, 1 H), 4.71 (s, 1 H), 2.99 (dt, J = 4.9, 11.0 Hz, 1 H), 2.64 - 2.58 (m, 1 H), 2.41 (dd, J = 8.1, 12.7 Hz, 1 H), 2.23 (dt, J = 3.1, 12.1 Hz, 1 H), 2.16 (dd, J = 6.3, 17.2 Hz, 1 H), 2.06 - 2.00 (m, 1 H), 1.90 (t, J = 11.7 Hz, 1 H), 1.85 (d, J = 12.5 Hz, 1 H), 1.76 (s, 3 H), 1.70 (d, J = 17.1 Hz, 1 H), 1.64 - 1.55 (m, 1 H), 1.55 - 1.39 (m, 9 H), 1.30 - 1.21 (m, 1 H), 1.17 (d, J = 13.1 Hz, 1 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.95 (s, 3 H). ¹³C NMR (126MHz, CHLOROFORM-d) δ 170.8, 167.4, 149.3, 148.4, 146.3, 145.9, 141.1, 138.6, 129.9, 128.8, 126.8, 123.9, 123.9, 121.2, 110.4, 104.8, 77.3, 68.1, 52.6, 49.9, 49.3, 45.2, 41.6, 41.5, 40.4, 37.2, 36.5, 36.0, 33.3, 32.7, 29.2, 29.2, 26.9, 24.9, 20.8, 19.4, 19.2, 16.1, 15.4, 14.2.
- 15
- 20 **Example 187A:** LC/MS: m/e 809.5 (M+H)⁺, 2.38 min (method 11).

Example 188

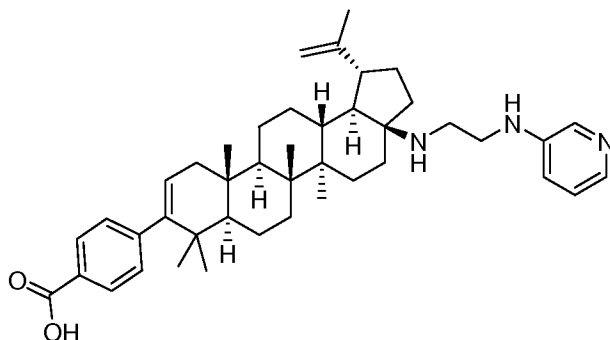
- 25 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-2-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



In a 1 dram vial under nitrogen were combined (2R)-1-[(1R)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (CAS# 158923-11-6) (2.101 mg, 3.79 μ mol), palladium(II) acetate (0.851 mg, 3.79 μ mol) and dry DME (0.5 ml). The contents of the vial were stirred for 10 min, and were then added all at once to a separate mixture of 2-bromopyridine (0.012 g, 0.076 mmol) and sodium tert-butoxide (0.032 g, 0.333 mmol) in dry DME (0.5 mL) contained in a separate 1 dram vial. The resulting mixture was allowed to stir very briefly (1 min) before TBDMSCl (0.025 g, 0.167 mmol) was added. The vial was shaken briefly, and solid methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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 bis HCl salt (0.050 g, 0.076 mmol) was added in one portion. A mild exotherm resulted upon the final addition. The mixture was heated to 110 °C for 15 min. LCMS indicated essentially complete consumption of starting material. To the mixture was added water (0.5 mL) and methanol (1.5 mL) and the resulting mixture was stirred for 2 days. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 6 gave the title compound (0.0092 g, 13.1% yield) as a beige powder bis TFA salt. LCMS: m/e 650.4 ($M+H$)⁺, 3.76 min (method 16). ¹H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 8.01 (d, $J=4.9$ Hz, 1H), 7.95 - 7.88 (m, $J=8.2$ Hz, 2H), 7.72 (t, $J=7.3$ Hz, 1H), 7.23 - 7.16 (m, $J=8.2$ Hz, 2H), 6.92 (d, $J=8.2$ Hz, 1H), 6.85 (t, $J=6.3$ Hz, 1H), 5.29 (d, $J=4.9$ Hz, 1H), 4.86 (s, 1H), 4.74 (br. s., 1H), 3.90 - 3.72 (m, 2H), 3.23 - 3.14 (m, 1H), 2.78 - 2.67 (m, 1H), 2.17 - 2.04 (m, 2H), 2.03 - 1.82 (m, 5H), 1.73 (s, 3H), 1.71 - 1.66 (m, 1H), 1.65 - 1.46 (m, 6H), 1.45 - 1.22 (m, 9H), 1.21 - 1.09 (m, 1H), 1.06 (s, 3H), 0.99 (br. s., 3H), 0.98 (br. s., 3H), 0.94 (s, 3H), 0.93 (br. s., 3H), 0.91 - 0.84 (m, $J=6.7, 3.4$ Hz, 1H).

Example 189

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-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.



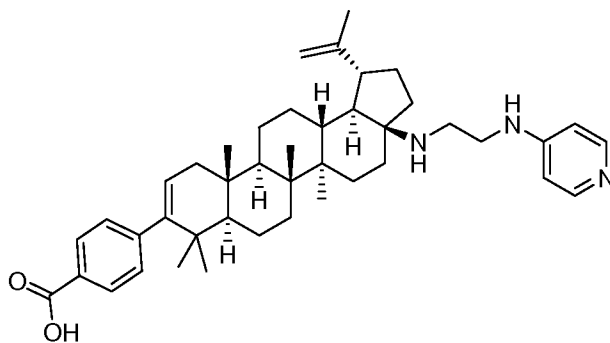
In a 1 dram vial under nitrogen were combined (2R)-1-[(1R)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (CAS# 158923-11-6) (2.101 mg, 3.79 μ mol), palladium(II) acetate (0.851 mg, 3.79 μ mol) and dry DME (0.5 mL). The contents of the vial were stirred for 10 min, and were then added all at once to a separate mixture of 3-bromopyridine (0.014 g, 0.091 mmol) and sodium tert-butoxide, 2.0M solution in THF (0.167 mL, 0.333 mmol) in dry DME (0.333 mL) contained in a separate 1 dram vial. The resulting mixture was allowed to stir very briefly (1 min) before solid methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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 bis HCl salt (0.050 g, 0.076 mmol) was added in one portion. The mixture was heated to 110 $^{\circ}$ C overnight. To the mixture was added lithium hydroxide monohydrate (6.4 mg, 0.152 mmol) with water (0.2 mL) and methanol (0.5 mL) and the resulting mixture was stirred for 4 days. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 7 gave the title compound (0.0407 g, 57.5% yield) as a beige powder bis TFA salt. LCMS: m/e 650.4 (M+H)⁺, 2.26 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of CDCl₃ and MeOD, MeOD lock) δ ppm 8.26 (d, J=2.4 Hz, 1H), 8.02 (d, J=4.9 Hz,

1H), 7.94 - 7.87 (m, $J=8.2$ Hz, 2H), 7.77 (dd, $J=8.9$, 1.5 Hz, 1H), 7.67 (dd, $J=8.9$, 5.2 Hz, 1H), 7.22 - 7.14 (m, 2H), 5.28 (dd, $J=6.3$, 1.7 Hz, 1H), 4.82 (s, 1H), 4.74 (s, 1H), 3.89 - 3.78 (m, 1H), 3.70 (dt, $J=14.6$, 4.5 Hz, 1H), 3.30 - 3.23 (m, 2H), 2.85 (td, $J=11.1$, 5.5 Hz, 1H), 2.21 - 2.05 (m, 3H), 2.03 - 1.94 (m, 2H), 1.94 - 1.85 (m, 1H),
 5 1.85 - 1.76 (m, 1H), 1.72 (s, 3H), 1.70 - 1.64 (m, 1H), 1.64 - 1.51 (m, 3H), 1.51 - 1.44 (m, 3H), 1.43 - 1.20 (m, 6H), 1.19 - 1.08 (m, 2H), 1.07 - 1.04 (m, 3H), 1.04 - 1.00 (m, 3H), 0.99 (s, 3H), 0.95 - 0.88 (m, 7H).

Example 190

10

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-4-ylamino)ethylamino)-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.



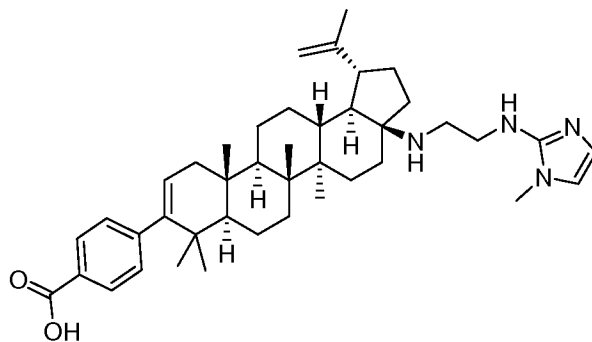
15

The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-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, except 4-bromopyridine hydrochloride (0.018 g, 0.091 mmol) was used in place of 3-bromopyridine, and an additional 1.2 equivalents of sodium tert-butoxide, 2.0M solution in THF (for a total of 5.6 equivalents, 0.212 mL, 0.424 mmol) was employed. The product was isolated after
 20 reverse phase preparative HPLC purification using Prep HPLC Method 7 as a beige solid (74 mg, 54% yield) bis TFA salt. LCMS: m/e 650.4 ($M+H$)⁺, 3.85 min (method 16). ¹H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 8.19 - 7.97 (m, 2H), 7.91 (d, $J=8.2$ Hz, 2H), 7.19 (d, $J=8.2$ Hz, 2H), 7.06 (br. s., 2H), 5.28

(d, $J=4.6$ Hz, 1H), 4.83 (s, 1H), 4.73 (s, 1H), 3.96 - 3.81 (m, 2H), 3.31 - 3.19 (m, 2H), 2.88 - 2.76 (m, 1H), 2.18 - 2.03 (m, 3H), 1.97 (dd, $J=10.4$, 6.4 Hz, 3H), 1.83 (d, $J=12.5$ Hz, 1H), 1.72 (s, 3H), 1.68 (br. s., 1H), 1.66 - 1.45 (m, 7H), 1.44 - 1.28 (m, 5H), 1.24 (d, $J=8.2$ Hz, 1H), 1.18 - 1.11 (m, 1H), 1.09 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

Example 191

- 10 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(1-methyl-1H-imidazol-2-ylamino)ethylamino)-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.



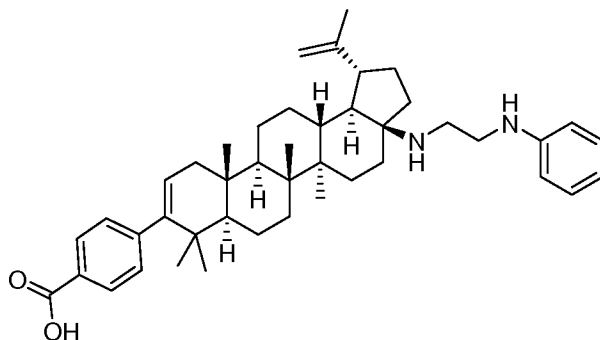
15

- The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-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, except 2-bromo-1-methyl-1H-imidazole (0.015 g, 8.88 μ L, 0.091 mmol) was used in place of 3-bromopyridine. Also, addition of LiOH, water and methanol were unnecessary for this example, as the ester hydrolysis occurred spontaneously during the course of the amination reaction. The product was isolated after reverse phase preparative HPLC purification using Prep HPLC Method 8 as a beige solid (38.1 mg, 51.5% yield) bis TFA salt. LCMS: m/e 653.4 ($M+H$)⁺, 3.88 min (method 16). ¹H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 7.91 (d, $J=8.2$ Hz, 2H), 7.19 (d, $J=7.9$ Hz, 2H), 6.86 (s, 1H), 6.83 - 6.79 (m, 1H), 5.28 (d, $J=5.5$ Hz, 1H), 4.84 (s, 1H), 4.73 (s, 1H), 4.71
- 20
- 25

(br. s., 1H), 3.98 - 3.82 (m, 2H), 3.58 (s, 3H), 3.25 (br. s., 1H), 2.89 - 2.78 (m, 1H), 2.18 - 2.07 (m, 3H), 2.05 - 1.92 (m, 3H), 1.90 - 1.79 (m, 1H), 1.72 (s, 4H), 1.69 (br. s., 1H), 1.62 - 1.54 (m, 3H), 1.53 - 1.47 (m, 3H), 1.46 - 1.34 (m, 5H), 1.28 - 1.20 (m, 2H), 1.18 - 1.12 (m, 1H), 1.11 (s, 3H), 1.09 - 1.03 (m, 4H), 1.01 (s, 3H), 0.93 (br. s., 3H), 0.93 (br. s., 3H).

Example 192

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(phenylamino)ethylamino)-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.



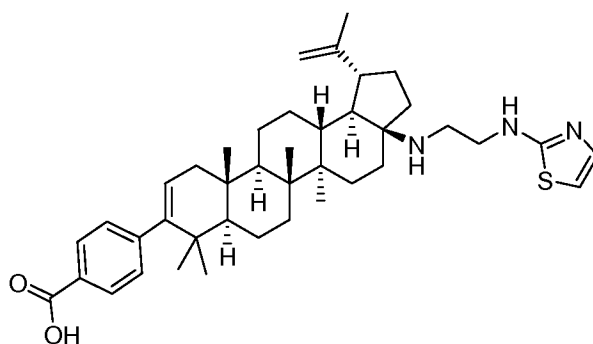
The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except bromobenzene (0.014 g, 9.58 μ L, 0.091 mmol) was used in place of 3-bromopyridine. The product was isolated after reverse phase preparative HPLC purification using Prep HPLC Method 7 as a beige solid (29.7 mg, 42% yield) bis TFA salt. LCMS: m/e 649.4 ($M+H$)⁺, 2.42 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 7.94 - 7.88 (m, $J=7.9$ Hz, 2H), 7.22 (t, $J=7.8$ Hz, 2H), 7.20 - 7.15 (m, $J=8.2$ Hz, 2H), 6.82 (t, $J=7.3$ Hz, 1H), 6.75 (d, $J=7.9$ Hz, 2H), 5.27 (d, $J=5.5$ Hz, 1H), 4.81 (s, 1H), 4.73 (s, 1H), 3.68 - 3.58 (m, 1H), 3.58 - 3.51 (m, 1H), 3.25 - 3.17 (m, 2H), 2.82 (td, $J=11.0, 5.2$ Hz, 1H), 2.18 - 2.05 (m, 2H), 2.01 - 1.92 (m, 2H), 1.90 (br. s., 1H), 1.83 - 1.72 (m, 2H), 1.71 (s, 3H), 1.68 (d, $J=17.4$ Hz, 1H), 1.64 - 1.46 (m, 6H), 1.45 -

1.30 (m, 5H), 1.27 - 1.11 (m, 4H), 1.10 - 1.02 (m, 2H), 1.02 - 0.99 (m, 6H), 0.98 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H).

Example 193

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Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(thiazol-2-ylamino)ethylamino)-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.



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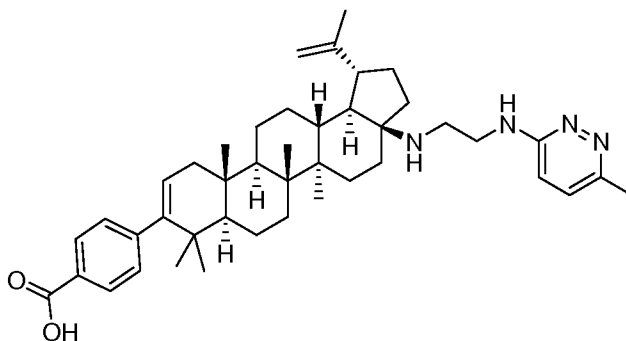
The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromothiazole (0.015 g, 0.091 mmol) was used in place of 3-bromopyridine. The product was isolated after reverse phase preparative HPLC purification using Prep HPLC Method 7 as a beige solid (12.8 mg, 18% yield) bis TFA salt. LCMS: m/e 656.4 ($M+H$)⁺, 2.38 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 7.91 (d, $J=8.2$ Hz, 2H), 7.19 (d, $J=8.2$ Hz, 2H), 7.08 (d, $J=3.7$ Hz, 1H), 6.68 (d, $J=4.0$ Hz, 1H), 5.28 (d, $J=4.6$ Hz, 1H), 4.86 (s, 1H), 4.74 (br. s., 1H), 3.69 (dd, $J=9.9$, 5.3 Hz, 1H), 3.43 - 3.36 (m, 1H), 2.13 (dd, $J=17.2$, 6.3 Hz, 1H), 2.05 (d, $J=15.0$ Hz, 1H), 2.01 - 1.79 (m, 6H), 1.73 (s, 4H), 1.70 - 1.46 (m, 8H), 1.46 - 1.27 (m, 6H), 1.27 - 1.22 (m, 2H), 1.22 - 1.10 (m, 2H), 1.07 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

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Example 194

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-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.



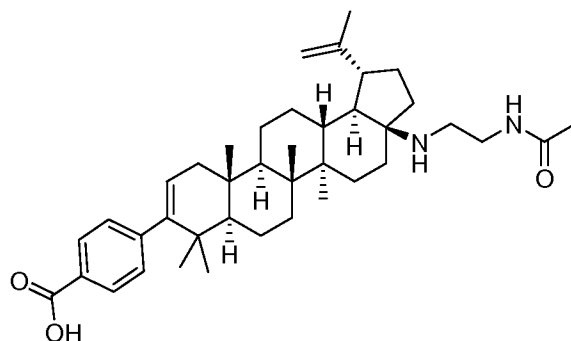
In a 1 dram vial under nitrogen were combined (2R)-1-[(1R)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (CAS# 158923-11-6) (2.52 mg, 4.55 μ mol), palladium(II) acetate (1.02 mg, 4.55 μ mol) and dry DME (0.5 ml). The contents of the vial were stirred for 10 min, and were then added all at once to a separate mixture of 3-bromo-6-methylpyridazine (0.017 g, 0.100 mmol) and sodium tert-butoxide, 2.0M solution in THF (0.200 mL, 0.400 mmol) in dry DME (0.500 mL) contained in a separate 1 dram vial. The resulting mixture was allowed to stir very briefly (1 min) before solid methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-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 bis HCl salt (0.060 g, 0.091 mmol) was added in one portion. The mixture was heated to 110 °C overnight. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound (0.0070 g, 8.3% yield) as a white glassy solid bis TFA salt. LCMS: m/e 665.5 (M+H)⁺, 2.22 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of CDCl₃ and MeOD, MeOD lock) δ ppm 7.90 (d, *J*=8.5 Hz, 2H), 7.49 - 7.42 (m, 1H), 7.32 - 7.23 (m, 1H), 7.18 (d, *J*=8.2 Hz, 2H), 5.27 (dd, *J*=6.0, 1.4 Hz, 1H), 4.88 (br. s., 1H), 4.72 (br. s., 1H), 3.94 - 3.84 (m, 1H), 3.84 - 3.73 (m, 1H), 3.26 - 3.13 (m, 1H), 2.84 (d, *J*=12.5 Hz, 1H), 2.57 (s, 3H), 2.12 (dd, *J*=16.9, 6.3 Hz, 1H), 2.05 (d, *J*=15.6 Hz, 1H), 2.01 - 1.91 (m, 2H), 1.91

- 1.74 (m, 2H), 1.70 (s, 3H), 1.69 - 1.59 (m, 2H), 1.59 - 1.43 (m, 4H), 1.43 - 1.28 (m, 4H), 1.28 - 1.18 (m, 4H), 1.18 - 1.06 (m, 2H), 1.05 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 - 0.89 (m, 3H).

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Example 195

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-acetamidoethylamino)-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.



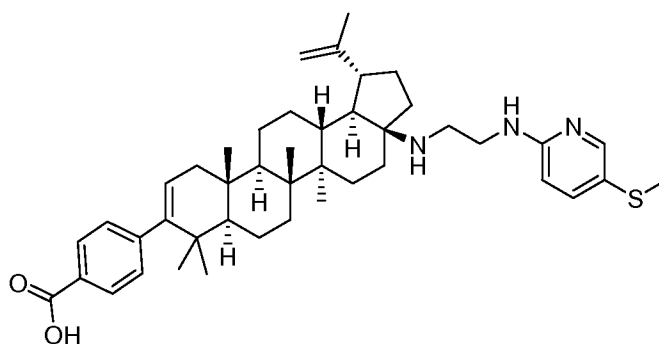
The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 4-bromopyrimidine (0.016 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. The reaction did not produce the intended product but instead produced the byproduct title compound as the major isolate. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (7.5 mg, 9.6% yield) mono TFA salt. LCMS: m/e 615.5 ($M+H$)⁺, 2.42 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 8.18 (s, 1H), 7.94 - 7.84 (m, $J=8.2$ Hz, 2H), 7.24 - 7.13 (m, $J=8.2$ Hz, 2H), 5.27 (d, $J=4.6$ Hz, 1H), 4.83 (s, 1H), 4.72 (br. s., 1H), 3.89 (s, 3H), 3.61 (br. s., 2H), 3.18 (br. s., 2H), 2.71 (td, $J=11.1, 6.3$ Hz, 2H), 2.12 - 1.92 (m, 6H), 1.90 - 1.76 (m, 3H), 1.76 - 1.66 (m, 5H),

1.66 - 1.43 (m, 9H), 1.42 - 1.33 (m, 3H), 1.24 (br. s., 2H), 1.17 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.92 (br. s., 3H).

Example 196

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Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(5-(methylthio)pyridin-2-ylamino)ethylamino)-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.



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The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-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, except 2-bromo-5-(methylthio)pyridine (0.020 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (5.2 mg, 5.9% yield) bis TFA salt. LCMS: m/e 696.5 (M+H)⁺, 2.34 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of CDCl₃ and MeOD, MeOD lock) δ ppm 8.03 (d, J=1.8 Hz, 1H), 7.93 - 7.88 (m, J=8.2 Hz, 2H), 7.61 - 7.57 (m, 1H), 7.21 - 7.14 (m, J=8.2 Hz, 2H), 6.71 (d, J=8.9 Hz, 1H), 5.27 (dd, J=6.1, 1.5 Hz, 1H), 4.87 (s, 1H), 4.75 (br. s., 1H), 4.72 (br. s., 1H), 3.80 - 3.72 (m, 1H), 3.72 - 3.63 (m, 1H), 3.18 - 3.09 (m, 1H), 2.72 - 2.64 (m, 1H), 2.39 (s, 3H), 2.11 (dd, J=17.1, 6.4 Hz, 1H), 2.08 - 2.01 (m, 1H), 2.00 - 1.90 (m, 3H), 1.90 - 1.74 (m, 3H), 1.72 (s, 3H), 1.71 - 1.66 (m, 2H), 1.65 - 1.44 (m, 7H), 1.44 - 1.33 (m, 3H),

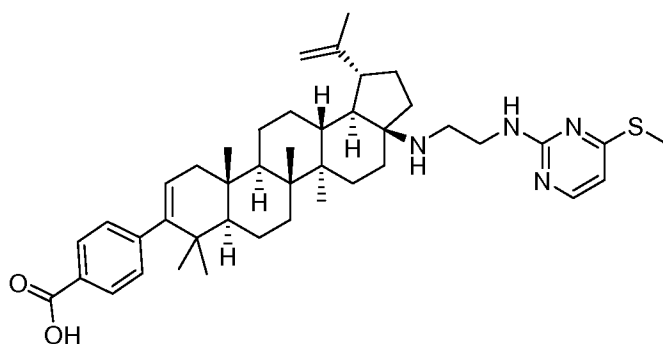
25

1.33 - 1.12 (m, 7H), 1.04 (s, 3H), 0.97 (s, 3H), 0.91 (br. s., 3H), 0.91 (br. s., 3H), 0.87 (s, 3H).

Example 197

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Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(4-(methylthio)pyrimidin-2-ylamino)ethylamino)-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.



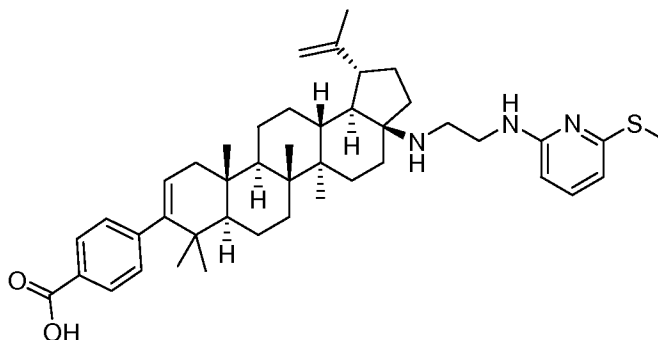
10

The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-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, except 2-chloro-4-(methylthio)pyrimidine (0.016 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (12.0 mg, 14% yield) bis TFA salt. LCMS: m/e 697.5 (M+H)⁺, 2.30 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of CDCl₃ and MeOD, MeOD lock) δ ppm 7.99 - 7.85 (m, 3H), 7.17 (d, J=8.2 Hz, 2H), 6.75 - 6.63 (m, 1H), 5.26 (d, J=4.6 Hz, 1H), 4.82 (s, 1H), 4.70 (br. s., 1H), 3.96 (s, 1H), 3.85 (br. s., 2H), 3.43 - 3.34 (m, 1H), 3.25 (br. s., 1H), 2.72 (br. s., 1H), 2.55 (s, 3H), 2.10 (dd, J=17.1, 6.4 Hz, 1H), 2.04 (d, J=15.3 Hz, 1H), 2.01 - 1.89 (m, 3H), 1.89 - 1.77 (m, 2H), 1.70 (s, 4H), 1.68 - 1.49 (m, 5H), 1.46 (d, J=7.3 Hz, 3H), 1.42 - 1.18 (m, 7H), 1.18 - 1.06 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.91 (br. s., 3H).

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Example 198

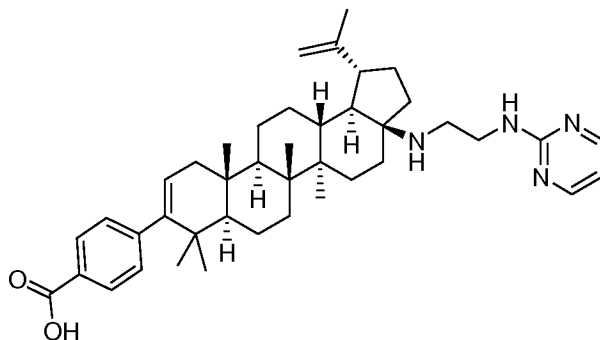
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-(methylthio)pyridin-2-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-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, except 2-bromo-6-(methylthio)pyridine (0.020 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (10.3 mg, 12% yield) bis TFA salt. LCMS: m/e 696.5 ($M+H$)⁺, 2.34 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of *CDCl*₃ and *MeOD*, *MeOD* lock) δ ppm 7.95 - 7.85 (m, $J=8.2$ Hz, 2H), 7.39 (t, $J=7.8$ Hz, 1H), 7.20 - 7.12 (m, $J=8.2$ Hz, 2H), 6.53 (d, $J=7.6$ Hz, 1H), 6.37 (d, $J=7.9$ Hz, 1H), 5.25 (d, $J=4.6$ Hz, 1H), 4.85 (s, 1H), 4.72 (br. s., 1H), 3.96 (s, 1H), 3.78 - 3.59 (m, 2H), 3.28 - 3.13 (m, 2H), 2.95 - 2.83 (m, 1H), 2.49 (s, 3H), 2.08 - 1.86 (m, 6H), 1.78 - 1.69 (m, 4H), 1.69 - 1.52 (m, 5H), 1.52 - 1.31 (m, 6H), 1.31 - 1.07 (m, 7H), 1.01 (s, 3H), 0.95 - 0.83 (m, 9H), 0.57 (s, 3H).

Example 199

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyrimidin-2-ylamino)ethylamino)-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.



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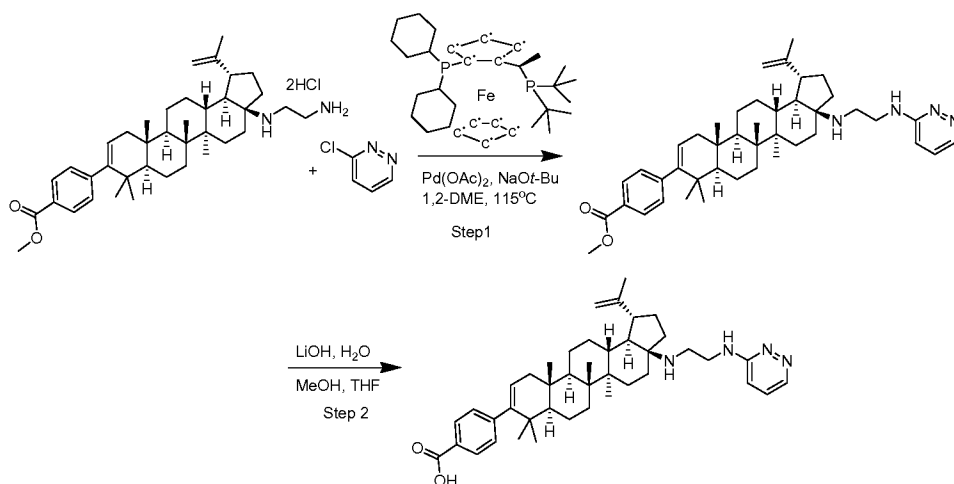
The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromopyrimidine (0.016 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (8.0 mg, 8.2% yield) bis TFA salt. LCMS: m/e 651.5 ($M+H$)⁺, 2.27 min (method 11).

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Example 200

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-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.

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Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-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 was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-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, except 3-chloropyridazine (0.011 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 9 gave the title compound as a white glassy solid (4.9 mg, 6.0% yield) bis TFA salt. LCMS: m/e 665.5 (M+H)⁺, 2.40 min (method 11).

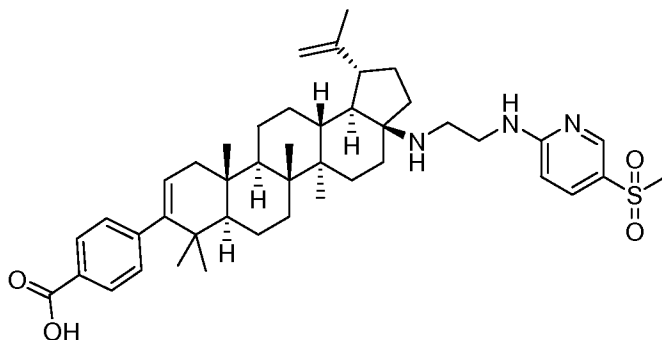
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

A solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-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 and lithium hydroxide monohydrate (2.3 mg,

0.055 mmol) in a mixture of water (0.5 mL), THF (0.25 mL) and MeOH (0.25 mL) was stirred at rt for 2.5 days. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 10 gave the title compound as a white solid (5.0 mg, 100% yield) bis TFA salt. LCMS: m/e 651.5 (M+H)⁺, 2.26 min (method 11).

Example 201

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(5-(methylsulfonyl)pyridin-2-ylamino)ethylamino)-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.



The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-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, except 2-bromo-5-(methylsulfonyl)pyridine (0.024 g, 0.100 mmol) was used in place of 3-chloropyridazine. Purification of the crude Step 2 mixture by reverse phase preparative HPLC using Prep HPLC Method 10 gave the title compound as an off-white solid (10.6 mg, 11.9% yield over 2 steps) bis TFA salt. LCMS: m/e 728.5 (M+H)⁺, 2.22 min (method 11). ¹H NMR (500 MHz, 1:1 mixture of CDCl₃ and MeOD, MeOD lock) δ ppm 8.61 (d, J =1.8 Hz, 1H), 7.95 - 7.87 (m, 3H), 7.19 (d, J =8.2 Hz, 2H), 6.80 (d, J =8.9 Hz, 1H), 5.29 (d, J =4.6 Hz, 1H), 4.90 (s, 1H), 4.82 (br. s., 1H), 3.96 - 3.85 (m, 1H), 3.85 - 3.71 (m, 1H), 3.42 (br. s., 1H), 3.37 (s, 3H), 3.27 - 3.18 (m, 1H), 3.10 (s, 3H), 2.70 (br. s., 1H), 2.14 (dd, J =17.2, 6.3 Hz, 1H), 2.10 - 1.95 (m, 5H), 1.91 - 1.77 (m, 3H), 1.74 (s, 3H), 1.71 (d, J =17.4

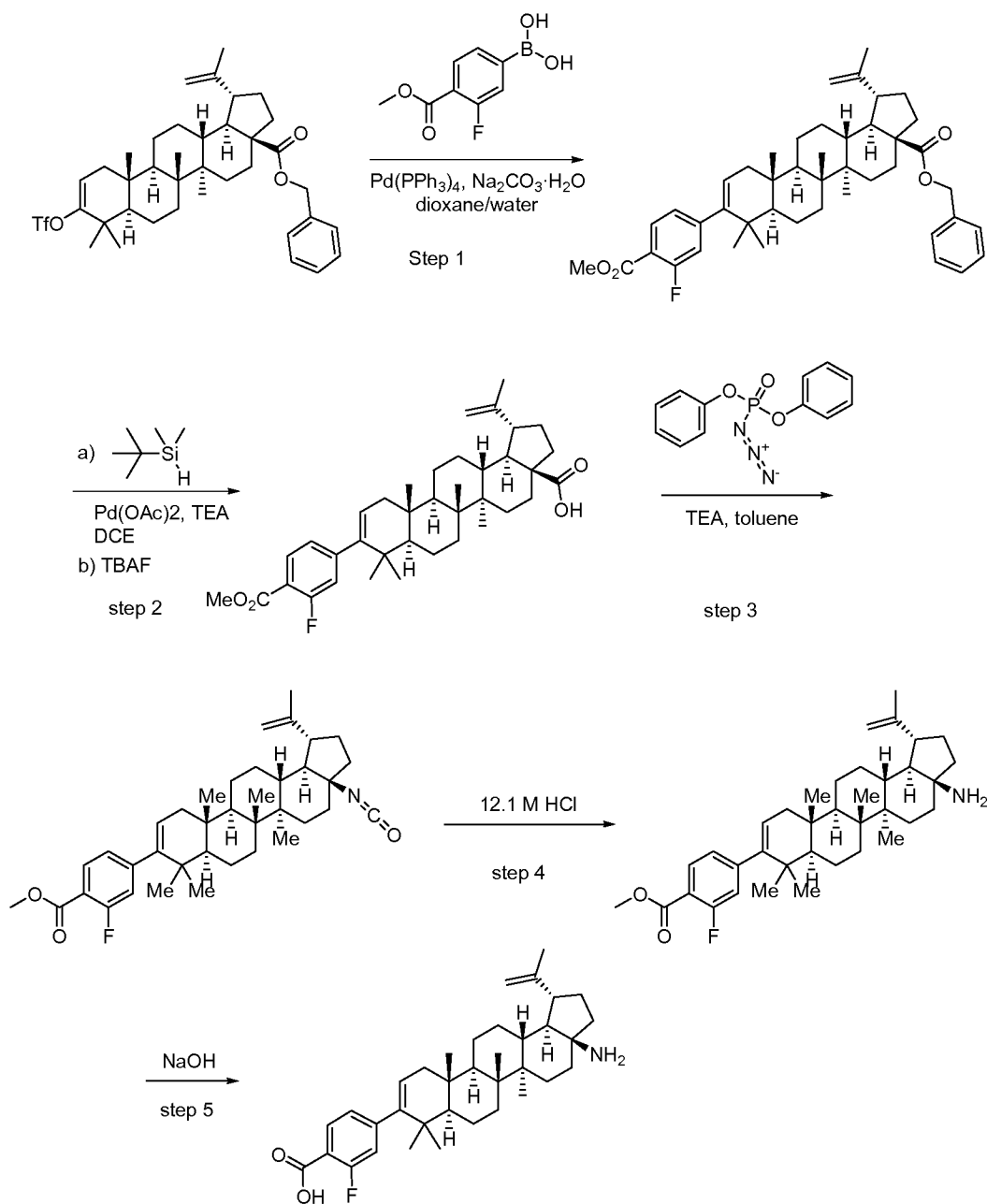
Hz, 2H), 1.65 - 1.47 (m, 6H), 1.47 - 1.34 (m, 3H), 1.34 - 1.11 (m, 6H), 1.06 (s, 3H), 1.00 (s, 3H), 0.94 (s, 6H), 0.93 (s, 3H).

Section 6. F-benzoic acid derivatives

5

Example A1

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
10 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)-2-fluorobenzoic acid.



Step 1. Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(3-fluoro-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]chrysene-3a-carboxylate.

A suspension of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(trifluoromethylsulfonyloxy)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysene-3a-carboxylate (4.0 g, 5.91 mmol), 3-fluoro-4-(methoxycarbonyl)phenylboronic acid (1.287 g, 6.50 mmol), sodium carbonate monohydrate (2.198 g, 17.73 mmol), and Pd(PPh₃)₄ (0.205 g, 0.177 mmol) in 1,4-dioxane (24 mL) and water (6 mL) was flushed with N₂ and the mixture was heated to reflux. After 2 h of heating, the mixture was cooled to rt. The mixture was diluted with water (40 mL) and was extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried with Na₂SO₄. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM and was filtered through a pad of celite and silica gel, washing with a 25% EtOAc in hexanes solution. The filtrate was concentrated under reduced pressure to give the title compound (3.59 g, 5.27 mmol, 89% yield) as a dark grey foam. The crude product was used in the next step with no additional purification. ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.80 (1 H, t, *J*=7.8 Hz), 7.29 - 7.42 (5 H, m), 6.96 (1 H, d, *J*=7.9 Hz), 6.91 (1 H, d, *J*=11.9 Hz), 5.28 - 5.33 (1 H, m), 5.16 (1 H, d, *J*=12.5 Hz), 5.09 (1 H, d, *J*=12.2 Hz), 4.73 (1 H, s), 4.59 (1 H, br. s.), 3.92 (3 H, s), 3.03 (1 H, td, *J*=10.8, 4.7 Hz), 2.20 - 2.33 (2 H, m), 2.09 (1 H, dd, *J*=17.1, 6.4 Hz), 1.81 - 1.97 (2 H, m), 1.68 (3 H, s), 0.96 (3 H, s), 0.92 (3 H, s), 0.92 (3 H, s), 0.91 (3 H, s), 0.81 (3 H, s), 0.79 - 1.75 (17 H, m).

Step 2. Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(3-fluoro-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]chrysene-3a-carboxylic acid.

To a solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(3-fluoro-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]chrysene-3a-carboxylate (3.59 g, 5.27 mmol) in DCE (25 mL) was added TEA (1.176 mL, 8.44 mmol), *t*-butyldimethylsilane (1.749 mL, 10.54 mmol), and palladium(II) acetate (0.118 g, 0.527 mmol). The mixture was flushed with N₂ and heated to 60 °C for 1 h. The mixture was cooled to rt and was filtered through a plug of celite and silica gel (washed with 25% EtOAc in hexanes). The filtrate was concentrated under reduced pressure. The residue was diluted with 25 mL of dioxane and TBAF (75% in water) (2.76 g, 7.91 mmol) was added. The mixture was stirred

for 30 minutes at rt then was diluted with 50 mL of 1N HCl. The solids that formed were collected by filtration and were washed with water to give the title compound (2.95 g, 4.99 mmol, 95% yield) as a white solid. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.83 (1 H, t, *J*=7.9 Hz), 6.90 - 7.00 (2 H, m), 5.34 (1 H, dd, *J*=6.1, 1.6 Hz), 4.77 (1 H, d, *J*=2.0 Hz), 4.64 (1 H, s), 3.94 (3 H, s), 3.04 (1 H, td, *J*=10.7, 4.8 Hz), 2.24 - 2.34 (2 H, m), 2.13 (1 H, dd, *J*=17.3, 6.3 Hz), 1.96 - 2.06 (2 H, m), 1.72 (3 H, s), 1.03 (3 H, s), 1.02 (3 H, s), 0.98 (3 H, s), 0.93 - 0.96 (6 H, m), 0.91 - 1.80 (17 H, m).

- 10 Step 3. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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-(3-fluoro-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]chrysene-3a-carboxylic acid (2.95 g, 4.99 mmol) in toluene (50 mL) and TEA (1.39 mL, 9.99 mmol) was added diphenyl phosphorazidate (1.614 mL, 7.49 mmol) and the mixture was heated to reflux. After 3 h, the reaction mixture was concentrated under reduced pressure, was adsorbed to silica gel, and was purified by flash chromatography using a 0-10% EtOAc in hexanes gradient to give the title compound as a white solid. The material was used in the next step with no additional purification. ¹H NMR (500 MHz, *Chloroform-d*) δ ppm 7.81 (1 H, t, *J*=7.8 Hz), 6.96 (1 H, dd, *J*=7.9, 1.5 Hz), 6.92 (1 H, dd, *J*=11.9, 1.5 Hz), 5.31 (1 H, dd, *J*=6.3, 1.7 Hz), 4.75 (1 H, s), 4.64 (1 H, s), 3.92 (3 H, s), 2.55 (1 H, td, *J*=10.8, 5.8 Hz), 2.05 - 2.16 (2 H, m), 1.76 - 1.92 (4 H, m), 1.68 (3 H, s), 1.09 - 1.11 (3 H, m), 0.97 (3 H, s), 0.96 (3 H, s), 0.94 (3 H, s), 0.92 (3 H, s), 0.88 - 1.75 (16 H, m).

- Step 4. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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)-2-fluorobenzoate dihydrochloride.

To a solution of crude methyl 2-fluoro-4-
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-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 (2.93 g, 4.99 mmol) in THF
5 (35 mL) was added 12N HCl (10 mL, 121 mmol). After stirring the mixture for 24 h,
the mixture was diluted with water (100 mL) until solids precipitated. The solids
were collected by filtration and were washed with water to afford the title compound
(2.75 g, 4.33 mmol, 87% yield), as an off-white solid that was used in the next step
with no additional purification. LCMS: m/e 562 (M+H)⁺, 1.96 min (method 2).

10

Step 5. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-
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)-2-fluorobenzoic acid.

15

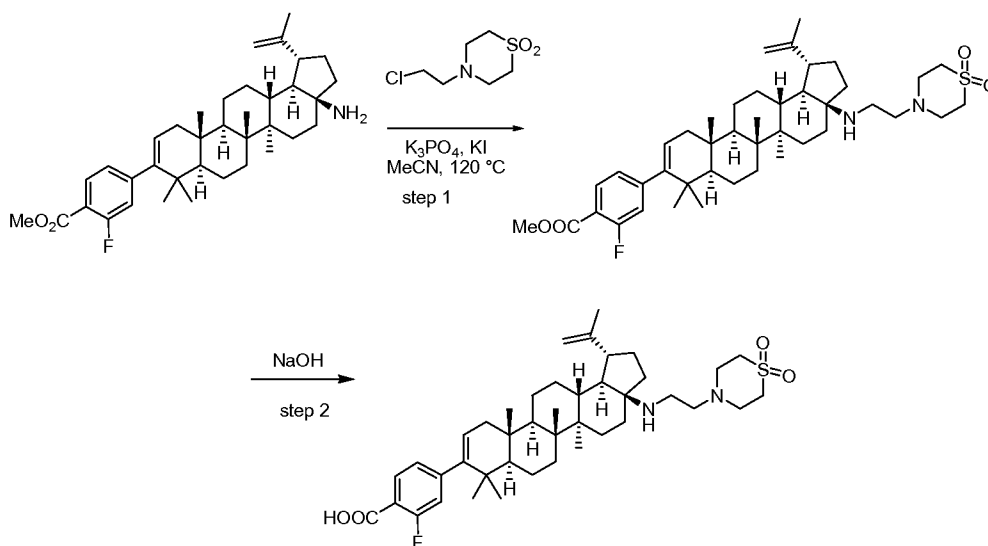
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate (100 mg, 0.178 mmol) in 1,4-dioxane (2
mL) was added 1N NaOH (0.890 mL, 0.890 mmol). Solids formed upon the addition
20 of the NaOH. The mixture was heated to 60 °C. After 20 minutes of heating, the
mixture still contained solids. The mixture was further diluted with 1 mL of MeOH
and 2 mL of dioxane then was heated to 60 °C overnight (solids did not completely
dissolve).

After 21 h of heating, the mixture was cooled to rt. The mixture was diluted with 3
25 mL of water and the solids that remained were collected by filtration and were washed
with water then with ether to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
3a-amino-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)-2-fluorobenzoic acid (67 mg, 0.113 mmol, 63.2% yield)
30 as a white solid. . LCMS: m/e 548.4 (M+H)⁺, 2.29 min (method 11).

Example A2

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-

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



- 10 Step 1. Preparation of benzoic acid, 4-
 [(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester.
- 15 To a sealable flask containing methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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)-2-fluorobenzoate, HCl (319 mg, 0.533 mmol) was added thiomorpholine, 4-(2-chloroethyl)-, 1,1-dioxide, HCl (385 mg, 1.644 mmol), potassium iodide (240 mg, 1.446 mmol), and phosphoric acid, potassium salt (500 mg, 2.356 mmol). The mixture was diluted with acetonitrile (10 mL), was flushed with N_2 , then the vial was sealed and heated to 120 °C for 115 h. The mixture was cooled to rt and was directly purified by flash chromatography using a 0-5% MeOH in DCM gradient. The fractions containing the expected product were
- 20

combined and were concentrated under reduced pressure to give the title compound (0.308 g, 0.426 mmol, 80% yield) as an off white foam. LCMS: m/e 723.5 (M+H)⁺, 1.94 min (method 2).

5 Step 2. Preparation of benzoic acid, 4-

[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, HCl.

10 To a solution of benzoic acid, 4-

[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester (0.308g, 0.426 mmol) in 1,4-

15 dioxane (5 mL) was added 1N sodium hydroxide (2.130 mL, 2.130 mmol). The mixture was heated to 70 °C for 18 h then was cooled to rt. To the mixture was added 1N HCl slowly until solids began to form. The solids were collected by filtration and were washed with water to give benzoic acid, 4-

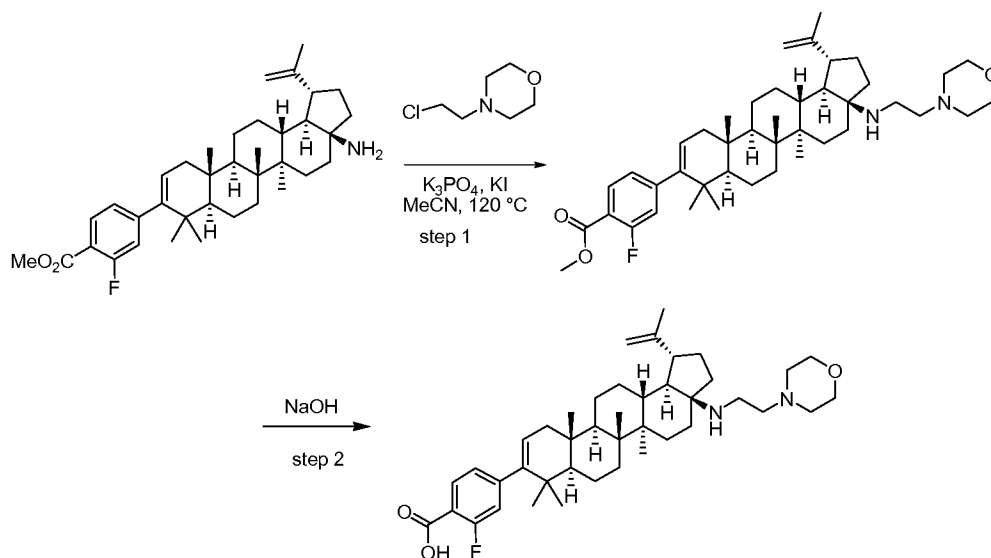
[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, HCl as an off-white solid (0.295g, 0.396 mmol, 93% yield). LCMS: m/e 709.5 (M+H)⁺, 1.66 min (method 2). ¹H NMR (500 MHz, *Acetic acid d4*) δ ppm 7.96 (1 H, t, J=7.8 Hz), 7.09 (1 H, dd, J=7.9, 1.5 Hz), 7.03 (1 H, d, J=11.9 Hz), 5.43 (1 H, d, J=4.6 Hz), 4.84 (1 H, s), 4.74 (1 H, s), 3.43 - 3.49 (1 H, m), 3.02 - 3.36 (11 H, m), 2.91 - 3.00 (1 H, m), 1.77 (3 H, s), 1.30 (3 H, s), 1.15 (3 H, s), 1.10 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.98 - 2.34 (22 H, m).

Example A3

30

Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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.



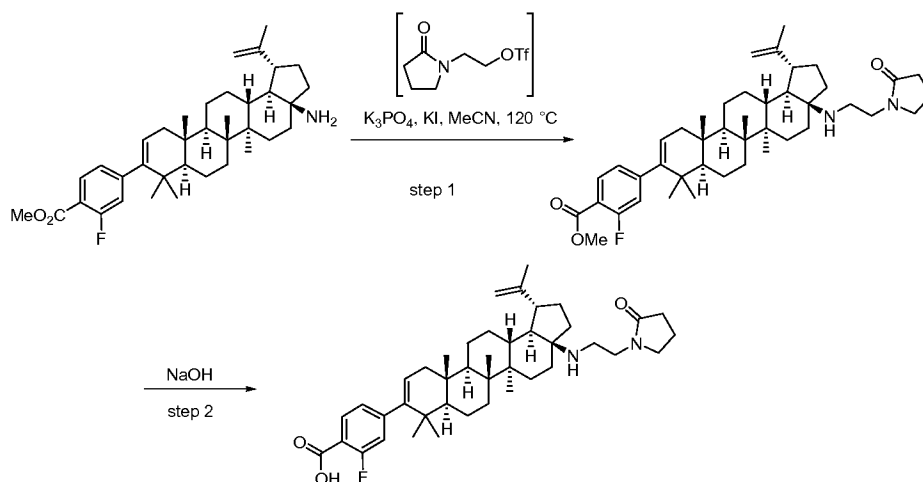
- 5 Step 1. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.
- 10 To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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)-2-fluorobenzoate, HCl (0.1 g, 0.167 mmol) was added 4-(2-chloroethyl)morpholine, HCl (0.093 g, 0.501 mmol),
- 15 phosphoric acid, potassium salt (0.156 g, 0.735 mmol) and potassium iodide (0.075 g, 0.451 mmol). The mixture was diluted with acetonitrile (3 mL), was flushed with N₂, and the vial was sealed and heated to 120 °C. After heating the mixture for 16 h, the it was cooled to rt. The crude product was adsorbed to silica gel then was purified by flash chromatography using a Thomson 12 g silica gel column and a 0-5% MeOH in
- 20 DCM gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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 (77 mg, 0.114 mmol, 68.3% yield) as an off-white foam. LCMS: m/e 675.5 (M+H)⁺, 1.91 min (method 2).

- 5 Step 2. Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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 methyl 2-fluoro-4-
- 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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 (0.075 g, 0.111 mmol) in 1,4-dioxane (1 mL) was added NaOH (1M) (0.5 mL, 0.500 mmol). The mixture was heated to 75 °C for 15 h
- 15 then was cooled to rt. The mixture was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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-
- 20 cyclopenta[a]chrysen-9-yl)benzoic acid (30 mg, 0.043 mmol, 38.8% yield) as a white solid. LCMS: m/e 661.5 (M+H)⁺, 1.66 min (method 2). ¹H NMR (500 MHz, *Acetic Acid d*₄) δ ppm 7.96 (1 H, t, *J*=7.9 Hz), 7.09 (1 H, dd, *J*=8.2, 1.2 Hz), 7.03 (1 H, d, *J*=11.6 Hz), 5.42 (1 H, d, *J*=4.6 Hz), 4.86 (1 H, s), 4.74 (1 H, s), 3.89 - 3.99 (4 H, m), 3.53 - 3.69 (4 H, m), 3.29 (4 H, br. s.), 2.81 - 2.90 (1 H, m), 1.77 (3 H, s), 1.23 (3 H,
- 25 s), 1.13 (3 H, s), 1.08 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.85 - 2.26 (22 H, m).

Example A4

- Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
- 30 5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-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 2-fluoro-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-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 vial containing *N*-(2-hydroxyethyl)-2-pyrrolidone (0.5 mL, 4.42 mmol) was added DMAP (0.054 g, 0.442 mmol) and TEA (0.925 mL, 6.64 mmol). The mixture was diluted with d-chloroform (10 mL) and was cooled to 0 °C then triflic anhydride (0.822 mL, 4.87 mmol) was added slowly. The mixture turned a dark red color as the anhydride was added. The mixture was warmed to rt and stirred for 45 minutes. The 0.442 M solution was used directly as the alkylating agent for the following reaction.

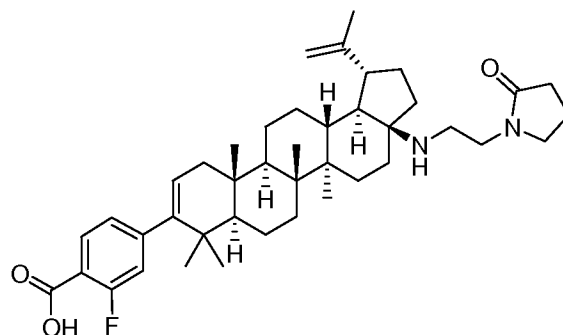
15

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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)-2-fluorobenzoate (50 mg, 0.089 mmol) was added potassium iodide (39.9 mg, 0.240 mmol) and phosphoric acid, potassium salt (83 mg, 0.392 mmol). The mixture was diluted with acetonitrile (1 mL) and the crude alkylating solution described above (1.007 mL, 0.445 mmol) was added. The mixture was flushed with N₂ and the vial was sealed and heated to 120 °C. After 15.5 h of heating, the mixture was cooled to rt. An additional 0.5 mL of the crude alkylating solution was added and the mixture was again heated to 120 °C. After

25

70.25 h, the mixture was cooled to rt. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 0-5% MeOH in DCM gradient and a Thomson 12 g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 2-fluoro-4-
 5 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-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 (25 mg, 0.037 mmol, 41.7% yield) as a yellow film. LCMS: m/e 673.5 (M+H)⁺, 2.03 min (method 2).

10 Step 2. Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-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.

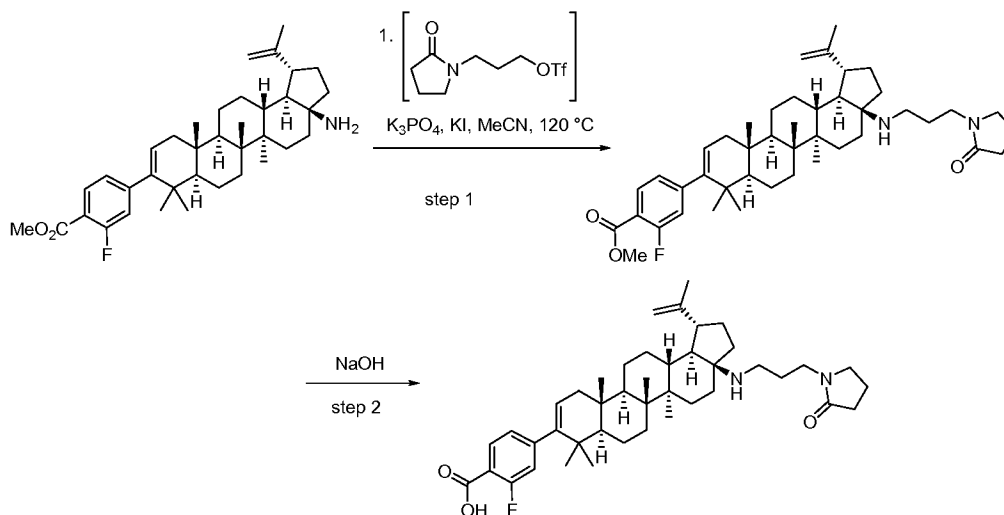


To a solution of methyl 2-fluoro-4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-
 20 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.025 g, 0.037 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.5 mL, 0.500 mmol). The mixture was warmed to 60 °C for 15.
 5h then was cooled to rt and purified by prep HPLC. The fractions containing the
 25 expected product were combined and concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-
 3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-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 (11 mg, 0.016 mmol, 42.2% yield) as a white solid. LCMS: m/e 659.5 ($M+H$)⁺, 1.77 min (method 2). ¹H NMR (500MHz, CHLOROFORM-*d*) δ 7.82 (t, $J=6.9$ Hz, 1H), 6.91 (d, $J=6.1$ Hz, 1H), 6.86 (d, $J=11.9$ Hz, 1H), 5.27 (d, $J=4.6$ Hz, 1H), 4.71 (s, 1H), 4.58 (s, 1H), 3.54 - 3.43 (m, 3H), 3.39 - 3.31 (m, 1H), 1.68 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H), 2.75 - 0.66 (m, 29H).

Example A5

- 10 Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-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.



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- Step 1. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-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 vial containing 1-(3-hydroxypropyl)-2-pyrrolidone (0.5 mL, 3.84 mmol) was added DMAP (0.047 g, 0.384 mmol) and TEA (0.803 mL, 5.76 mmol). The mixture was diluted with *d*-chloroform (10 mL) and was cooled to 0 °C. To the

cooled solution was added trifluoromethanesulfonic anhydride (0.714 mL, 4.23 mmol) slowly. The mixture turned dark red as the anhydride was added. The mixture was slowly warmed to rt as the ice bath melted. After 1h of stirring at rt, ¹HNMR showed no starting material remained. The crude reaction mixture was used directly in the following reaction with no purification.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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)-2-fluorobenzoate (50 mg, 0.089 mmol) was added potassium iodide (39.9 mg, 0.240 mmol) and phosphoric acid, potassium salt (83 mg, 0.392 mmol). The mixture was diluted with acetonitrile (1 mL) and 3-(2-oxopyrrolidin-1-yl)propyl trifluoromethanesulfonate (the crude solution prepared above) (1.0 mL, 0.384 mmol) was added. The mixture was flushed with N₂, then the vial was sealed and heated to 120 °C. After 15.5 h of heating, the mixture was cooled to rt. An additional 0.5 mL of the above crude solution containing the triflate was added and the mixture was again heated to 120 °C. After heating the mixture for an additional 70.25 h, the mixture was cooled to rt. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 0-5% MeOH in DCM gradient and a Thomson 12 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-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, 0.023 mmol, 26.2% yield) as a yellow film. LCMS: m/e 687.5 (M+H)⁺, 2.04 min (method 2).

Step 2. Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-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 methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-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-

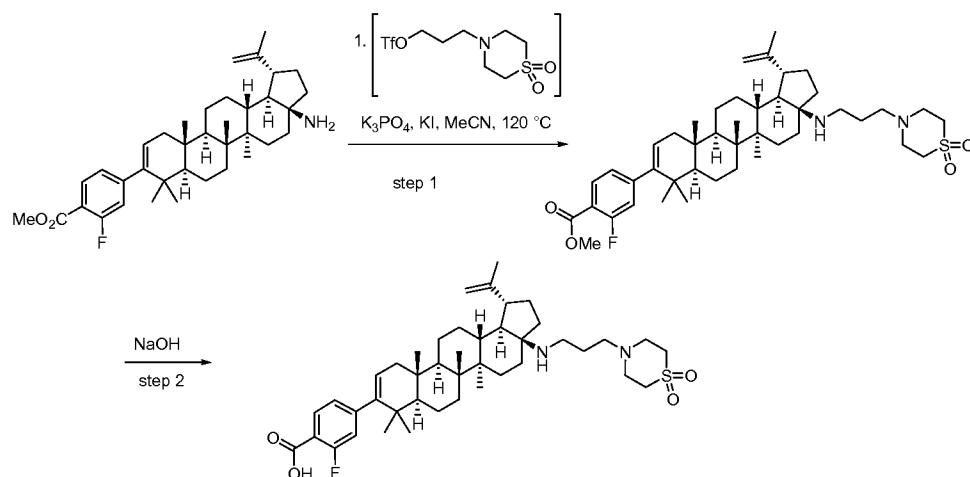
cyclopenta[a]chrysen-9-yl)benzoate (16 mg, 0.023 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.25 mL, 0.250 mmol). The mixture was heated to 60 °C overnight for 15.25h then was cooled to rt. The mixture was directly loaded onto the prep HPLC for purification. The fractions containing the expected product were
 5 combined and concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-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, 8.02 μmol, 34.5% yield) as a clear,
 10 colorless film. LCMS: m/e 673.5 (M+H)⁺, 1.75 min (method 2). ¹H NMR (500MHz, *Acetic acid d*₄) δ 7.96 (t, *J*=7.9 Hz, 1H), 7.09 (dd, *J*=7.9, 1.2 Hz, 1H), 7.03 (d, *J*=11.9 Hz, 1H), 5.42 (d, *J*=4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.58 - 3.40 (m, 4H), 3.26 - 3.16 (m, 2H), 2.94 - 2.85 (m, 1H), 2.56 - 2.48 (m, 2H), 1.76 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 2.29 - 0.85 (m, 26H).

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Example A6

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

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Step 1. Preparation of benzoic acid, 4-

[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester.

To a vial containing *N*-(3-hydroxypropyl)thiomorpholine-1,1-dioxide (0.15 g, 0.776 mmol) was added DMAP (9.48 mg, 0.078 mmol) and TEA (0.162 mL, 1.164 mmol). The mixture was diluted with d-chloroform (2 mL) and was cooled to 0 °C. To the cooled solution was added trifluoromethanesulfonic anhydride (0.144 mL, 0.854 mmol) slowly. The mixture turned orange as the anhydride was added and became a thick gel which did not stir well. After 2 h the mixture was diluted with an additional 1 mL of d-chloroform and was used directly in the following reaction as the crude reaction mixture.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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)-2-fluorobenzoate (50 mg, 0.089 mmol) was added potassium iodide (39.9 mg, 0.240 mmol) and phosphoric acid, potassium salt (83 mg, 0.392 mmol). The mixture was diluted with acetonitrile (1 mL) and a solution of the crude mixture from the reaction above (1.718 mL, 0.445 mmol) was added. The mixture was flushed with N₂ and the vial was sealed and heated to 120 °C. After stirring the mixture for 66 h it was cooled to rt. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 12 g Thomson silica gel column and a 0-5% MeOH in DCM gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester (43 mg, 0.058 mmol, 65.6% yield) as a yellow film. LCMS: m/e 737.5 (M+H)⁺, 1.88 min (method 2).

Step 2. Preparation of benzoic acid, 4-

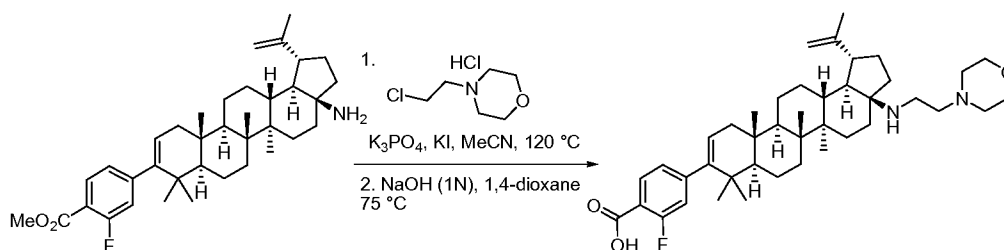
[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-.

To a solution of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester (0.043 g, 0.058 mmol) in 1,4-dioxane (1 mL) was added NaOH (1M) (0.5 mL, 0.500 mmol). The mixture was heated to 60 °C for 15.25h and was cooled to rt. The mixture was directly loaded onto the prep HPLC for purification. The fractions containing the expected product were combined and concentrated under reduced pressure to give benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro- (13.2 mg, 0.017 mmol, 29.4% yield) as a white solid. LCMS: m/e 723.5 (M+H)⁺, 1.62 min (method 2). ¹H NMR (400MHz, *Acetic acid d4*) δ 7.92 (t, J=7.9 Hz, 1H), 7.04 (d, J=8.0 Hz, 1H), 6.98 (d, J=11.8 Hz, 1H), 5.38 (d, J=4.8 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.71 (br. s., 4H), 3.48 (br. s., 4H), 3.25 (t, J=7.5 Hz, 4H), 2.82 (br. s., 1H), 2.46 - 2.30 (m, 2H), 1.72 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.24 - 0.82 (m, 22H).

Example A7

Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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 2-fluoro-4-

5 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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 sealable flask containing methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-
 10 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)-2-fluorobenzoate hydrochloride (0.1 g, 0.167 mmol) was added 4-(2-chloroethyl)morpholine hydrochloride (0.093 g, 0.501 mmol), phosphoric acid, potassium salt (0.156 g, 0.735 mmol) and potassium iodide (0.075 g, 0.451 mmol). The mixture was diluted with acetonitrile (3mL), was flushed
 15 with nitrogen, then the vial was sealed and heated to 120 °C. After heating the mixture for 16h, the mixture was cooled to rt. The crude product was adsorbed to silica gel then was purified by flash chromatography using a Thomson 12g silica gel column and a 0-5% methanol in dichloromethane gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give
 20 methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-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 (77 mg, 0.114 mmol, 68.3 % yield) as an off-white foam. LCMS: m/e 675.5 (M+H)⁺, 1.91 min (method 2).

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Step 2. To a solution of methyl 2-fluoro-4-

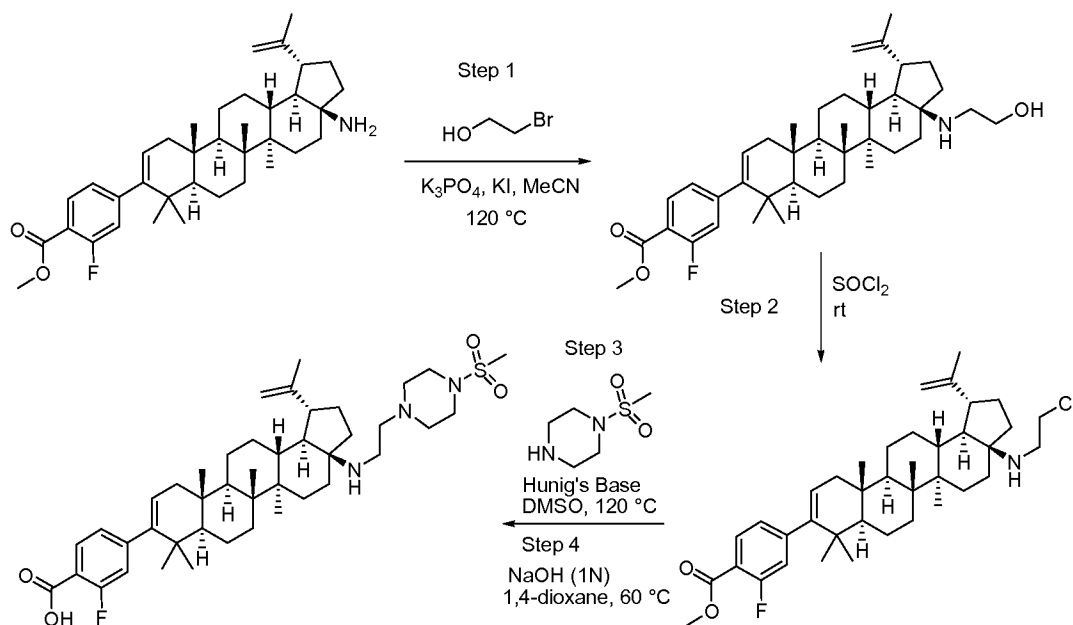
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoate (0.075 g, 0.111 mmol) in 1,4-Dioxane (1 mL) was added NaOH (1M) (0.5 mL, 0.500 mmol). The mixture was heated to 75 °C for 15h then was cooled to rt. The mixture was acidified with 1N HCl (3 mL) and was concentrated under reduced pressure. The residue was diluted with 15 mL of water and the solids that remained were collected by filtration and were washed with water then with ether. The compound was dissolved in DMF and methanol and was purified by prep HPLC. Fractions containing the expected product were combined and concentrated under reduced pressure to give 2-fluoro-4-
5 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-
10 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 (30 mg, 0.043 mmol, 38.8 % yield) as a white solid. LCMS: m/e 661.5 (M+H)⁺, 1.67 min (method 2). ¹H NMR (500 MHz, *Acetic acid d₄*) ppm 7.96 (1 H, t, *J*=7.9 Hz), 7.09 (1 H, dd, *J*=8.2, 1.2 Hz), 7.03 (1
15 H, d, *J*=11.6 Hz), 5.42 (1 H, d, *J*=4.6 Hz), 4.86 (1 H, s), 4.74 (1 H, s), 3.89 - 3.99 (4 H, m), 3.53 - 3.69 (4 H, m), 3.29 (4 H, br. s.), 2.81 - 2.90 (1 H, m), 1.77 (3 H, s), 1.23 (3 H, s), 1.13 (3 H, s), 1.08 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.85 - 2.26 (22 H, m).

Example A8

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**Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethylamino)-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-
25 cyclopenta[a]chrysen-9-yl)benzoic acid**



Step 1. Preparation of methyl 2-fluoro-4-

- 5 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-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 sealable flask containing methyl 4-

- 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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)-2-fluorobenzoate, HCl (1.0 g, 1.671 mmol) was added potassium iodide (0.694 g, 4.18 mmol), phosphoric acid, potassium salt (1.774 g, 8.36 mmol) and 2-bromoethanol (0.475 mL, 6.69 mmol). The mixture
- 15 was diluted with acetonitrile (15 mL) and the vial was sealed and heated to 120 °C for 21h then was cooled to rt and was diluted with water (50 mL). The solids were collected by filtration then were washed with water. The solids were purified by flash chromatography in silica gel using a 0-5% methanol in dichloromethane gradient with 0.1% ammonium hydroxide added to the mixture. The fractions containing the
- 20 expected product were combined and were concentrated under reduced pressure. The product was repurified a second time using a 0-20% EtOAc in hexanes gradient with 0.1% TEA added to the mixture. The fractions containing the product combined and were concentrated under reduced pressure to give methyl 2-fluoro-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-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 (0.135g, 0.223 mmol, 13% yield) as an off-white solid. LCMS: m/e 606.7 (M+H)⁺, 2.02 min (method 2).

Step 2. Preparation of methyl 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-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)-2-fluorobenzoate, HCl.

To a flask containing methyl 2-fluoro-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-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 (0.135 g, 0.223 mmol) was added thionyl chloride (2.5 ml, 34.3 mmol). The clear, colorless solution was stirred at rt for 2.5h the reaction was carefully quenched with water (20 mL) and the solids that formed were collected by filtration and were washed with water. The expected product, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-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)-2-fluorobenzoate, HCl (0.173 g, 0.262 mmol, 117 % yield), was isolated as an off-white solid which was directly used in the next step with no additional purification. LCMS: m/e 624.6 (M+H)⁺, 2.42 min (method 11).

Step 3. Preparation of methyl 2-fluoro-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-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)-2-fluorobenzoate, HCl (0.147 g, 0.223 mmol) in DMSO (2 mL) was added 1-methanesulfonyl-piperazine (0.073 g, 0.446 mmol) and Hunig's Base (0.195 mL, 1.115 mmol). Upon addition of the base, the solids dissolved. The solution was heated to 120 °C for 2h then was cooled to rt, was diluted with water (20 mL) and was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (2 x 30 mL) then with brine (20 mL), then were dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography in silica gel using a 0-50% ethyl acetate in hexanes gradient with 0.1% triethyl amine added to the mixture. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-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 (0.056 g, 0.074 mmol, 33.4 % yield) as an off-white solid. LCMS: m/e 752.7 (M+H)⁺, 1.95 min (method 2).

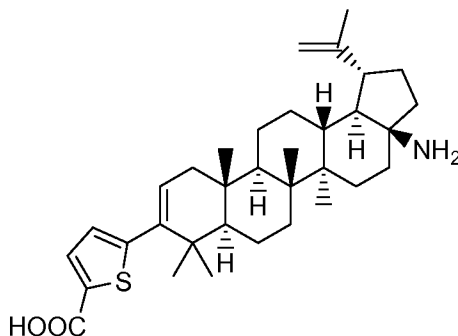
Step 4. To a solution of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.056 g, 0.074 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.372 mL, 0.372 mmol). The mixture was heated to 60 °C for 6.5 h then was cooled to rt. The mixture was diluted with methanol and 1,4-dioxane, was filtered through a plug of glass wool and was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-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 (30.1 mg, 0.039 mmol, 52.0 % yield) as a white solid. LCMS: m/e 738.6 (M+H)⁺, 1.66 min (method 2). ¹H NMR (400MHz, Acetic acid d₄) δ7.92 (t, J=7.9 Hz, 1H), 7.04 (dd, J=8.0, 1.5 Hz, 1H), 7.01 - 6.96 (m,

1H), 5.38 (d, $J=5.0$ Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.59 - 3.25 (m, 8H), 3.15 (br. s., 4H), 2.90 (s, 3H), 2.94 - 2.81 (m, 1H), 1.72 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.23 - 0.83 (m, 22H).

5 Section B. Amines (Continued)

Example B1

Preparation of 5-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-
 10 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)thiophene-2-carboxylic acid

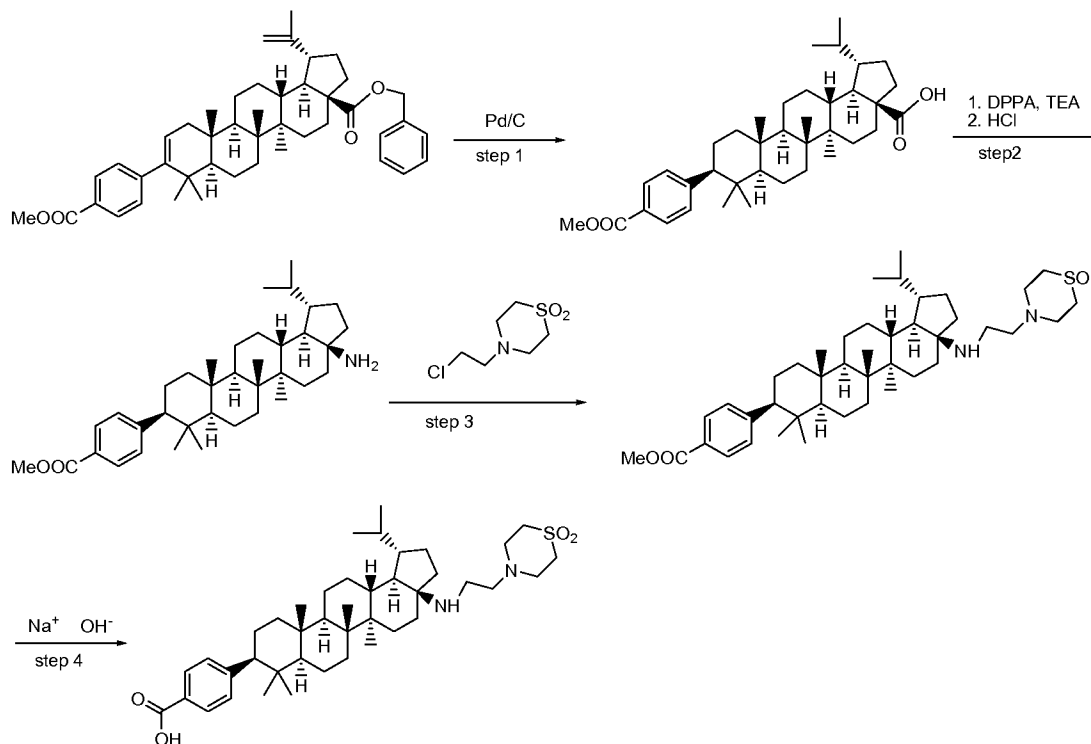


The title compound was prepared following the method described above for
 15 the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-
 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)-2-fluorobenzoic acid using 5-(methoxycarbonyl)thiophen-
 2-ylboronic acid as the coupling reagent in Step 1. The product was isolated as a
 20 white solid (2.7 mg, 44%). LCMS: m/e 536.30 ($M+H$)⁺, 2.25 min (method 10). ¹H
 NMR (500MHz, Acetic) δ 7.77 (d, $J=4.0$ Hz, 1H), 6.98 (d, $J=3.7$ Hz, 1H), 5.87 (d,
 $J=4.3$ Hz, 1H), 4.88 (s, 1H), 4.75 (s, 1H), 2.79 (td, $J=10.5, 6.7$ Hz, 1H), 2.35 - 2.13
 (m, 4H), 1.98 - 1.85 (m, 4H), 1.83 - 1.07 (m, 14H), 1.77 (s, 3H), 1.19 (s, 3H), 1.14 (s,
 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H).

25

Example B2

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



5

Step 1. Preparation of (1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid

- A mixture of palladium on carbon (67.4 mg, 0.063 mmol) and
 10 (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 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]chrysene-3a-carboxylate (140 mg, 0.211 mmol) in methanol (2mL) was stirred at 20 °C under hydrogen at 1 atmosphere of pressure for 20 hours. The
 15 reaction mixture was filtered through a celite pad to remove Pd/C. The filtrates were concentrated under reduced pressure to provide the title compound as a white solid (100 mg, 82%). LCMS: m/e 577.33 (M+H)⁺, 3.22 min (method 10).

Step 2. Preparation of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A mixture of (1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-9-
5 (4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (100 mg, 0.173 mmol), diphenyl phosphorazidate (0.056 mL, 0.260 mmol) and triethylamine (0.072 mL, 0.520 mmol) in toluene (4 mL) was refluxed for 18 hours. TLC indicated the consumption of starting material and the formation of desired product. The mixture was cooled to
10 room temperature, filtered through a silica gel pad and the filtrates were concentrated under reduced pressure to produce the desired intermediate as colorless oil. To this intermediate (70 mg, 0.122 mmol) in THF (4 mL) was added HCl (0.037 mL, 1.220 mmol). The reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was purified by chromatography in silica gel with 20-70% ethyl
15 acetate/hexanes to provide the title compound as white solid (50mg, 50%). LCMS: m/e 548.49 (M+H)⁺, 2.58 min (method 11).

Step 3. Preparation of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A mixture of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.091 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide (54.1 mg, 0.274 mmol), potassium phosphate (77 mg, 0.365 mmol) and potassium iodide
25 (36.4 mg, 0.219 mmol) in acetonitrile (2 mL) was heated up at 120 °C for 20 hours. The reaction mixture was quenched with distilled water (5 mL), extracted with dichloromethane (3x 5 mL), the organic phases were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the crude product as a yellow solid (40 mg, 62%). LCMS: m/e 709.53 (M+H)⁺, 2.46 min (method 11).

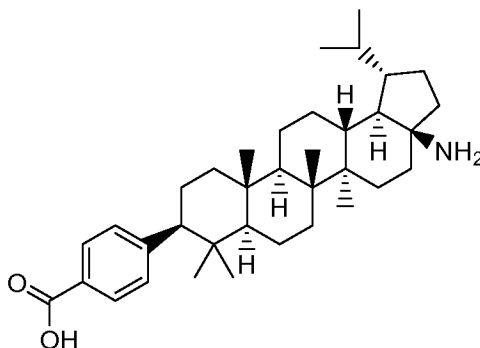
30

Step 4. Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.056 mmol) and sodium hydroxide (0.564 mL, 0.564 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and purified by HPLC to provide the title compound as white solid (30 mg, 73%). LCMS: m/e 695.46 (M+H)⁺, 2.55 min (method 10). ¹H NMR (500MHz, Acetic) δ 8.02 (d, $J=8.5$ Hz, 2H), 7.36 (d, $J=8.5$ Hz, 2H), 3.44 - 3.36 (m, 1H), 3.35 - 3.21 (m, 6H), 3.19 - 2.99 (m, 5H), 2.50 (dd, $J=13.0, 2.9$ Hz, 1H), 2.34 - 1.01 (m, 26H), 1.28 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.93 (d, $J=6.7$ Hz, 3H), 0.85 (d, $J=6.7$ Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Example B3

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

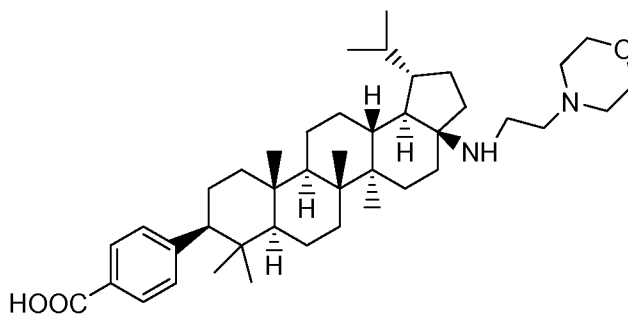


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoic acid using methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate as the starting material in Step 5. The product was isolated as a white solid (12 mg, 47%).

LCMS: m/e 532.43 (M-H)⁻, 2.37 min (method 10). ¹H NMR (500MHz, METHANOL- d_4) δ 7.84 (d, $J=8.2$ Hz, 2H), 7.19 (d, $J=8.2$ Hz, 2H), 2.42 (dd, $J=13.0$, 2.9 Hz, 1H), 2.18 (qd, $J=13.3$, 3.1 Hz, 1H), 2.07 - 1.24 (m, 25H), 1.16 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.93 (d, $J=6.7$ Hz, 3H), 0.83 (d, $J=6.7$ Hz, 3H), 0.79 (s, 3H), 0.74 (s, 3H).

Example B4

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

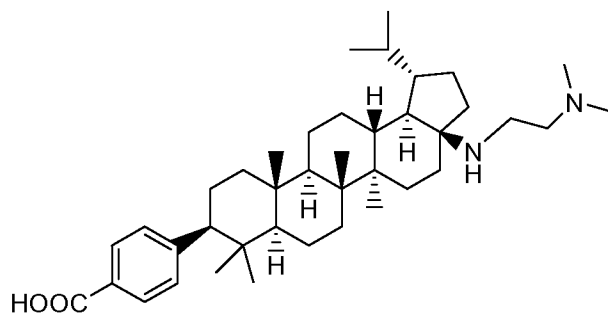


The title compound was prepared following the method described above for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(2-chloroethyl)morpholine as the alkylating reagent in Step 3. The product was isolated as a colorless oil (4 mg, 39%). LCMS: m/e 647.58 (M+H)⁺, 2.35 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.02 (d, $J=8.2$ Hz, 2H), 7.36 (d, $J=8.2$ Hz, 2H), 3.94 (d, $J=3.7$ Hz, 4H), 3.73 - 3.44 (m, 4H), 3.27 (br. s., 4H), 2.50 (d, $J=10.4$ Hz, 1H), 2.32 - 1.01 (m, 26H), 1.21 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 0.93 (d, $J=6.7$ Hz, 3H), 0.86 (d, $J=6.7$ Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

Example B5

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

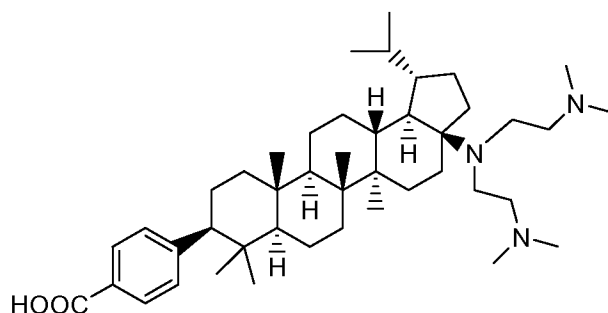
5



- The title compound was prepared following the method described above for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-
- 10 pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 2-chloro-N,N-dimethylethanamine as the alkylating reagent in Step 3. The product was isolated as a colorless oil (0.9 mg, 37%). LCMS: m/e 605.56 ($M+H$)⁺, 2.35 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.02 (d, $J=8.2$ Hz, 2H), 7.36 (d, $J=8.2$ Hz, 2H), 3.89 - 3.72 (m, 2H), 3.70 - 3.55 (m, 1H), 3.07 - 2.91 (m, 1H), 3.00 (s, 6H),
- 15 2.60 - 2.40 (m, 1H), 2.34 - 1.04 (m, 26H), 1.18 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.93 (d, $J=6.7$ Hz, 3H), 0.86 (d, $J=6.7$ Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

Example B6

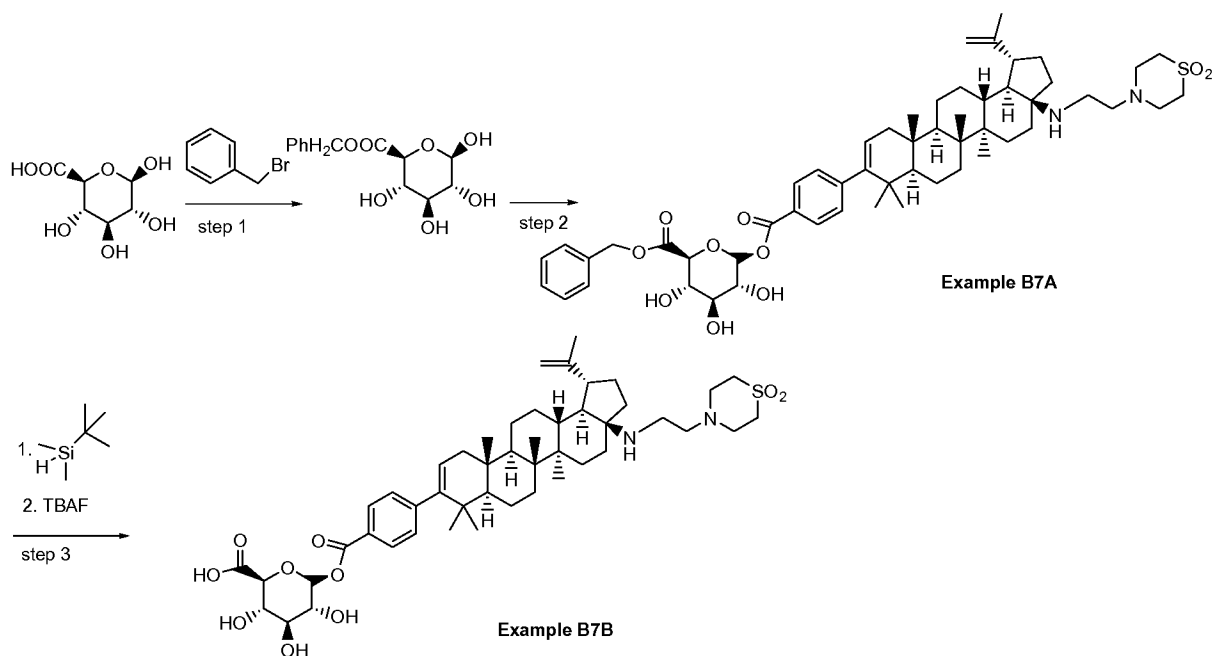
- 20 Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(bis(2-(dimethylamino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was obtained as a side product in the preparation 4-
 ((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-
 5 (dimethylamino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoic acid. The product was isolated as a colorless oil
 (0.7 mg, 26%). LCMS: m/e 676.63 (M+H)⁺, 2.33 min (method 11). ¹H NMR
 (500MHz, Acetic) δ 8.02 (d, J=8.2 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 4.33 - 4.09 (m,
 4H), 3.85 (br. s., 3H), 3.73 (br. s., 1H), 3.40 (s, 6H), 3.01 (s, 6H), 2.50 (d, J=14.0 Hz,
 10 1H), 2.37 - 1.04 (m, 26H), 1.17 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.93 (d, J=6.7 Hz,
 3H), 0.87 (d, J=6.7 Hz, 3H), 0.8s (s, 3H), 0.79 (s, 3H).

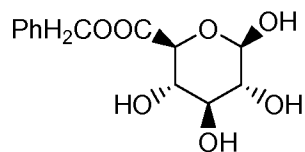
Example B7A and B7B

15 Preparation of (2S,3S,4S,5R,6R)-6-((4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
 dioxidothiomorpholino)ethyl)amino)-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)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-
 20 carboxylic acid



Step 1. Preparation of (2S,3S,4S,5R,6R)-benzyl 3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-carboxylate

5



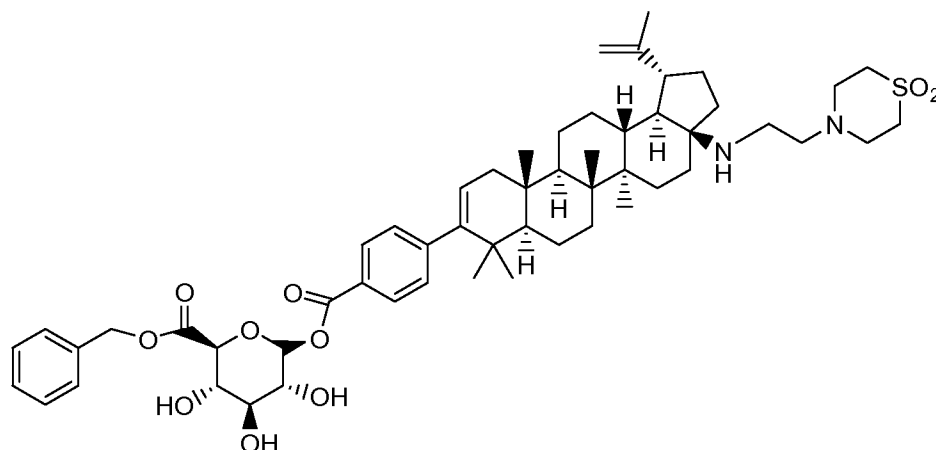
To a solution of (2S,3S,4S,5R,6R)-3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-carboxylic acid (1 g, 5.15 mmol) and TBAF in THF (6.18 mL, 6.18 mmol) in DMF (7 mL) was slowly added (bromomethyl)benzene (0.925 g, 5.41 mmol) at 0°C. The clear solution was warmed up to room temperature slowly and let it stir for 17 hours. TLC indicated the reaction was completed (20% iPrOH/CH₂Cl₂). The solvent was removed and the reaction residue was purified by silica gel chromatography with 10-20% iPrOH/CH₂Cl₂ to provide the desired product as a colorless oil (950 mg, 65%).

15 LCMS: m/e 283.31 (M-H)⁻, 2.55 min (method 10).

Step 2. Preparation of (2S,3S,4S,5R,6R)-benzyl 6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-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-

20

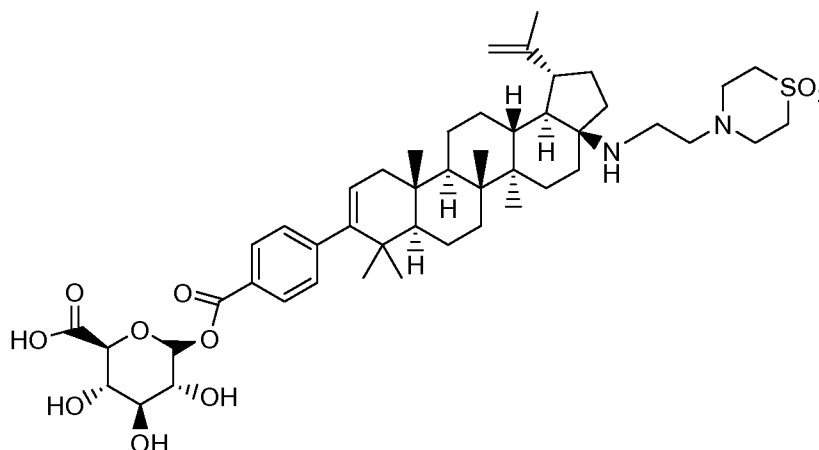
cyclopenta[a]chrysen-9-yl)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylate



- 5 A mixture of (2S,3S,4S,5R)-benzyl 3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-carboxylate (61.7 mg, 0.217 mmol), 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-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-
- 10 cyclopenta[a]chrysen-9-yl)benzoic acid (100 mg, 0.145 mmol), HATU (88 mg, 0.232 mmol) and N-methylmorpholine (0.048 mL, 0.434 mmol) in dioxane (3 mL) was stirred overnight at room temperature. The reaction mixture was filtered, the clear solution was purified by prep HPLC with acetonitrile/water/ammonium acetate to provide the desired product as white solid (20 mg, 14%). LCMS: m/e 957.7 (M+H)⁺,
- 15 2.36 min (method 6). ¹H NMR (500MHz, Acetic) δ 8.05 (d, J=8.2 Hz, 2H), 7.58 - 7.14 (m, 7H), 5.95 (d, J=7.6 Hz, 1H), 5.38 (d, J=4.6 Hz, 1H), 5.26 (s, 2H), 4.84 (s, 1H), 4.74 (s, 1H), 4.30 (d, J=9.5 Hz, 1H), 4.05 - 3.78 (m, 3H), 3.46 (d, J=11.9 Hz, 1H), 3.38 - 3.22 (m, 6H), 3.20 - 3.11 (m, 3H), 3.07 (br. s., 2H), 2.95 (dt, J=10.8, 5.5 Hz, 1H), 2.42 - 1.01 (m, 22H), 1.77 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H),
- 20 1.03 (s, 3H), 1.00 (s, 3H).

- Step 3. Preparation of (2S,3S,4S,5R,6R)-6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-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-
- 25

cyclopenta[a]chrysen-9-yl)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid

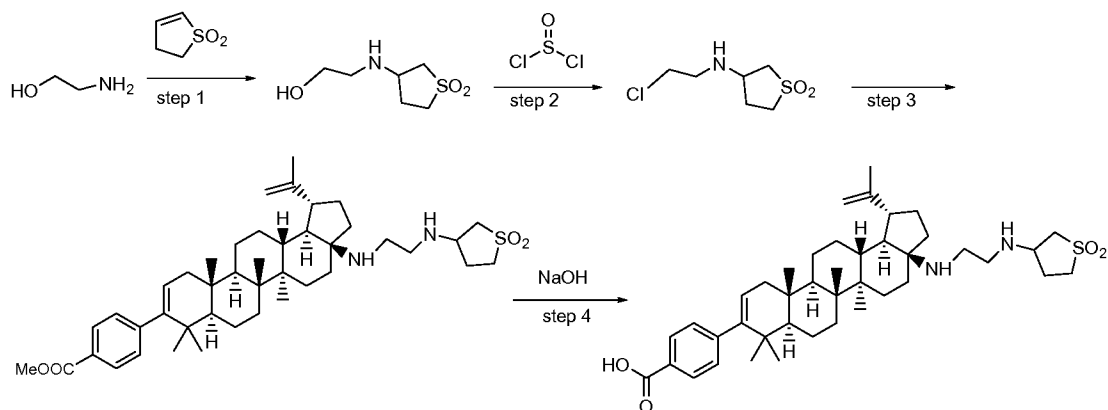


- 5 A mixture of (2S,3S,4S,5R,6R)-benzyl 6-((4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
 dioxidomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-
 10 carboxylate (8 mg, 8.36 μmol), tert-butyldimethylsilane (1.943 mg, 0.017 mmol),
 palladium acetate (3.75 mg, 0.017 mmol) and triethylamine (5.82 μl , 0.042 mmol) in
 dichloroethane (1 mL) was heated up at 60 $^{\circ}\text{C}$ for 2 hours. The reaction mixture was
 cooled to room temperature, filtered and the filtrates were concentrated to provide the
 residue. To this residue in THF (1.0 mL) was added TBAF (10.93 mg, 0.042 mmol),
 15 the reaction mixture was stirred for 1 hours. The reaction mixture was then purified
 by prep. HPLC to provide the desired product as a colorless oil (4 mg, 52%). LCMS:
 m/e 867.69 ($\text{M}+\text{H}^+$), 2.42 min (method 10). ^1H NMR (500MHz, Acetic) δ 8.06 (d,
 $J=8.2$ Hz, 2H), 7.31 (d, $J=8.2$ Hz, 2H), 5.96 (d, $J=7.9$ Hz, 1H), 5.37 (d, $J=4.4$ Hz,
 1H), 4.84 (s, 1H), 4.74 (s, 1H), 4.40 - 4.16 (m, 1H), 4.02 - 3.76 (m, 3H), 3.46 (d,
 20 $J=12.3$ Hz, 1H), 3.37 - 3.22 (m, 6H), 3.20 - 3.11 (m, 3H), 3.07 (br. s., 2H), 3.00 - 2.82
 (m, 1H), 2.37 - 1.03 (m, 22H), 1.76 (s, 3H), 1.29 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H),
 1.02 (s, 3H), 0.99 (s, 3H).

Example B8

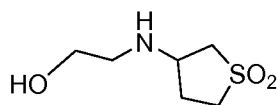
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

5



Step 1. Preparation of 3-((2-hydroxyethyl)amino)tetrahydrothiophene 1,1-dioxide

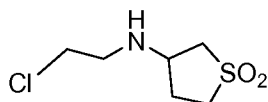
10



A mixture of 2-aminoethanol (310 mg, 5.08 mmol), triethylamine (514 mg, 5.08 mmol) and 2,3-dihydrothiophene 1,1-dioxide (200 mg, 1.693 mmol) in ethanol (3 mL) was heated up at 78 °C for 16 hours. TLC indicated the starting material was consumed and desired product was formed (30% methanol/ethyl acetate). The reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel chromatography with 0-35% methanol/ethyl acetate to provide the title compound as a colorless oil (260 mg, 86%). ¹H NMR (400MHz, CHLOROFORM-d) δ 3.78 - 3.56 (m, 3H), 3.38 - 3.21 (m, 2H), 3.14 - 3.00 (m, 1H), 2.94 (dd, *J*=13.3, 6.0 Hz, 1H), 2.85 - 2.68 (m, 2H), 2.53 - 2.34 (m, 1H), 2.22 - 2.03 (m, 1H).

20

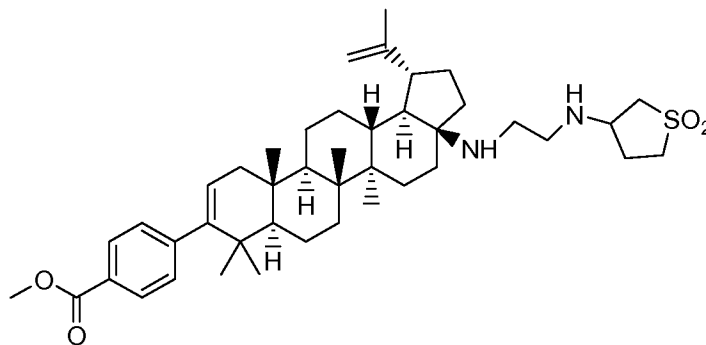
Step 2. Preparation of 3-((2-chloroethyl)amino)tetrahydrothiophene 1,1-dioxide



25

A mixture of 3-((2-hydroxyethyl)amino)tetrahydrothiophene 1,1-dioxide (260 mg, 1.451 mmol) and sulfurous dichloride (863 mg, 7.25 mmol) in dichloroethane (3 mL) was heated up at 78 °C for 3 hours. The mixture was cooled to room temperature and concentrated under reduced pressure to provide the black oil. To this black oil
 5 was added THF(5 mL) and dichloromethane (5 mL), grey-white solid was observed. The solid was filtered and collected to provide the desired product as a grey solid (230 mg, 80%). LCMS: m/e 198.1 (M+H)⁺, 0.60 min (method 6).

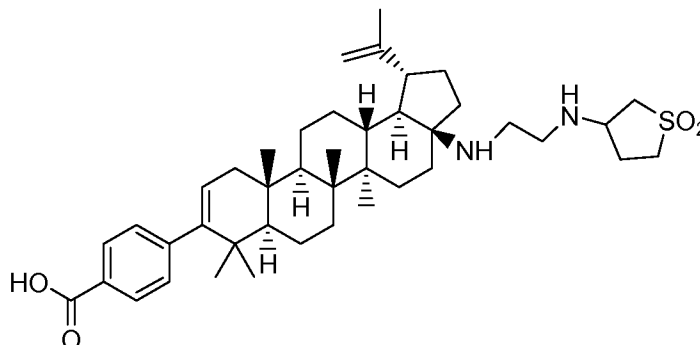
Step 3. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-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, 0.092 mmol), 3-((2-chloroethyl)amino)tetrahydrothiophene 1,1-dioxide (45.4 mg, 0.230 mmol),
 20 potassium phosphate (58.5 mg, 0.276 mmol) and potassium iodide (30.5 mg, 0.184 mmol) in acetonitrile (1 mL) was heated up at 120 °C for 18 hours. The reaction mixture was quenched with distilled water (3 mL), extracted with dichloromethane (3x 3 mL), the organic phases were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the crude product as a white solid
 25 (40mg, 62%). LCMS: m/e 705.48 (M+H)⁺, 2.44 min (method 11).

Step 4. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-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

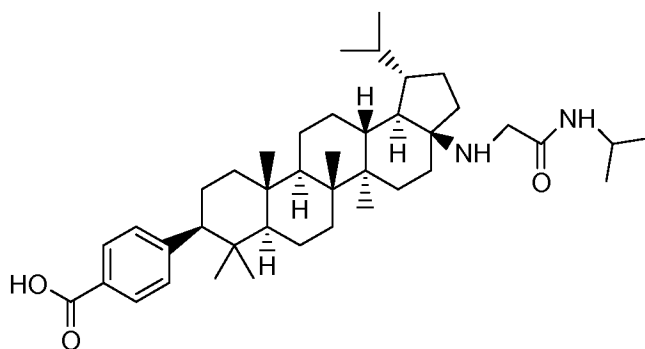
A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.057 mmol) and sodium hydroxide (0.567 mL, 0.567 mmol) in dioxane (1 mL) was heated up at 78 °C for 3 hours. The reaction mixture was cooled to room temperature, filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (26 mg, 63%). LCMS: m/e 691.46 (M+H)⁺, 2.24 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.04 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 5.37 (d, J=4.9 Hz, 1H), 4.87 (s, 1H), 4.75 (s, 1H), 4.06 (quin, J=7.7 Hz, 1H), 3.67 - 3.45 (m, 4H), 3.44 - 3.34 (m, 1H), 3.33 - 3.11 (m, 2H), 2.92 - 2.80 (m, 1H), 2.77 - 2.59 (m, 1H), 2.42 - 2.29 (m, 1H), 2.26 - 1.02 (m, 23H), 1.77 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

20

Example B9

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-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

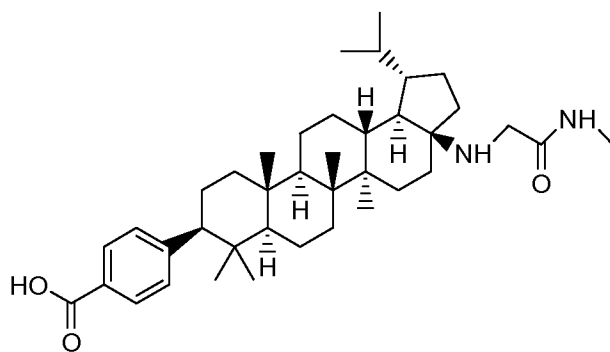
25



A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-
 (isopropylamino)-2-oxoethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 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 (15 mg, 0.024 mmol) and Pd/C (7.61 mg,
 7.16 μ mol) in methanol (1 mL) and ethyl acetate (1.000 mL) was stirred for 12 hours
 at room temperature under hydrogen at 1 atmosphere of pressure. The reaction
 mixture was filtered and the solution was purified by HPLC to provide the title
 10 compound as a white solid (6 mg, 38%). LCMS: m/e 633.48 ($M+H$)⁺, 2.62 min
 (method 10). ¹H NMR (500MHz, Acetic) δ 8.02 (d, $J=8.2$ Hz, 2H), 7.36 (d, $J=8.5$
 Hz, 2H), 4.17 (d, $J=15.6$ Hz, 1H), 4.09 (quin, $J=6.6$ Hz, 1H), 3.82 (d, $J=15.3$ Hz, 1H),
 2.50 (dd, $J=13.1, 2.7$ Hz, 1H), 2.34 - 1.05 (m, 26H), 1.27 (s, 3H), 1.19 (s, 3H), 1.18 (s,
 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.94 (d, $J=6.7$ Hz, 3H), 0.86 (d, $J=6.7$ Hz, 3H), 0.84
 15 (s, 3H), 0.80 (s, 3H).

Example B10

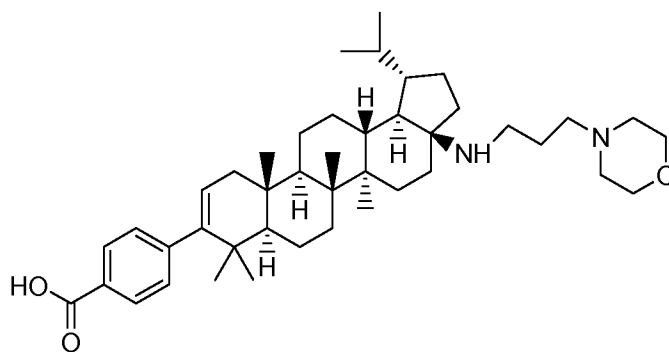
Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-
 20 5a,5b,8,8,11a-pentamethyl-3a-((2-(methylamino)-2-oxoethyl)amino)icosahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-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-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylamino)-2-oxoethyl)amino)-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 the starting material. The product was isolated as a white solid (3 mg, 28%). LCMS: m/e 605.45 ($M+H$)⁺, 2.58 min (method 10). ¹H NMR (500MHz, Acetic) δ 8.02 (d, $J=8.2$ Hz, 2H), 7.36 (d, $J=8.2$ Hz, 2H), 4.22 (d, $J=15.6$ Hz, 1H), 3.85 (d, $J=15.6$ Hz, 1H), 2.87 (s, 3H), 2.50 (dd, $J=13.1, 2.4$ Hz, 1H), 2.35 - 1.02 (m, 26H), 1.28 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.95 (d, $J=6.7$ Hz, 3H), 0.87 (d, $J=6.7$ Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Example B11

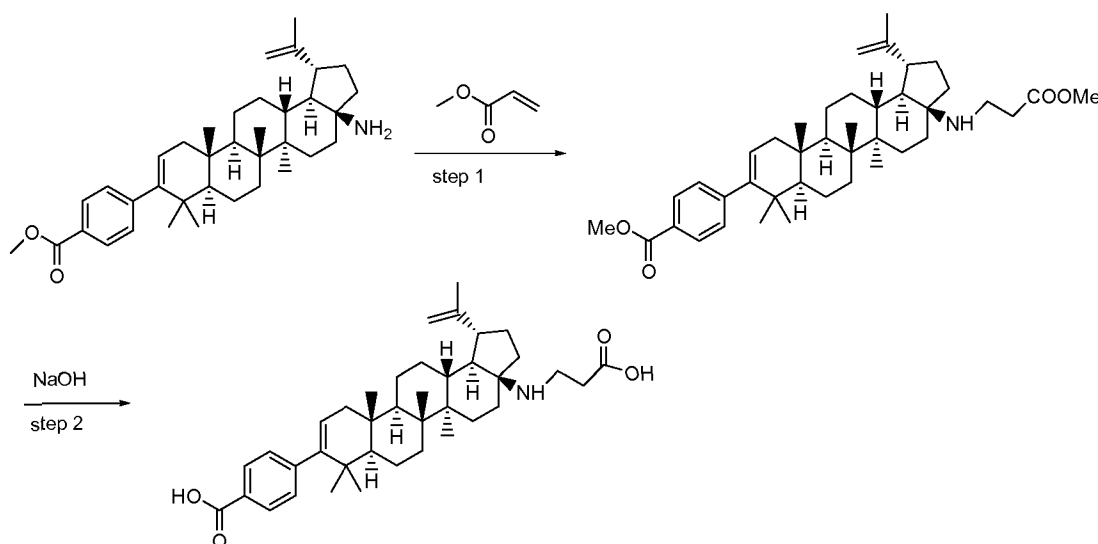
Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((3-morpholinopropyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



- The title compound was prepared following the method described above for the synthesis 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-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-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((3-morpholinopropyl)amino)-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 the starting material. The product was isolated as a white solid (5 mg, 40%). LCMS: m/e 659.55 ($M+H$)⁺, 2.86 min (method 10). ¹H NMR (500MHz, Acetic) δ 8.04 (d, $J=8.5$ Hz, 2H), 7.30 (d, $J=8.2$ Hz, 2H), 5.38 (d, $J=4.6$ Hz, 1H), 3.98 (br. s., 4H), 3.47 - 3.14 (m, 6H), 2.58 - 2.34 (m, 1H), 2.30 - 1.04 (m, 27H), 1.21 (s, 3H), 1.11 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.93 (d, $J=6.7$ Hz, 4H), 0.86 (d, $J=6.7$ Hz, 3H).

Example B12

- 20 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxyethyl)amino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((3-methoxy-3-oxopropyl)amino)-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 mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 amino-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, 0.037 mmol), methyl acrylate (0.013 mL,
 0.147 mmol) and triethylamine (0.026 mL, 0.184 mmol) in ethanol (1 mL) was
 refluxed for 5 hours. The reaction mixture was cooled to room temperature and then
 concentrated under reduced pressure to provide the desired product as a yellow oil (15
 mg 65%). LCMS: m/e 630.43 ($M+H$)⁺, 3.81 min (method 10).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-
 carboxyethyl)amino)-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

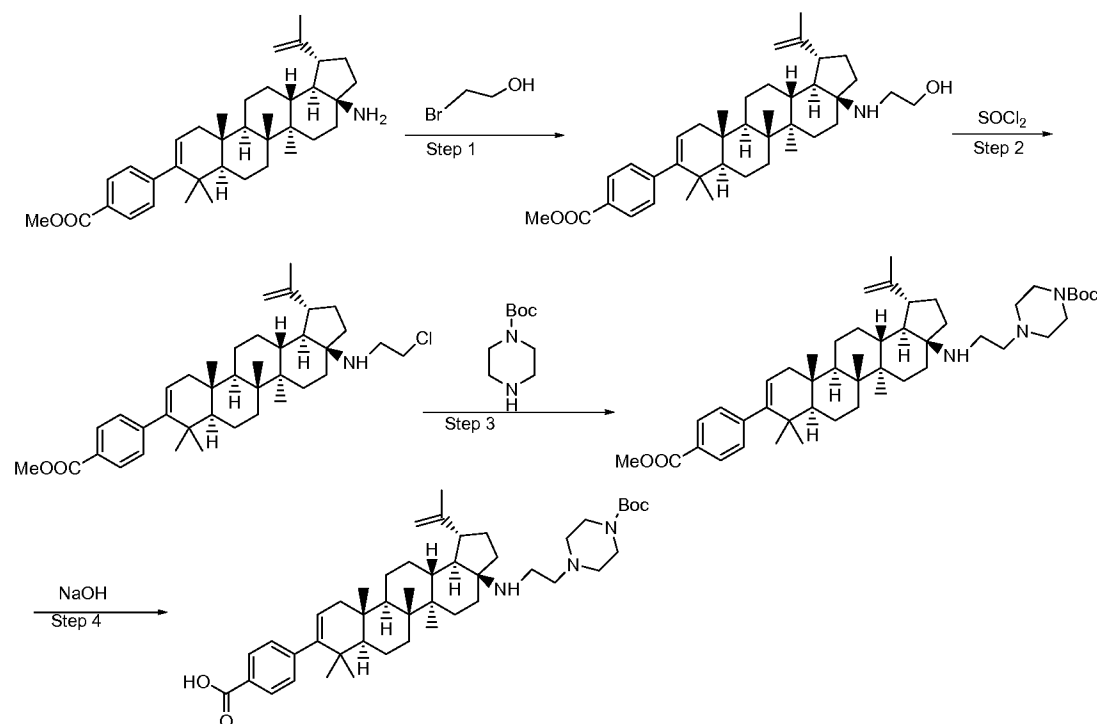
A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-
 methoxy-3-oxopropyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoate (15 mg, 0.024 mmol) and sodium hydroxide
 (0.238 mL, 0.238 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The

reaction mixture was cooled to room temperature and then filtered, the clear solution was purified by HPLC to provide the title compound as a white solid (5 mg, 33%).

LCMS: m/e 602.43 ($M+H$)⁺, 2.25 min (method 10). ¹H NMR (500MHz, Acetic) δ 8.04 (d, $J=8.2$ Hz, 2H), 7.30 (d, $J=8.2$ Hz, 2H), 5.37 (d, $J=4.9$ Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.39 (t, $J=4.4$ Hz, 2H), 3.17 - 3.02 (m, 1H), 2.98 - 2.80 (m, 2H), 2.31 - 1.02 (m, 22H), 1.77 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B13

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-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 mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 5 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 (1500 mg, 2.76 mmol), 2-bromoethanol (1034 mg, 8.27 mmol), potassium phosphate (1756 mg, 8.27 mmol) and potassium iodide (916 mg, 5.52 mmol) in acetonitrile (10 mL) was heated up at 120 °C for 15 hours. The reaction mixture was poured into distilled water (40 mL). The white precipitate
10 was filtered and washed with distilled water (100 mL). The white solid was dried under vacuum to provide the desired product (1.4g, 86%). LCMS: m/e 588.5 (M+H)⁺, 2.40 min (method 11).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
15 ((2-chloroethyl)amino)-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 mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 20 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 (1400 mg, 2.381 mmol) and thionyl chloride (1.738 mL, 23.81 mmol) in dichloroethane (15 mL) was heated up at 60 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to provide the desired product as brown solid (1.3g, 90%). LCMS: m/e 606.48 (M+H)⁺, 2.46 min
25 (method 11).

Step 3. Preparation of tert-butyl 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
30 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)amino)ethyl)piperazine-1-carboxylate

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-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 (230 mg, 0.379 mmol), Hunig's Base (0.331 mL,

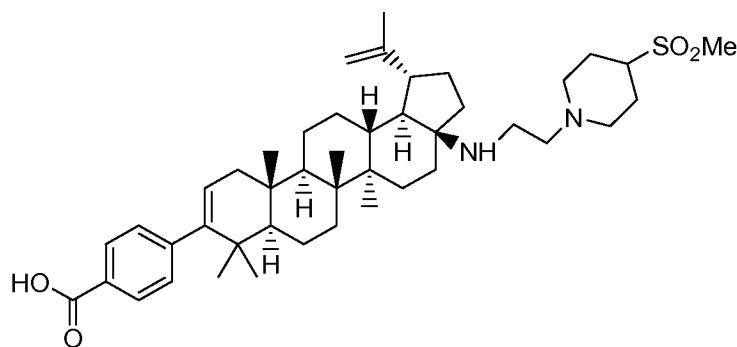
1.895 mmol) and tert-butyl piperazine-1-carboxylate (141 mg, 0.759 mmol) in DMSO (3 mL) was heated up at 120 °C for 1 hour. The reaction mixture was quenched with water (10 mL), extracted with ethyl acetate (3x8 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the crude, the crude was purified by silica gel chromatography with 0-30% ethyl acetate/hexanes to provide the desired product as a white solid (150 mg, 52%).
LCMS: m/e 756.66 (M+H)⁺, 2.50 min (method 11).

Step 4. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-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

A mixture of tert-butyl 4-(2-(((1R,3aS,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)amino)ethyl)piperazine-1-carboxylate (4 mg, 5.29 μmol) and sodium hydroxide (0.053 mL, 0.053 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and the clear solution was purified by HPLC to provide the desired product as white solid (1.6 mg, 39%).
LCMS: m/e 742.65 (M-H)⁻, 2.68 min (method 10). ¹H NMR (500MHz, Acetic) δ 8.03 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 5.37 (d, J=4.6 Hz, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 3.73 (br. s., 4H), 3.66 - 3.45 (m, 4H), 3.21 (br. s., 4H), 2.98 - 2.75 (m, 1H), 2.31 - 1.00 (m, 22H), 1.77 (s, 3H), 1.50 (s, 9H), 1.23 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B14

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-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



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-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-(methylsulfonyl)piperidine as the alkylating reagent in Step 3. The product was isolated as a white solid (200 mg, 84%).

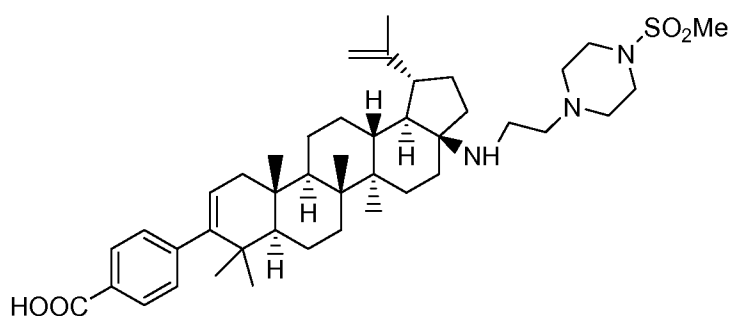
LCMS: m/e 719.58 ($M+H$)⁺, 2.31 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.04 (d, $J=8.5$ Hz, 2H), 7.30 (d, $J=8.2$ Hz, 2H), 5.37 (d, $J=4.6$ Hz, 1H), 4.87 (s, 1H), 4.75 (s, 1H), 3.76-3.70 (m, 2H), 3.68 - 3.54 (m, 4H), 3.48 - 3.29 (m, 1H), 3.18 - 3.03 (m, 2H), 3.02 (s, 3H), 2.84 (td, $J=11.8, 4.7$ Hz, 1H), 2.46 - 1.03 (m, 26H), 1.77 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

15

Example B15

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-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

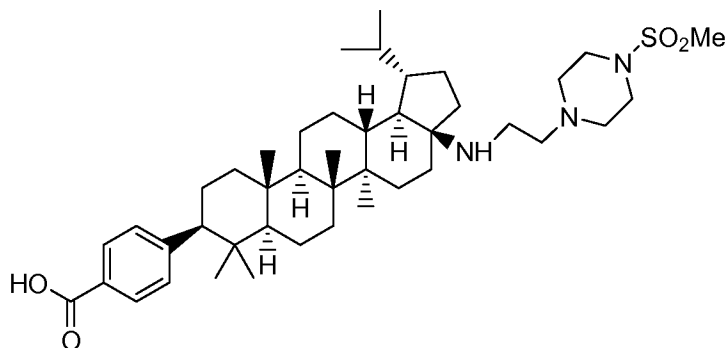
20



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-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 1-(methylsulfonyl)piperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (220 mg, 89%). LCMS: m/e 720.58 (M+H)⁺, 2.25 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.04 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 5.37 (d, J=4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.74 - 3.38 (m, 7H), 3.37 - 3.25 (m, 1H), 3.17 (br. s., 4H), 2.94 (s, 3H), 2.91 - 2.80 (m, 1H), 2.35 - 1.01 (m, 22H), 1.77 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B16

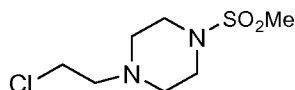
Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described in Example B2 for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine (prepared as described below) as the alkylating reagent in Step 3. The product was isolated as a white solid (11 mg, 56%).

LCMS: m/e 724.6 (M+H)⁺, 2.44 min (method 10). ¹H NMR (500MHz, Acetic) δ 8.02 (d, $J=8.2$ Hz, 2H), 7.36 (d, $J=8.2$ Hz, 2H), 3.63 - 3.29 (m, 7H), 3.25 - 3.14 (m, 1H), 3.13 - 2.99 (m, 4H), 2.93 (s, 3H), 2.50 (dd, $J=13.0, 2.6$ Hz, 1H), 2.32 - 0.98 (m, 26H), 1.25 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 0.93 (d, $J=6.7$ Hz, 3H), 0.86 (d, $J=6.7$ Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

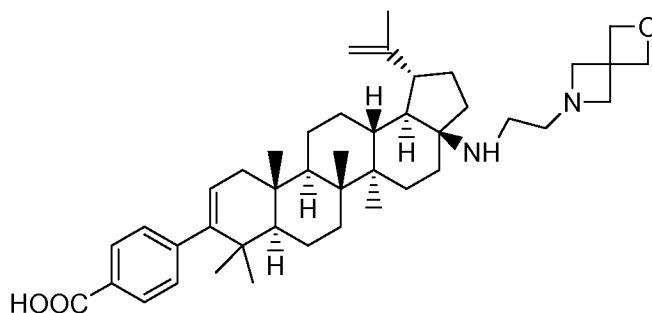
Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine



A mixture of 1-(methylsulfonyl)piperazine (250 mg, 1.522 mmol), potassium carbonate (1262 mg, 9.13 mmol) and 1-bromo-2-chloroethane (1092 mg, 7.61 mmol) in acetonitrile (5 mL) was stirred for 6 hours at room temperature. LCMS indicated the formation of desired product. The reaction mixture was filtered to remove the white precipitate, then quenched with distilled water (10 mL), extracted with ethyl acetate (3x8 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the clean desired product as white solid (100 mg, 29%). LCMS: m/e 227.15 (M+H)⁺, 1.21 min (method 10).

Example B17

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)ethyl)amino)-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



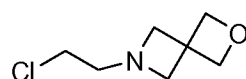
25

The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-

dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-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 6-(2-chloroethyl)-2-oxa-6-

- 5 3. The product was isolated as a white solid (1.1 mg, 18%). LCMS: m/e 655.53 (M+H)⁺, 2.29 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.04 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.5 Hz, 2H), 5.37 (d, J=4.9 Hz, 1H), 4.93 (s., 4H), 4.86 (s, 1H), 4.75 (br. s., 1H), 4.71 - 4.32 (m, 4H), 4.05 - 3.86 (m, 2H), 3.70 - 3.40 (m, 2H), 3.00 - 2.66 (m, 1H), 2.25 - 1.05 (m, 22H), 1.76 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H),
10 1.02 (s, 3H), 1.00 (s, 3H).

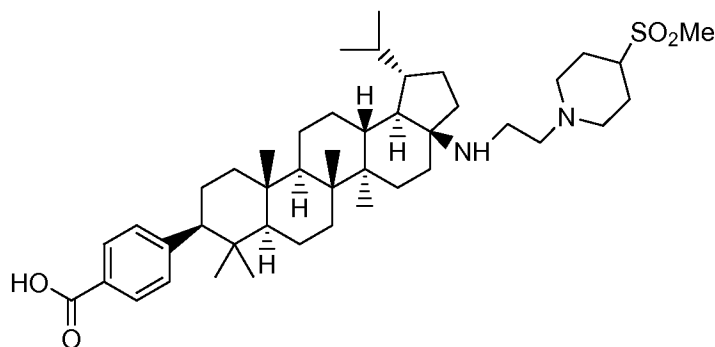
Preparation of 6-(2-chloroethyl)-2-oxa-6-azaspiro[3.3]heptane



- 15 The title compound was prepared following the method described above for the synthesis of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine using 2-oxa-6-azaspiro[3.3]heptane as the starting reagent. The product was isolated as colorless oil (10 mg, 12%). LCMS: m/e 162.15 (M+H)⁺, 0.87 min (method 10).

20 Example B18

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

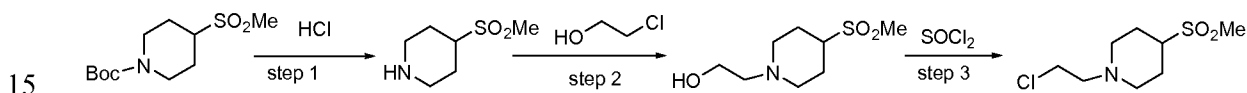


25

The title compound was prepared following the method described in above for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylcosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)-4-(methylsulfonyl)piperidine (prepared as described below) as the alkylating reagent in Step 3. The product was isolated as a white solid (24 mg, 36%).

LCMS: m/e 723.56 ($M+H$)⁺, 2.28 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.02 (d, $J=8.2$ Hz, 2H), 7.36 (d, $J=8.2$ Hz, 2H), 3.77 - 3.63 (m, 2H), 3.62 - 3.54 (m, 3H), 3.50 (d, $J=5.5$ Hz, 1H), 3.35 (td, $J=11.4$, 3.7 Hz, 1H), 3.08 - 2.89 (m, 2H), 3.02 (s, 3H), 2.50 (d, $J=13.1$ Hz, 1H), 2.42 - 2.29 (m, 2H), 2.28 - 1.03 (m, 28H), 1.21 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 1.01 (d, $J=11.3$ Hz, 1H), 0.93 (d, $J=6.7$ Hz, 4H), 0.86 (d, $J=6.7$ Hz, 4H), 0.83 (s, 3H), 0.79 (s, 3H).

Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperidine



Step 1. Preparation of 4-(methylsulfonyl)piperidine



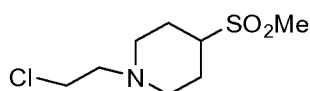
A mixture of tert-butyl 4-(methylsulfonyl)piperidine-1-carboxylate (1.5 g, 5.70 mmol) and hydrogen chloride (7.12 mL, 28.5 mmol) in THF (20 mL) was stirred at 20 °C for 15 hours. TLC indicated the formation of desired product, the reaction mixture was filtered and the pale yellow solid was collected to provide desired product (1 g, 88%). LCMS: m/e 163.96 ($M+H$)⁺, 0.25 min (method 10).

Step 2. Preparation of 2-(4-(methylsulfonyl)piperidin-1-yl)ethanol



A mixture of 4-(methylsulfonyl)piperidine hydrochloride (900 mg, 4.51 mmol), 2-bromoethanol (1126 mg, 9.01 mmol) and potassium carbonate (1869 mg, 13.52 mmol) in acetonitrile (4 mL) was heated up at 60 °C for 13 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to provide the crude, the crude was purified by 0-35% ethyl acetate/methanol to provide the desired product as colorless oil (620 mg, 66%). LCMS: m/e 208.1 (M+H)⁺, 0.27 min (method 6).

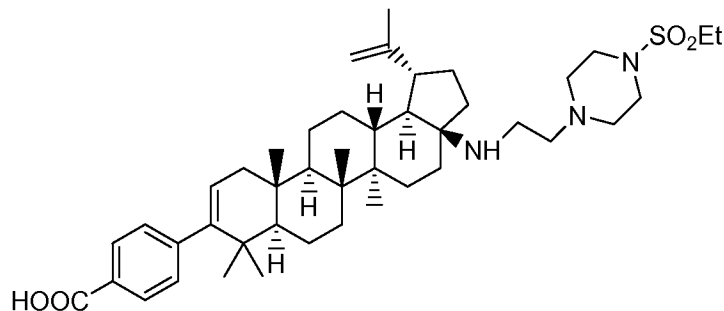
Step 3. Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperidine



A mixture of 2-(4-(methylsulfonyl)piperidin-1-yl)ethanol (620 mg, 2.99 mmol) and thionyl chloride (1.092 mL, 14.95 mmol) in dichloroethane (5 mL) was heated up at 74 °C for 4 hours. The reaction mixture was concentrated under reduced pressure to provide the crude, to the crude was added THF (10 mL), the grey precipitate was observed and collected. The solid was dried under vacuum for 20 hour to provide the desired product as grey solid (400mg, 59%). LCMS: m/e 226.1 (M+H)⁺, 1.00 min (method 6).

Example B19

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ethylsulfonyl)piperazin-1-yl)ethyl)amino)-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

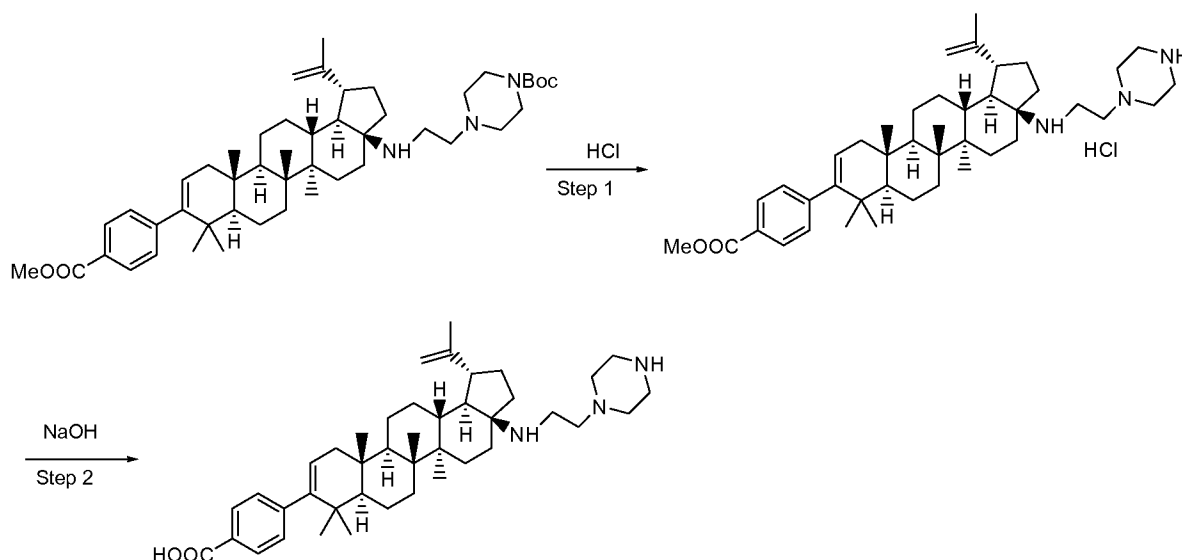


The title compound was prepared following the method described in above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(ethylsulfonyl)piperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (11 mg, 53%).

LCMS: m/e 734.56 ($M+H$)⁺, 2.28 min (method 11). ¹H NMR (400MHz, Acetic) δ 7.99 (d, $J=8.5$ Hz, 2H), 7.26 (d, $J=8.3$ Hz, 2H), 5.34 (d, $J=4.5$ Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.63 - 3.28 (m, 7H), 3.26 - 3.16 (m, 1H), 3.14 - 2.98 (m, 6H), 2.95 - 2.75 (m, 1H), 2.33 - 1.06 (m, 22H), 1.73 (s, 3H), 1.32 (t, $J=7.4$ Hz, 3H), 1.23 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Example B20

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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

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

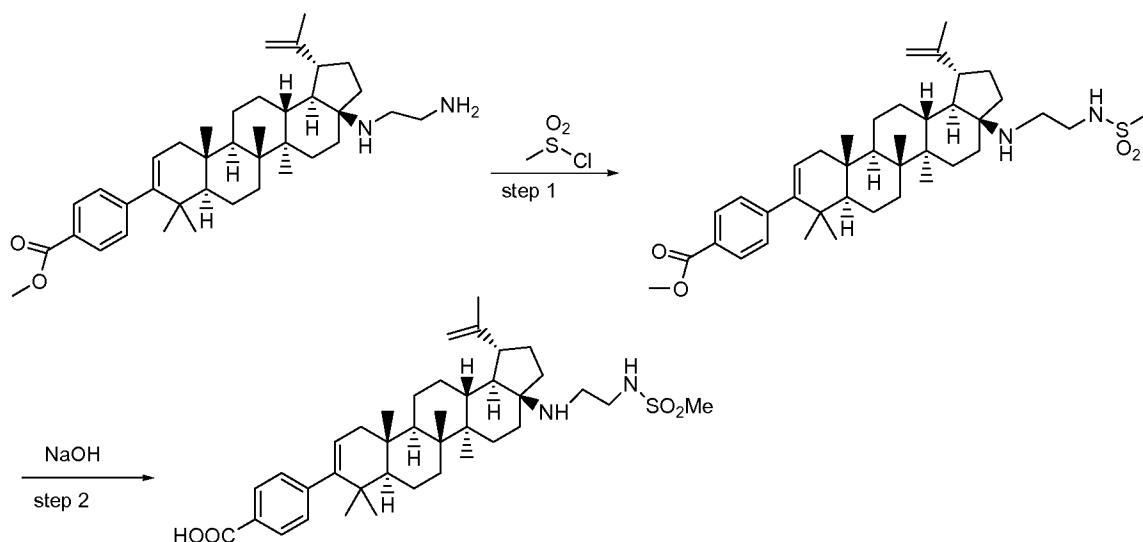
A mixture of tert-butyl 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperazine-1-carboxylate (150 mg, 0.198 mmol) and HCl (0.248 mL, 0.992 mmol) in THF (4 mL) was stirred at 20 °C for 18 hours. The reaction mixture was concentrated under reduced pressure to provide the desired product as brown solid (120 mg, 87%). LCMS: m/e 656.7 (M+H)⁺, 1.62 min (method 11).

Step 2. Preparation of 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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

A mixture of methyl 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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 (7.5 mg, 0.011 mmol) and sodium hydroxide (0.057 mL, 0.057 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and the clear solution was purified by HPLC to provide the desired product as white solid (2.3 mg, 31%). LCMS: m/e 642.62 (M+H)⁺, 2.29 min (method 11). ¹H NMR (400MHz, Acetic) δ 8.00 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 5.34 (d, J=4.8 Hz, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 3.59 - 3.28 (m, 6H), 3.25 - 3.11 (m, 1H), 3.09 - 2.73 (m, 6H), 2.31 - 1.15 (m, 22H), 1.73 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

Example B21

Preparation of 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
5 5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-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.

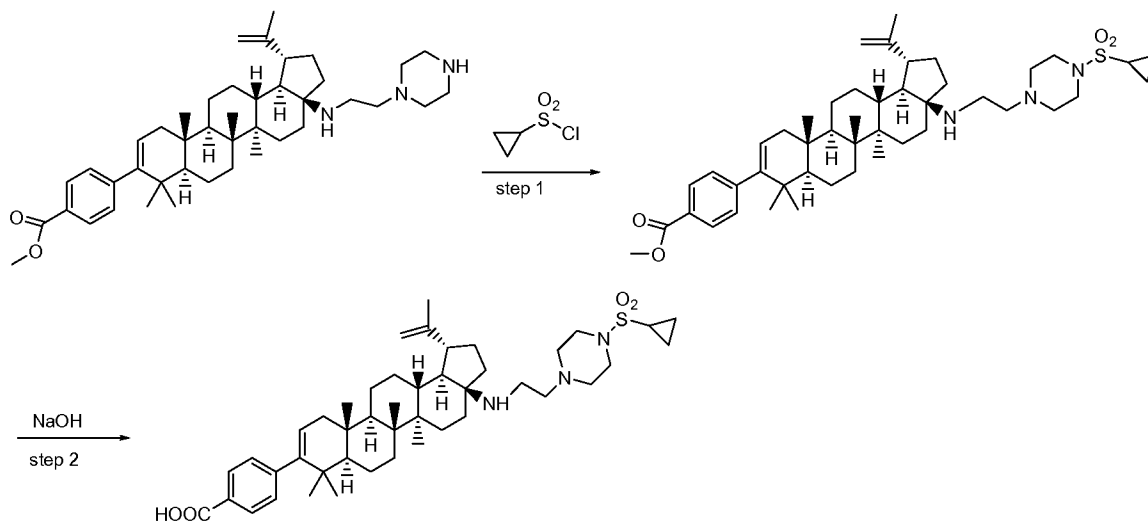
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
((2-aminoethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
10 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)benzoate (15 mg, 0.026 mmol) and Hunig's Base (0.013
mL, 0.077 mmol) in dichloromethane (1 mL) was added methanesulfonyl chloride
(3.81 mg, 0.033 mmol) in dichloromethane (1 mL). The reaction mixture was stirred
at 20 °C for 2 hours. The reaction mixture was diluted with distilled water (3 mL),
15 extracted with dichloromethane (3x3 mL), the extracts were combined, dried over
sodium sulfate, filtered and concentrated under reduced pressure to provide the
desired product as a yellow solid (15 mg, 88%). LCMS: m/e 665.55 (M+H)⁺, 2.44
min (method 11).

20 Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-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.

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-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, 0.023 mmol) and sodium hydroxide (0.113 mL, 0.113 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (7 mg, 45%). LCMS: m/e 651.52 (M+H)⁺, 2.28 min (method 11). ¹H NMR (400MHz, Acetic) δ 7.99 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 5.33 (d, J=4.5 Hz, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 3.53 (br. s., 2H), 3.36 - 3.26 (m, 2H), 3.07 (s, 3H), 2.96 - 2.75 (m, 1H), 2.30 - 2.11 (m, 3H), 1.84 - 1.06 (m, 19H), 1.74 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Example B22

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-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,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-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 methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-
5 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 (26 mg, 0.040 mmol) and Hunig's Base (0.035 mL, 0.198 mmol) in dichloromethane (1 mL) was added a solution of cyclopropanesulfonyl chloride (11.14 mg, 0.079 mmol) in dichloromethane (1 mL) at room temperature. The reaction mixture was stirred for 2 hours at 20 °C or LCMS
10 indicated the formation of desired product and consumption of starting material. The reaction mixture was diluted with distilled water (4 mL), extracted with dichloromethane (3x4 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the desired product as a yellow solid (30 mg, 100%). LCMS: m/e 760.61 (M+H)⁺, 2.40 min (method 11).

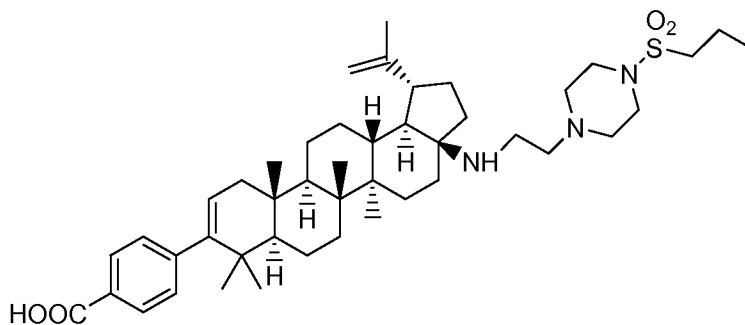
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Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic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

20 A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-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 (30 mg, 0.039 mmol) and sodium hydroxide (0.395 mL, 0.395 mmol) in dioxane (0.5 mL) was heated up at 80 °C for 3 hours. The
25 reaction mixture was filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (13 mg, 42%). LCMS: m/e 746.58 (M+H)⁺, 2.27 min (method 11). ¹H NMR (400MHz, Acetic) δ 7.99 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 5.34 (d, J=4.8 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.63 - 3.44 (m, 5H), 3.43 - 3.26 (m, 2H), 3.24 - 3.13 (m, 1H), 3.05 (d, J=4.3 Hz, 4H), 2.86 (br. s., 1H),
30 2.58 - 2.40 (m, 1H), 2.27 - 1.02 (m, 22H), 1.73 (s, 3H) 1.24 (s, 3H), 1.13 (d, J=4.5 Hz, 2H), 1.10 (s, 3H), 1.06 (s, 3H), 1.02 (d, J=4.5 Hz, 2H), 0.97 (s, 3H), 0.96 (s, 3H).

Example B23

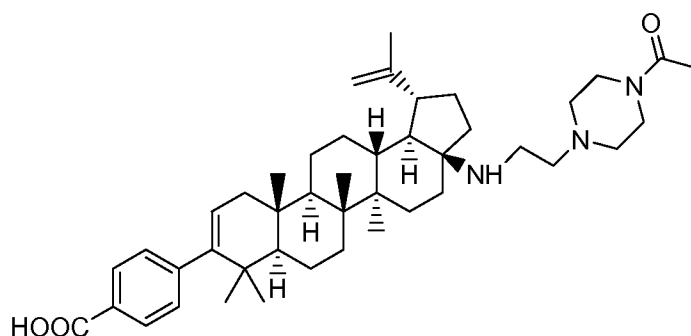
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-(propylsulfonyl)piperazin-1-yl)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described in above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-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 propane-1-sulfonyl chloride as the reagent in Step 1. The product was isolated as a white solid (8 mg, 48%). LCMS: m/e 748.6 (M+H)⁺, 2.30 min (method 11). ¹H NMR (400MHz, Acetic) δ 7.99 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 5.34 (d, J=4.5 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.59 - 3.26 (m, 7H), 3.23 - 3.11 (m, 1H), 3.09 - 2.95 (m, 6H), 2.93 - 2.80 (m, 1H), 2.27 - 1.02 (m, 24H), 1.73 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.05 (t, J=8.3 Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Example B24

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-acetylpiperazin-1-yl)ethyl)amino)-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



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-

5 (cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-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 acetyl chloride as the reagent in Step 1. The product was isolated as a white solid (5.4 mg, 35%). LCMS: m/e 684.67 ($M+H$)⁺, 2.27 min (method 11). ¹H NMR (400MHz, Acetic) δ 7.99 (d, $J=8.3$ Hz, 2H), 7.26 (d, $J=8.5$ Hz, 2H), 5.33 (d, $J=4.8$ Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 4.09 - 3.89 (m, 1H), 3.85 (br. s., 3H), 3.68 (br. s., 4H), 3.53 - 3.14 (m, 4H), 2.92 - 2.66 (m, 1H), 2.28 - 1.01 (m, 22H), 2.17 (s, 3H), 1.73 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

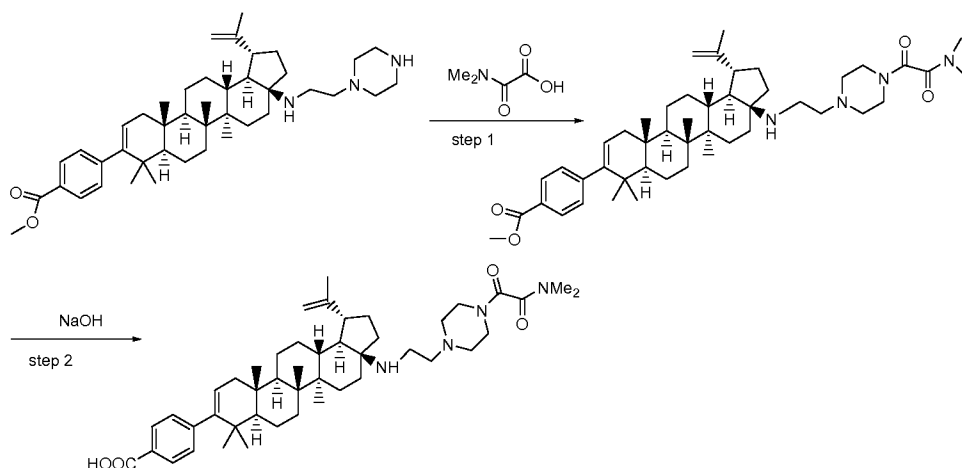
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Example B25

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-

(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-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-

20 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((2-(4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-
 5 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 mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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-
 10 cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.076 mmol), 2-(1H-
 benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate (29.4
 mg, 0.091 mmol), N-ethyl-N-isopropylpropan-2-amine (11.82 mg, 0.091 mmol) and
 2-(dimethylamino)-2-oxoacetic acid (26.8 mg, 0.229 mmol) in dichloromethane (2
 mL) was stirred at 20 °C for 2 hours. The reaction mixture was diluted with distilled
 15 water (5 mL), extracted with ethyl acetate (3x4 mL), the extracts were combined,
 dried over sodium sulfate, filtered and concentrated under reduced pressure to provide
 the desired product as a yellow oil (40 mg, 70%). LCMS: m/e 755.68 (M+H)⁺, 2.42
 min (method 11).

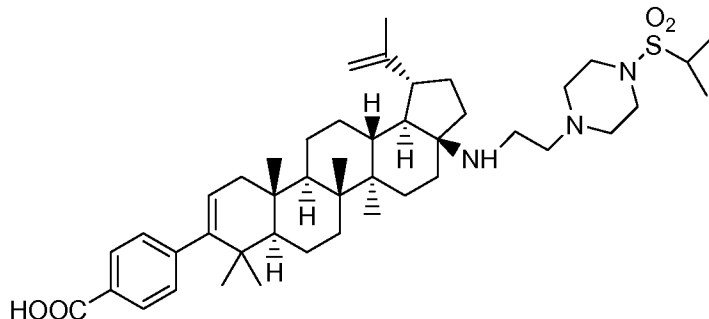
20 Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-
 (dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-
 25 (4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-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, 0.053 mmol) and sodium hydroxide (0.530 mL, 0.530 mmol) in dioxane (1 mL) was heated up at 82 °C for 3 hours. The reaction mixture was cooled to room temperature, filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (17 mg, 41%). LCMS: m/e 741.65 (M+H)⁺, 2.29 min (method 11). ¹H NMR (400MHz, Acetic) δ 7.99 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 5.33 (d, J=4.5 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.14 - 3.78 (m, 2H), 3.75 - 3.36 (m, 6H), 3.22 (br s., 4H), 3.03 (s, 3H), 3.00 (s, 3H), 2.92 - 2.75 (m, 1H), 2.29 - 1.05 (m, 22H), 1.73 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Example B26

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(isopropylsulfonyl)piperazin-1-yl)ethyl)amino)-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



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-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 propane-2-sulfonyl chloride as the reagent in Step 1. The product was isolated as a colorless oil (6 mg, 36%). LCMS: m/e 748.63 (M+H)⁺, 2.31 min (method 11). ¹H NMR (400MHz, Acetic) δ 7.99 (d, J=8.0 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 5.33 (d, J=5.3 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 3.80 - 3.55 (m, 8H), 3.49 - 3.25 (m, 5H), 2.92 - 2.68 (m, 1H), 2.32 - 1.04 (m,

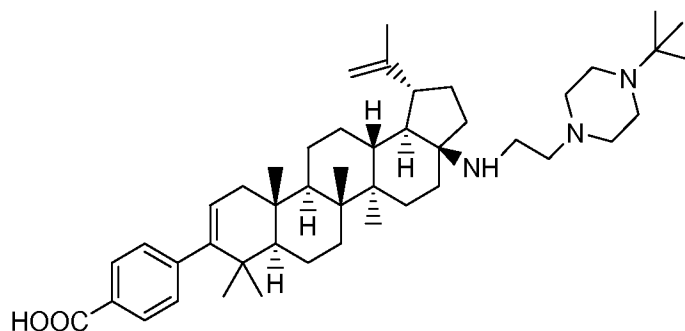
22H), 1.73 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Example B27

5

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butyl)piperazin-1-yl)ethyl)amino)-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

10

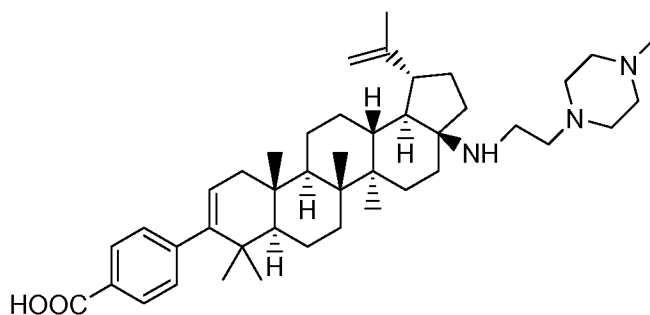


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(tert-butyl)piperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (9 mg, 40%).

LCMS: m/e 698.67 ($M+H$)⁺, 2.27 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.04 (d, $J=8.0$ Hz, 2H), 7.30 (d, $J=8.0$ Hz, 2H), 5.38 (d, $J=5.2$ Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.77 (br. s., 2H), 3.51 - 2.82 (m, 11H), 2.41 - 1.16 (m, 22H), 1.77 (s, 3H), 1.49 (s, 9H), 1.30 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H).

Example B28

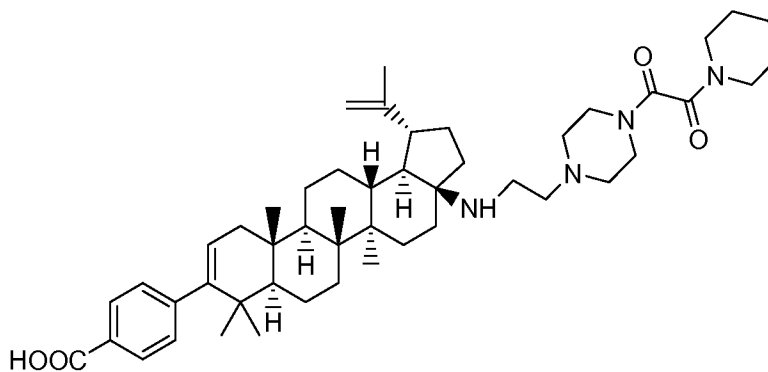
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-methylpiperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described in above for
 5 the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-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 1-methylpiperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (3 mg, 19%). LCMS: m/e
 10 656.62 (M+H)⁺, 2.19 min (method 11). ¹H NMR (500MHz, Acetic) δ 8.04 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 5.38 (d, J=5.7 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.73 (br. s., 1H), 3.62 - 2.85 (m, 12H), 2.94 (s, 3H), 2.34 - 1.15 (m, 22H), 1.77 (s, 3H), 1.29 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H).

15 Example B29

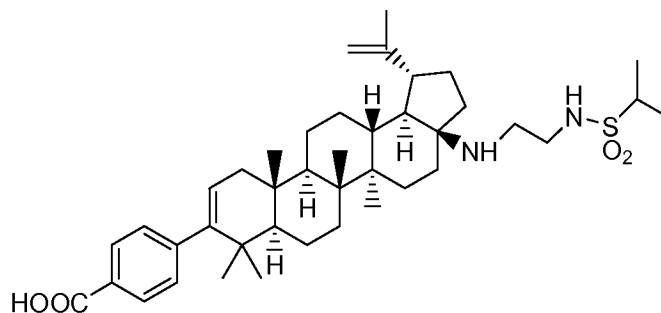
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(2-oxo-2-(piperidin-1-yl)acetyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-
 20 1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-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 2-oxo-2-(piperidin-1-yl)acetic acid as the acid in Step 1. The product was isolated as a white solid (1.1 mg, 18%). LCMS: m/e 781.7 ($M+H$)⁺, 1.72 min (method 11). ¹H NMR (500MHz, CHLOROFORM-*d*) δ 7.99 (d, $J=8.4$ Hz, 2H), 7.24 (d, $J=8.4$ Hz, 2H), 5.31 (d, $J=4.6$ Hz, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 3.84 (dd, $J=7.6, 2.7$ Hz, 1H), 3.68 - 3.56 (m, 3H), 3.49 (t, $J=4.9$ Hz, 2H), 3.43 - 3.30 (m, 2H), 2.93 - 2.63 (m, 9H), 2.60 - 1.05 (m, 28H), 1.72 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B30

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(1-methylethylsulfonamido)ethyl)amino)-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

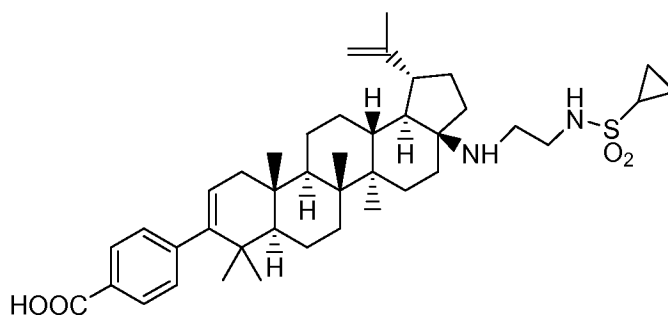
The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using propane-2-sulfonyl chloride as the reagent in Step 1. The product was isolated as a colorless oil (3.5 mg, 34%). LCMS: m/e 679.55 ($M+H$)⁺, 2.36 min (method 11). ¹H NMR (400MHz, CHLOROFORM-*d*)

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δ 9.56 (br. s., 1H), 7.98 (d, $J=8.5$ Hz, 2H), 7.23 (d, $J=8.3$ Hz, 2H), 6.91 (t, $J=6.3$ Hz, 1H), 5.94 (br. s., 1H), 5.18 (d, $J=4.5$ Hz, 1H), 4.87 (s, 1H), 4.71 (s, 1H), 3.88 - 3.69 (m, 1H), 3.63 - 3.49 (m, 1H), 3.37 - 3.16 (m, 3H), 2.90 - 2.68 (m, 1H), 2.26 - 1.07 (m, 22H), 1.70 (s, 3H), 1.44 (dd, $J=8.8, 6.8$ Hz, 6H), 1.20 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H).

Example B31

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(cyclopropanesulfonamido)ethyl)amino)-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



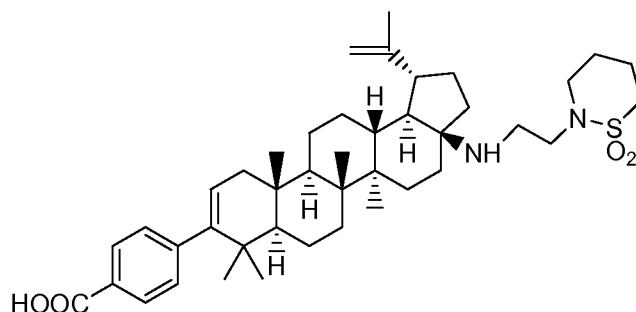
15

The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-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 cyclopropanesulfonyl chloride as the reagent in Step 1. The product was isolated as a colorless oil (3.5 mg, 34%). LCMS: m/e 677.52 ($M+H$)⁺, 2.32 min (method 11). ¹H NMR (400MHz, CHLOROFORM-d) δ 9.55 (br. s., 1H), 7.98 (d, $J=8.3$ Hz, 2H), 7.23 (d, $J=8.3$ Hz, 2H), 6.76 (br. s., 1H), 5.99 (br. s., 1H), 5.21 (d, $J=5.0$ Hz, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 3.92 - 3.71 (m, 1H), 3.69 - 3.55 (m, 1H), 3.23 (br. s., 2H), 2.91 - 2.70 (m, 1H), 2.63 - 2.44 (m, 1H), 2.25 - 1.02 (m, 26H), 1.70 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H).

25

Example B32

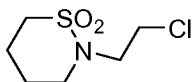
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-
1,2-thiazinan-2-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)benzoic acid



10 The title compound was prepared following the method described above for
the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-
dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-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 1-(2-chloroethyl)-4-
15 (methylsulfonyl)piperazine (prepared as described below) as the alkylating reagent in
Step 3. The product was isolated as a white solid (5.2 mg, 36%). LCMS: m/e 691.55
(M+H)⁺, 2.35 min (method 11). ¹H NMR (400MHz, CHLOROFORM-d) δ 7.99 (d,
J=8.3 Hz, 2H), 7.23 (d, *J*=8.5 Hz, 2H), 5.27 (d, *J*=4.5 Hz, 1H), 4.82 (s, 1H), 4.70 (s,
1H), 3.87 - 3.74 (m, 1H), 3.72 - 3.48 (m, 3H), 3.39 (br. s., 2H), 3.18 - 3.08 (m, 2H),
20 2.96 - 2.78 (m, 1H), 2.34 - 1.10 (m, 26H), 1.71 (s, 3H), 1.23 (s, 3H), 1.05 (s, 3H), 0.99
(s, 3H), 0.96 (s, 3H), 0.96 (s, 3H).

Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine

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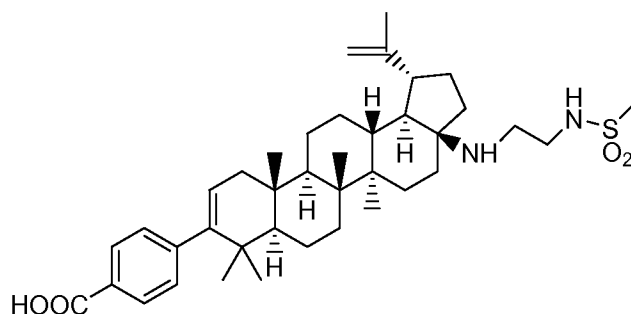


The title compound was prepared following the method described in previously for the synthesis of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine using 1,2-thiazinane 1,1-dioxide as the starting reagent and sodium hydride as the base. The product was isolated as colorless oil (120 mg, 41%). LCMS: m/e 198.08 (M+H)⁺,

5 1.24 min (method 11).

Example B33

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-
10 (ethylsulfonamido)ethyl)amino)-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

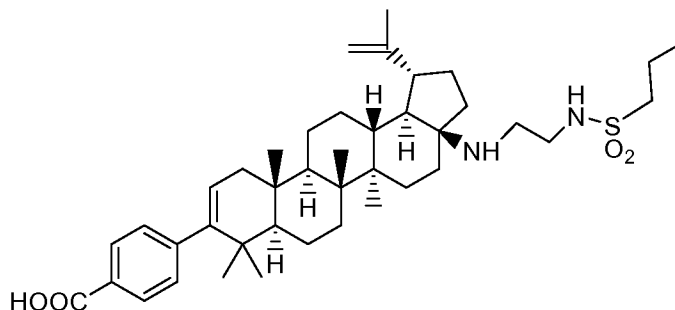


15

The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-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-
20 cyclopenta[a]chrysen-9-yl)benzoic acid using ethanesulfonyl chloride as the reagent in Step 1. The product was isolated as a white solid (8.7 mg, 56%). LCMS: m/e 665.46 (M+H)⁺, 2.29 min (method 11). ¹H NMR (500MHz, CHLOROFORM-d) δ 9.27 (br. s., 1H), 8.00 (d, J=7.1 Hz, 2H), 7.25 (d, J=7.1 Hz, 2H), 6.84 (br. s., 1H), 6.07 (br. s., 1H), 5.24 (d, J=6.3 Hz, 1H), 4.85 (s, 1H), 4.73 (s, 1H), 3.84 - 3.68 (m, 1H),
25 3.54 (d, J=14.8 Hz, 1H), 3.37 - 3.21 (m, 2H), 3.17 (q, J=7.4 Hz, 2H), 2.83-2.76 (m, 1H), 2.36 - 0.95 (m, 22H), 1.72 (s, 3H), 1.46 (t, J=7.4 Hz, 3H), 1.20 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.95 (s, 3H).

Example B34

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(propylsulfonamido)ethyl)amino)-
 5 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



10 The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-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 propane-1-sulfonyl chloride as the
 15 reagent in Step 1. The product was isolated as a white solid (9 mg, 49%). LCMS: m/e 679.48 ($M+H$)⁺, 2.34 min (method 11). ¹H NMR (500MHz, CHLOROFORM-d) δ 9.36 (br. s., 1H), 8.00 (d, $J=8.4$ Hz, 2H), 7.25 (d, $J=8.2$ Hz, 2H), 6.81 (br. s., 1H), 6.04 (br. s., 1H), 5.31 - 5.19 (m, 1H), 4.86 (s, 1H), 4.73 (s, 1H), 3.85 - 3.67 (m, 1H), 3.54 (d, $J=14.7$ Hz, 1H), 3.38 - 3.18 (m, 2H), 3.15 - 3.07 (m, 2H), 2.80 (td, $J=11.2$, 5.9 Hz,
 20 1H), 2.26 - 0.95 (m, 24H), 1.71 (s, 3H), 1.20 (s, 3H), 1.12 (t, $J=7.4$ Hz, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H).

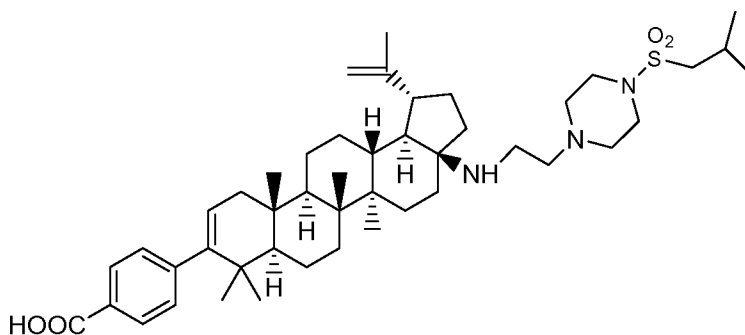
General procedure for the preparation of examples B35-B-52.

25 To the corresponding substituted sulfonyl chloride reagent (sulfonylating agent) (0.075 mmol) was added a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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 (29 mg, 0.044 mmol) and DIPEA (0.039 mL, 0.221 mmols) in DCE (1 mL) at room temperature. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated to provide the dry residue.
- 5 To the residue in dioxane (0.8 mL) was added a solution of lithium hydroxide monohydrate (14.7 mg, 0.35 mmol) in water (0.2 mL). The reaction mixture was agitated at 350 rpm on an Innova platform shaker at 70° C overnight. The solvent was removed and DMF (1.5 mL) was added. The mixture was filtered and the clear solution was purified by HPLC to provide the desired products with yield ranged from
- 10 6-50% over two steps.

Example B35

- Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-
- 15 (isobutylsulfonyl)piperazin-1-yl)ethyl)amino)-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

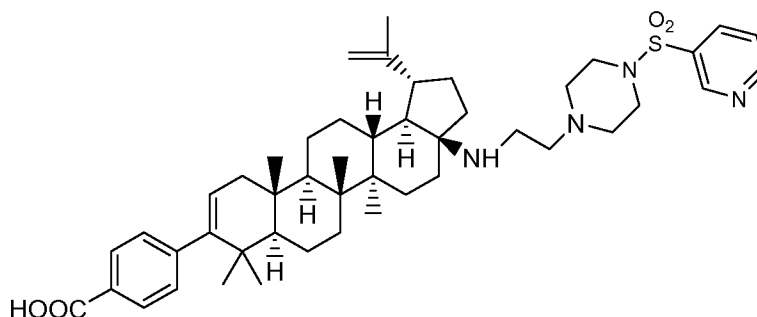
- The title compound was prepared to provide 11.9 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described
- 25 above using isobutanesulfonyl chloride as the sulfonylating agent. LCMS: m/e 762.8 (M+H)⁺, 3.65 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.87 (d, J=8.2 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 5.25 (d, J=4.9 Hz, 1H), 4.70 (s, 1H), 4.57 (s, 1H), 3.17

(br. s., 4H), 3.00 - 2.82 (m, 2H), 2.70 - 2.53 (m, 5H), 2.48 - 2.30 (m, 4H), 2.24 - 2.03 (m, 2H), 2.00 - 1.83 (m, 2H), 1.80-1.01 (m, 19H), 1.67 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H).

5

Example B36

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-(pyridin-3-ylsulfonyl)piperazin-1-yl)ethyl)amino)-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



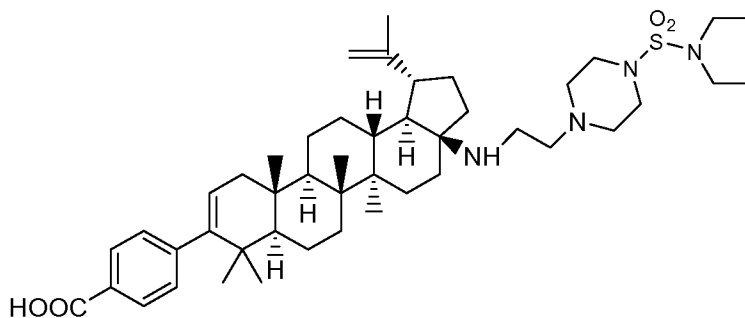
The title compound was prepared to provide 12.7 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using pyridine-3-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 783.8 (M+H)⁺, 3.42 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 8.95 (d, J=2.1 Hz, 1H), 8.89 (dd, J=4.7, 1.4 Hz, 1H), 8.32 - 8.16 (m, 1H), 7.88 (d, J=8.2 Hz, 2H), 7.73 (dd, J=7.9, 4.9 Hz, 1H), 7.25 (d, J=7.9 Hz, 2H), 5.25 (d, J=4.9 Hz, 1H), 4.64 (d, J=1.8 Hz, 1H), 4.53 (s, 1H), 3.11 - 2.92 (m, 4H), 2.65 - 2.46 (m, 5H), 2.45 - 2.20 (m, 4H), 2.05 (dd, J=17.4, 6.4 Hz, 1H), 1.91 - 1.76 (m, 2H), 1.73 - 0.99 (m, 19H), 1.63 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.61 (s, 3H).

25

Example B37

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(N,N-diethylsulfamoyl)piperazin-1-yl)ethyl)amino)-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

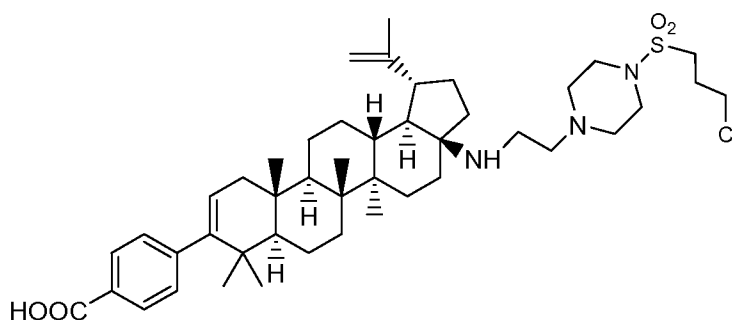


The title compound was prepared to provide 10.6 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using dimethylsulfamoyl chloride as the sulfonylating agent. LCMS: m/e 777.8 (M+H)⁺, 3.82 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.87 (d, J=7.9 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 5.25 (d, J=4.6 Hz, 1H), 4.70 (d, J=2.1 Hz, 1H), 4.56 (s, 1H), 3.22 (q, J=7.1 Hz, 4H), 3.08 (br. s., 4H), 2.69 - 2.57 (m, 1H), 2.56 - 2.47 (m, 4H), 2.44 - 2.31 (m, 4H), 2.08 (dd, J=17.5, 6.3 Hz, 1H), 1.95 - 1.00 (m, 21H), 1.67 (s, 3H), 1.12 (t, J=7.0 Hz, 6H), 1.09 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H).

20

Example B38

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((3-chloropropyl)sulfonyl)piperazin-1-yl)ethyl)amino)-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

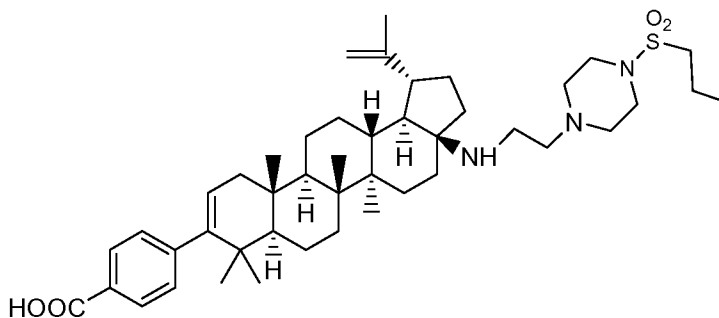


The title compound was prepared to provide 10.9 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 3-chloropropanesulfonyl chloride as the sulfonylating agent. LCMS: m/e 782.7 (M+H)⁺, 3.59 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.87 (d, J=7.9 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 5.25 (d, J=4.9 Hz, 1H), 4.70 (d, J=2.1 Hz, 1H), 4.57 (s, 1H), 3.76 (t, J=6.4 Hz, 2H), 3.26 - 3.13 (m, 6H), 2.63 (td, J=10.5, 4.9 Hz, 1H), 2.56 (d, J=7.6 Hz, 4H), 2.48 - 2.33 (m, 4H), 2.21 - 2.04 (m, 3H), 1.98 - 1.83 (m, 2H), 1.83 - 1.02 (m, 19H), 1.67 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

15

Example B39

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(butylsulfonyl)piperazin-1-yl)ethyl)amino)-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

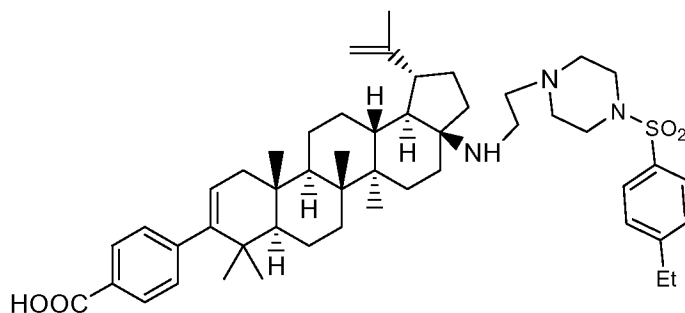


The title compound was prepared to provide 13.6 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using butane-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 762.8 (M+H)⁺, 3.66 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.87 (d, $J=8.2$ Hz, 2H), 7.22 (d, $J=8.2$ Hz, 2H), 5.25 (d, $J=4.6$ Hz, 1H), 4.70 (d, $J=2.1$ Hz, 1H), 4.56 (s, 1H), 3.19 (br. s., 4H), 3.12 - 2.96 (m, 2H), 2.63 (td, $J=10.8, 5.3$ Hz, 1H), 2.55 (br. s., 4H), 2.47 - 2.30 (m, 4H), 2.08 (dd, $J=17.2, 6.3$ Hz, 1H), 1.98 - 1.83 (m, 2H), 1.82 - 1.02 (m, 23H), 1.67 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.91 (t, $J=4.7$ Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

15

Example B40

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-ethylphenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-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

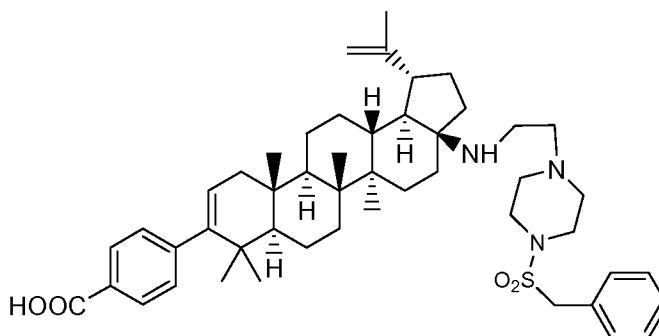


The title compound was prepared to provide 3.7 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described

above using 4-ethyl-benzene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 810.9 (M+H)⁺, 4.12 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.89 (d, J=8.2 Hz, 2H), 7.68 (d, J=8.2 Hz, 2H), 7.49 (d, J=8.2 Hz, 2H), 7.24 (d, J=8.2 Hz, 2H), 5.26 (d, J=4.9 Hz, 1H), 4.63 (br. s., 1H), 4.55 (br. s., 1H), 3.03 - 2.90 (m, 4H), 2.71 (q, J=7.7 Hz, 2H), 2.52 (d, J=1.5 Hz, 5H), 2.49 - 2.34 (m, 4H), 2.06 (dd, J=17.7, 6.4 Hz, 1H), 1.80 (d, J=9.8 Hz, 2H), 1.75 - 1.01 (m, 19H), 1.63 (s, 3H), 1.21 (t, J=7.5 Hz, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H).

Example B41

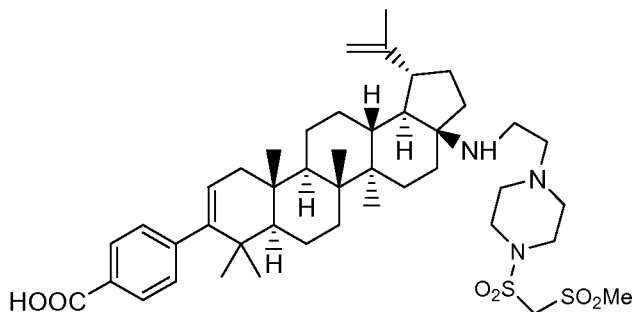
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(benzylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 16.4 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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 following the general procedure as described above using phenyl-methanesulfonyl chloride as the sulfonylating agent. LCMS: m/e 796.8 (M+H)⁺, 3.73 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.87 (d, J=8.2 Hz, 2H), 7.46 - 7.41 (m, 2H), 7.41 - 7.31 (m, 3H), 7.22 (d, J=8.2 Hz, 2H), 5.25 (d, J=4.6 Hz, 1H), 4.72 (d, J=1.5 Hz, 1H), 4.58 (s, 1H), 4.53 - 4.39 (m, 2H), 3.11 (br. s., 4H), 2.64 - 2.54 (m, 1H), 2.53 - 2.45 (m, 2H), 2.46 - 2.29 (m, 6H), 2.09 (dd, J=17.2, 6.3 Hz, 1H), 1.96 - 1.80 (m, 3H), 1.78 - 1.02 (m, 18H), 1.68 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H).

Example B42

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 5 pentamethyl-3a-((2-(4-(((methylsulfonyl)methyl)sulfonyl)piperazin-1-
 yl)ethyl)amino)-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



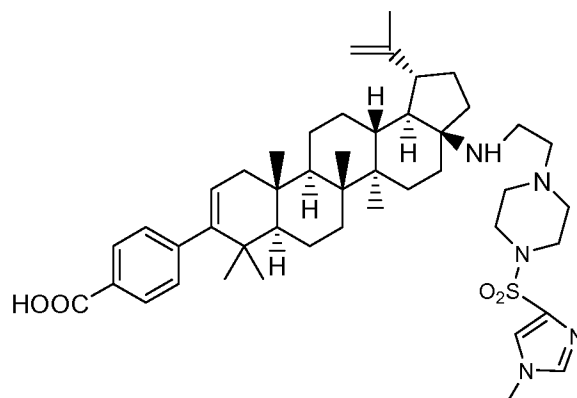
10

The title compound was prepared to provide 5.5 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 (piperazin-1-yl)ethyl)amino)-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-
 15 cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described
 above using methanesulfonyl-methanesulfonyl chloride as the sulfonylating agent.
 LCMS: m/e 798.8 (M+H)⁺, 3.28 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ
 7.87 (d, $J=7.9$ Hz, 2H), 7.22 (d, $J=7.9$ Hz, 2H), 5.29 (s, 2H), 5.25 (d, $J=4.6$ Hz, 1H),
 4.70 (s, 1H), 4.57 (s, 1H), 3.29 (br. s., 8H), 3.19 (s, 3H), 2.64 - 2.55 (m, 1H), 2.48 -
 20 2.34 (m, 4H), 2.08 (dd, $J=17.2, 6.3$ Hz, 1H), 1.97 - 1.80 (m, 3H), 1.79 - 0.99 (m,
 18H), 1.67 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Example B43

25 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-3a-((2-(4-((1-methyl-1H-imidazol-4-yl)sulfonyl)piperazin-1-
 yl)ethyl)amino)-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

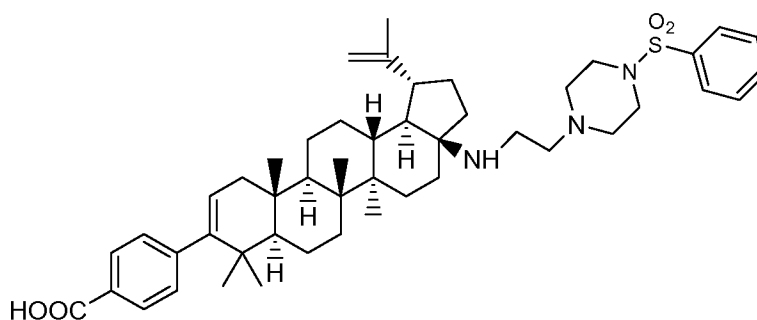
The title compound was prepared to provide 17 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-

- 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 following the general procedure as described above using 1-methyl-1H-imidazole-4-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 786.8 ($M+H$)⁺, 3.08 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.92 - 7.84 (m, 3H), 7.77 (s, 1H), 7.23 (d, $J=7.9$ Hz, 2H), 5.26 (d, $J=4.9$ Hz, 1H), 4.66 (d, $J=1.8$ Hz, 1H), 4.55 (s, 1H), 3.73 (s, 3H), 3.04 (br. s., 4H), 2.63 - 2.47 (m, 5H), 2.45 - 2.26 (m, 4H), 2.08 (dd, $J=17.4, 6.4$ Hz, 1H), 1.91 - 1.77 (m, 2H), 1.77 - 1.00 (m, 19H), 1.65 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H).

20

Example B44

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(phenylsulfonyl)piperazin-1-yl)ethyl)amino)-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

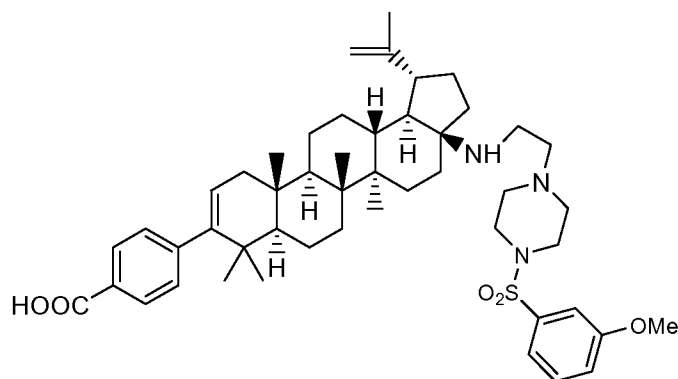


The title compound was prepared to provide 3.9 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described
 above using benzenesulfonyl chloride as the sulfonylating agent. LCMS: m/e 782.8
 (M+H)⁺, 4.98 min (method 15). ¹H NMR (500MHz, DMSO-d₆) δ 7.89 (d, J=8.2 Hz,
 10 2H), 7.78 (d, J=7.0 Hz, 2H), 7.75 - 7.62 (m, 3H), 7.26 (d, J=7.9 Hz, 2H), 5.25 (d,
 J=4.9 Hz, 1H), 4.64 (br. s., 1H), 4.54 (br. s., 1H), 2.92 (br. s., 4H), 2.57 (br. s., 5H),
 2.47 - 2.27 (m, 4H), 2.05 (dd, J=17.4, 6.4 Hz, 1H), 1.93 - 1.77 (m, 2H), 1.76 - 0.98
 (m, 19H), 1.63 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.58 (s,
 3H).

15

Example B45

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((3-
 methoxyphenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-
 20 (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

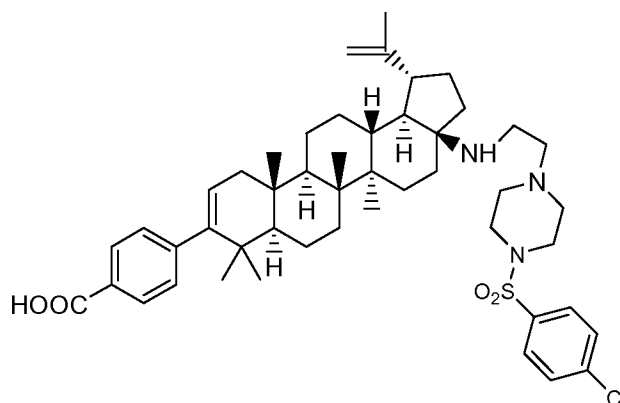


The title compound was prepared to provide 3.2 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described
 above using 3-methoxybenzenesulfonyl chloride as the sulfonylating agent. LCMS:
 m/e 812.8 (M+H)⁺, 4.98 min (method 15). ¹H NMR (500MHz, DMSO-d₆) δ 7.89 (d,
 10 J=8.2 Hz, 2H), 7.64 - 7.51 (m, 1H), 7.34 (d, J=7.9 Hz, 1H), 7.28 - 7.13 (m, 4H), 5.25
 (d, J=4.6 Hz, 1H), 4.64 (s, 1H), 4.53 (s, 1H), 3.85 (s, 3H), 3.03 - 2.87 (m, 4H), 2.64 -
 2.51 (m, 5H), 2.46 - 2.22 (m, 4H), 2.05 (dd, J=17.2, 6.3 Hz, 1H), 1.93 - 1.76 (m, 2H),
 1.75 - 0.98 (m, 19H), 1.63 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.87 (s,
 3H), 0.63 (s, 3H).

15

Example B46

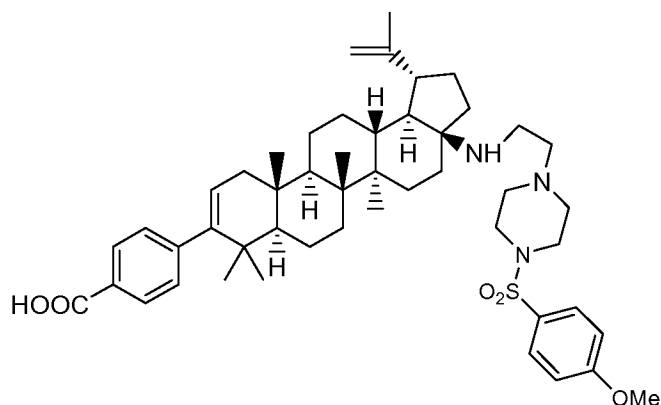
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-
 chlorophenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-
 20 (prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-
 1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 2.1 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 above using 4-chlorobenzene-1-sulfonyl chloride as the sulfonylating agent. LCMS:
 m/e 816.8 (M+H)⁺, 3.94 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.89 (d,
 10 J=8.2 Hz, 2H), 7.81 (d, J=8.5 Hz, 2H), 7.73 (d, J=8.9 Hz, 2H), 7.24 (d, J=7.9 Hz,
 2H), 5.25 (d, J=4.6 Hz, 1H), 4.66 (br. s., 1H), 4.57 (br. s., 1H), 2.96 (br. s., 4H), 2.71 -
 2.55 (m, 4H), 2.51 - 2.30 (m, 5H), 2.06 (dd, J=17.4, 6.4 Hz, 1H), 1.98 - 1.79 (m, 2H),
 1.78 - 0.89 (m, 19H), 1.65 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.93 (s, 3H), 0.92 (s,
 3H), 0.80 (s, 3H).

Example B47

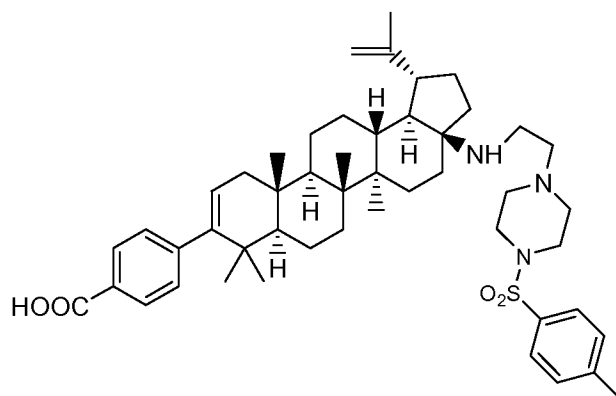
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-
 methoxyphenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-
 20 (prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-
 1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 9.5 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 above using 4-methoxybenzene-1-sulfonyl chloride as the sulfonylating agent.
 LCMS: m/e 812.8 (M+H)⁺, 3.69 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ
 10 7.89 (d, $J=8.2$ Hz, 2H), 7.70 (d, $J=8.9$ Hz, 2H), 7.24 (d, $J=8.2$ Hz, 2H), 7.16 (d, $J=8.9$
 Hz, 2H), 5.25 (d, $J=4.6$ Hz, 1H), 4.63 (d, $J=2.1$ Hz, 1H), 4.53 (s, 1H), 3.83 (s, 3H),
 2.91 (s, 4H), 2.61 - 2.46 (m, 5H), 2.41 (br. s., 2H), 2.36 - 2.22 (m, 2H), 2.05 (dd,
 $J=17.5, 6.3$ Hz, 1H), 1.90 - 1.75 (m, 2H), 1.74 - 1.03 (m, 19H), 1.63 (s, 3H), 0.98 (s,
 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.75 (s, 3H).
 15

Example B48

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-tosylpiperazin-1-yl)ethyl)amino)-
 20 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

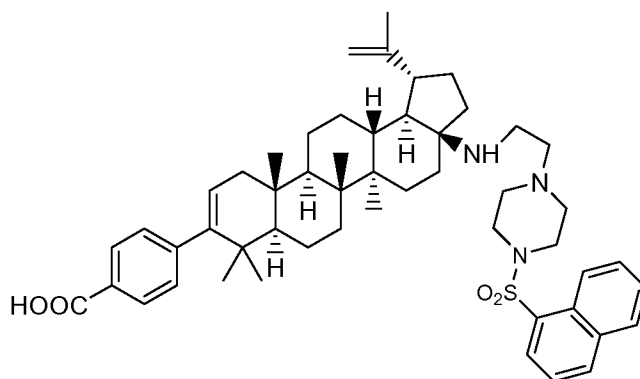


The title compound was prepared to provide 4.6 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described
 above using 4-methylbenzene-1-sulfonyl chloride as the sulfonylating agent. LCMS:
 m/e 796.8 (M+H)⁺, 3.91 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.88 (d,
 10 J=8.2 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 7.46 (d, J=8.2 Hz, 2H), 7.24 (d, J=7.9 Hz,
 2H), 5.25 (d, J=4.6 Hz, 1H), 4.62 (d, J=2.1 Hz, 1H), 4.53 (s, 1H), 2.91 (s, 4H), 2.59 -
 2.45 (m, 5H), 2.41 (s, 5H), 2.36 - 2.25 (m, 2H), 2.06 (dd, J=17.4, 6.4 Hz, 1H), 1.88 -
 1.74 (m, 2H), 1.73 - 0.99 (m, 19H), 1.63 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 (s,
 3H), 0.91 (s, 3H), 0.81 (s, 3H).

15

Example B49

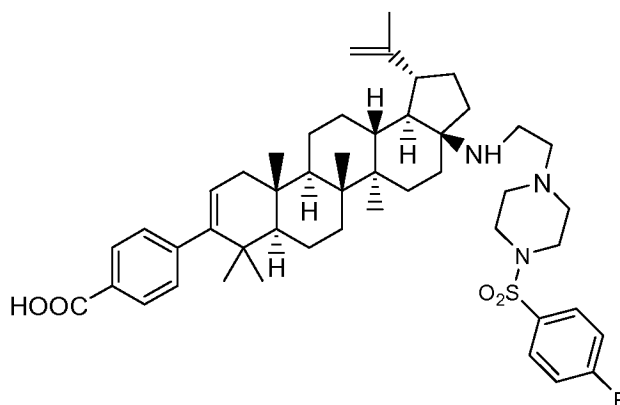
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
 pentamethyl-3a-((2-(4-(naphthalen-1-ylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-
 20 1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 3.0 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 above using naphthalene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e
 832.8 (M+H)⁺, 4.00 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 8.75 (d,
 10 J=8.5 Hz, 1H), 8.29 (d, J=7.9 Hz, 1H), 8.17 (d, J=7.3 Hz, 1H), 8.10 (d, J=8.2 Hz,
 1H), 7.90 (d, J=7.9 Hz, 2H), 7.81 - 7.62 (m, 3H), 7.28 (d, J=7.9 Hz, 2H), 5.24 (d,
 J=5.5 Hz, 1H), 4.62 (br. s., 1H), 4.52 (br. s., 1H), 3.08 (br. s., 4H), 2.52 (br. s., 5H),
 2.45 - 2.22 (m, 4H), 2.02 (dd, J=17.7, 6.1 Hz, 1H), 1.91 - 1.74 (m, 2H), 1.73 - 1.02
 (m, 19H), 1.61 (s, 3H), 1.06 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H), 0.48 (s,
 15 3H).

Example B50

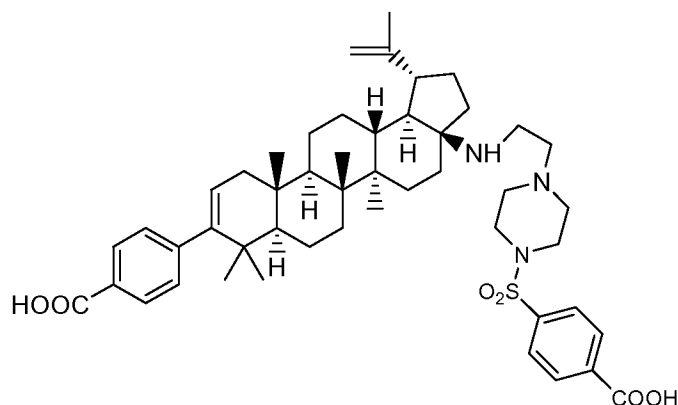
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-
 20 (fluorophenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-
 (prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-
 1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 5.7 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 above using 4-fluorobenzene-1-sulfonyl chloride as the sulfonylating agent. LCMS:
 m/e 800.8 (M+H)⁺, 4.95 min (method 15). ¹H NMR (500MHz, DMSO-d₆) δ 7.93 -
 10 7.80 (m, 4H), 7.50 (t, J=8.7 Hz, 2H), 7.24 (d, J=7.9 Hz, 2H), 5.25 (d, J=4.9 Hz, 1H),
 4.64 (d, J=2.1 Hz, 1H), 4.53 (s, 1H), 3.05 - 2.84 (m, 4H), 2.64 - 2.47 (m, 5H), 2.40
 (br. s., 2H), 2.35 - 2.22 (m, 2H), 2.05 (dd, J=17.2, 6.3 Hz, 1H), 1.90 - 0.97 (m, 21H),
 1.63 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.67 (s, 3H).

15 Example B51

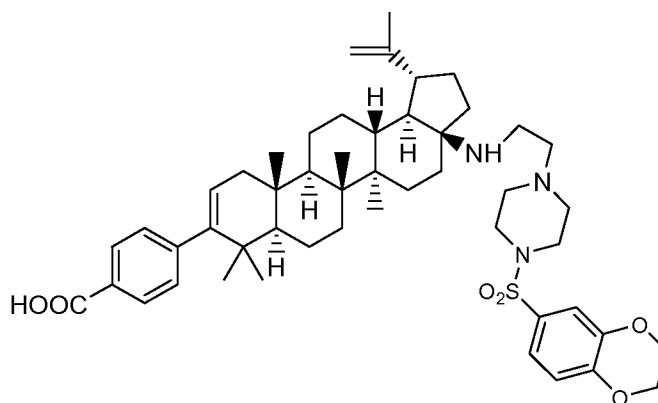
Preparation of 4-((4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-
 carboxyphenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 20 cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperazin-1-yl)sulfonyl)benzoic acid



The title compound was prepared to provide 10.1 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 above using 4-(chlorosulfonyl)benzoic acid as the sulfonylating agent. LCMS: m/e
 826.8 (M+H)⁺, 2.75 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 8.18 (d,
 10 J=8.2 Hz, 2H), 7.89 (dd, J=8.4, 3.8 Hz, 4H), 7.25 (d, J=8.2 Hz, 2H), 5.23 (d, J=4.9
 Hz, 1H), 4.63 (s, 1H), 4.54 (s, 1H), 3.10 - 2.93 (m, 4H), 2.68 - 2.53 (m, 5H), 2.49 -
 2.32 (m, 4H), 2.03 (dd, J=17.2, 6.0 Hz, 1H), 1.90 - 1.76 (m, 2H), 1.75 - 0.99 (m,
 19H), 1.63 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H).

15 Example B52

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((2,3-
 dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)piperazin-1-yl)ethyl)amino)-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-
 20 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 13.2 mg from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 above using 2,3-dihydro-1,4-benzodioxine-6-sulfonyl chloride as the sulfonylating
 agent. LCMS: m/e 840.8 ($M+H$)⁺, 3.66 min (method 14). ¹H NMR (500MHz, DMSO-
 10 d₆) δ 7.88 (d, $J=8.2$ Hz, 2H), 7.31 - 7.18 (m, 4H), 7.08 (d, $J=8.2$ Hz, 1H), 5.25 (d,
 $J=4.6$ Hz, 1H), 4.64 (d, $J=2.1$ Hz, 1H), 4.54 (s, 1H), 4.42 - 4.21 (m, 4H), 2.91 (s, 4H),
 2.62 - 2.51 (m, 5H), 2.41 (br. s., 2H), 2.36 - 2.26 (m, 2H), 2.06 (dd, $J=17.4$, 6.4 Hz,
 1H), 1.90 - 1.76 (m, 2H), 1.75 - 0.88 (m, 19H), 1.64 (s, 3H), 0.98 (s, 3H), 0.93 (s,
 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.78 (s, 3H).

15

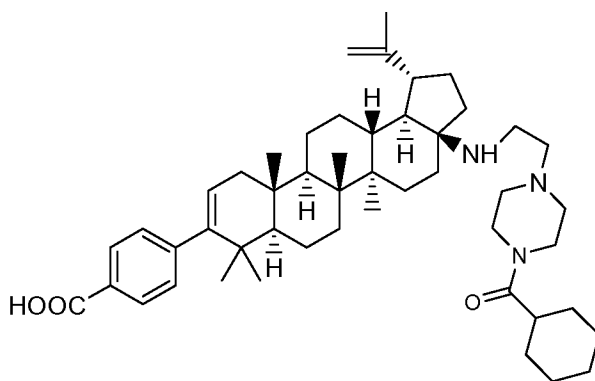
General procedure for the preparation of examples B53-B64

A solution of the corresponding substituted carboxylic acid (acylating agent)
 (0.039 mmol) and HATU (14.78 mg, 0.039 mmol) in DMF (0.5 mL) was stirred for
 20 10 minutes, then a solution of methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 (piperazin-1-yl)ethyl)amino)-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 (17 mg, 0.026 mmol) and DIPEA (0.018 mL,
 25 0.104 mmol) in DMF (0.500 mL) was introduced. The reaction mixture was agitated
 at 350 rpm on an Innova platform shaker at room temperature overnight. The solvent

was evaporated to provide the dry residue. To the residue in dioxane (0.8 mL) was added the lithium hydroxide monohydrate (8.70 mg, 0.207 mmol) dissolved in water (0.2 mL). The reaction mixture was stirred at 80°C overnight. The solvent was removed and DMF (1.0 mL) was added. The mixture was filtered and the clear solution was purified by HPLC to provide the desired products with yield ranged from 2-31% over two steps.

Example B53

- 10 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclohexanecarbonyl)piperazin-1-yl)ethyl)amino)-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

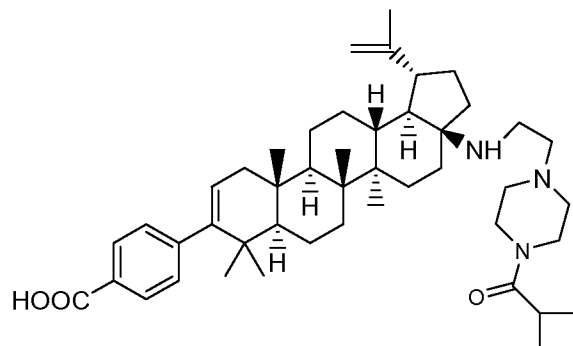


15

- The title compound (4.9 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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 following the general procedure as described above using cyclohexanecarboxylic acid as the acylating agent. LCMS: m/e 752.8 (M+H)⁺, 3.90 min (method 14). ¹H NMR (500MHz, DMSO-d₆) δ 7.85 (d, J=8.2 Hz, 2H), 7.19 (d, J=8.2 Hz, 2H), 5.24 (d, J=4.9 Hz, 1H), 4.70 (s, 1H), 4.56 (s, 1H), 3.49 (br. s., 4H), 2.70 - 2.53 (m, 4H), 2.48 - 2.31 (m, 5H), 2.31 - 2.18 (m, 1H), 2.08 (dd, J=17.4, 6.1 Hz, 1H), 1.99 - 1.79 (m, 3H), 1.78 - 1.00 (m, 28H), 1.67 (s, 3H), 1.08 (s., 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).
- 25

Example B54

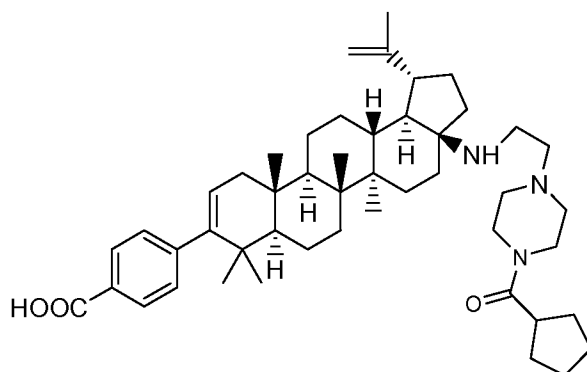
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-
 5 (cyclobutanecarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



10 The title compound (3.1 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 15 above using cyclobutanecarboxylic acid as the acylating agent. LCMS: m/e 724.8 (M+H)⁺, 3.66 min (method 14). ¹H NMR (500MHz, METHANOL-d₄) δ 7.89 (d, J=8.2 Hz, 2H), 7.17 (d, J=8.2 Hz, 2H), 5.30 (d, J=4.6 Hz, 1H), 4.79 (s, 1H), 4.68 (s, 1H), 3.83 - 3.54 (m, 2H), 3.53 - 3.38 (m, 3H), 2.91 (d, J=2.1 Hz, 1H), 2.85 - 2.71 (m, 2H), 2.62 (d, J=10.1 Hz, 3H), 2.55 - 2.39 (m, 2H), 2.36 - 1.18 (m, 29H), 1.75 (s, 3H),
 20 1.22 (s., 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H).

Example B55

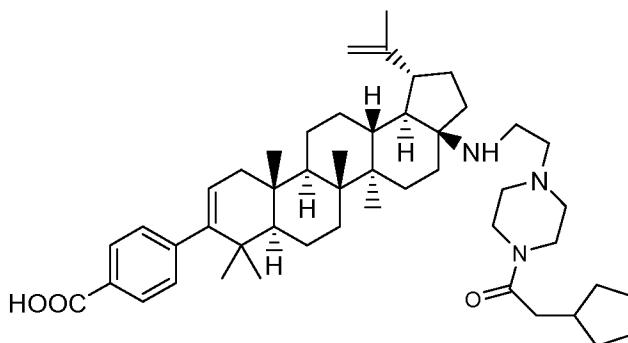
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-
 25 (cyclopentanecarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (3.1 mg) was prepared from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 5 (piperazin-1-yl)ethyl)amino)-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 following the general procedure as described
 above using cyclopentanecarboxylic acid as the acylating agent. LCMS: m/e 738.8
 (M+H)⁺, 3.84 min (method 14). ¹H NMR (500MHz, METHANOL-d₄) δ 7.89 (d,
 10 $J=8.2$ Hz, 2H), 7.17 (d, $J=8.2$ Hz, 2H), 5.30 (d, $J=4.6$ Hz, 1H), 4.79 (s, 1H), 4.69 (s,
 1H), 3.78 - 3.52 (m, 4H), 3.13 - 3.01 (m, 2H), 2.97 - 2.89 (m, 1H), 2.86 - 2.73 (m,
 2H), 2.72 - 2.61 (m, 3H), 2.60 - 2.41 (m, 2H), 2.20 - 1.80 (m, 8H), 1.75 (s, 3H), 1.74 -
 1.18 (m, 22H), 1.23 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

15 Example B56

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-
 cyclopentylacetyl)piperazin-1-yl)ethyl)amino)-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-
 20 cyclopenta[a]chrysen-9-yl)benzoic acid

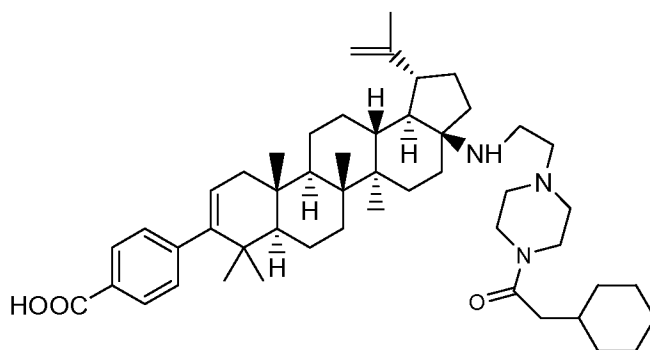


The title compound (3.1 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using cyclopentylacetic acid as the acylating agent. LCMS: m/e 752.9 (M+H)⁺, 3.93 min (method 14). ¹H NMR (500MHz, METHANOL-d₄) δ 7.89 (d, J=8.2 Hz, 2H), 7.17 (d, J=8.2 Hz, 2H), 5.30 (d, J=4.6 Hz, 1H), 4.80 (s, 1H), 4.69 (s, 1H), 3.70 (br. s., 1H), 3.66 - 3.53 (m, 3H), 3.12 - 3.01 (m, 1H), 2.95 - 2.89 (m, 1H), 2.86 - 2.72 (m, 2H), 2.71 - 2.61 (m, 3H), 2.60-2.54 (m, 1H), 2.51 - 2.47 (m, 1H), 2.45 (d, J=7.3 Hz, 2H), 2.27 - 1.90 (m, 6H), 1.89 - 1.79 (m, 3H), 1.76 (s, 3H), 1.73 - 1.18 (m, 22H), 1.23 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

15

Example B57

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-cyclohexylacetyl)piperazin-1-yl)ethyl)amino)-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



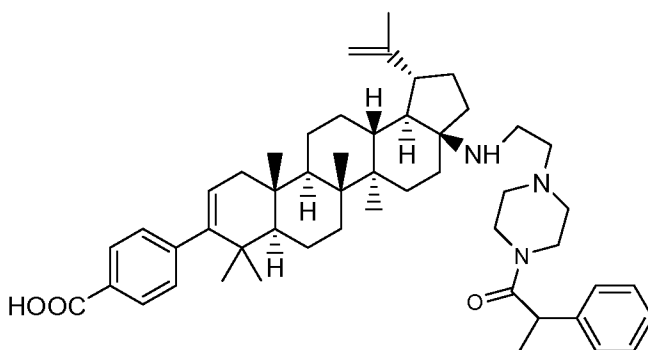
The title compound (3.4 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described

above using cyclopentylacetic acid as the acylating agent. LCMS: m/e 766.9 ($M+H$)⁺, 4.09 min (method 14). ¹H NMR (500MHz, METHANOL- d_4) δ 7.89 (d, $J=8.2$ Hz, 2H), 7.17 (d, $J=8.2$ Hz, 2H), 5.30 (d, $J=4.9$ Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.72 (dd, $J=10.5, 6.0$ Hz, 1H), 3.67 - 3.53 (m, 3H), 3.11 - 3.01 (m, 1H), 2.92 (d, $J=10.7$ Hz, 1H), 2.87 - 2.72 (m, 2H), 2.71 - 2.60 (m, 3H), 2.60 - 2.53 (m, 1H), 2.51 - 2.41 (m, 1H), 2.31 (d, $J=6.4$ Hz, 2H), 2.20 - 1.90 (m, 5H), 1.84 (td, $J=12.1, 3.4$ Hz, 1H), 1.75 (s, 3H), 1.75 - 1.02 (m, 27H), 1.23 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

10

Example B58

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(2-phenylpropanoyl)piperazin-1-yl)ethyl)amino)-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



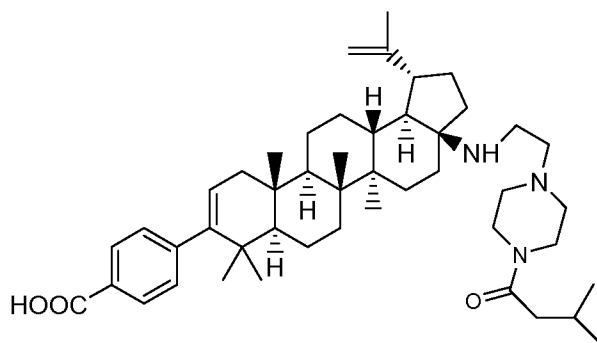
The title compound (4.1 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 2-phenylpropionic acid as the acylating agent. LCMS: m/e 774.9 ($M+H$)⁺, 3.87 min (method 14). ¹H NMR (500MHz, METHANOL- d_4) δ 7.89 (d, $J=7.0$ Hz, 2H), 7.41 - 7.31 (m, 2H), 7.29 - 7.22 (m, 3H), 7.18 (dd, $J=8.2, 3.1$ Hz, 2H), 5.30 (d, $J=4.9$ Hz, 1H), 4.77 (s, 1H), 4.67 (s, 1H), 4.11 (quin, $J=6.4$ Hz, 1H), 3.89 -

3.44 (m, 4H), 2.99 - 2.92 (m, 1H), 2.86 - 2.67 (m, 3H), 2.67 - 2.57 (m, 1H), 2.51 (d, $J=13.7$ Hz, 2H), 2.46 - 2.27 (m, 2H), 2.21 - 2.09 (m, 2H), 2.07 - 1.85 (m, 4H), 1.80 - 1.15 (m, 16H), 1.74 (s, 3H), 1.40 (d, $J=6.7$ Hz, 3H), 1.09 (d, $J=8.5$ Hz, 3H), 1.07 (d, $J=13$ Hz, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H).

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Example B59

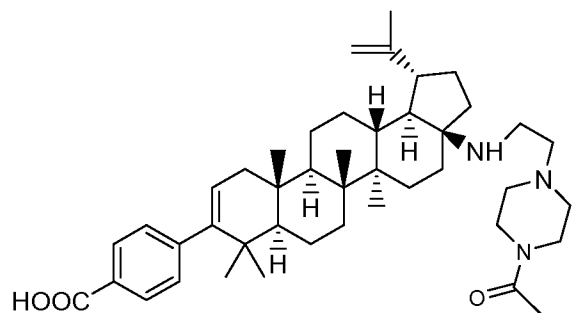
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(3-methylbutanoyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (3.3 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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 following the general procedure as described above using isovaleric acid as the acylating agent. LCMS: m/e 726.8 ($M+H$)⁺, 3.71 min (method 14). ¹H NMR (500MHz, METHANOL-d₄) δ 7.89 (d, $J=8.2$ Hz, 2H), 7.17 (d, $J=8.2$ Hz, 2H), 5.30 (d, $J=4.9$ Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.77 - 3.55 (m, 4H), 3.09 - 3.02 (m, 1H), 2.91 (br. s., 1H), 2.86 - 2.72 (m, 2H), 2.71 - 2.60 (m, 3H), 2.59 - 2.52 (m, 1H), 2.52 - 2.43 (m, 1H), 2.31 (d, $J=7.3$ Hz, 2H), 2.21 - 1.80 (m, 7H), 1.76 (s, 3H), 1.73 - 1.08 (m, 16H), 1.22 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.99 (d, $J=6.4$ Hz, 6H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B60

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-propionylpiperazin-1-yl)ethyl)amino)-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

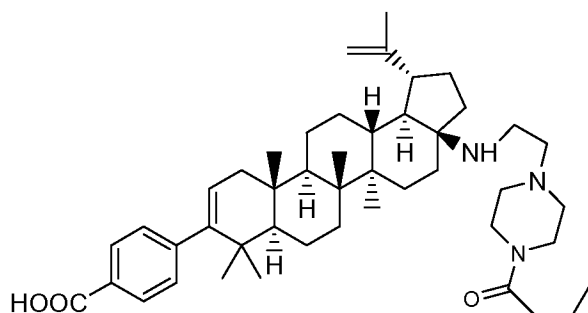
The title compound (5.5 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using propionic acid as the acylating agent. LCMS: m/e 698.8 ($M+H$)⁺, 3.39 min (method 14). ¹H NMR (500MHz, DMSO-*d*₆) δ 7.87 (d, $J=8.2$ Hz, 2H), 7.22 (d, $J=7.9$ Hz, 2H), 5.25 (d, $J=4.9$ Hz, 1H), 4.70 (s, 1H), 4.56 (s, 1H), 3.52 - 3.43 (m, 4H), 3.11 (br. s., 2H), 2.71 - 2.53 (m, 2H), 2.47 - 2.20 (m, 7H), 2.08 (dd, $J=17.2$, 6.3 Hz, 1H), 1.97 - 1.80 (m, 3H), 1.79 - 1.03 (m, 18H), 1.67 (s, 3H), 1.08 (s, 3H), 0.99 (t, $J=8.0$ Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

15

Example B61

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-butyrylpiperazin-1-yl)ethyl)amino)-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

25

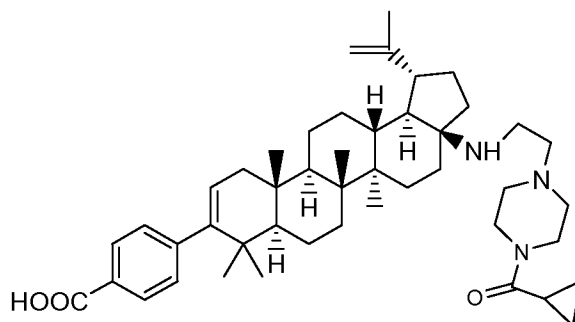


The title compound (1.2 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using butyric acid as the acylating agent. LCMS: m/e 712.8 ($M+H$)⁺, 4.97 min (method 15). ¹H NMR (500MHz, METHANOL-d₄) δ 7.89 (d, $J=8.2$ Hz, 2H), 7.16 (d, $J=8.2$ Hz, 2H), 5.30 (d, $J=4.6$ Hz, 1H), 4.78 (s, 1H), 4.68 (s, 1H), 3.79 - 3.55 (m, 4H), 3.12 - 2.98 (m, 1H), 2.97 - 2.82 (m, 2H), 2.78 (td, $J=10.9, 5.0$ Hz, 1H), 2.71 - 2.61 (m, 3H), 2.60 - 2.54 (m, 1H), 2.52 - 2.44 (m, 1H), 2.40 (t, $J=7.5$ Hz, 2H), 2.19 - 1.80 (m, 6H), 1.75 (s, 3H), 1.73 - 1.04 (m, 18H), 1.23 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.99 (t, $J=7.5$ Hz, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

15

Example B62

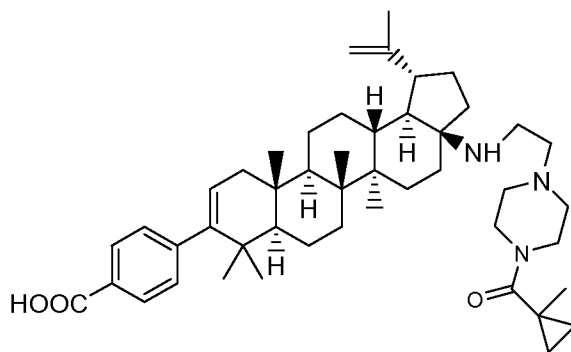
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropanecarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (0.9 mg) was prepared from methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 (piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-
 5 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 following the general procedure as described
 above using cyclopropanecarboxylic acid as the acylating agent. LCMS: m/e 710.8
 (M+H)⁺, 4.41 min (method 15). ¹H NMR (500MHz, METHANOL-d₄) δ 7.88 (d,
 J=7.9 Hz, 2H), 7.16 (d, J=7.9 Hz, 2H), 5.30 (d, J=4.9 Hz, 1H), 4.78 (s, 1H), 4.67 (s,
 10 1H), 3.84 (br. s., 2H), 3.77 - 3.50 (m, 2H), 3.09 - 2.97 (m, 1H), 2.94 - 2.81 (m, 2H),
 2.77 (td, J=10.5, 5.3 Hz, 1H), 2.73 - 2.57 (m, 4H), 2.48 (br. s., 1H), 2.21 - 1.82 (m,
 8H), 1.75 (s, 3H), 1.73 - 1.07 (m, 15H), 1.24 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.97
 (s, 3H), 0.97 (s, 3H), 0.93 - 0.87 (m, 2H), 0.87 - 0.79 (m, 2H).

15 Example B63

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



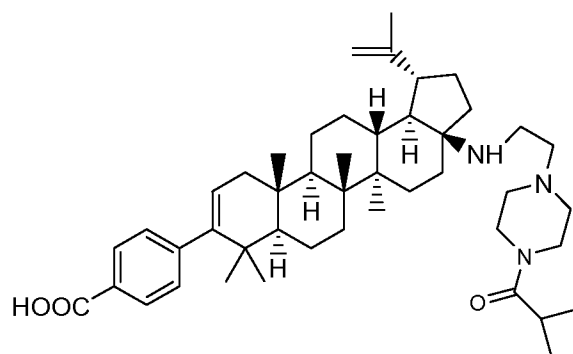
The title compound (0.9 mg) was prepared from methyl 4-
 25 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-
 (piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 1-methylcyclopropane-1-carboxylic acid as the acylating agent. LCMS: m/e 724.8 (M+H)⁺, 4.49 min (method 15). ¹H NMR (500MHz, METHANOL-d₄) δ 7.89 (d, J=8.2 Hz, 2H), 7.16 (d, J=8.2 Hz, 2H), 5.30 (d, J=4.6 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.90 - 3.63 (m, 4H), 3.09 - 2.98 (m, 1H), 2.96 - 2.82 (m, 2H), 2.81 - 2.73 (m, 1H), 2.71 - 2.61 (m, 3H), 2.54 (br. s., 2H), 2.24 - 2.12 (m, 1H), 2.11 - 1.82 (m, 5H), 1.75 (s, 3H), 1.72 - 1.14 (m, 16H), 1.32 (s., 3H), 1.23 (s., 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.93 - 0.88 (m, 2H), 0.68 - 0.58 (m, 2H).

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Example B64

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-isobutyrylpiperazin-1-yl)ethyl)amino)-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



The title compound (0.4 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-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 following the general procedure as described above using isobutyric acid as the acylating agent. LCMS: m/e 712.8 (M+H)⁺, 4.46 min (method 15). ¹H NMR (500MHz, METHANOL-d₄) δ 7.88 (d, J=8.2 Hz, 2H), 7.15 (d, J=7.9 Hz, 2H), 5.30 (d, J=4.9 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.77 - 3.54 (m, 4H), 2.97 (dt, J=13.4, 6.6 Hz, 2H), 2.86 - 2.71 (m, 3H), 2.70 - 2.51 (m, 4H), 2.46

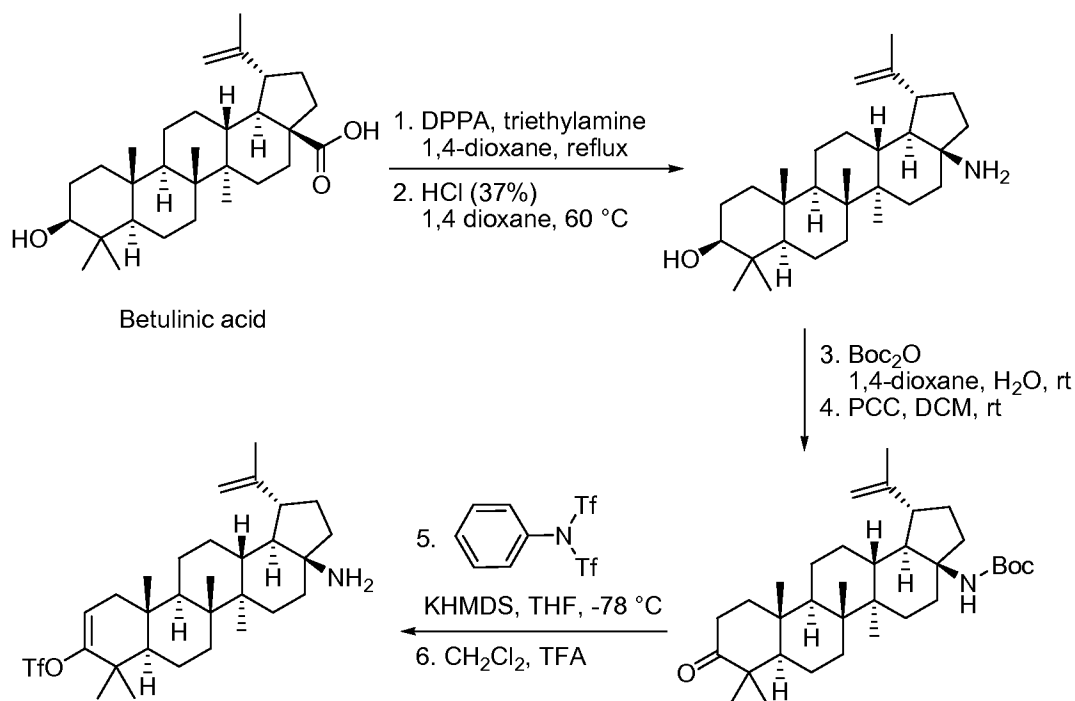
(br. s., 1H), 2.15 (dd, $J=17.1, 6.4$ Hz, 1H), 2.08 - 1.82 (m, 5H), 1.75 (s, 3H), 1.73 - 1.18 (m, 16H), 1.22 (s, 3H), 1.11 (d, $J=6.7$ Hz, 6H), 1.10 (s, 3H), 1.05 (s, 3H), 0.97 (s., 3H), 0.97 (s., 3H),

5

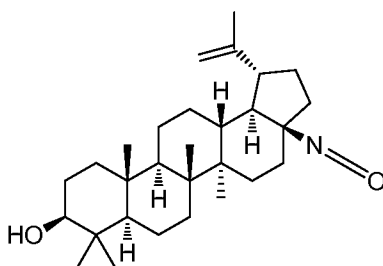
Example B65

Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-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 trifluoromethanesulfonate

10

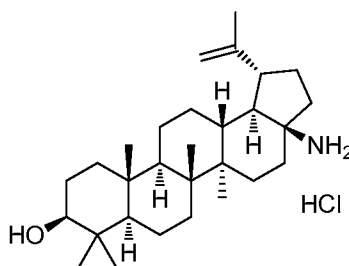


15 **Step 1. Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol**



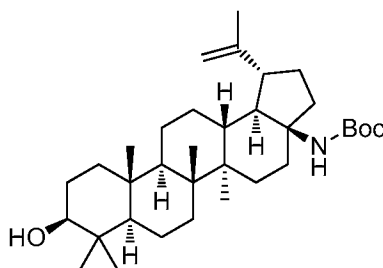
To a suspension of betulinic acid (10 g, 21.90 mmol) in 1,4-Dioxane (100 mL) was added triethylamine (9.16 mL, 65.7 mmol) and diphenyl phosphorazidate (7.08 mL, 32.8 mmol). The mixture was heated to reflux. Upon heating, all solids dissolved. After heating the mixture for 26h, the mixture was cooled to rt and was concentrated under reduced pressure. The residue was diluted with 100 mL of water and was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography in silica gel using a 0-15% EtOAc in hexanes gradient and a Thomson 240g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure. A second batch of less-pure product was concentrated and was repurified using a Thomson 240g column and the same gradient. The fractions containing the expected product were combined with the first batch to give (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (7.76 g, 17.10 mmol, 78 % yield) as a white solid. ¹H NMR (400MHz, *chloroform-d*) δ = 4.75 (s, 1H), 4.67 - 4.62 (m, 1H), 3.20 (dt, $J=11.3$, 5.6 Hz, 1H), 2.55 (td, $J=10.9$, 5.9 Hz, 1H), 2.17 - 2.03 (m, 1H), 1.92 - 1.76 (m, 5H), 1.69 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 0.85 (s, 3H), 0.78 (s, 3H), 1.74 - 0.66 (m, 19H).

Step 2. Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl



To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (7.76 g, 17.10 mmol) in 1,4-dioxane (100 mL) was added HCl (37%) (21.07 mL, 257 mmol). The mixture was heated to 60 °C for 15h of heating then was cooled to rt and was concentrated under reduced pressure. The residue was dissolved in dichloromethane and methanol and was concentrated two additional times to give (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl (7.75 g, 16.70 mmol, 98 % yield) as an off-white foam. The crude product was used in the next step with no purification.

Step 3. Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate

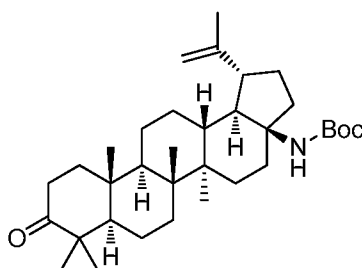


To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl (7.76 g, 16.72 mmol) in 1,4-Dioxane (100 mL) was added water (25 mL), sodium bicarbonate (4.21 g, 50.2 mmol) and Boc anhydride (5.82 mL, 25.08 mmol). The mixture was stirred at rt for 16h then the mixture was diluted with 100 mL of water and was extracted with ethyl acetate (3 x 100 mL). The combined organic

layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give tert-butyl

((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate as an off-white foam. ¹H NMR (500MHz, *chloroform-d*) δ = 4.74 (d, *J*=1.6 Hz, 1H), 4.64 - 4.62 (m, 1H), 4.34 (br. s., 1H), 3.24 - 3.18 (m, 1H), 2.63 - 2.35 (m, 3H), 2.06 - 1.93 (m, 1H), 1.71 (s, 3H), 1.46 (s, 9H), 1.04 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H), 0.79 (s, 3H), 1.77 - 0.68 (m, 22H).

- 10 Step 4. Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate



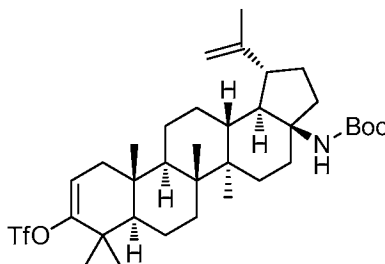
15

To a solution of the resulting tert-butyl

((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate in dichloromethane (100 mL) was added pyridinium chlorochromate (4.69 g, 21.74 mmol). The mixture was stirred at rt for 5h then an additional 1.0g of PCC was added and the mixture was stirred at rt for 1h. The mixture was filtered through a plug of silica gel and celite which was washed with a solution of 25% ethyl acetate in hexanes. The filtrate was concentrated under reduced pressure to give tert-butyl

- 20 ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate as a light-yellow foam. ¹H NMR (500MHz, CHLOROFORM-*d*) δ = 4.74 (d, *J*=1.7 Hz, 1H), 4.63 (t, *J*=1.7 Hz, 1H), 4.34 (br. s., 1H), 2.65 - 2.34 (m, 5H), 2.05 - 1.88 (m, 2H), 1.71 (s, 3H), 1.47 (s, 9H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 1.76 - 0.93 (m, 18H).

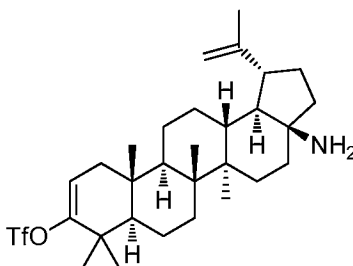
Step 5. Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate



A solution of the resulting tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate in THF (100 mL) was cooled to -78 °C. To the solution was added KHMDS (0.91M in THF) (40.4 mL, 36.8 mmol). The mixture was stirred for 20 minutes at -78 °C then a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl)sulfonyl methanesulfonamide (7.47 g, 20.90 mmol) in THF (100 mL) was added via canula. The mixture was stirred at -78 °C for 5h then was quenched with 100 mL of water and was extracted with ethyl acetate (3 x 75 mL). The combined organic layers were dried with magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was taken up in a small amount of DCM and methanol and the yellow solids that formed were removed by filtration. The filtrate was again concentrated and treated with methanol and the solids that formed were again removed by filtration. The filtrate was concentrated and was adsorbed to silica gel and was then purified by flash chromatography using a 0-50% ethyl acetate in hexanes gradient and a Thomson 240g silica gel column. The fractions containing the deprotected product were combined and were concentrated under reduced pressure to give a mixture of products. The expected product was repurified by flash chromatography using a 0-10% EtOAc in hexanes gradient and a 240g Thomson silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-

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 trifluoromethanesulfonate (1.31g, 1.99 mmol, 11.9% over
 3 steps). ¹H NMR (500MHz, CHLOROFORM-d) δ = 5.57 (dd, J =6.7, 1.8 Hz, 1H),
 5 4.73 (s, 1H), 4.62 (s, 1H), 4.32 (br. s., 1H), 2.64 - 2.31 (m, 3H), 2.16 (dd, J =17.0, 6.8
 Hz, 1H), 2.04 - 1.94 (m, 1H), 1.70 (s, 3H), 1.45 (s, 9H), 1.13 (s, 3H), 1.06 (s, 3H),
 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82 - 0.86 (m, 18H).

Step 6. Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-
 10 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 trifluoromethanesulfonate



15

To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-
 butoxycarbonyl)amino)-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 trifluoromethanesulfonate (0.2 g, 0.304 mmol) in
 20 dichloromethane (2 mL) was added trifluoroacetic acid (0.5 mL, 6.49 mmol). The
 mixture was stirred at rt for 1.5h then was concentrated under reduced pressure. The
 residue was diluted with saturated aqueous sodium bicarbonate (20 mL) and was
 extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried
 with Na₂SO₄. The drying agent was removed by filtration and the filtrate was
 25 concentrated and adsorbed to silica gel then was purified by flash chromatography
 using a 12-100% ethyl acetate in hexanes gradient and a 12g Thomson silica gel
 column. The fractions containing the expected product were combined and were
 concentrated under reduced pressure to give
 (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-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 trifluoromethanesulfonate (0.109 g, 0.195 mmol, 64.3 % yield) as an off-white solid. ¹H NMR (500MHz, *chloroform-d*) δ = 5.57 (dd, *J*=6.8, 1.9 Hz, 1H), 4.73 (d, *J*=1.6 Hz, 1H), 4.63 - 4.60 (m, 1H), 2.54 (td, *J*=10.9, 5.3 Hz, 1H), 2.17 (dd, *J*=17.1, 6.9 Hz, 1H), 2.08 - 1.99 (m, 1H), 1.70 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82 - 0.91 (m, 20H).

10 Biology Data for the Examples

- “ μ M” means micromolar;
- “mL” means milliliter;
- “ μ l” means microliter;
- 15 • “mg” means milligram;
- “ μ g” means microgram;

The materials and experimental procedures used to obtain the results reported in Tables 1-2 are described below.

- 20 *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 μ g/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),
- 25 100 units/ml penicillin G and 100 μ g/ml streptomycin. The proviral DNA clone of NL₄₋₃ was obtained from the NIH AIDS Research and Reference Reagent Program. A recombinant NL₄₋₃ 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
- 30 transfection of the altered proviral clone of NL₄₋₃. 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 2.

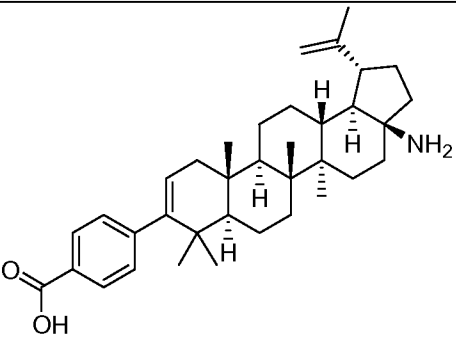
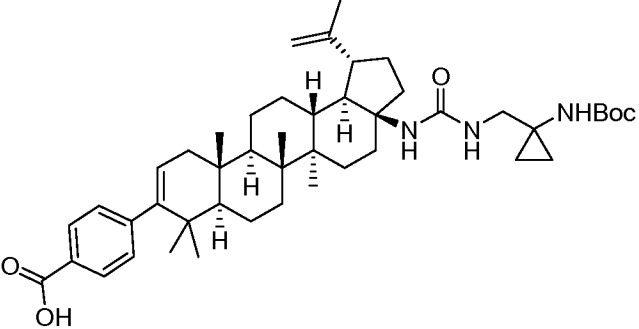
Table 1 is the key for the data in Table 2.

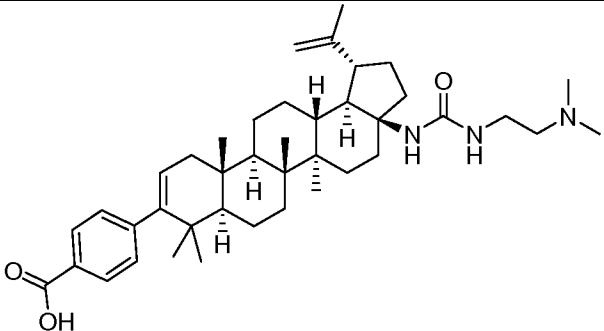
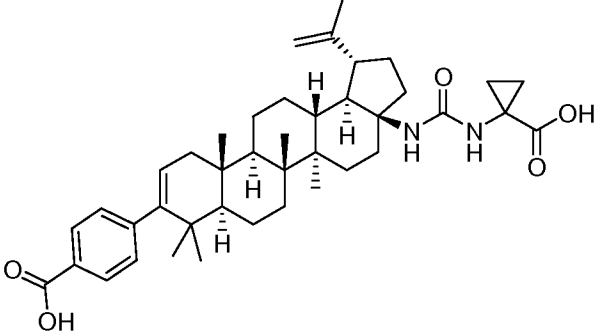
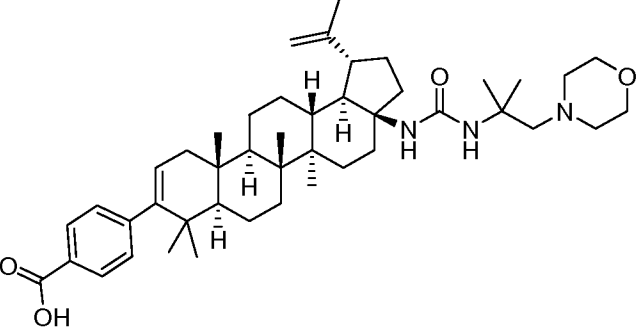
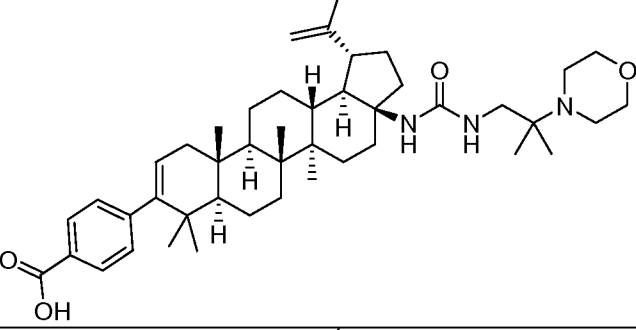
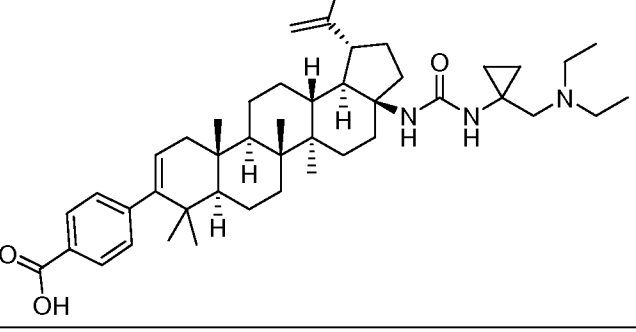
Results

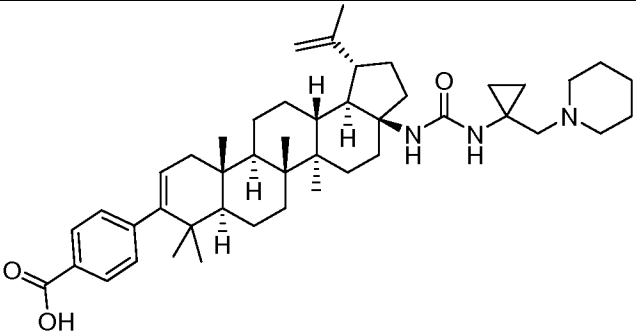
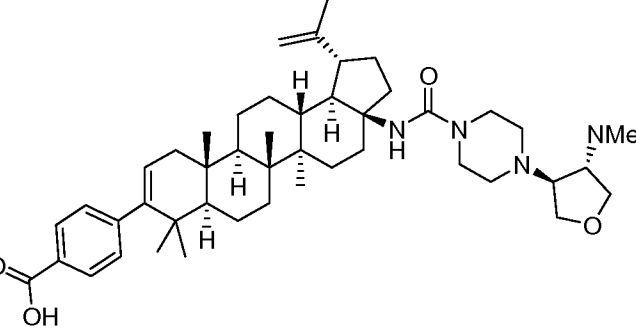
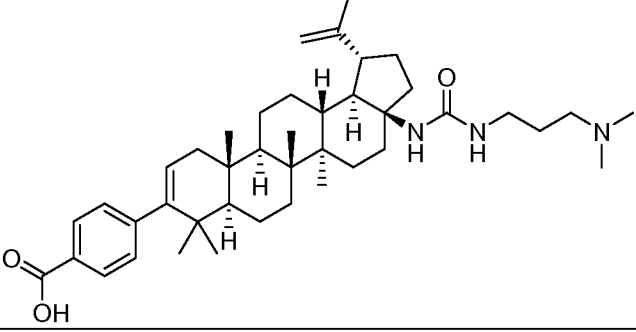
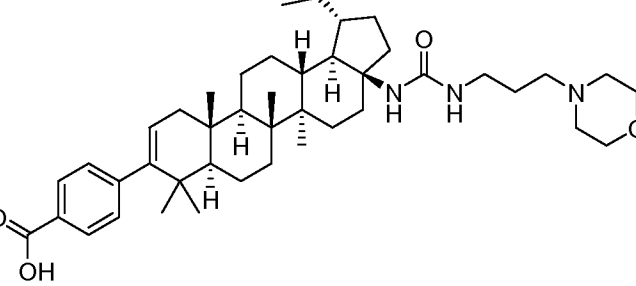
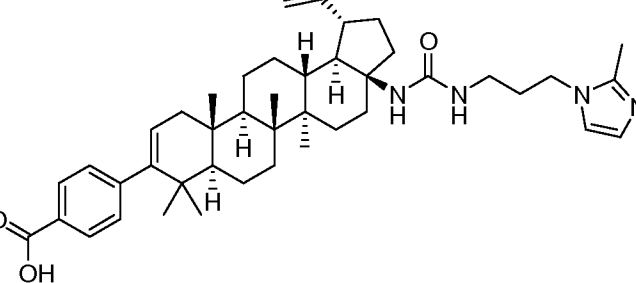
Table 1. Biological Data Key for EC_{50}

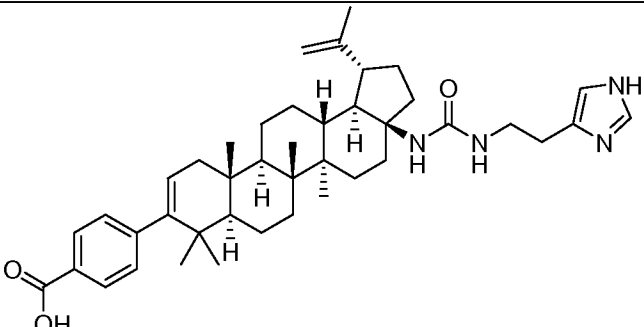
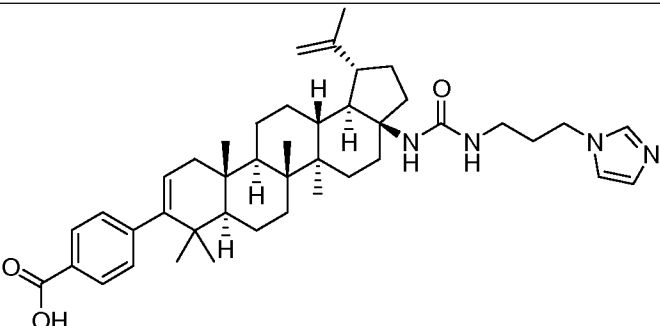
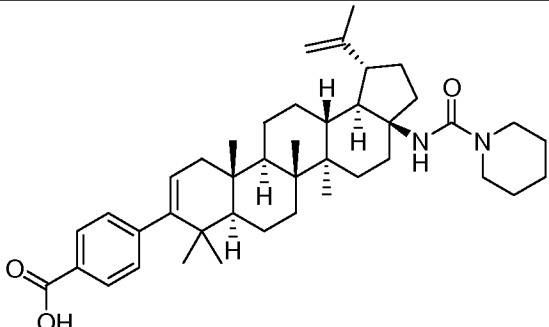
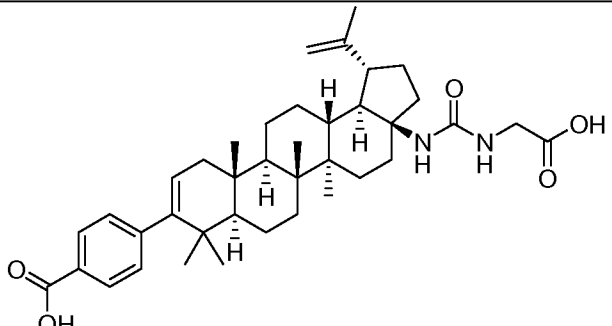
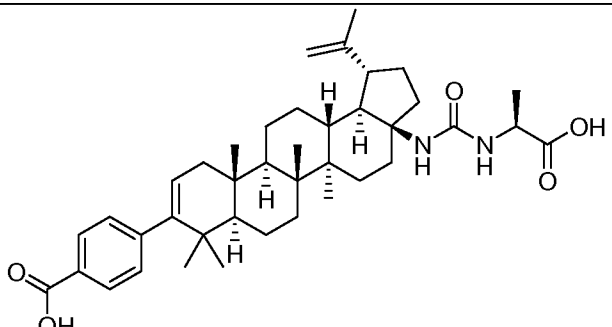
Compounds with $\text{EC}_{50} > 0.1 \mu\text{M}$	Compounds with $\text{EC}_{50} < 0.1 \mu\text{M}$
Group "B"	Group "A"

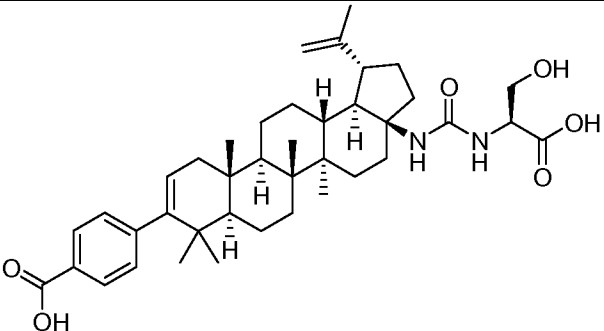
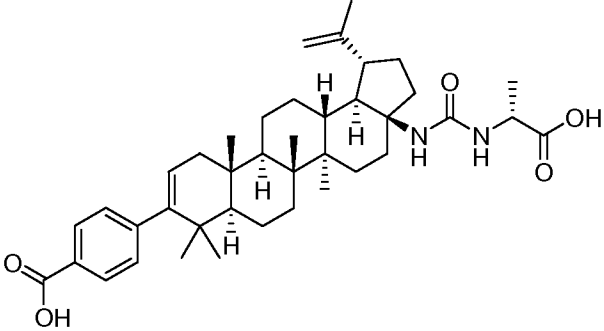
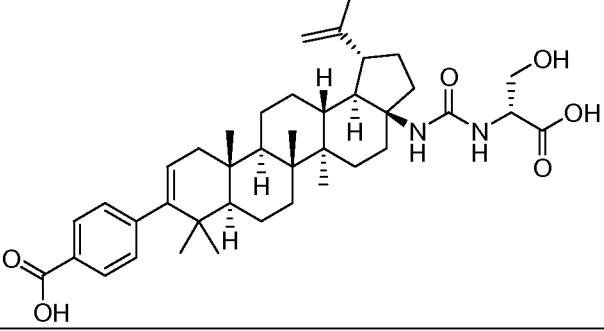
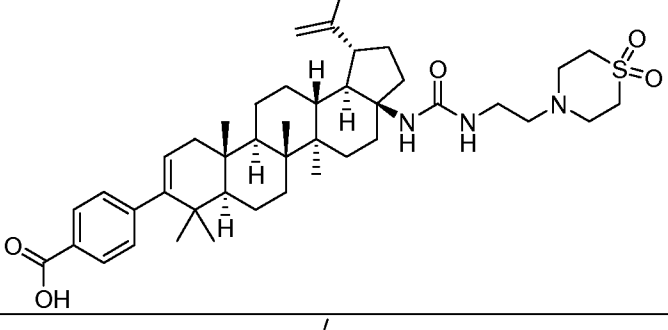
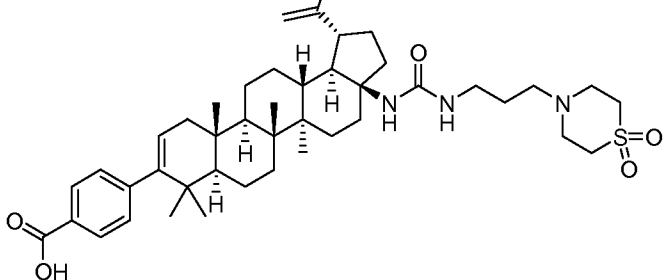
Table 2

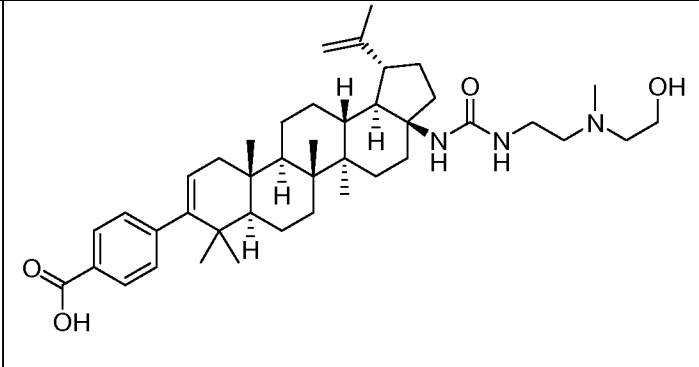
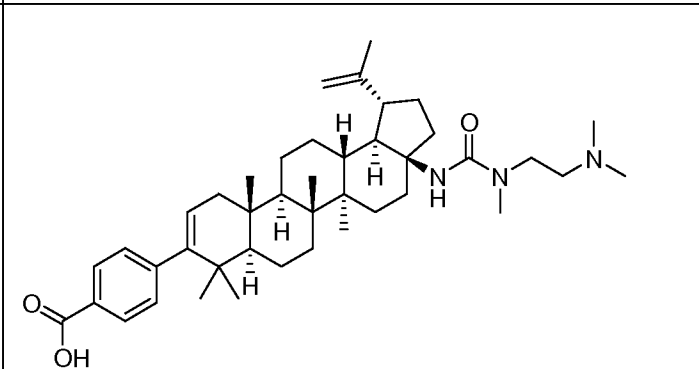
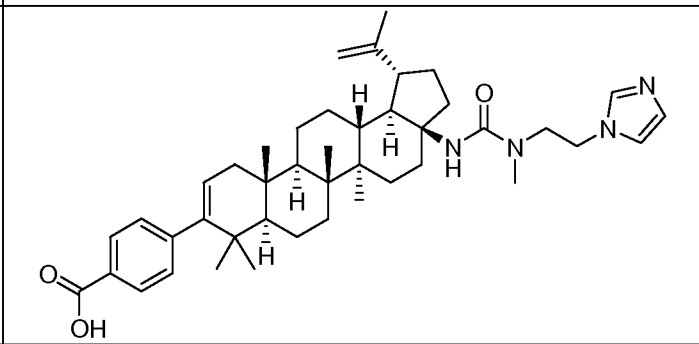
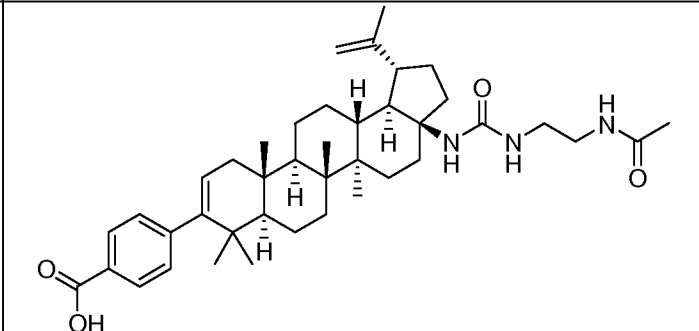
Example #	Structure	EC_{50} (μM)
1		A
2		A

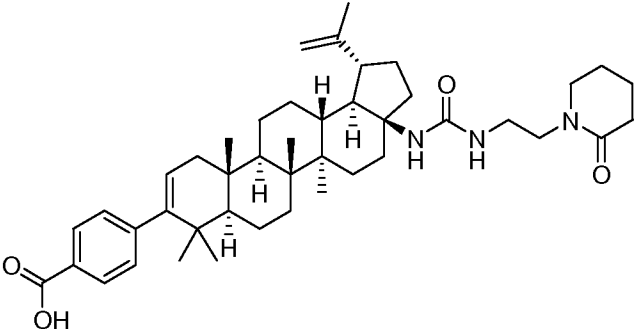
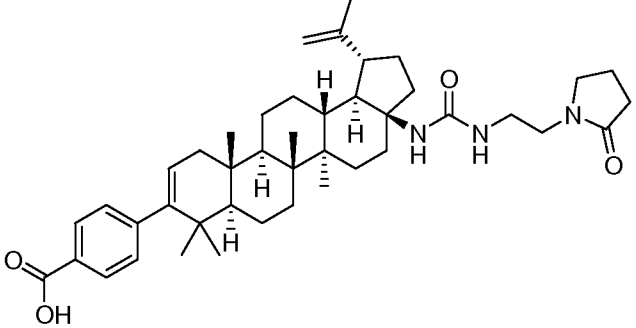
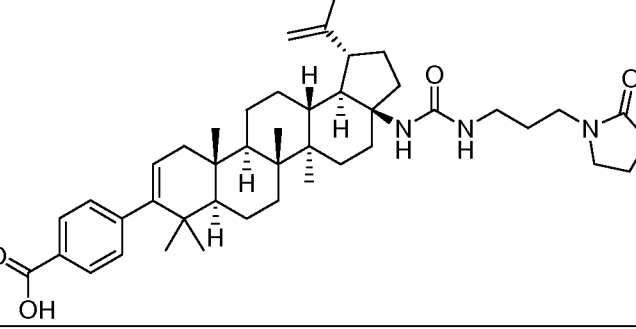
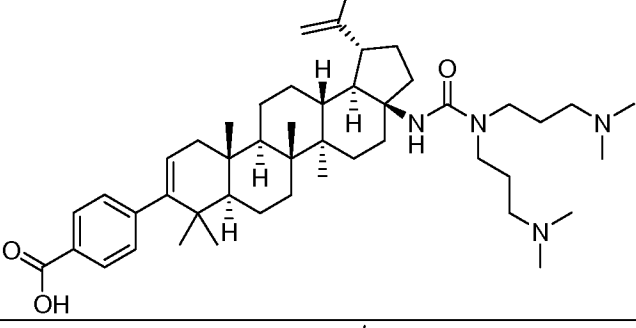
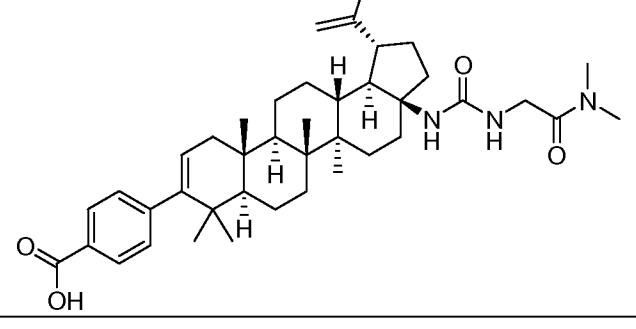
3		0.004
4		B
5		A
6		A
7		A

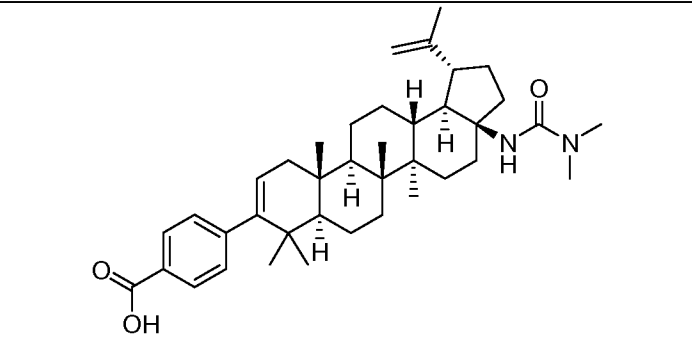
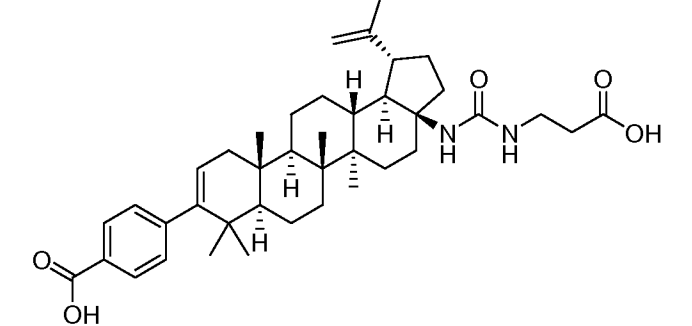
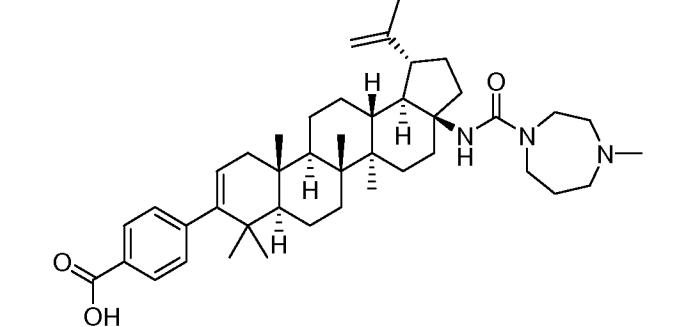
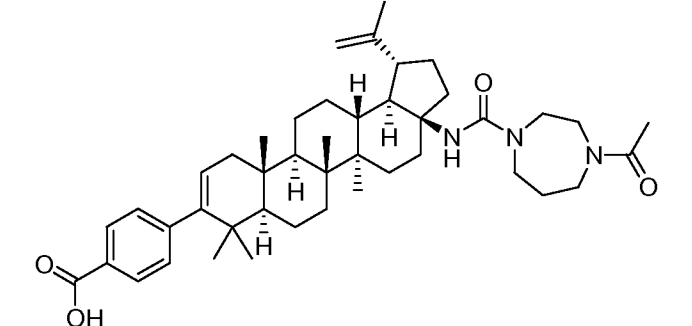
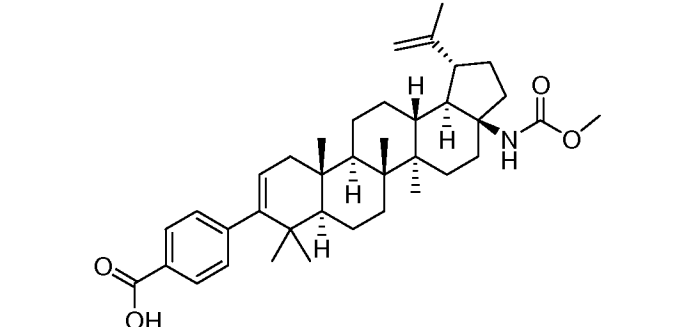
8		A
9		0.003
10		A
11		A
12		A

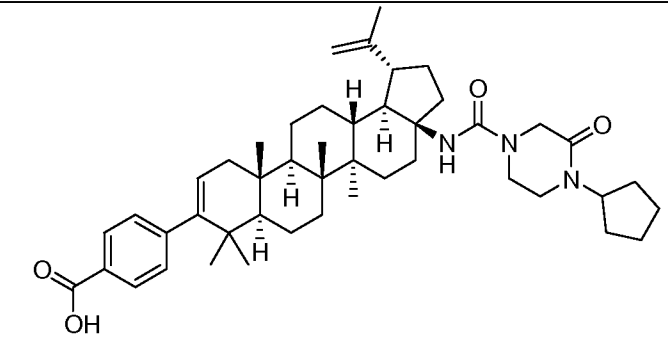
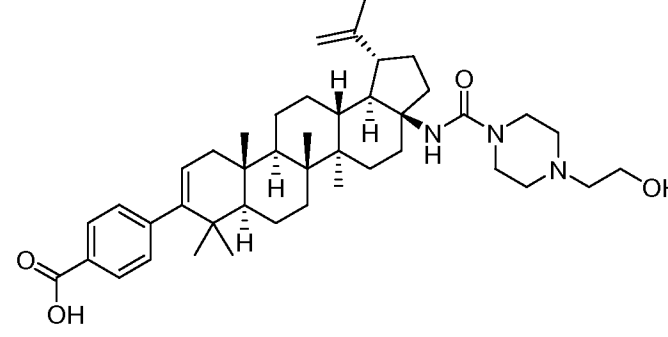
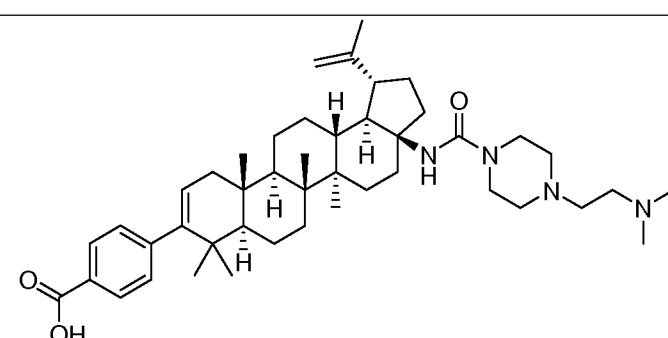
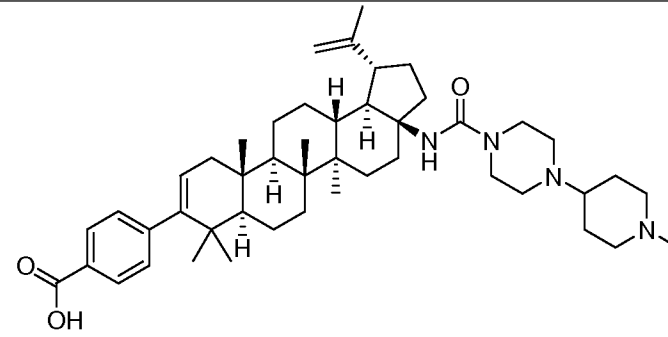
13		A
14		A
15		A
16		A
17		A

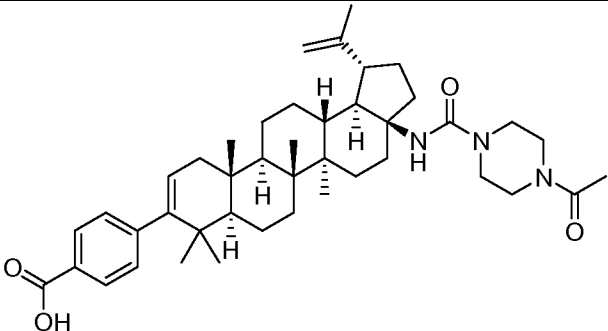
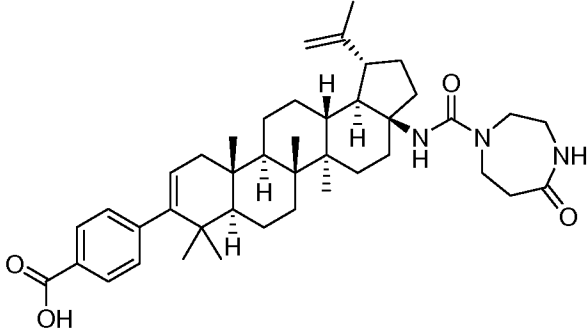
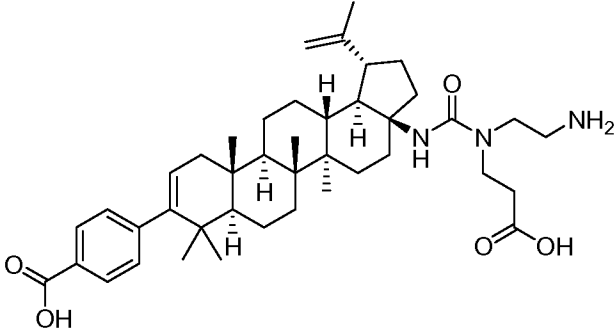
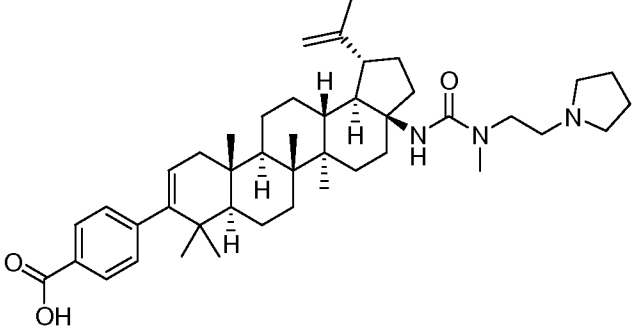
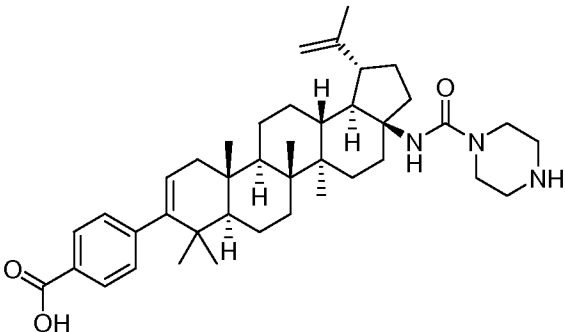
18		0.25
19		A
20		0.4
21		A
22		A

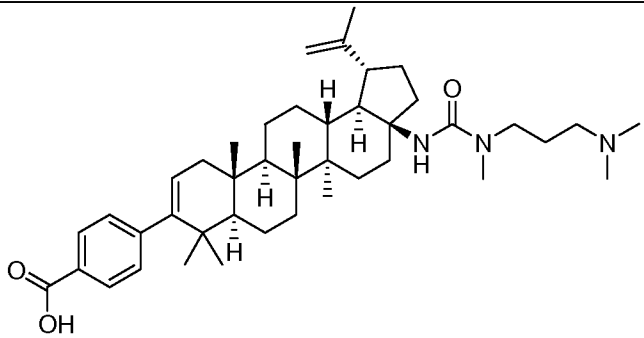
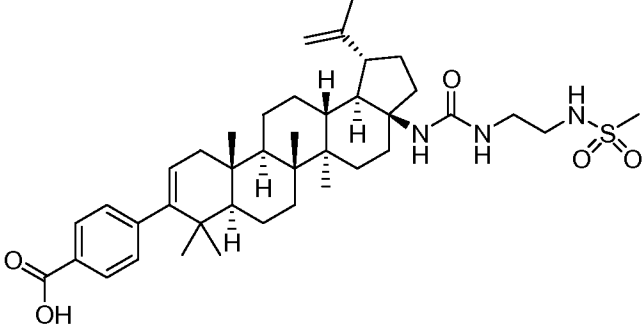
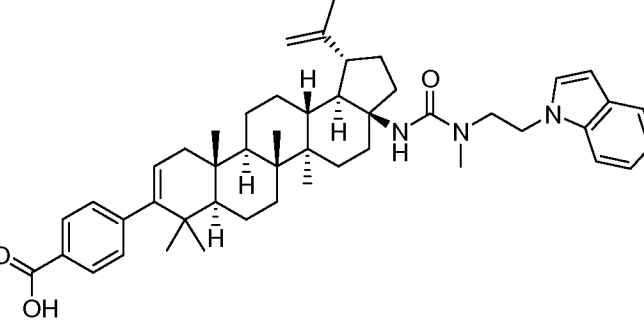
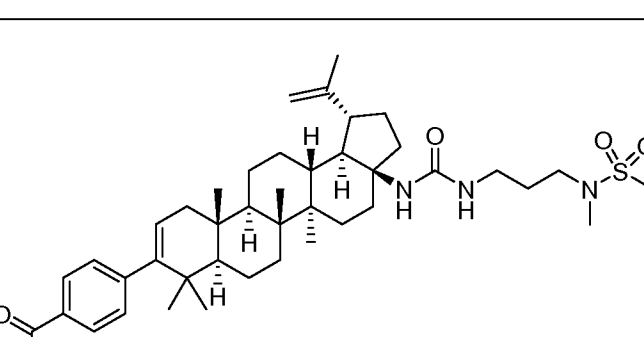
23		A
24		A
25		A
26		A

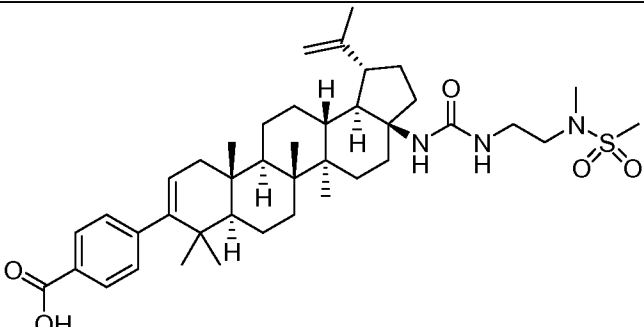
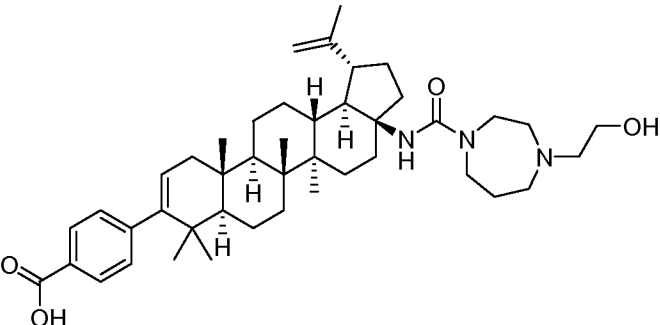
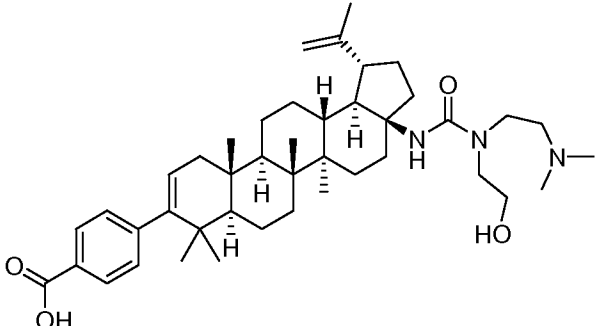
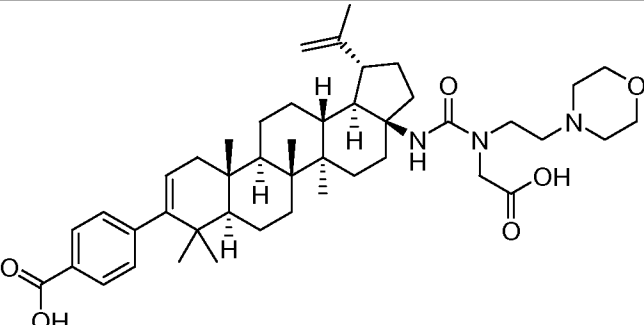
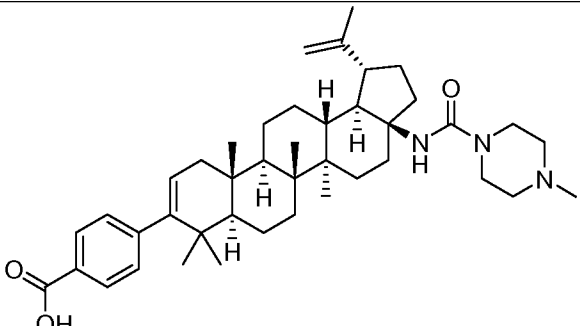
27		A
28		0.004
29		0.01
30		A
31		A

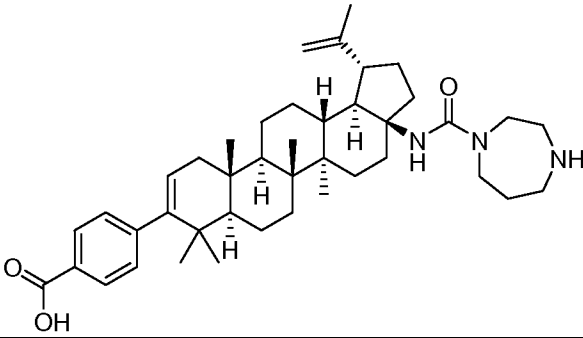
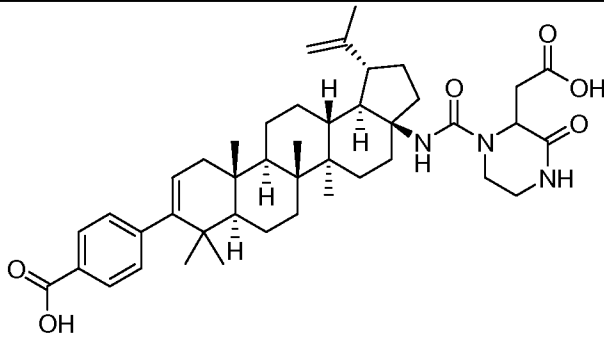
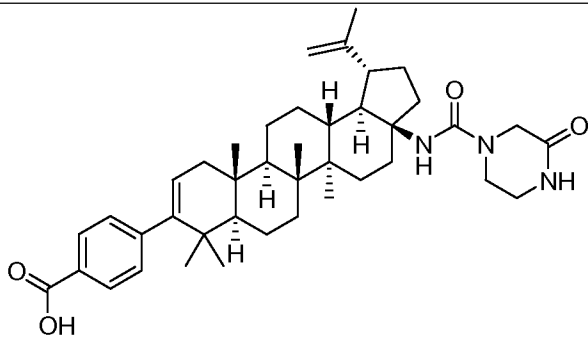
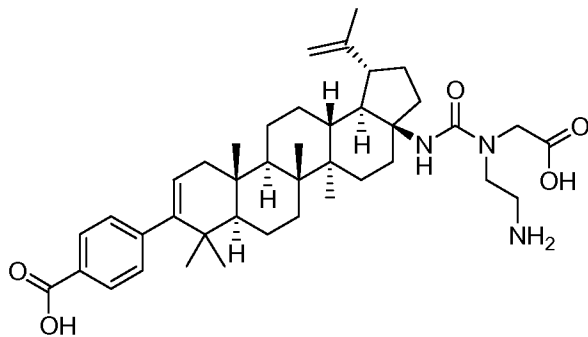
32		0.01
33		A
34		0.002
35		A
36		A

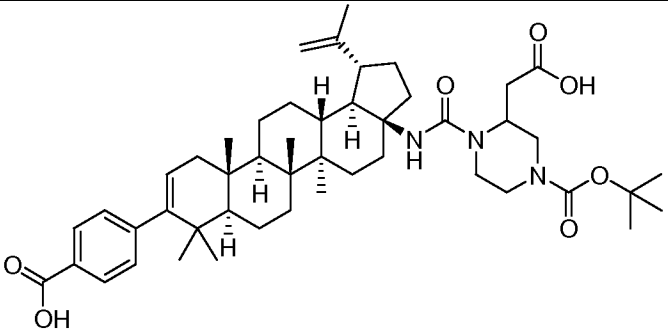
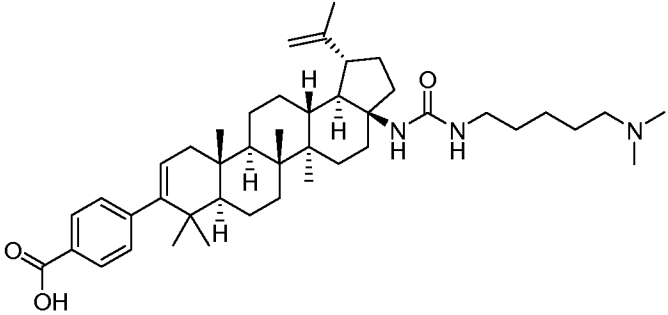
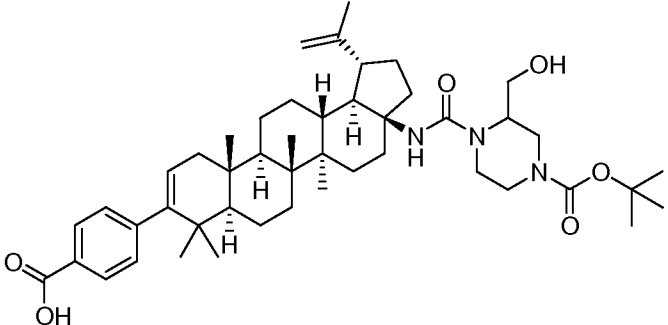
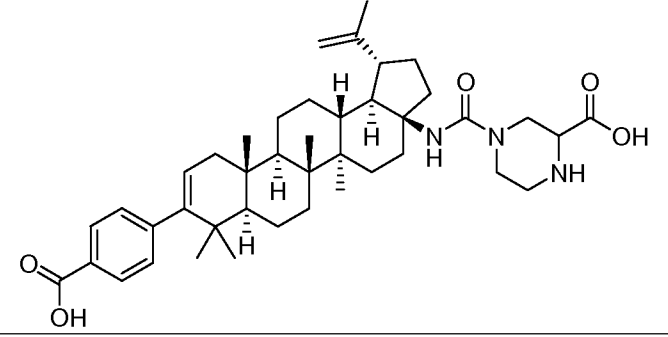
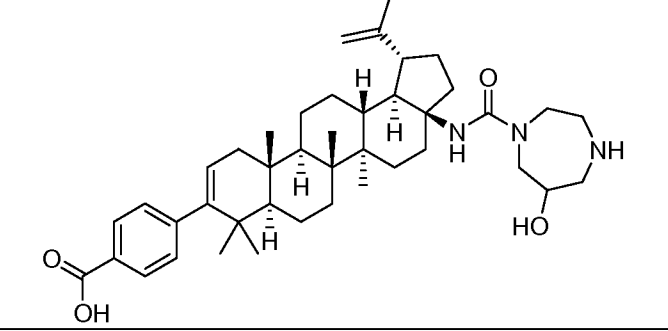
37		0.004
38		A
39		A
40		A
41		A

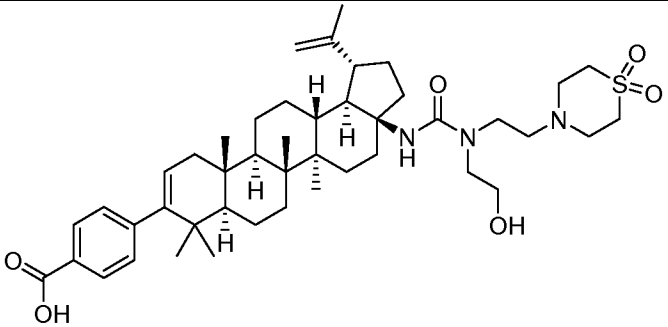
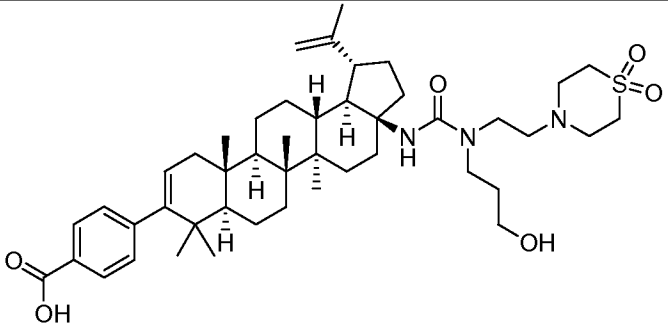
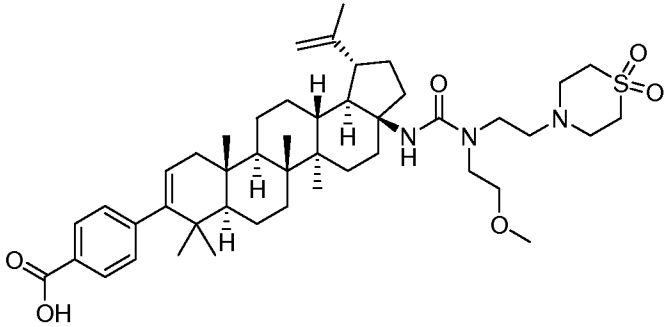
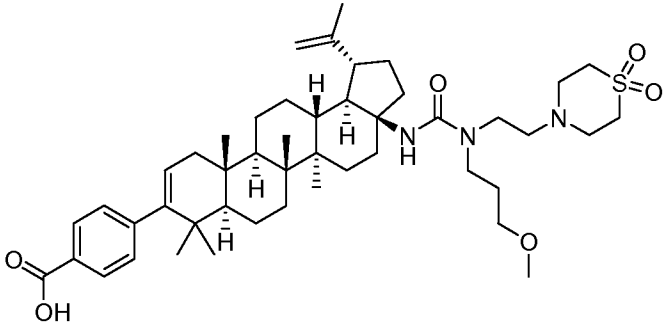
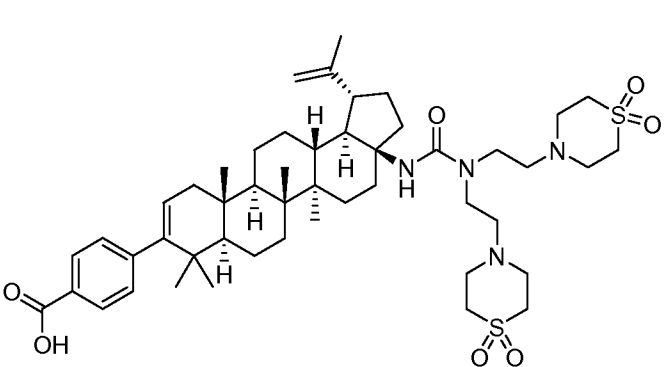
		
42		A
43		0.03
44		A
45		A

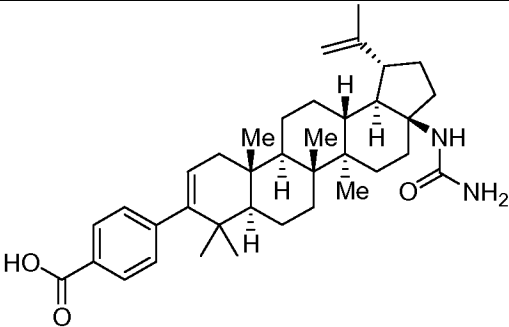
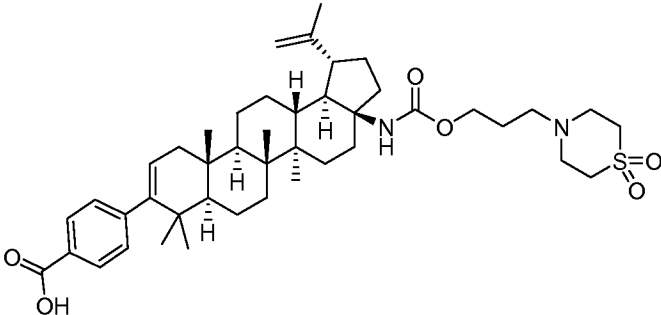
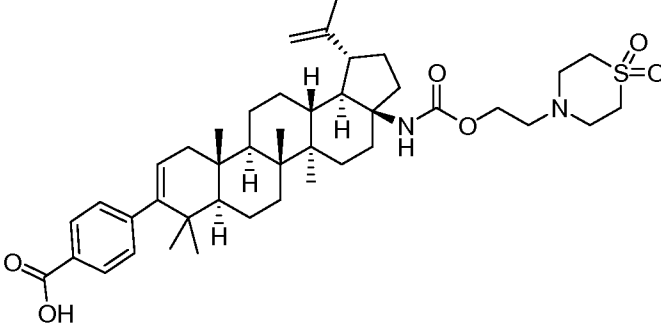
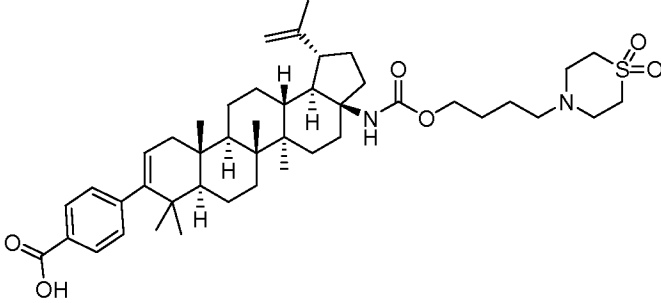
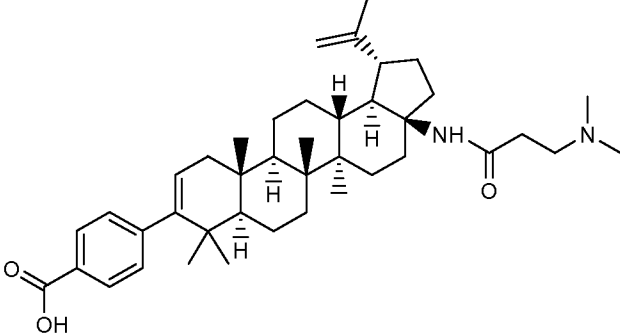
46		A
47		A
48		A
49		A

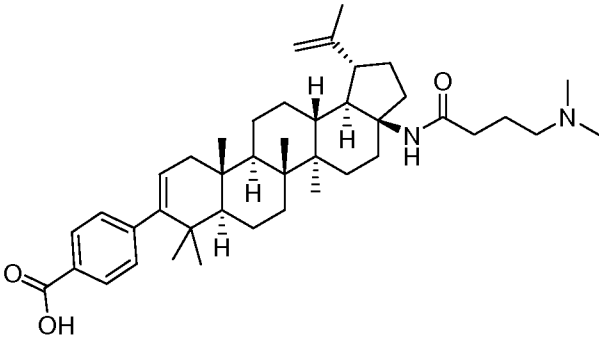
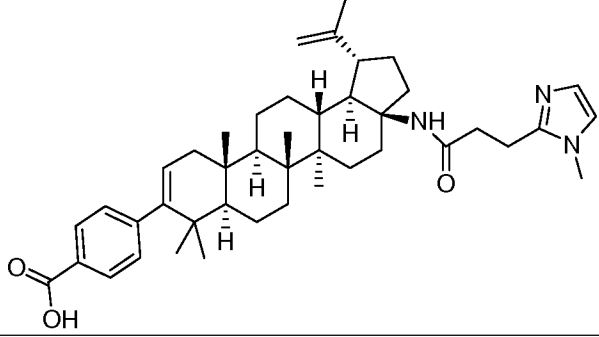
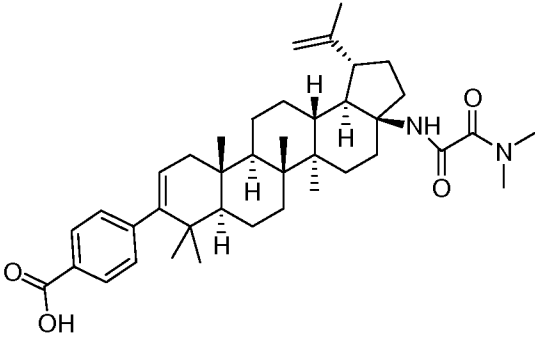
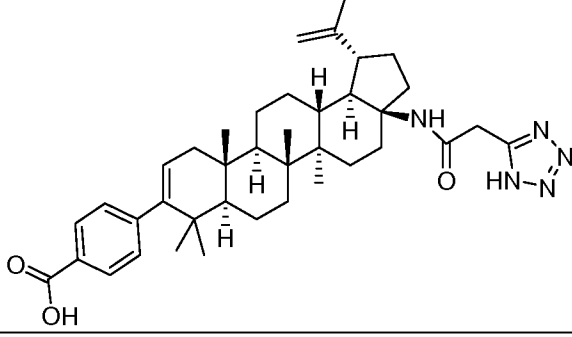
50		A
51		A
52		A
53		A
54		A

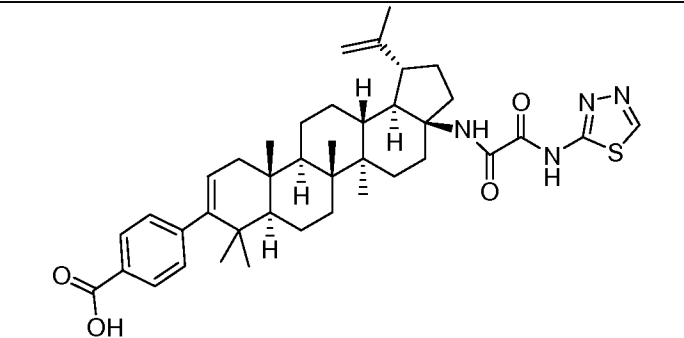
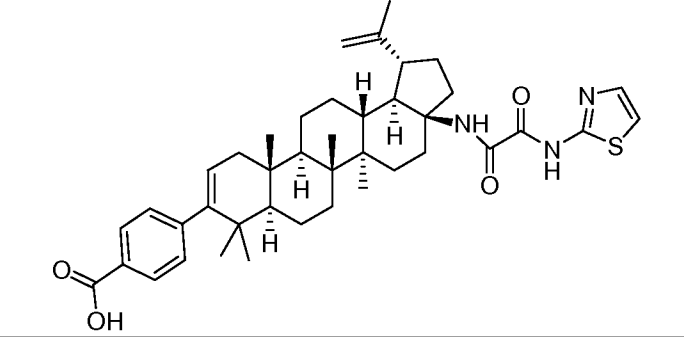
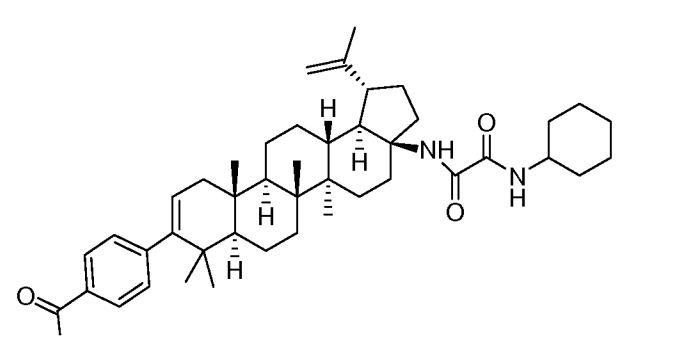
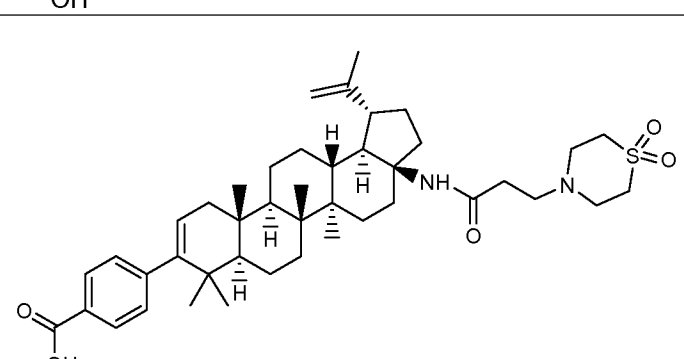
55		A
56		A
57		A
58		A
59		A

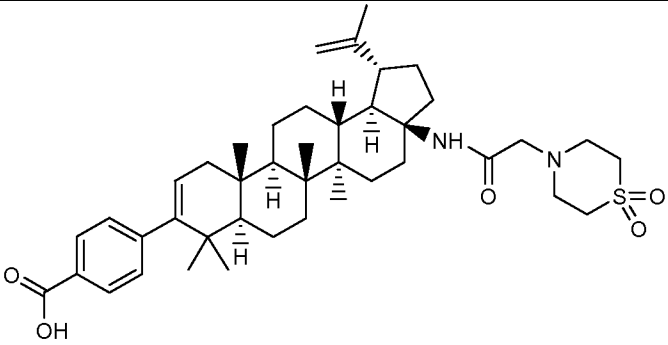
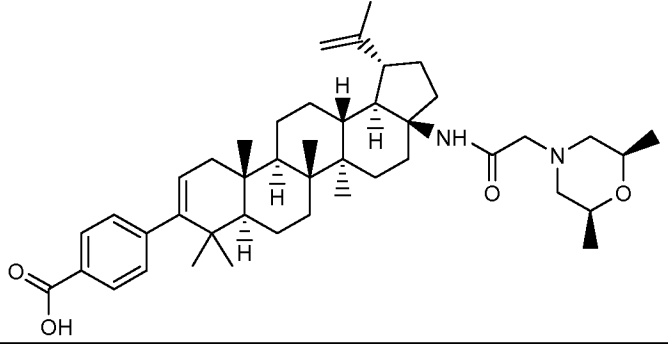
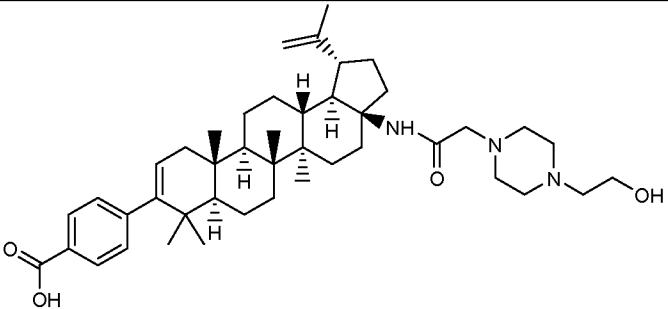
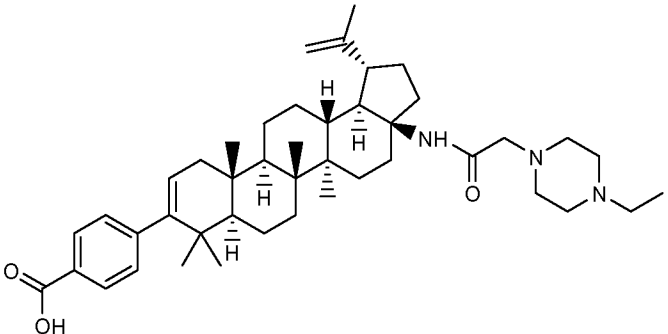
		
60		A
61		A
62		A
63		A
64		A

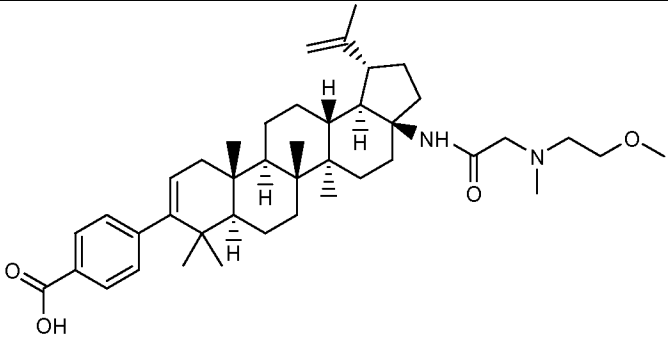
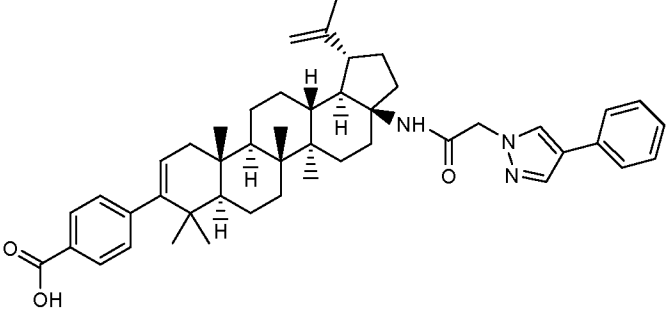
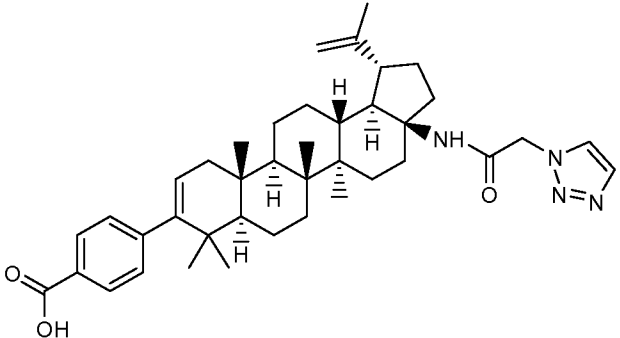
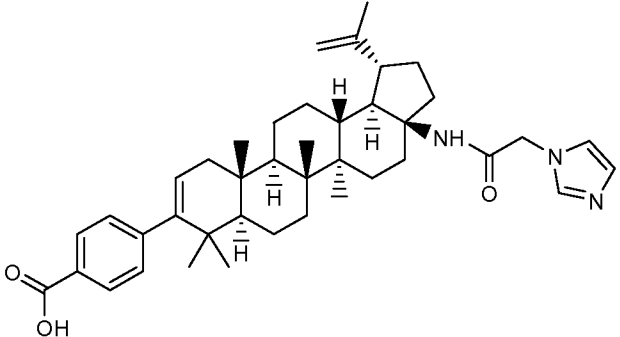
65		A
66		A
67		A
68		A
69		A

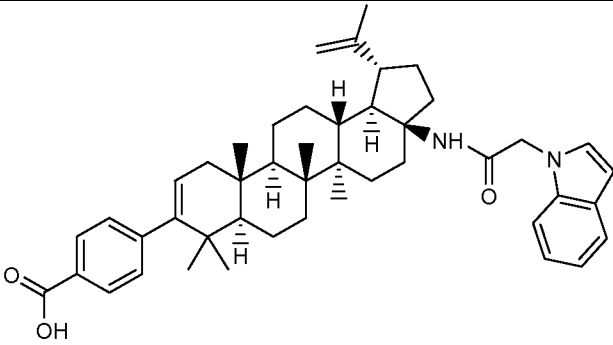
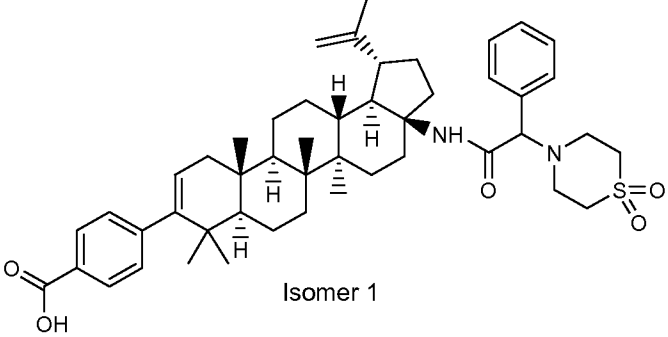
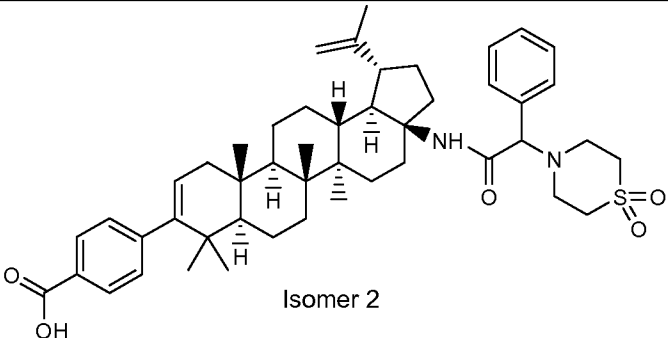
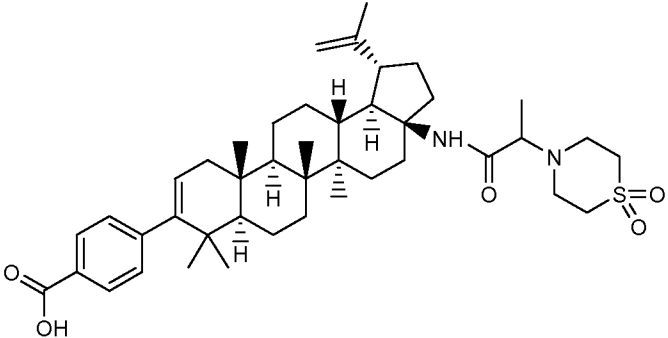
69-1		A
70		A
71		A
72		A
73		A

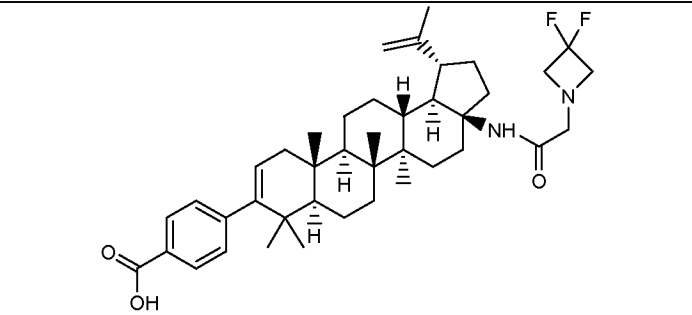
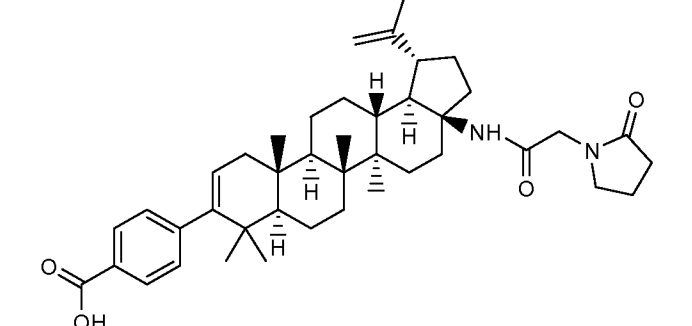
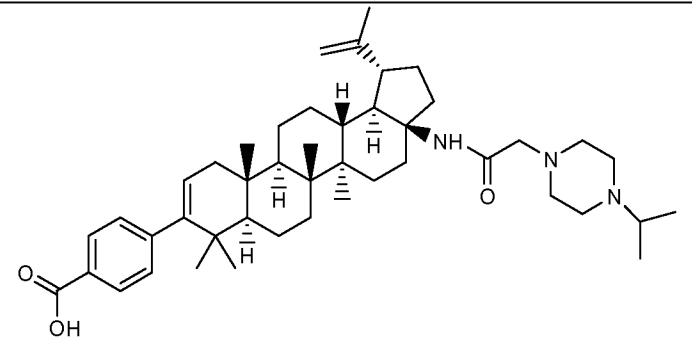
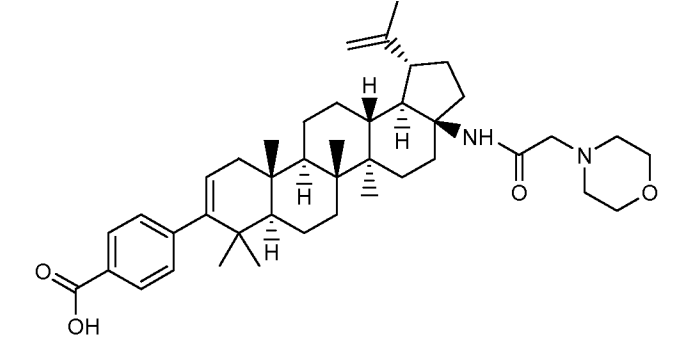
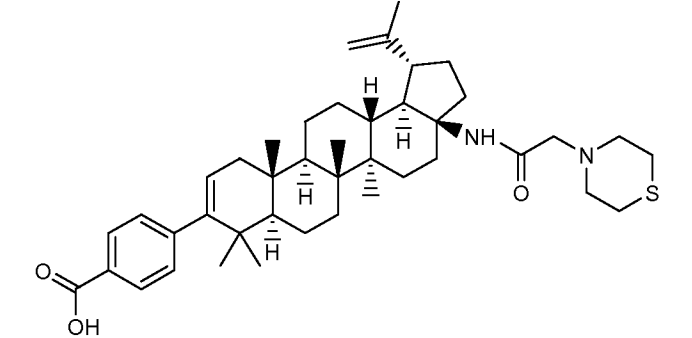
74		A
75		A
76		A
77		A

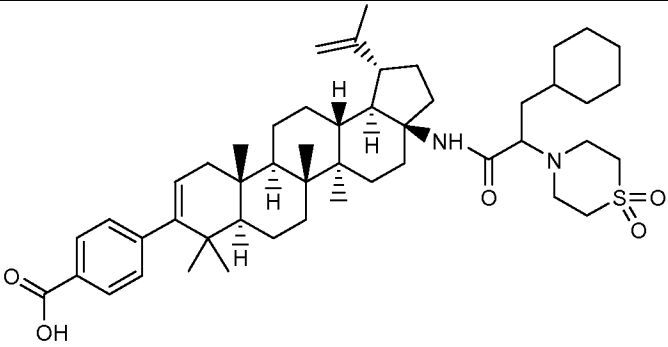
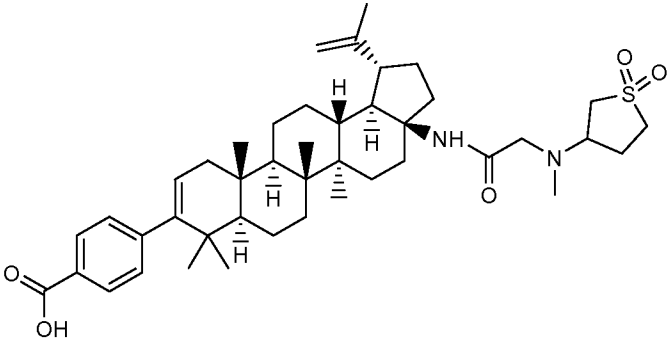
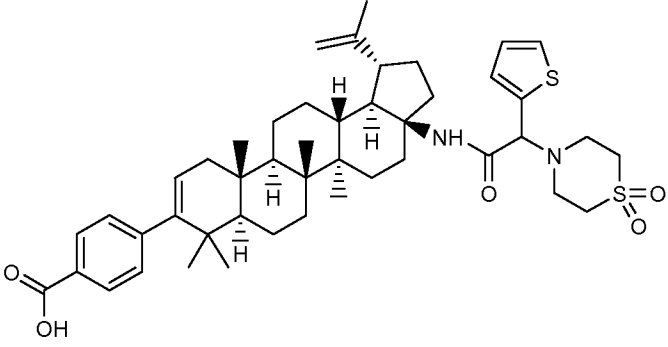
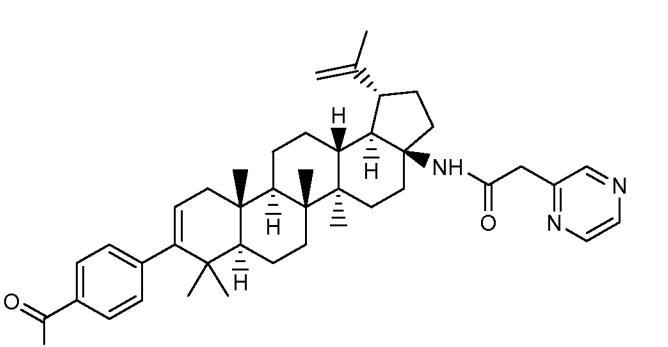
78	 <chem>CC1=C(C(CCC2=C(C(=C(C=C2)C(=O)O)C)C)C)CCC3=C(C)CCC4=C3C(=C(C=C4)NCC(=O)NC5=NC=NC=S5)C1</chem>	A
79	 <chem>CC1=C(C(CCC2=C(C(=C(C=C2)C(=O)O)C)C)C)CCC3=C(C)CCC4=C3C(=C(C=C4)NCC(=O)NC5=NC=CS5)C1</chem>	A
80	 <chem>CC1=C(C(CCC2=C(C(=C(C=C2)C(=O)O)C)C)C)CCC3=C(C)CCC4=C3C(=C(C=C4)NCC(=O)NC5=CC=CC=C5)C1</chem>	0.11
81	 <chem>CC1=C(C(CCC2=C(C(=C(C=C2)C(=O)O)C)C)C)CCC3=C(C)CCC4=C3C(=C(C=C4)NCC(=O)NCC5=CC=CC=C5S(=O)(=O)5)C1</chem>	A

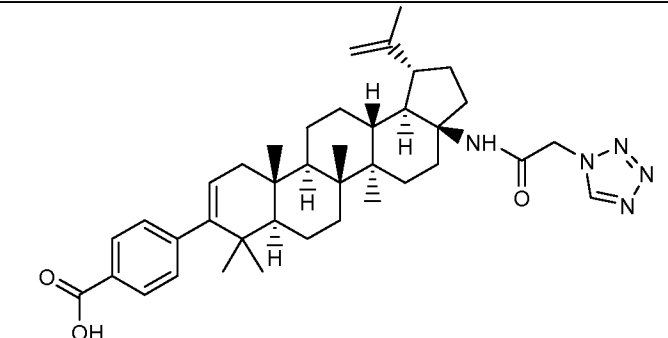
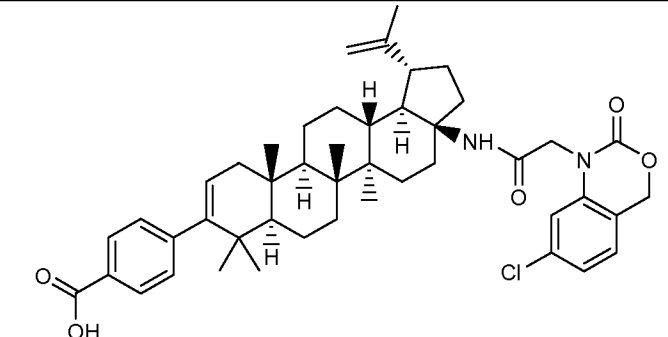
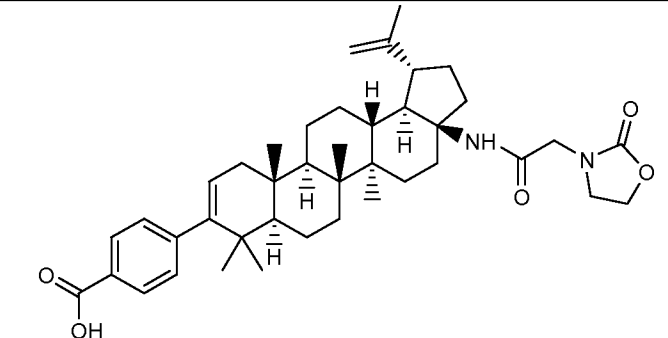
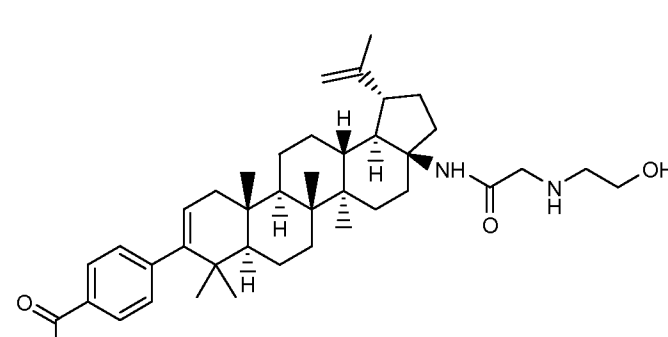
82		A
83		A
84		A
85		A

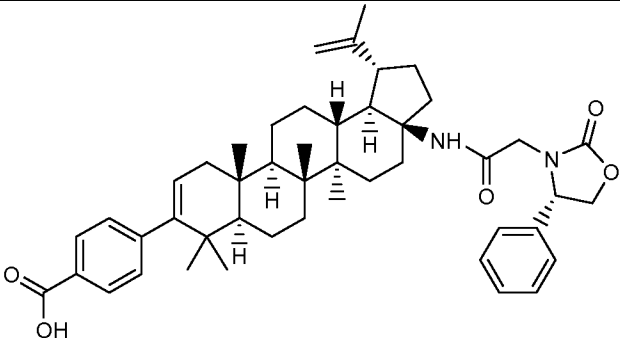
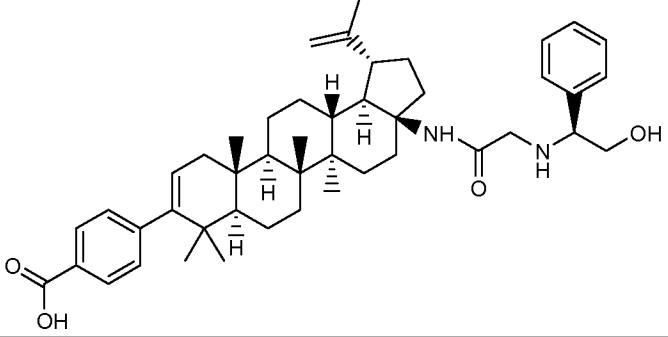
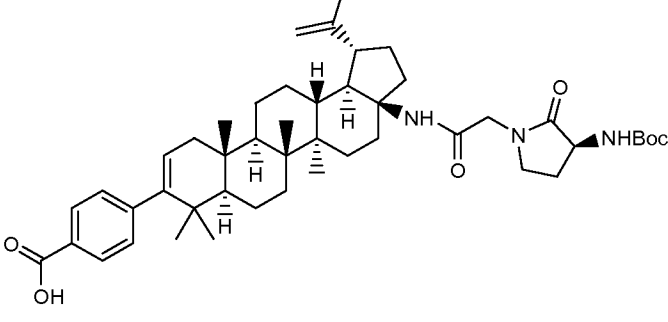
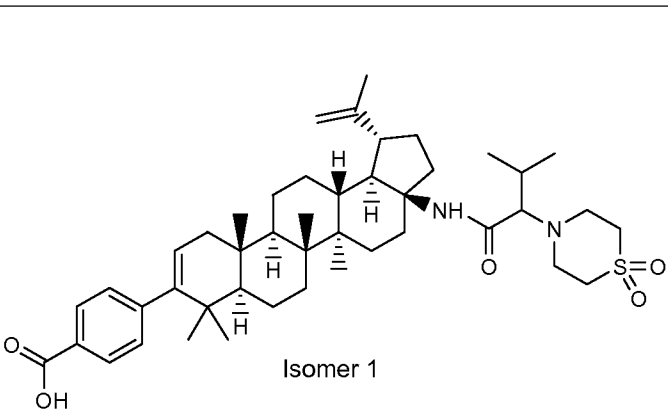
86		A
87		A
88		A
89		A
90		0.02

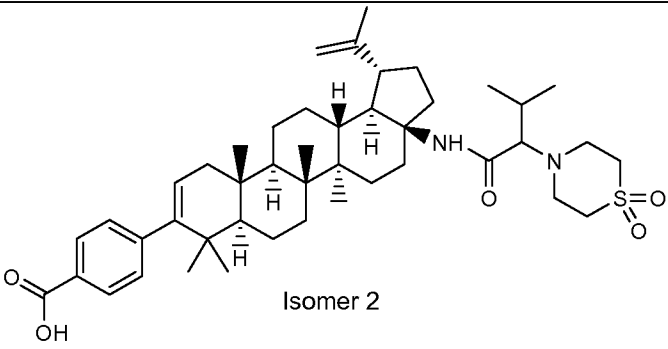
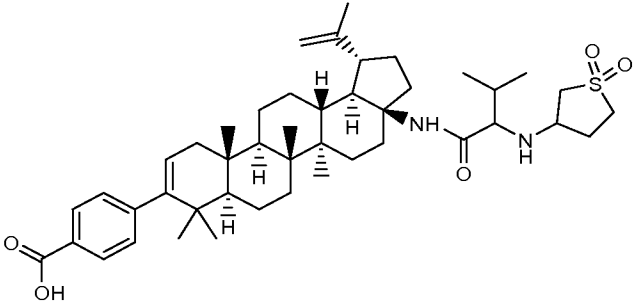
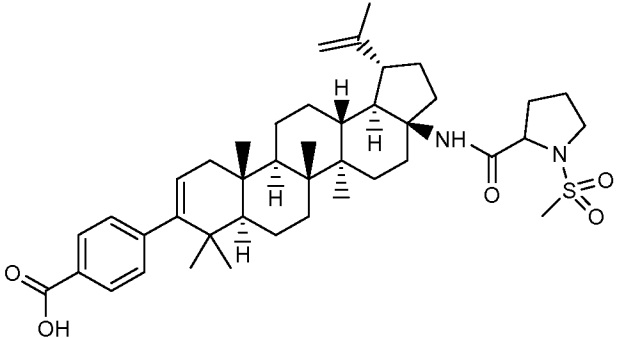
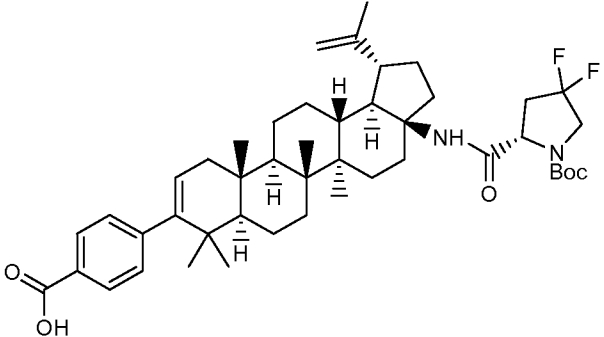
		
91	 Isomer 1	A
92	 Isomer 2	A
93		A

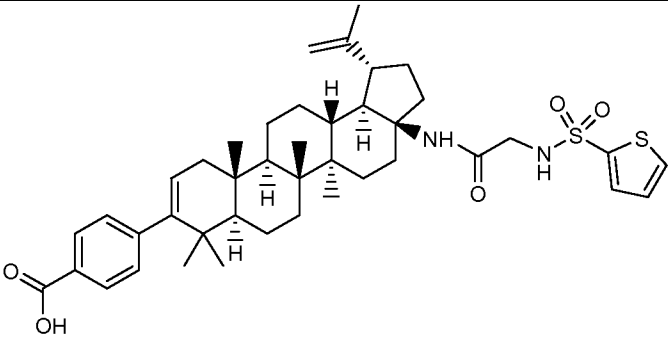
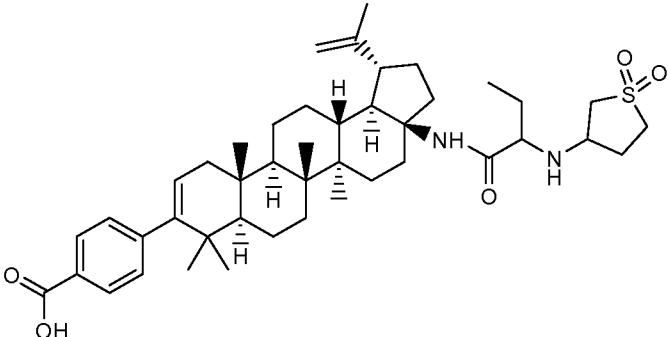
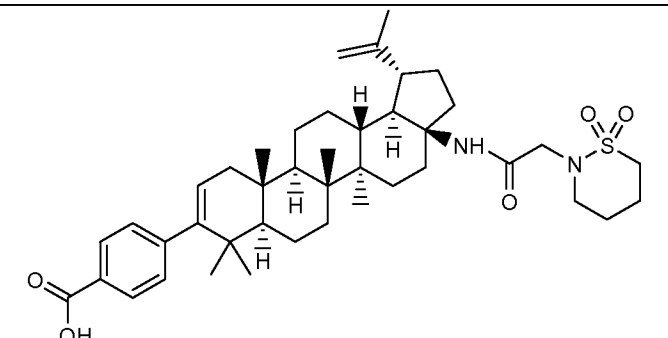
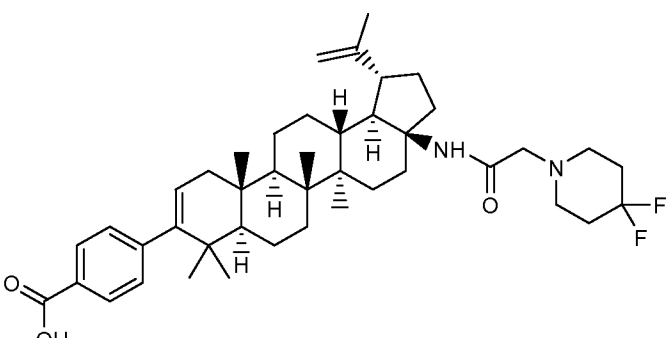
94		A
95		A
96		A
97		A
98		A
99		A

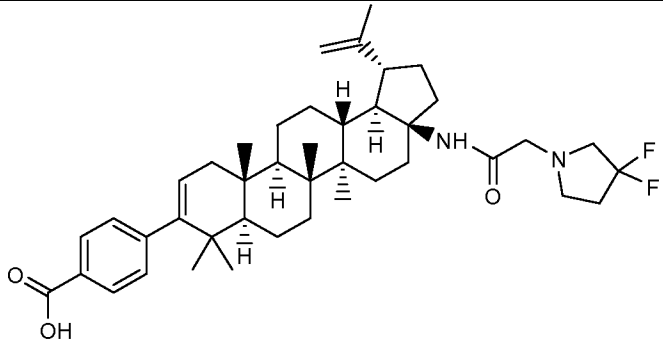
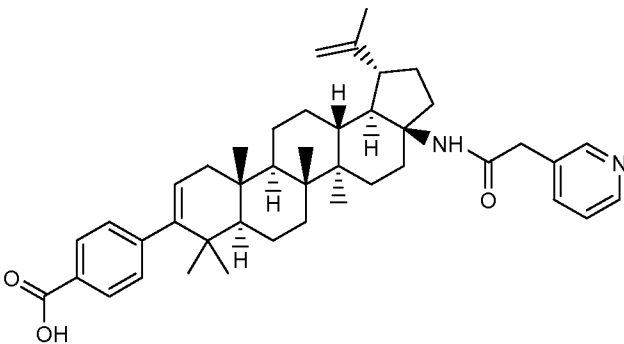
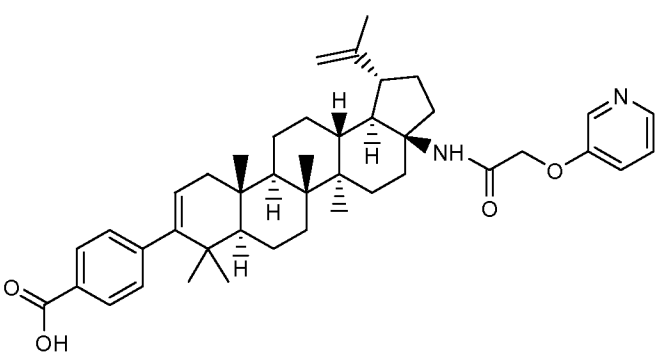
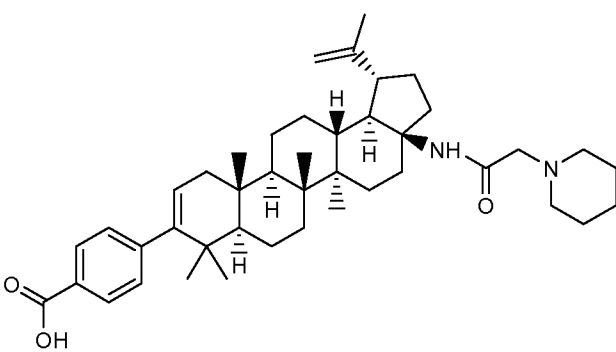
		
100		A
101		A
102		A

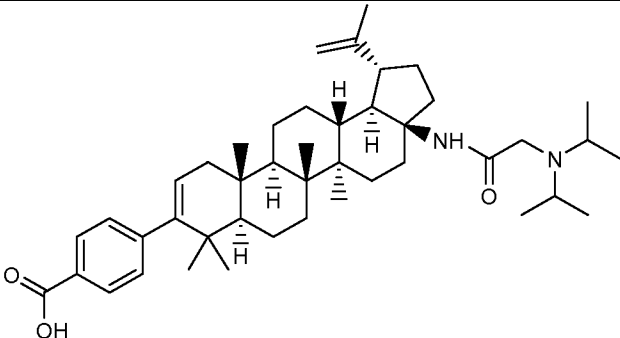
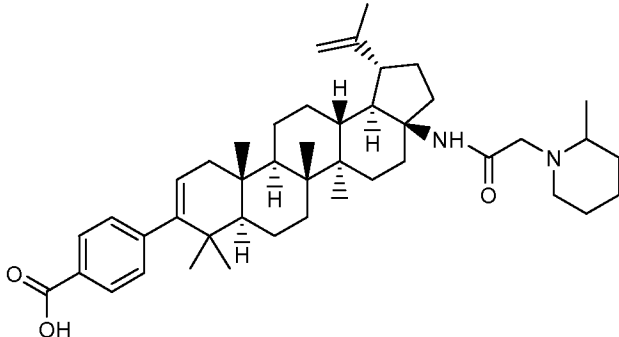
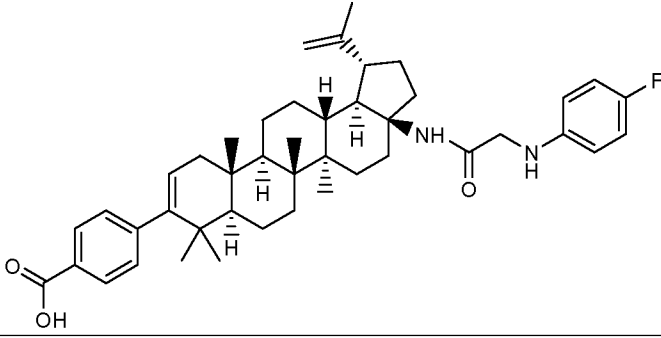
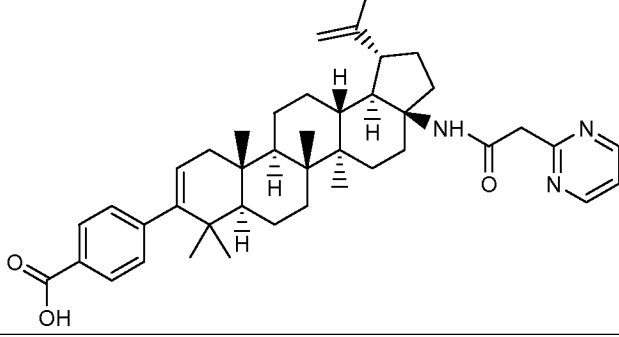
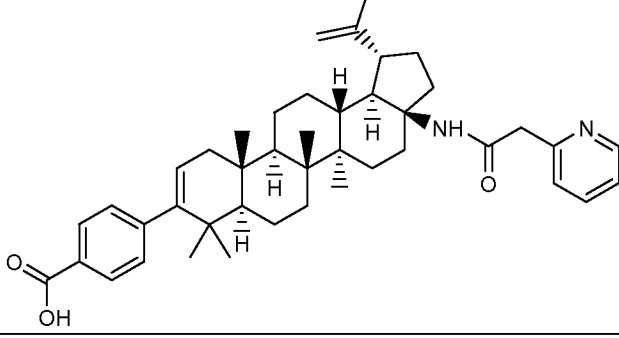
103		A
104		A
105		A
106		A
107		A

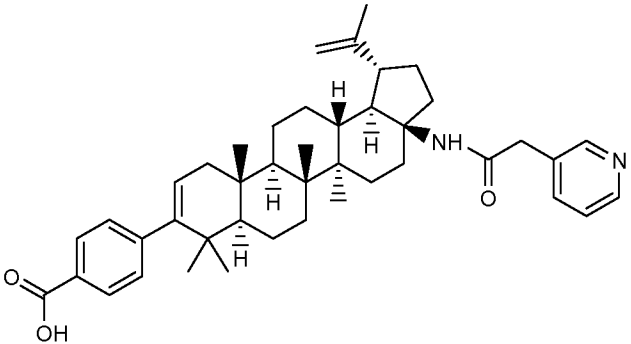
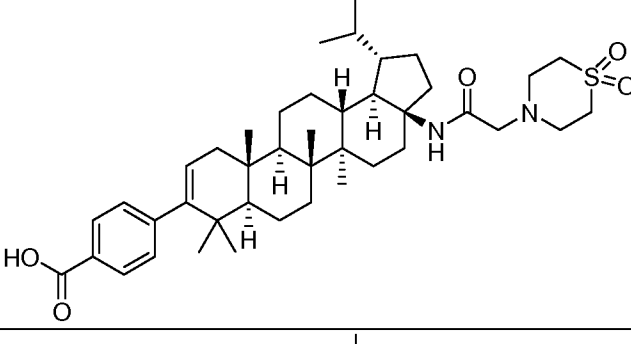
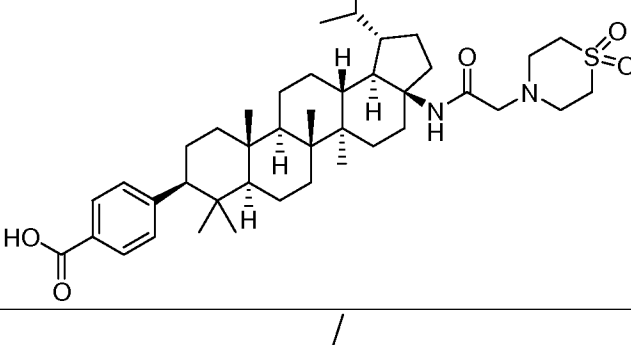
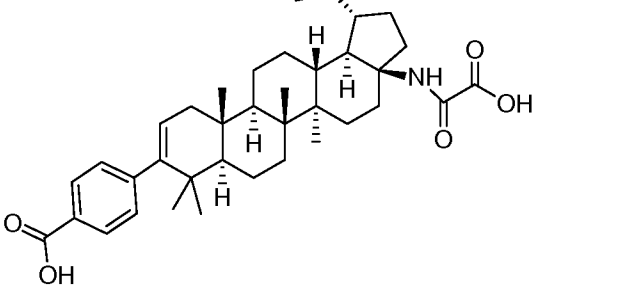
		
108		A
109		A
110	 Isomer 1	A

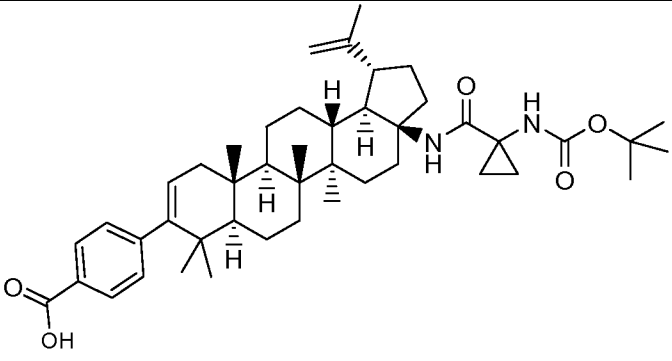
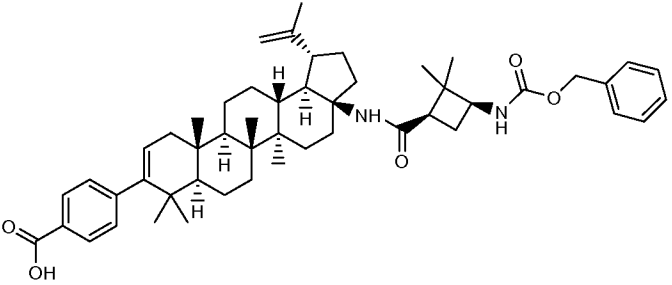
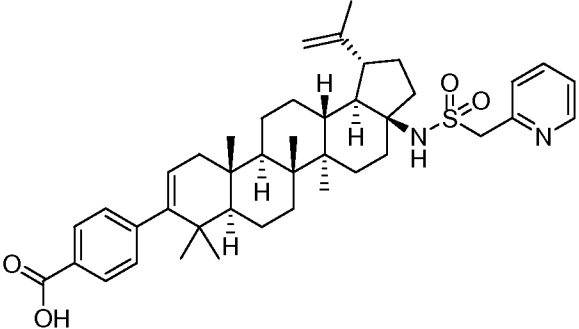
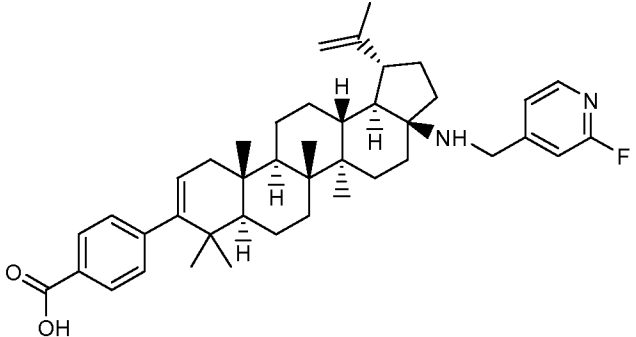
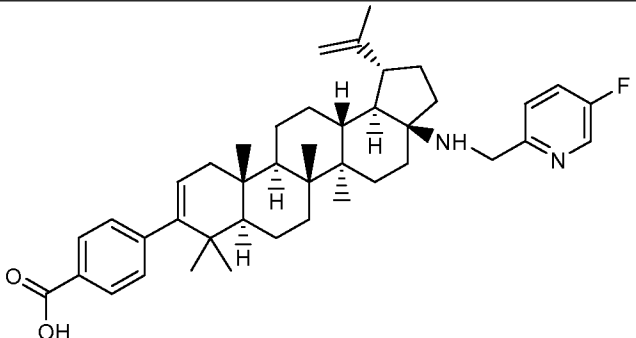
111	 Isomer 2	A
112		A
113		A
114		A
115		A

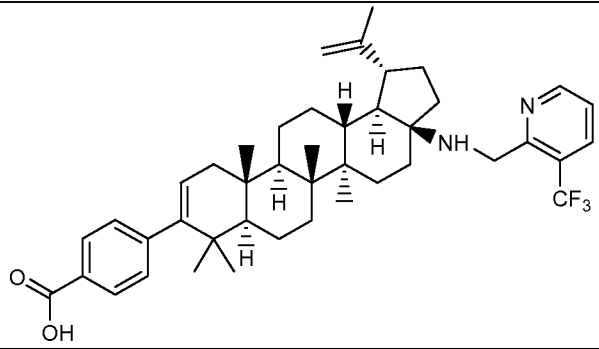
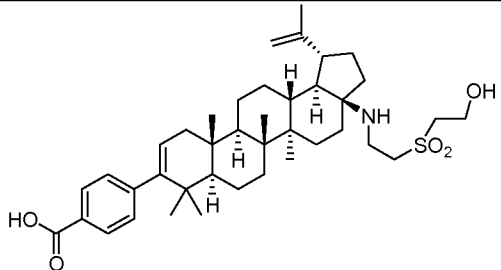
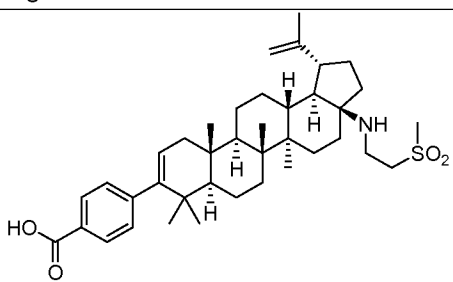
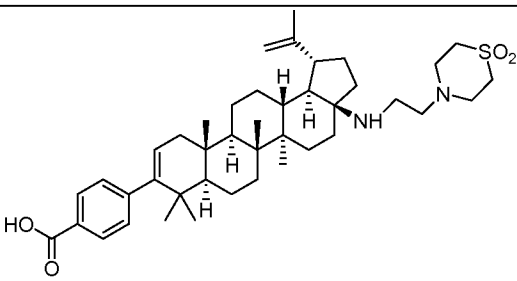
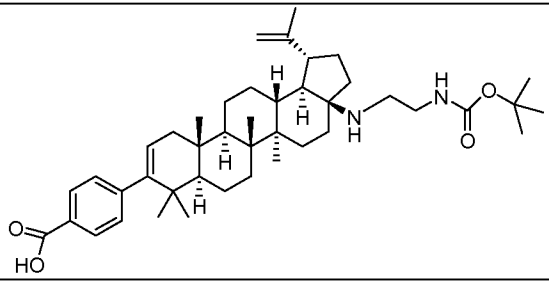
		
116		A
117		A
118		A

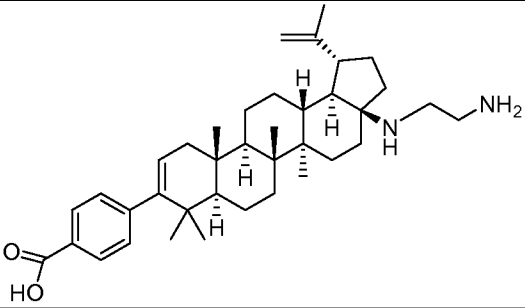
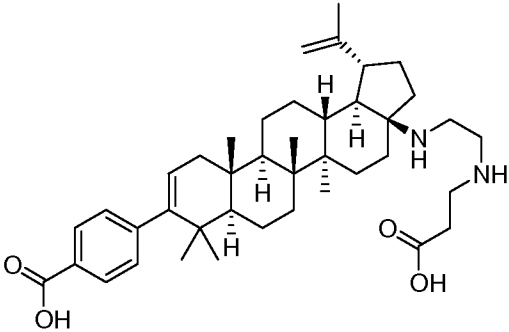
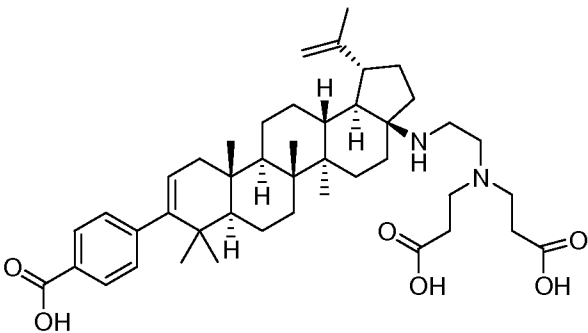
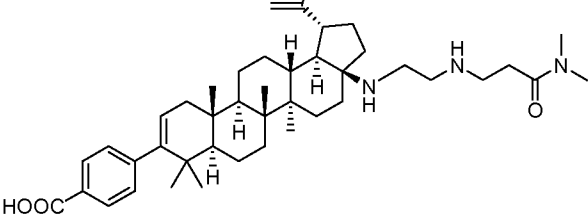
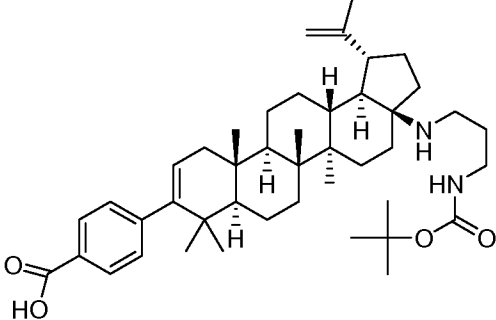
119		A
120		A
121		A
122		A
123		A

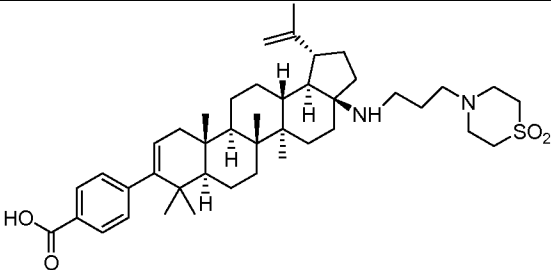
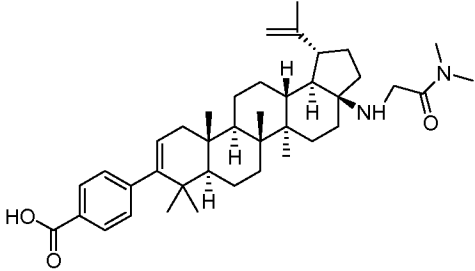
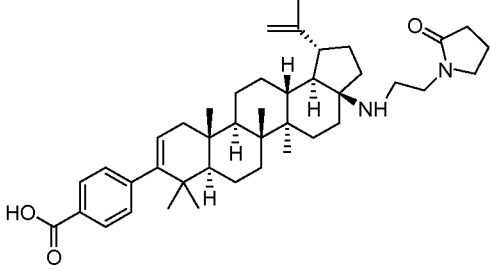
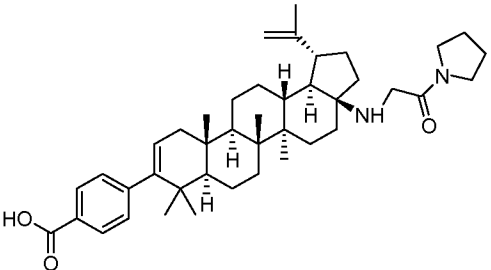
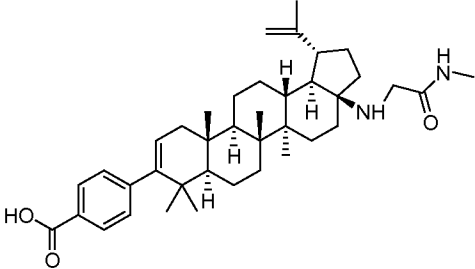
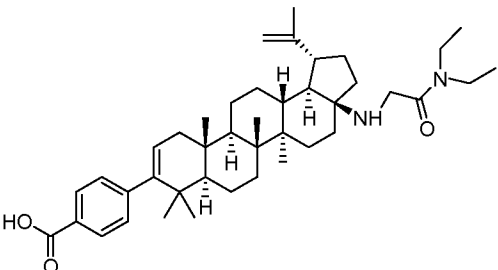
		
124		A
125		A
126		A
127		A

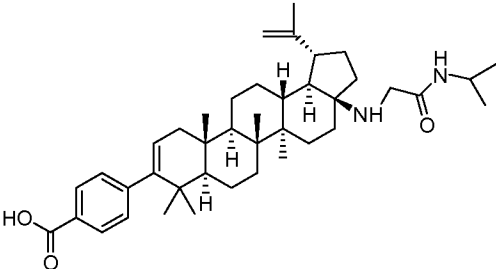
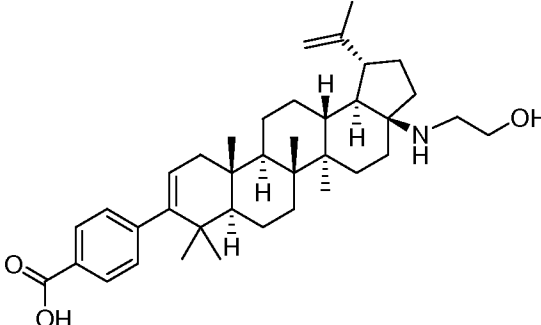
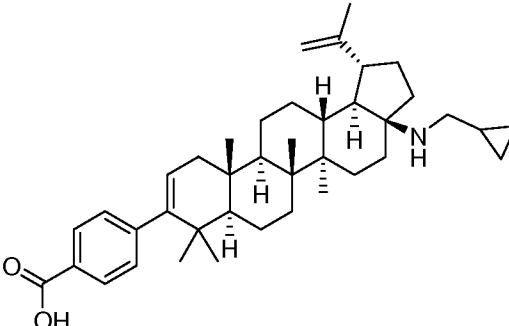
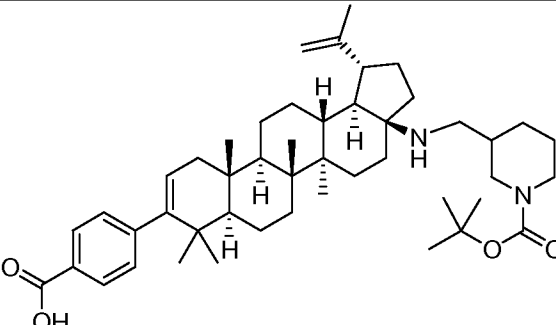
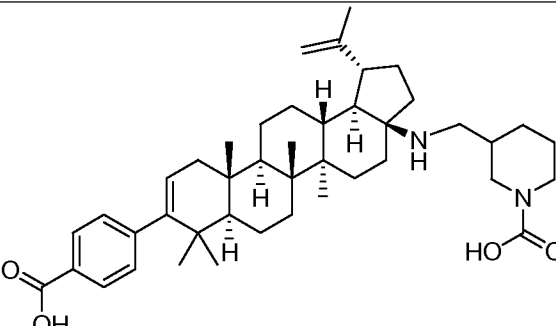
128		A
129		A
130		A
130-1		B

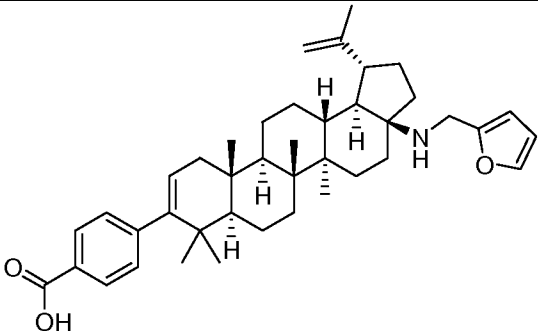
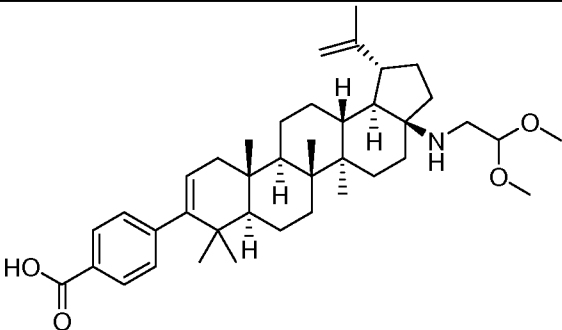
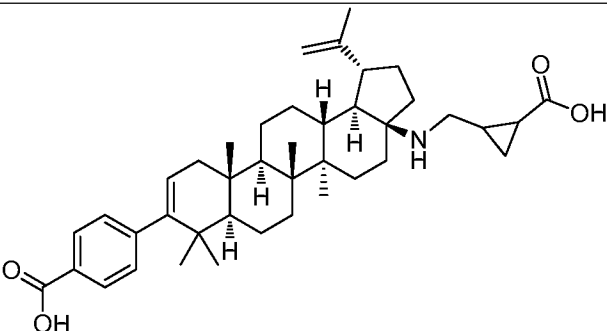
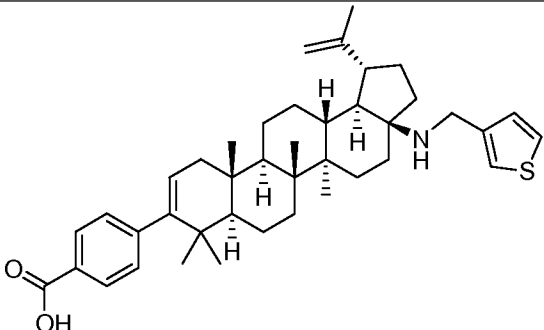
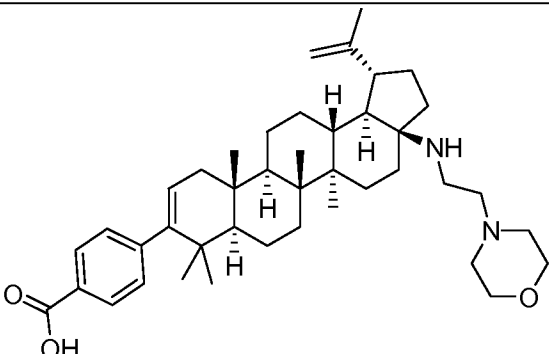
130-2		A
130-3		A
131		A
132		A
133		0.03

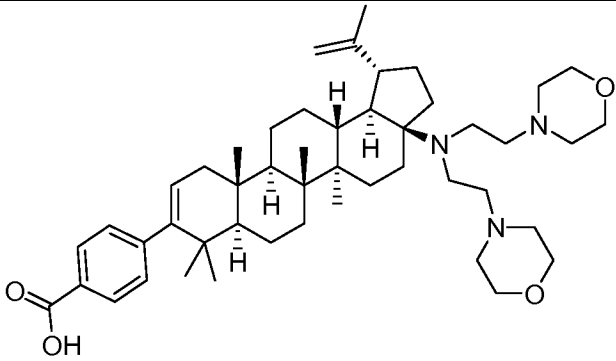
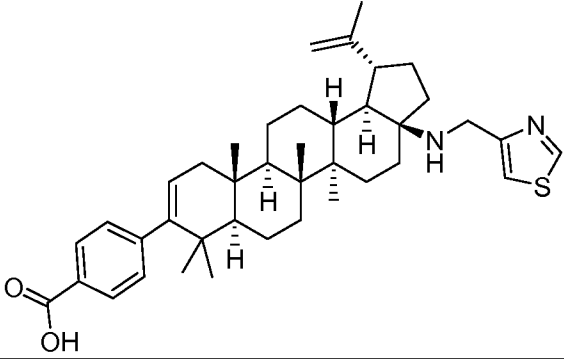
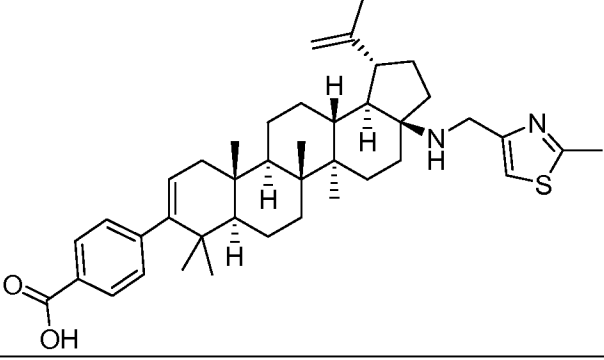
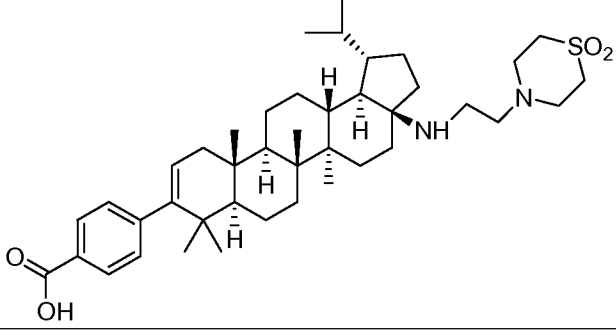
134		0.10
135		A
136		A
137		A
138		A
139		A

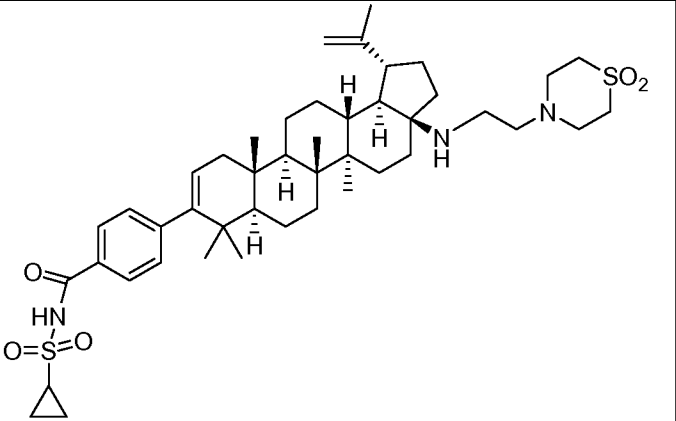
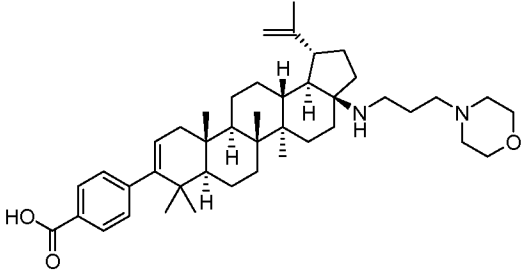
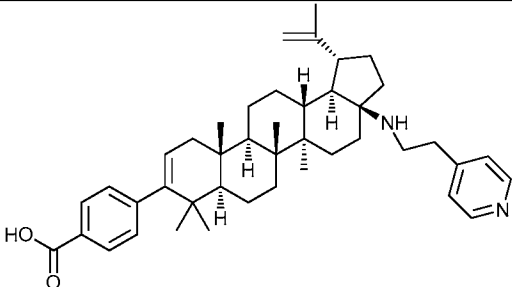
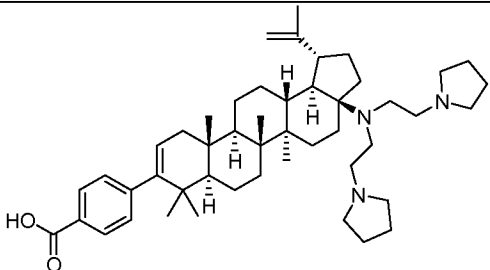
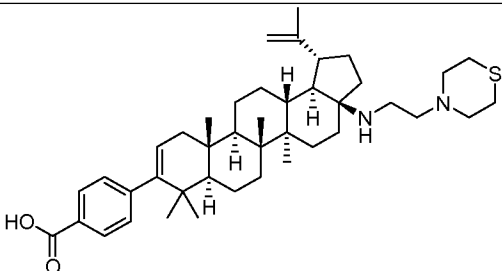
		
140		0.009
141		A
142		A
143		A

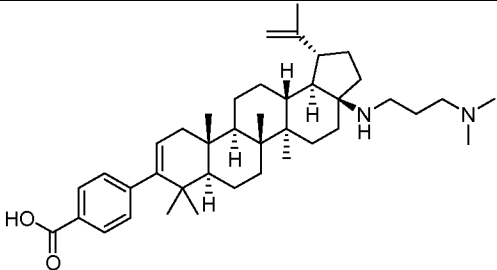
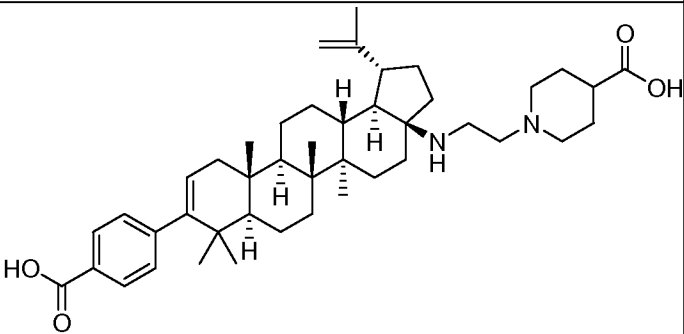
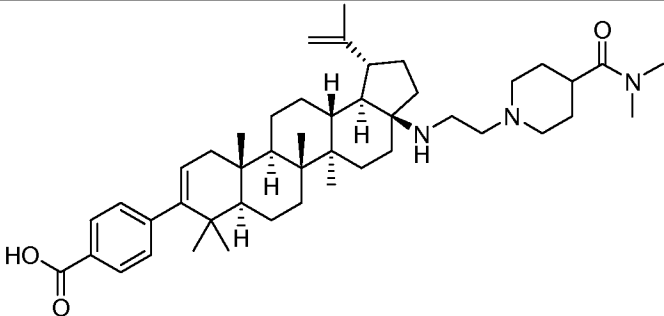
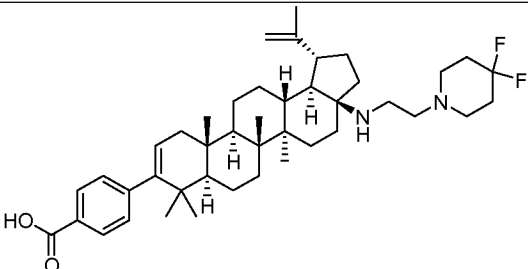
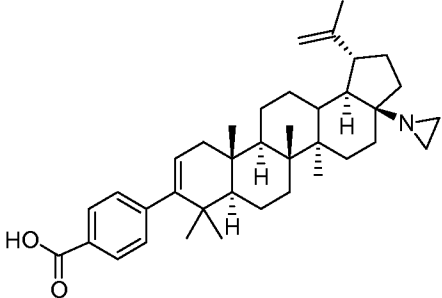
144		A
145		A
146		A
147		A
148		A
149		A

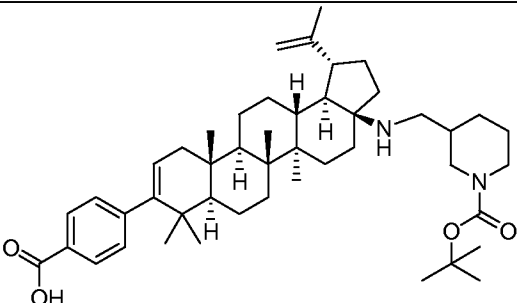
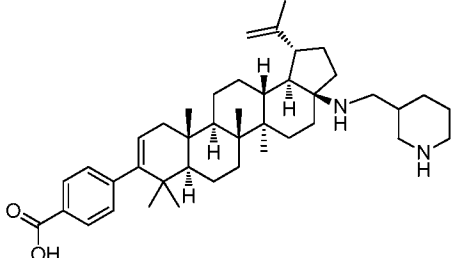
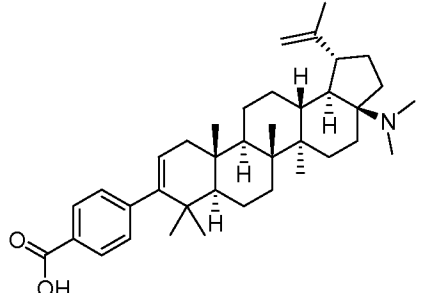
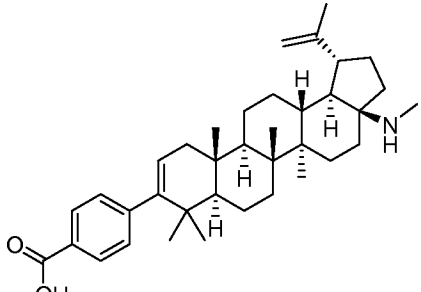
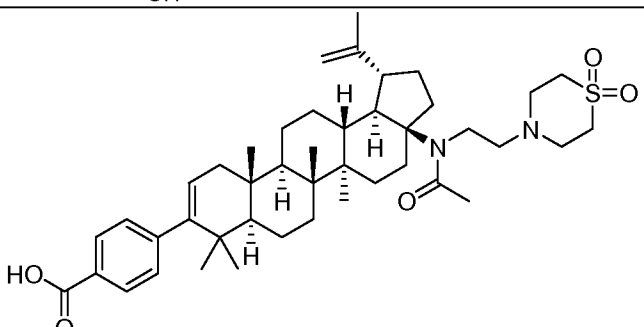
150		A
151		A
152		A
153		B
154		A

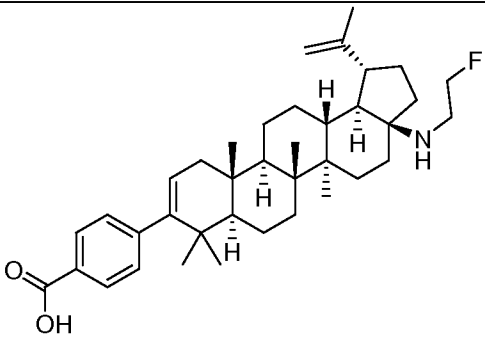
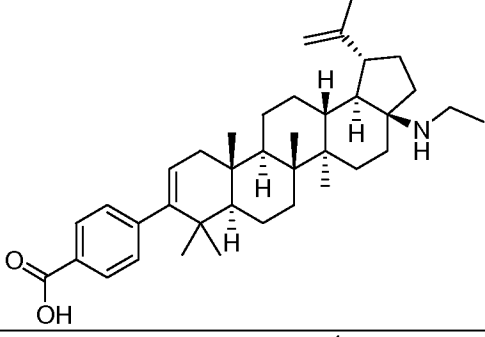
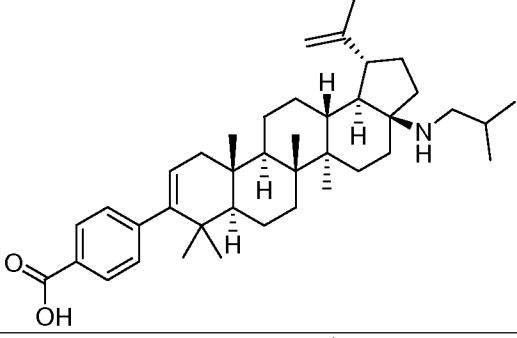
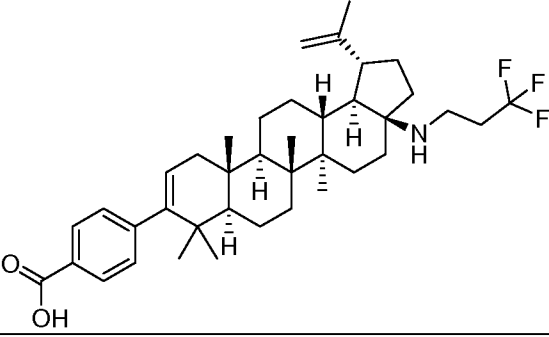
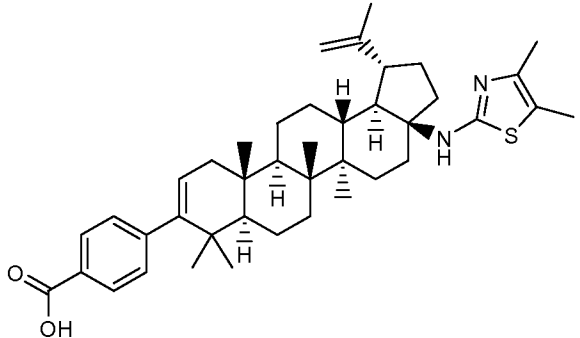
155		A
156		0.12
157		A
158		A
159		A

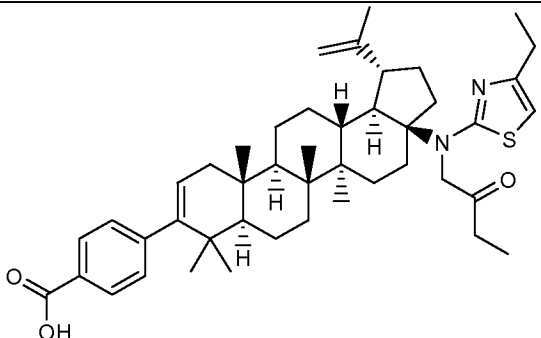
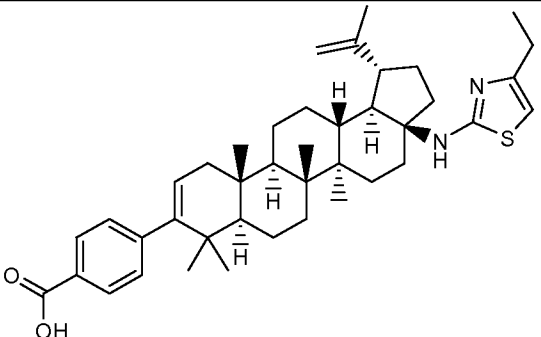
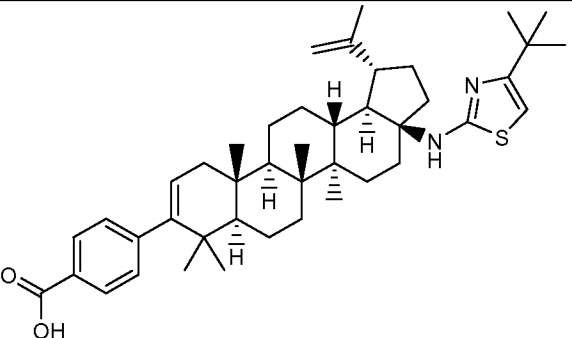
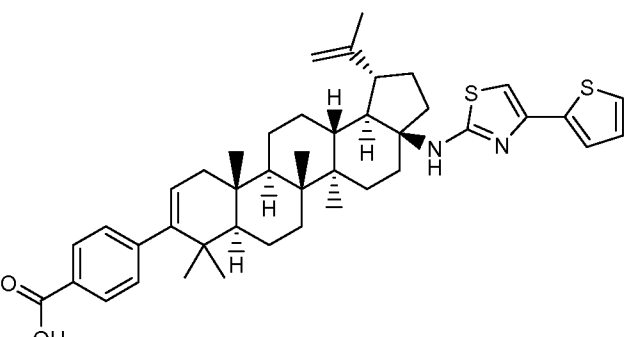
160		A
161		A
162		A
163		A

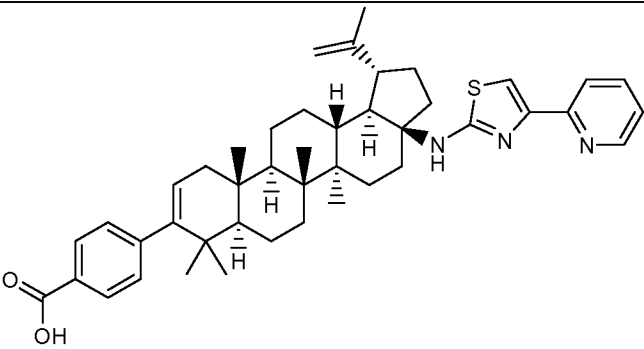
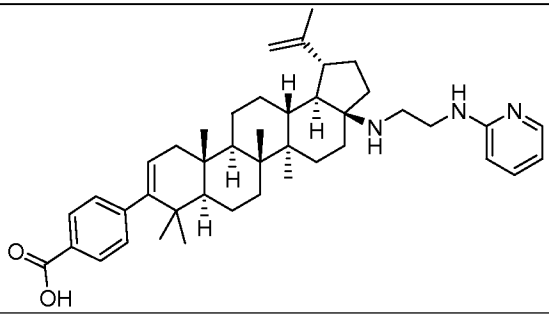
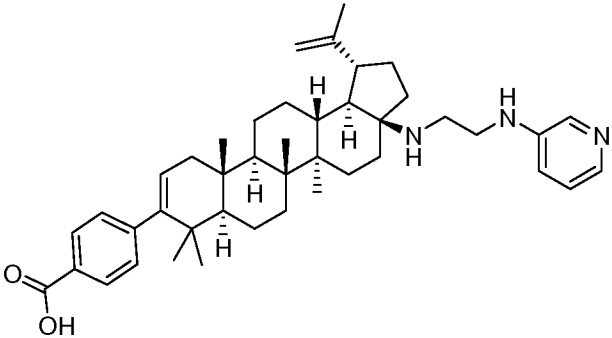
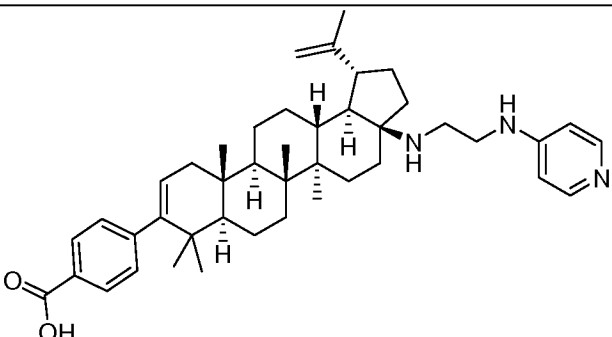
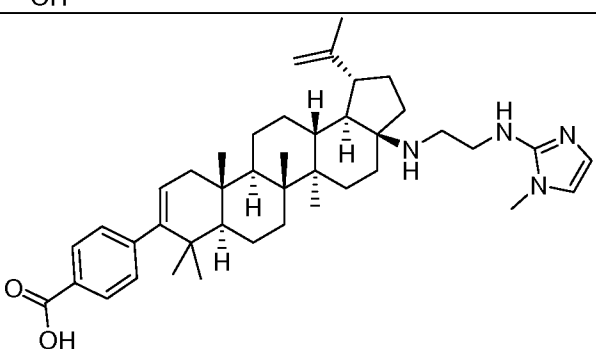
164		A
165		A
166		A
167		0.004
168		A

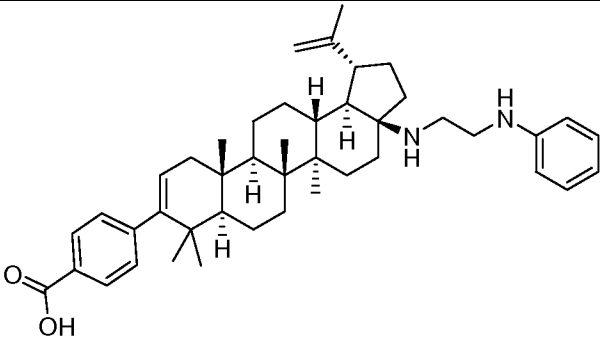
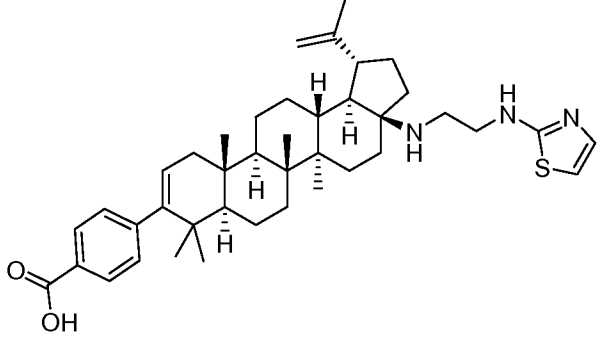
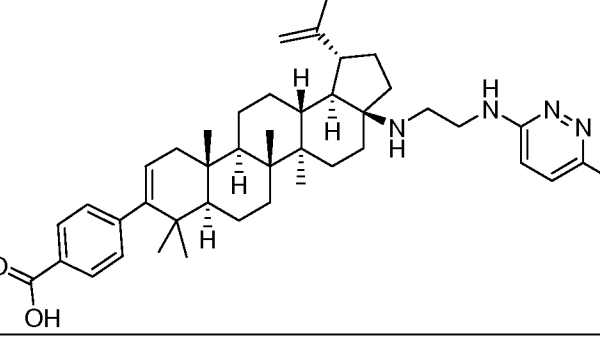
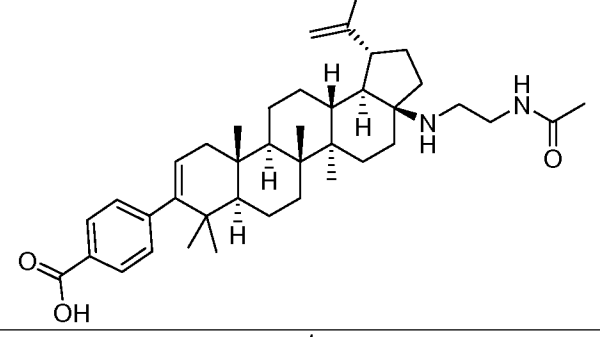
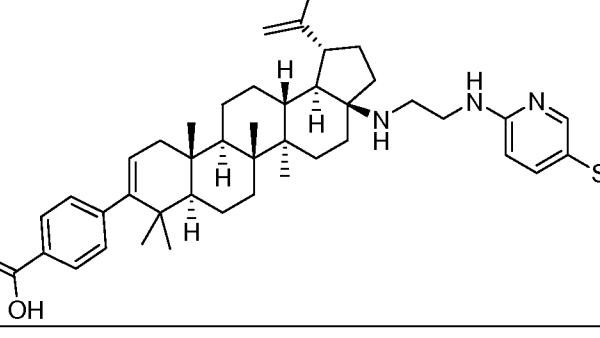
169		A
170		A
171		A
172		A
173		A

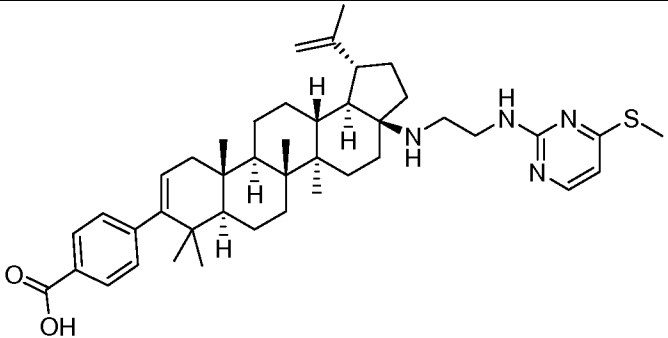
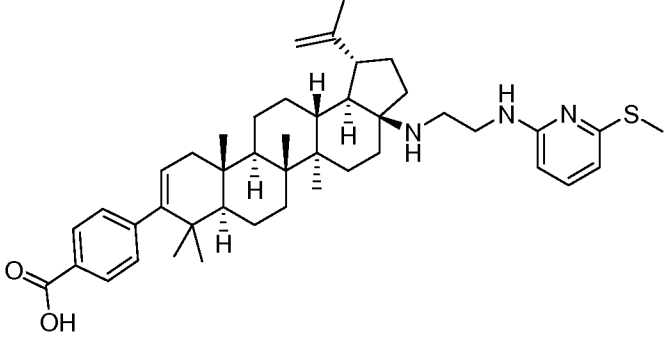
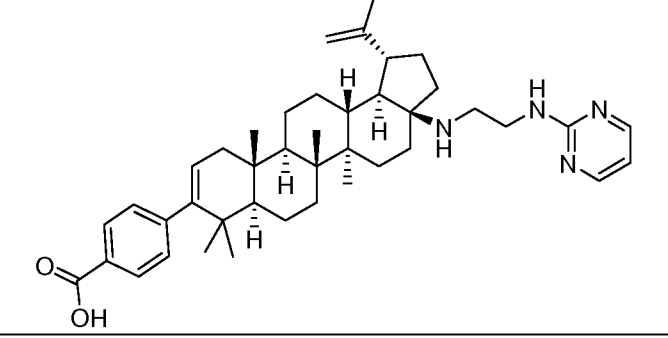
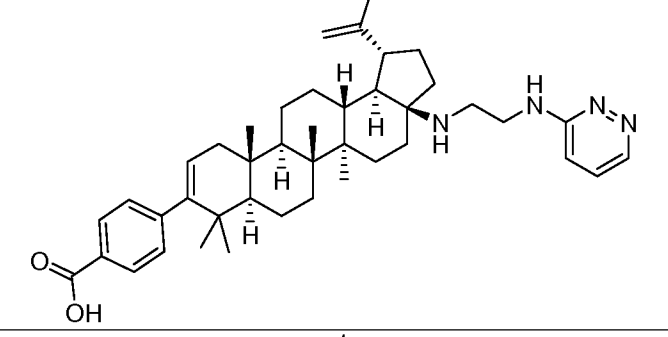
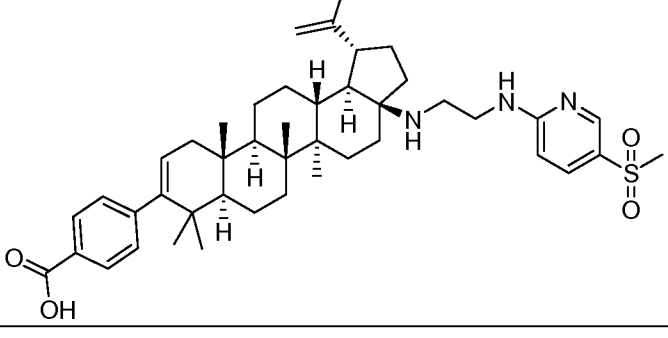
174		0.3
175		0.01
176		A
177		0.009
178		A

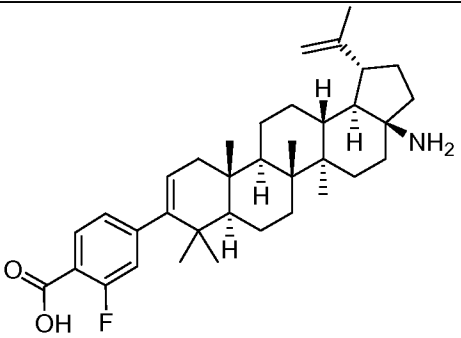
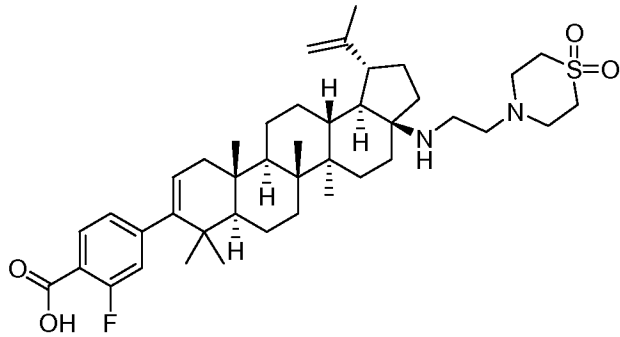
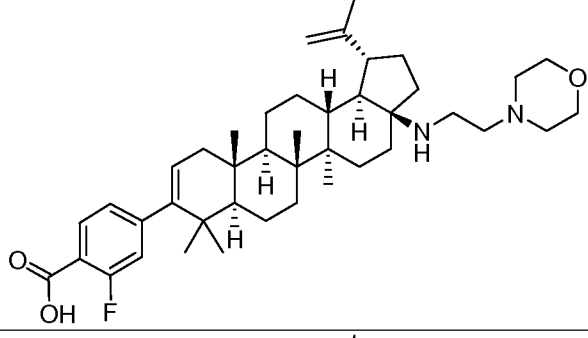
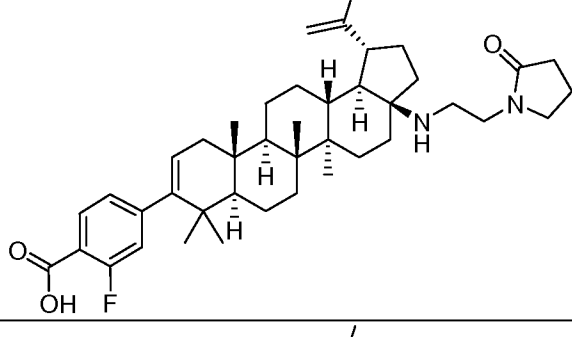
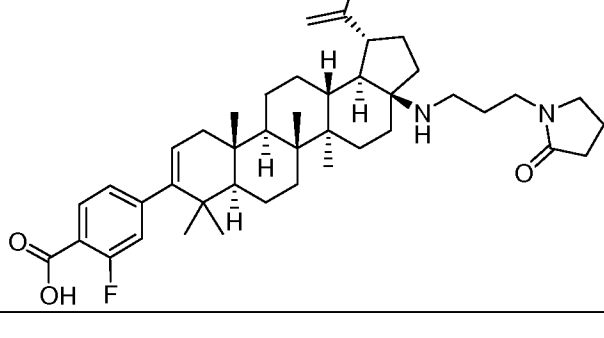
179		A
180		A
181		A
182		B
183		A

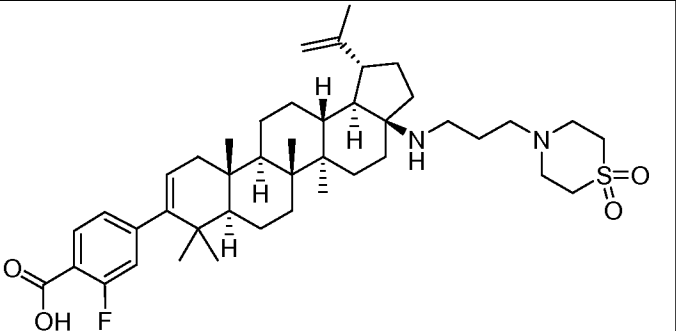
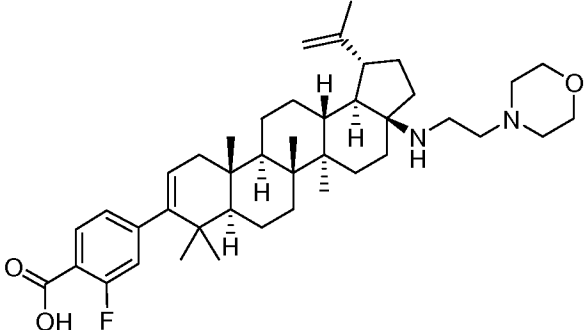
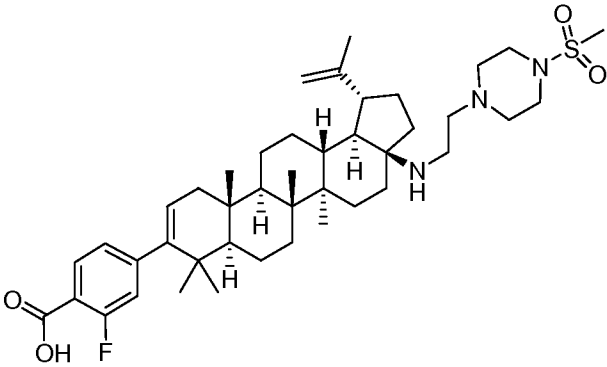
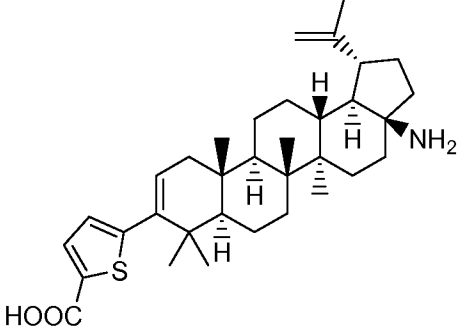
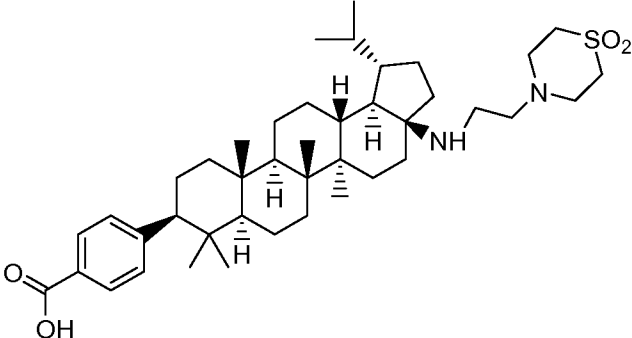
184A		0.39
184B		A
185		B
186		B

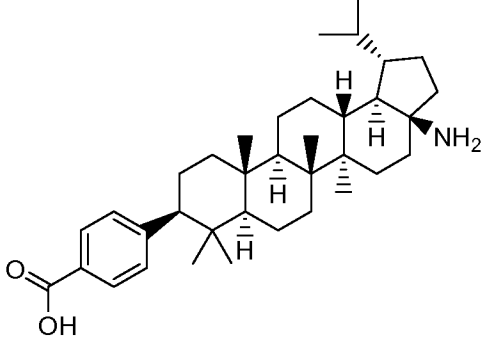
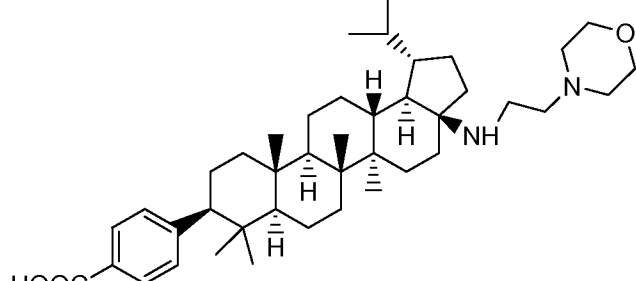
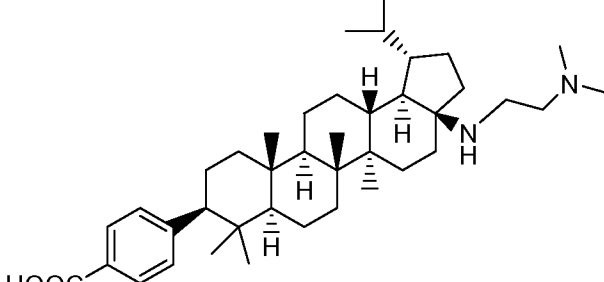
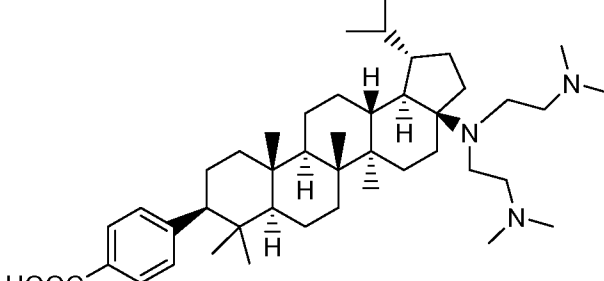
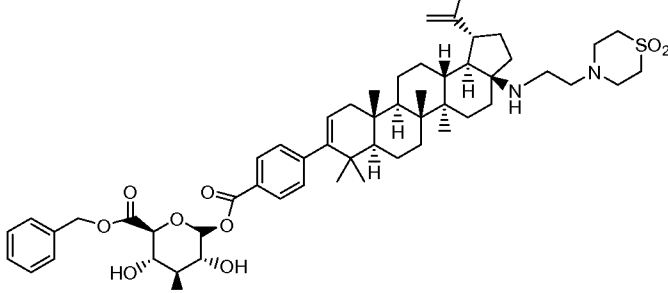
187		A
188		0.001
189		A
190		A
191		A

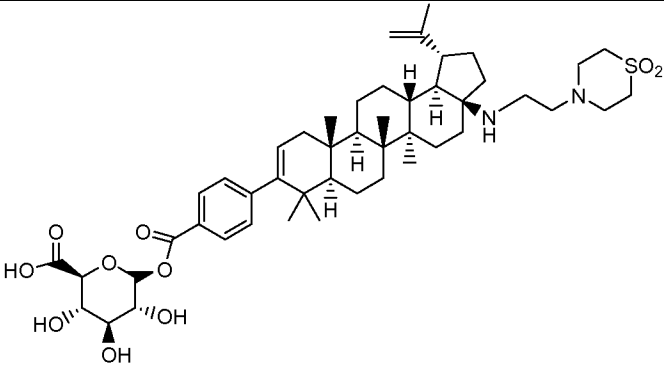
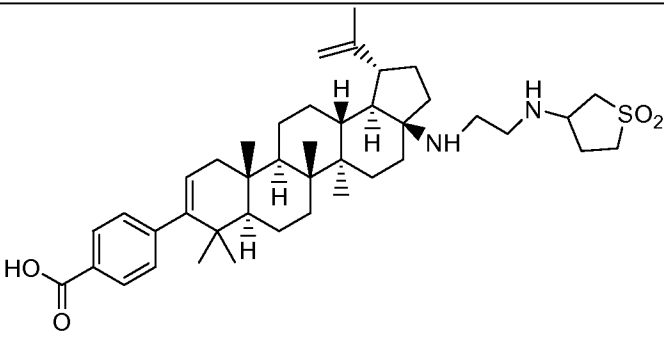
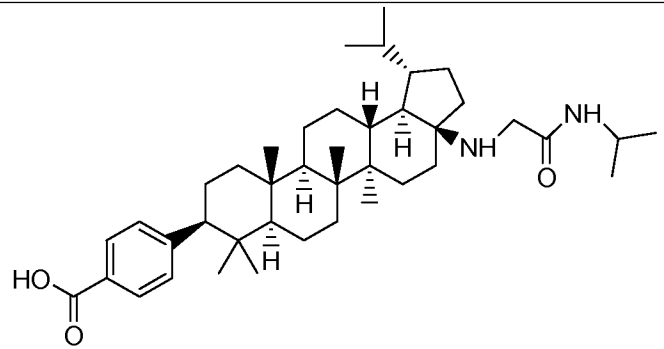
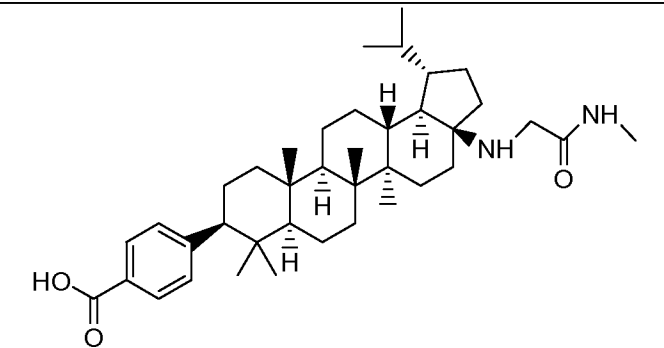
192		A
193		0.02
194		A
195		A
196		A

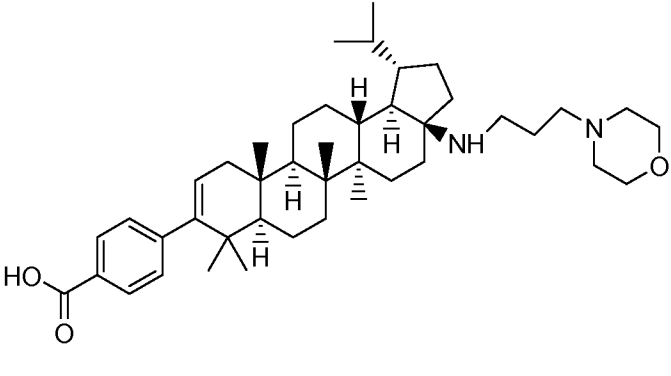
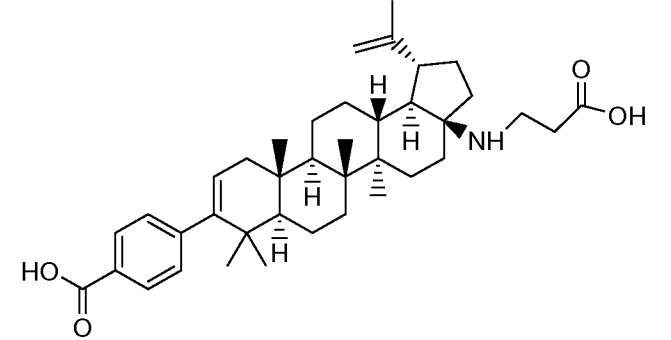
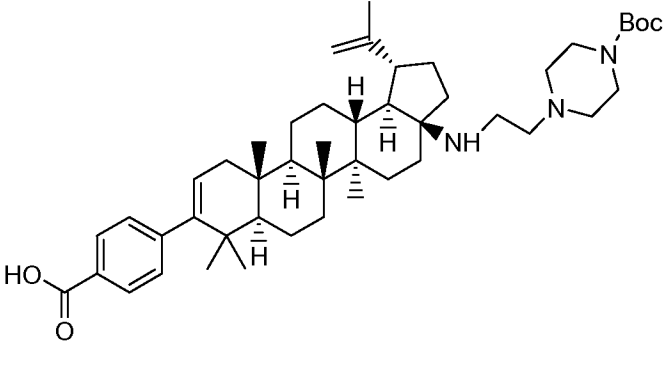
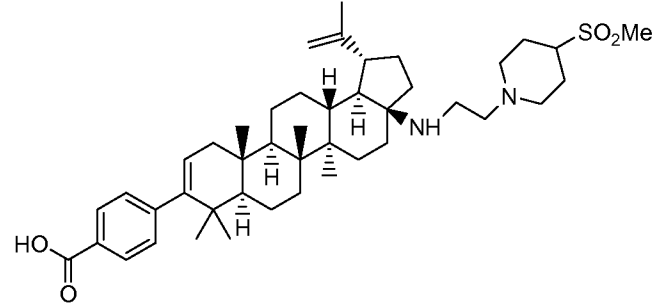
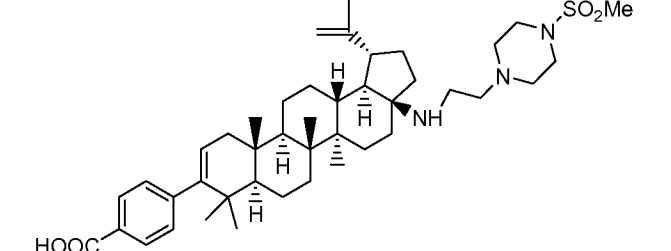
197		A
198		A
199		A
200		A
201		A

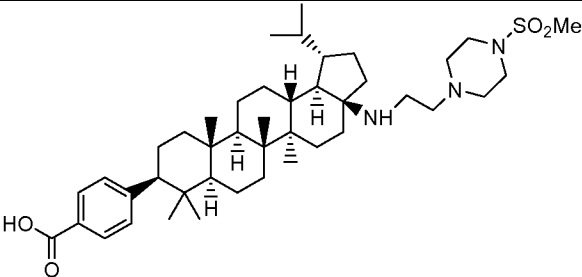
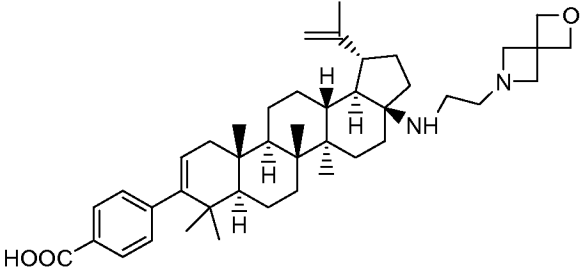
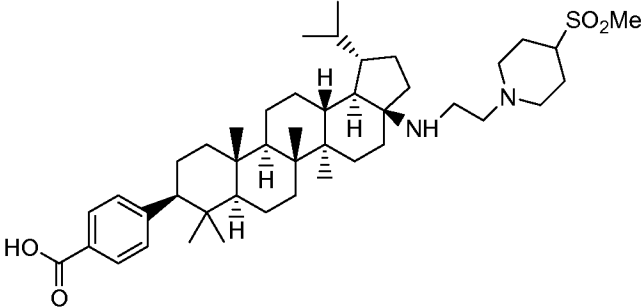
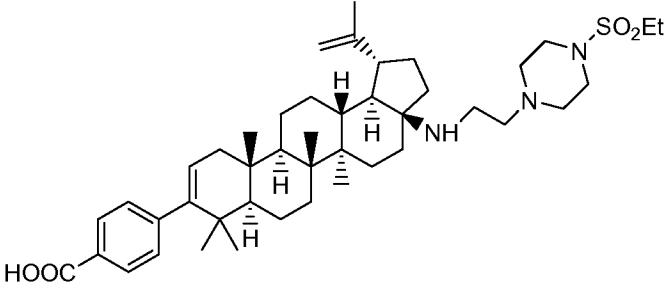
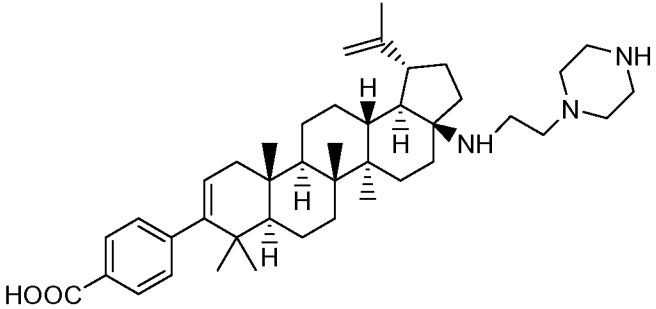
A1	 <chem>CC1=C[C@H]2[C@@H]3[C@H]([C@@H]1CC[C@@H]2[C@]3(C)C[C@@H]4[C@@]5(CC[C@H]4[C@H]5CC=C6[C@@]3(CC[C@@H](C6)C(=O)O)C)C)C</chem>	A
A2	 <chem>CC1=C[C@H]2[C@@H]3[C@H]([C@@H]1CC[C@@H]2[C@]3(C)C[C@@H]4[C@@]5(CC[C@H]4[C@H]5CC=C6[C@@]3(CC[C@@H](C6)C(=O)O)C)C)C)C</chem>	A
A3	 <chem>CC1=C[C@H]2[C@@H]3[C@H]([C@@H]1CC[C@@H]2[C@]3(C)C[C@@H]4[C@@]5(CC[C@H]4[C@H]5CC=C6[C@@]3(CC[C@@H](C6)C(=O)O)C)C)C)C</chem>	A
A4	 <chem>CC1=C[C@H]2[C@@H]3[C@H]([C@@H]1CC[C@@H]2[C@]3(C)C[C@@H]4[C@@]5(CC[C@H]4[C@H]5CC=C6[C@@]3(CC[C@@H](C6)C(=O)O)C)C)C)C</chem>	A
A5	 <chem>CC1=C[C@H]2[C@@H]3[C@H]([C@@H]1CC[C@@H]2[C@]3(C)C[C@@H]4[C@@]5(CC[C@H]4[C@H]5CC=C6[C@@]3(CC[C@@H](C6)C(=O)O)C)C)C)C</chem>	A

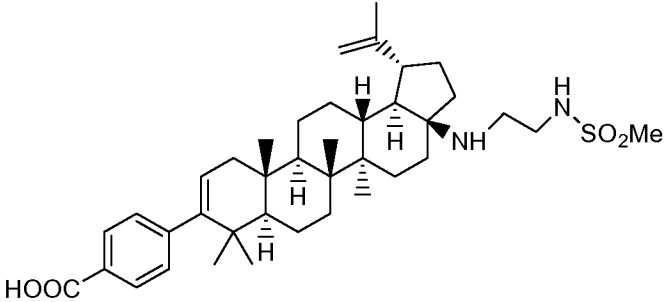
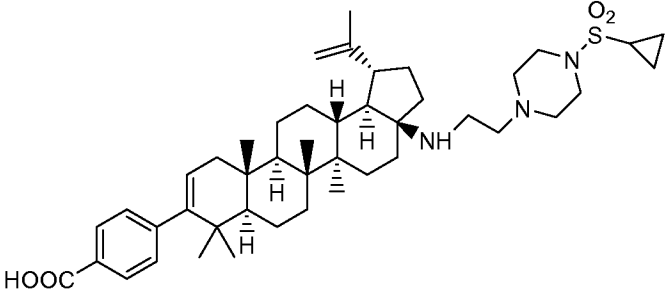
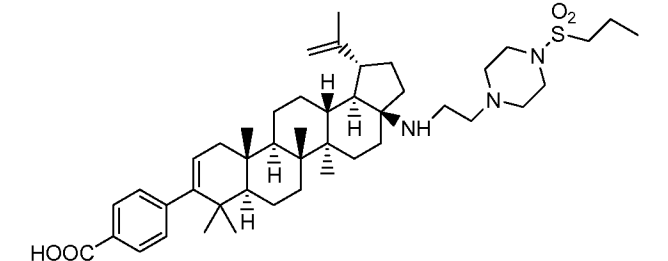
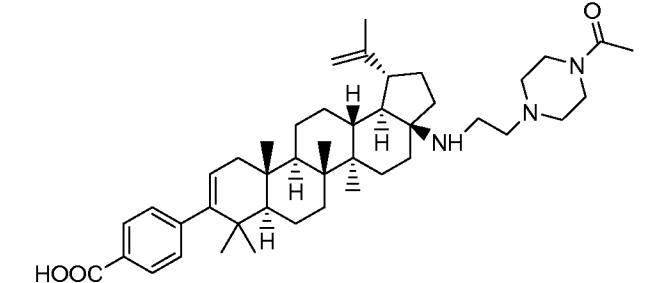
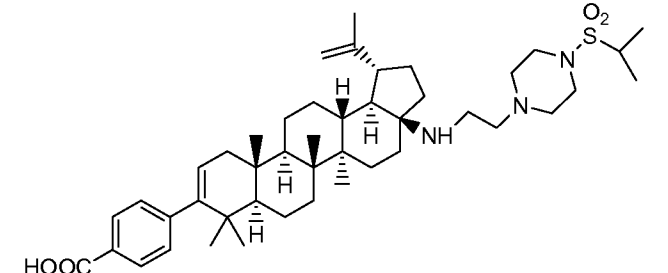
A6		A
A7		A
A8		A
B1		A
B2		A

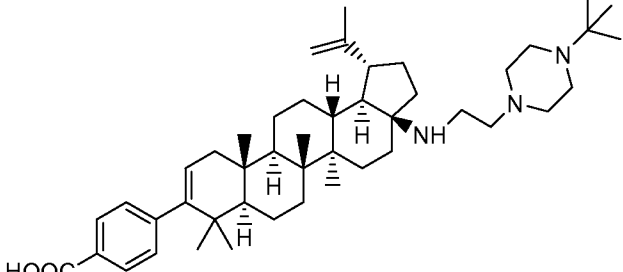
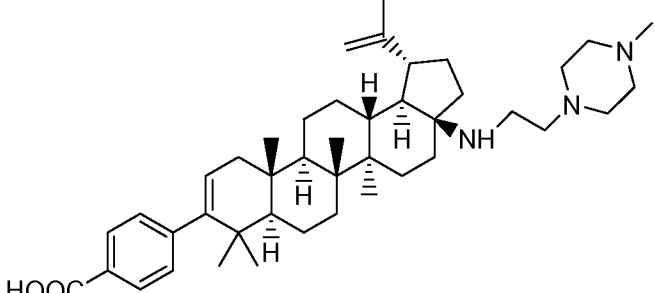
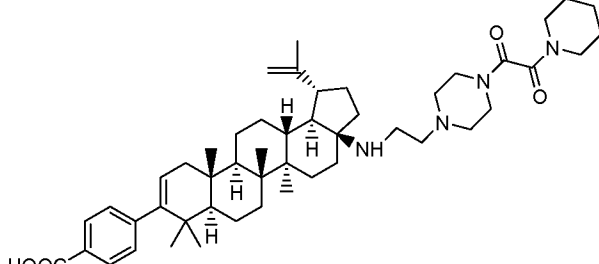
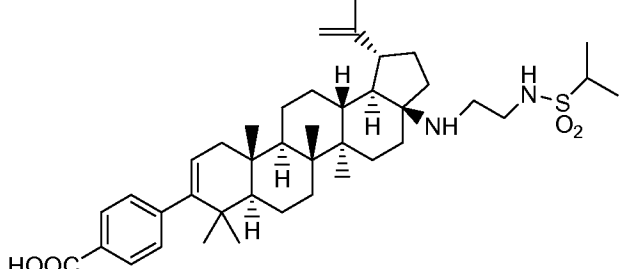
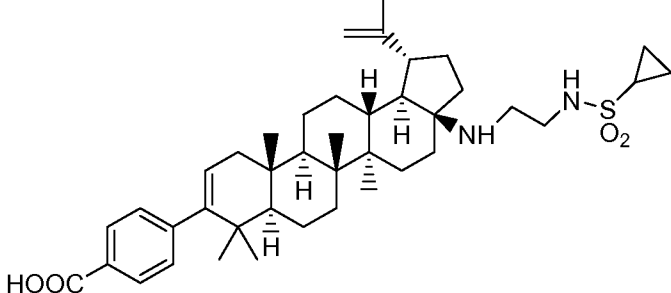
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B4		A
B5		A
B6		A
B7A		A

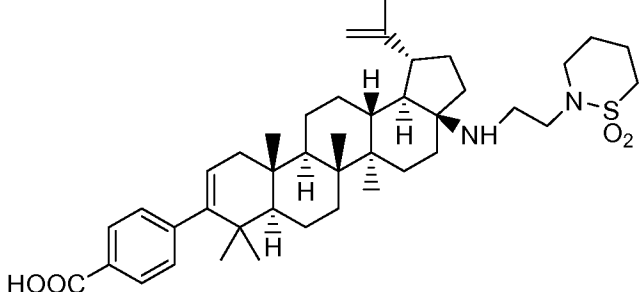
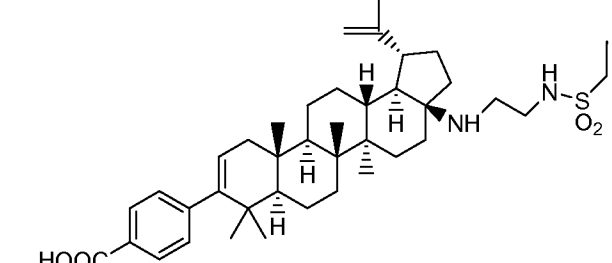
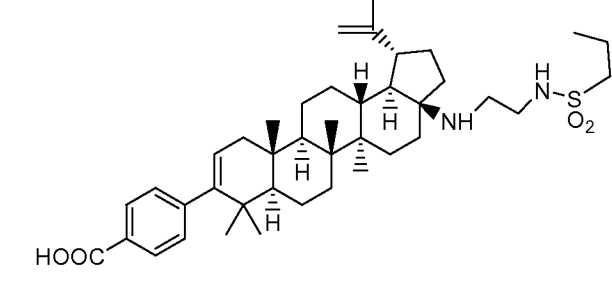
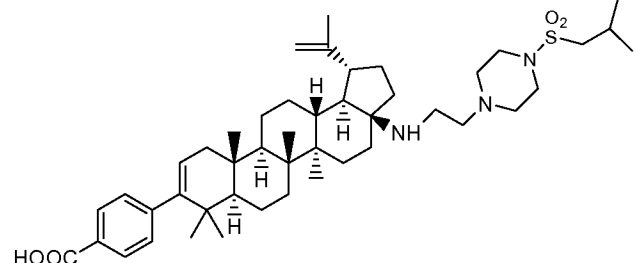
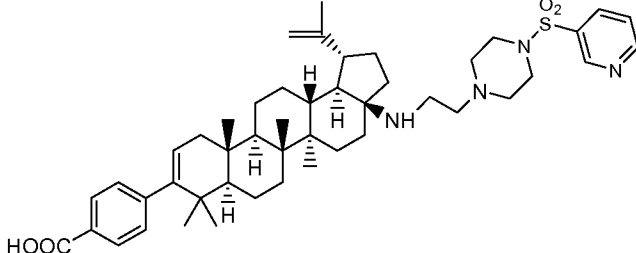
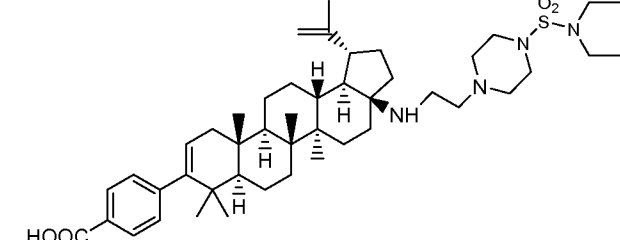
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B8		A
B9		0.01
B10		A

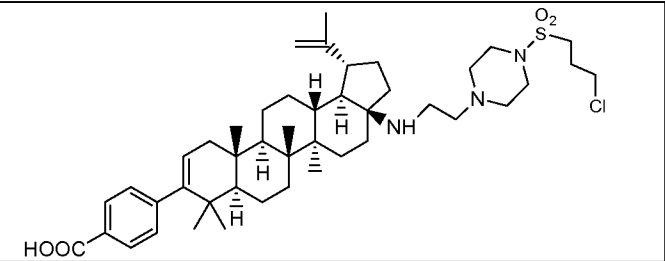
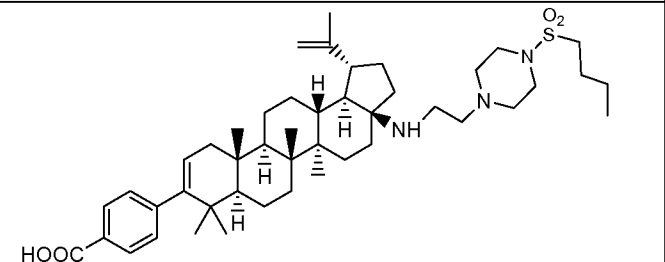
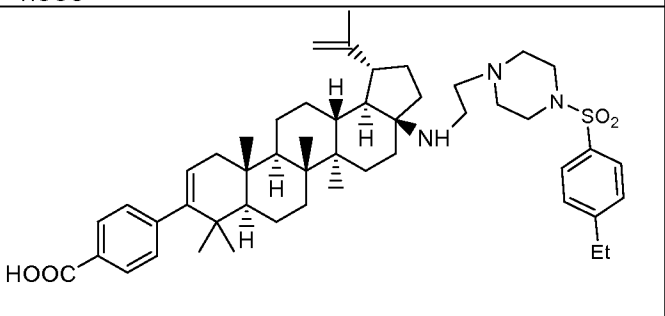
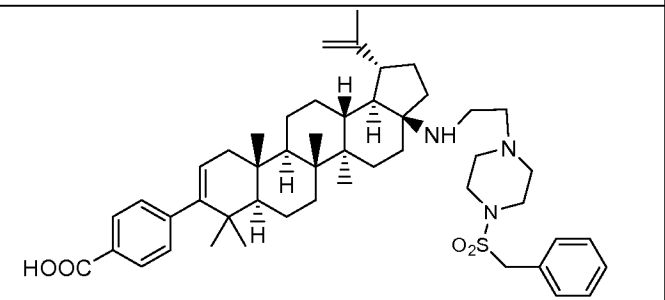
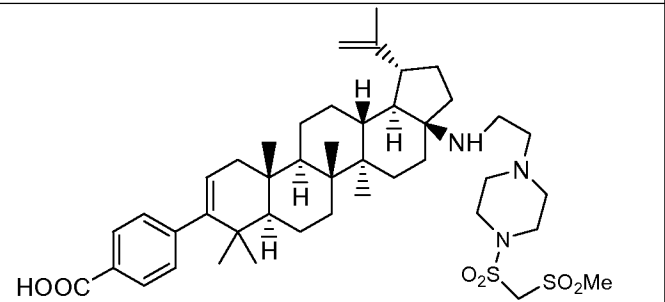
B11		A
B12		A
B13		A
B14		A
B15		A

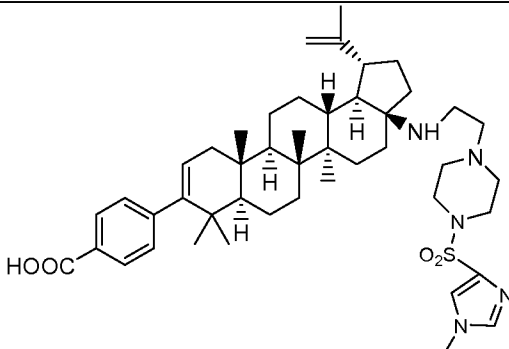
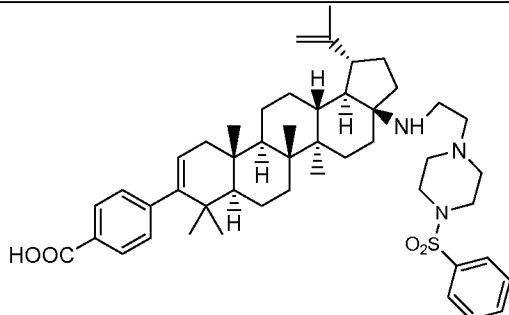
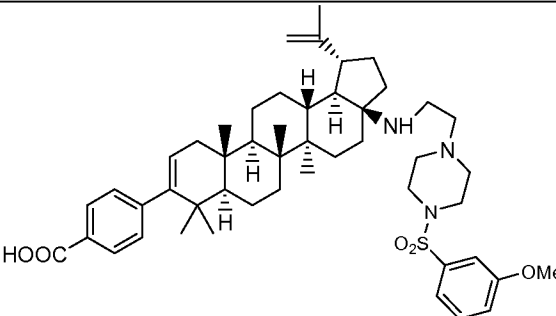
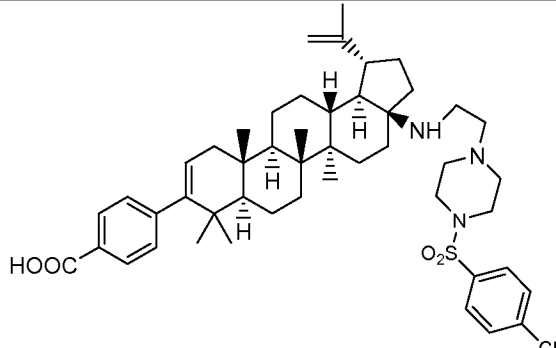
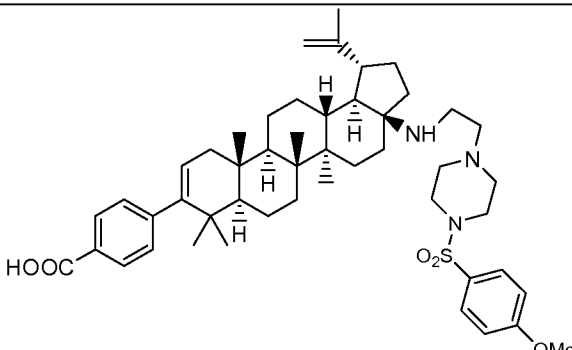
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B17		A
B18		A
B19		A
B20		A

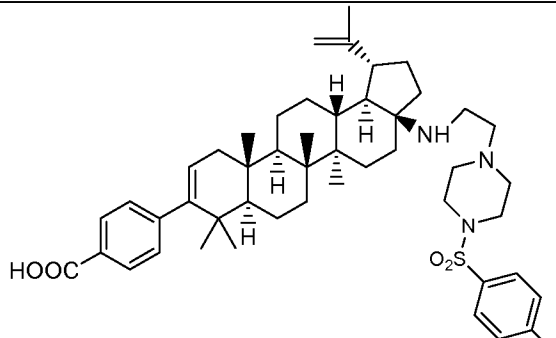
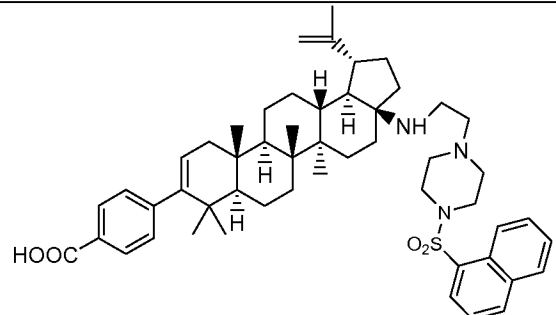
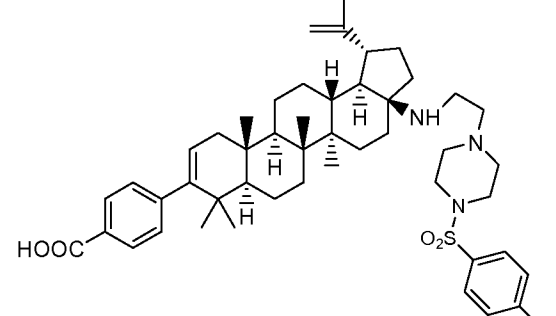
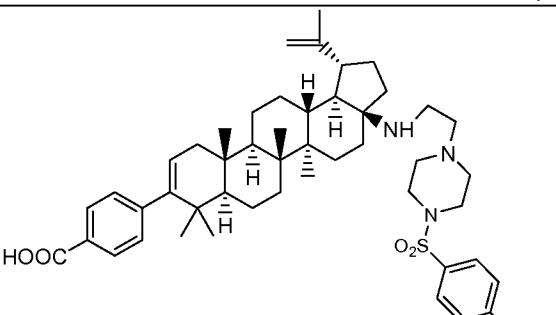
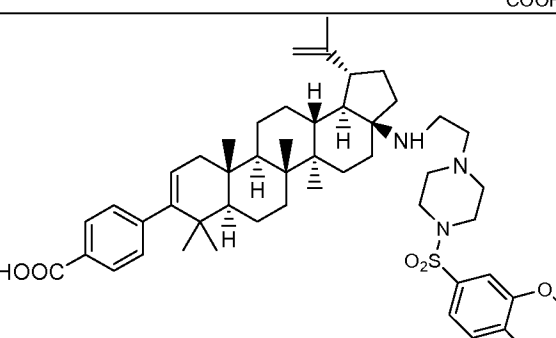
B21		A
B22		A
B23		A
B24		A
B25	+	A
B26		A

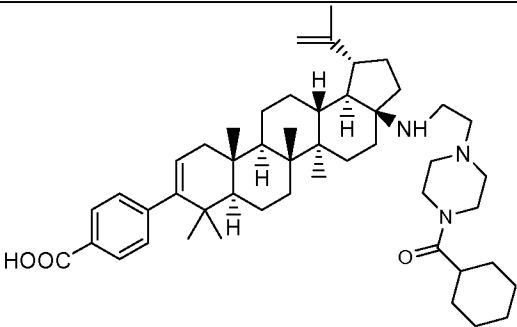
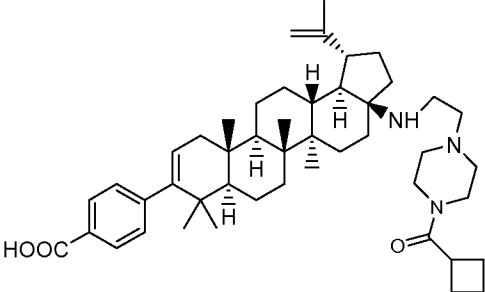
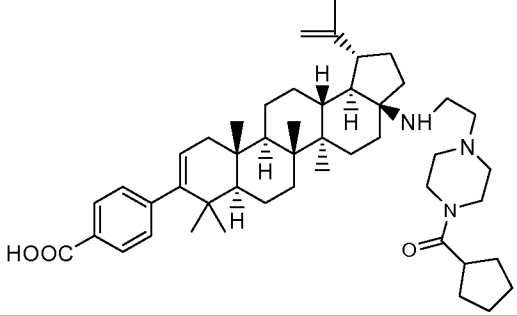
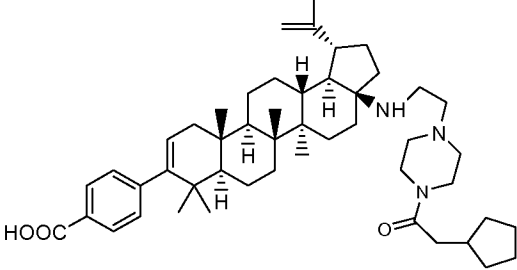
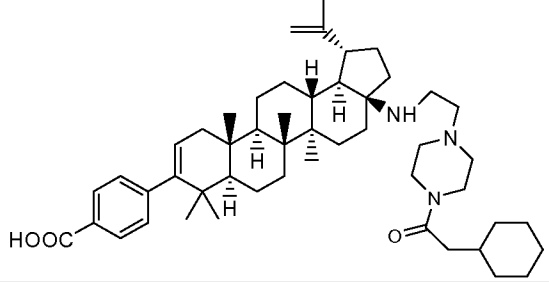
B27		A
B28		A
B29		A
B30		A
B31		A

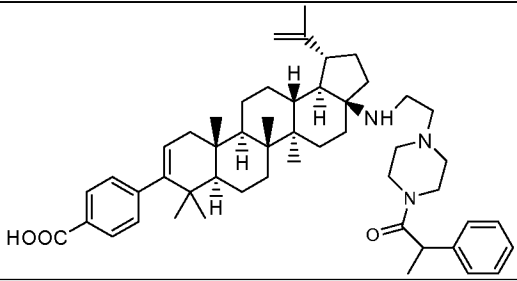
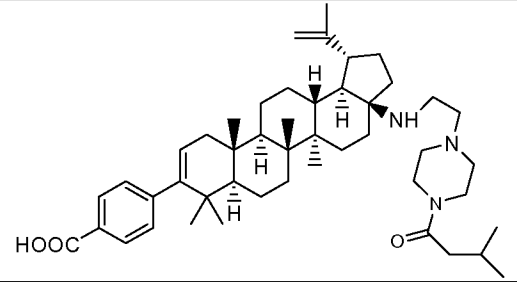
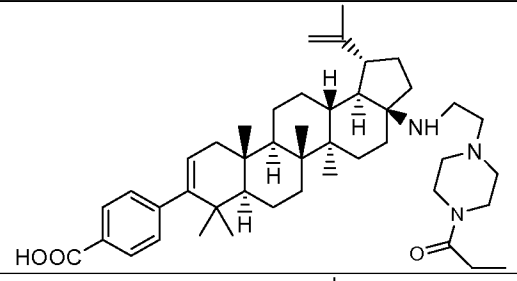
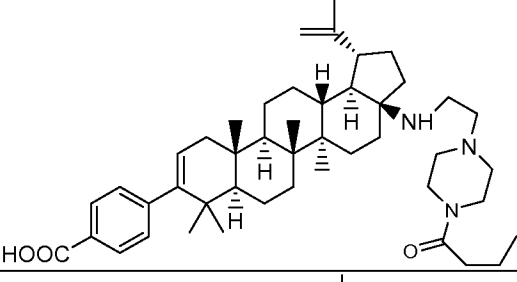
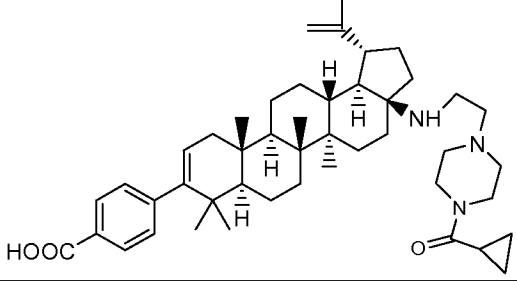
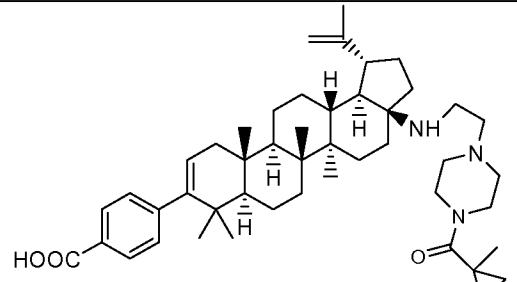
B32		A
B33		0.005
B34		A
B35		A
B36		A
B37		A

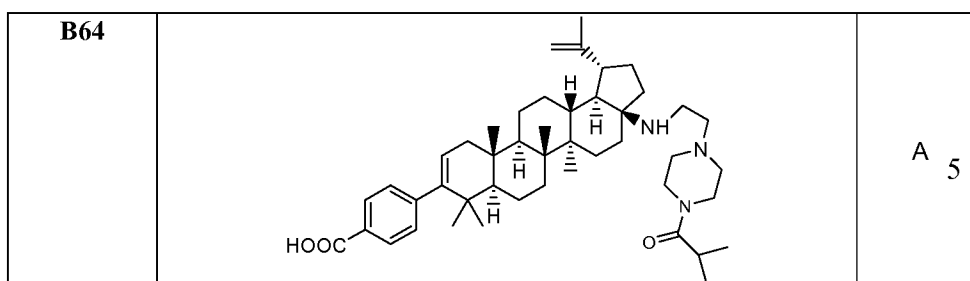
B38		A
B39		A
B40		A
B41		A
B42		A

B43		A
B44		A
B45		0.004
B46		A
B47		A

B48		A
B49		A
B50		A
B51		A
B52		A

B53		A
B54		A
B55		A
B56		A
B57		A

B58		A
B59		A
B60		A
B61		A
B62		A
B63		A



10

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

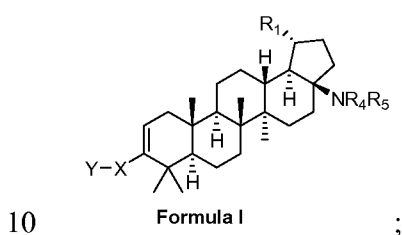
15 herein, will become apparent to those skilled in the art from the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

CLAIMS

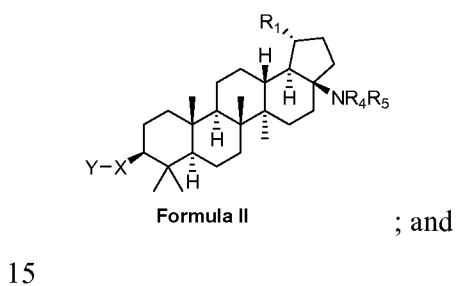
What is claimed is:

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

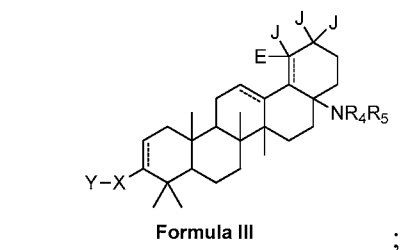
a compound of formula I



a compound of formula II



a compound of formula III



- 20 wherein R₁ is isopropenyl or isopropyl;

J and E are -H or -CH₃, and E is absent when the double bond is present;

X is a phenyl or heteroaryl ring substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C₁₋₆ alkyl, -C₁₋₆ alkoxy, and -COOR₂;

5

R₂ is -H, -C₁₋₆ alkyl, -alkylsubstituted C₁₋₆ alkyl or-arylsubstituted C₁₋₆ alkyl;

Y is selected from the group of -COOR₂, -C(O)NR₂SO₂R₃, -C(O)NHSO₂NR₂R₂, -NR₂SO₂R₂, -SO₂NR₂R₂, -C₃₋₆ cycloalkyl-COOR₂, -C₂₋₆ alkenyl-COOR₂, -C₂₋₆ alkynyl-COOR₂, -C₁₋₆ alkyl-COOR₂, -NHC(O)(CH₂)_n-COOR₂, -SO₂NR₂C(O)R₂, -tetrazole, and -CONHOH,

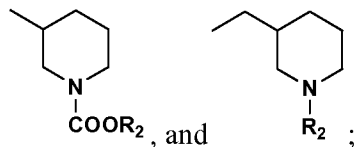
10

wherein n=1-6;

R₃ is -C₁₋₆ alkyl or -alkylsubstituted C₁₋₆ alkyl;

15

R₄ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-C(OR₃)₂-C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-Q₁, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₁, aryl, heteroaryl, substituted heteroaryl, -COR₆, -COCOR₆, -SO₂R₇, -SO₂NR₂R₂,



wherein Q₁ is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF₃, -OR₂, -COOR₂, -NR₈R₉, -CONR₁₀R₁₁ and -SO₂R₇;

25 R₅ is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₁₀, -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

with the proviso that only one of R₄ or R₅ can be selected from the group of -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

30 or R₄ and R₅ are taken together with the adjacent N to form



R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆ cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -NR₁₃R₁₄, and -OR₁₅;

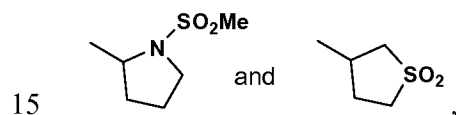
5 wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂,
-COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

R₇ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, aryl, and heteroaryl;

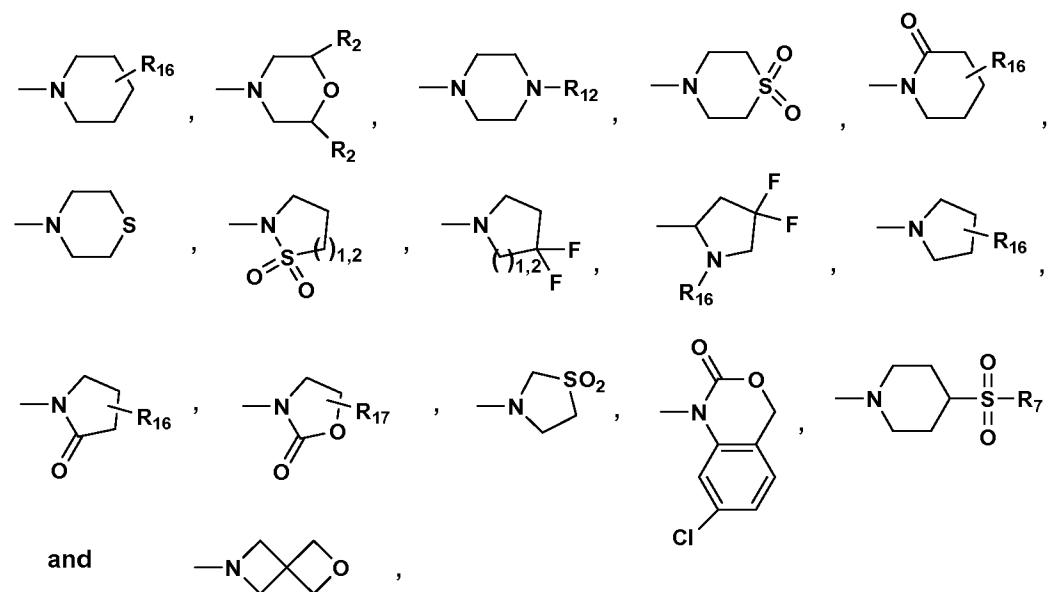
10

R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-Q₂, and -COOR₃,

and R_8 and R_9 can also be independently selected from the group of



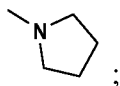
or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



20 with the proviso that only one of R_8 or R_9 can be $-\text{COOR}_3$;

R₁₀ and R₁₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl and -C₃₋₆ cycloalkyl,

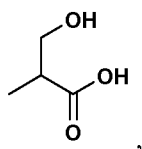
or R₁₀ and R₁₁ are taken together with the adjacent N to form a cycle such as



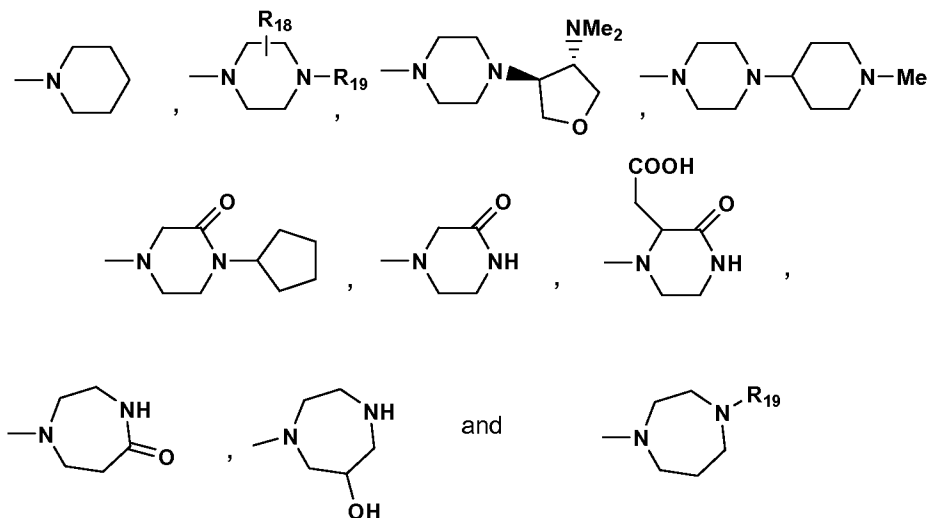
5

R₁₂ is selected from the group of -C₁₋₆ alkyl, -NR₂R₂, -C₁₋₆ alkyl-OH, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -COR₇, -COONR₂₂R₂₃, -SOR₇, and -SONR₂₄R₂₅;

10 R₁₃ and R₁₄ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃, C₁₋₆ substituted alkyl-Q₃ and



or R₁₃ and R₁₄ are taken together with the adjacent N to form a cycle selected from the group of:



15

Q₃ is selected from the group of heteroaryl, substituted heteroaryl, -NR₂₀R₂₁, -CONR₂R₂, -COOR₂, -OR₂, and -SO₂R₃;

20 R₁₅ is selected from the group of -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃ and -C₁₋₆ substituted alkyl-Q₃;

R₁₆ is selected from the group of -H, -C₁₋₆ alkyl, -NR₂R₂, and -COOR₃;

R₁₇ is selected from the group of -H, -C₁₋₆ alkyl, -COOR₃, and aryl;

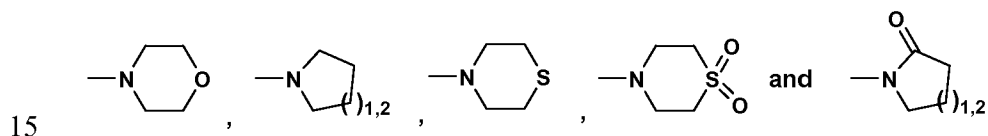
5

R₁₈ is selected from the group of -COOR₂ and -C₁₋₆ alkyl-COOR₂;

R₁₉ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-Q₄, -COR₃, -COOR₃,
wherein Q₄ is selected from the group of -NR₂R₂ and -OR₂;

10

R₂₀ and R₂₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆
substituted alkyl, -C₁₋₆ substituted alkyl-OR₂, and -COR₃,
or R₂₀ and R₂₁ are taken together with the adjacent N to form a cycle selected from the
group of

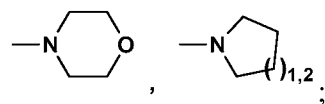


with the proviso that only one of R₂₀ or R₂₁ can be -COR₃;

R₂₂ and R₂₃ are independently selected from the group of H, -C₁₋₆ alkyl, -C₁₋₆
substituted alkyl, and -C₁₋₆ cycloalkyl,

20

or R₂₂ and R₂₃ are taken together with the adjacent N to form a cycle selected from the
group of



R₂₄ and R₂₅ are independently from the group of H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl,

25

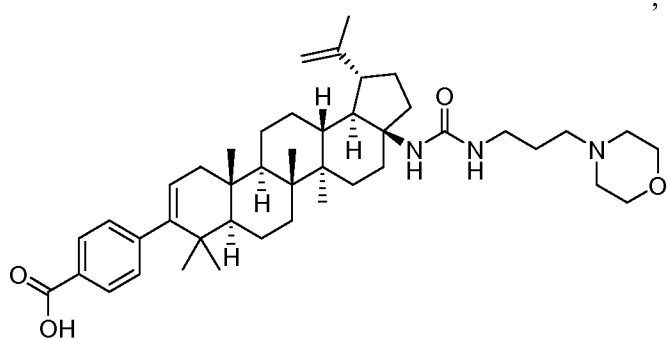
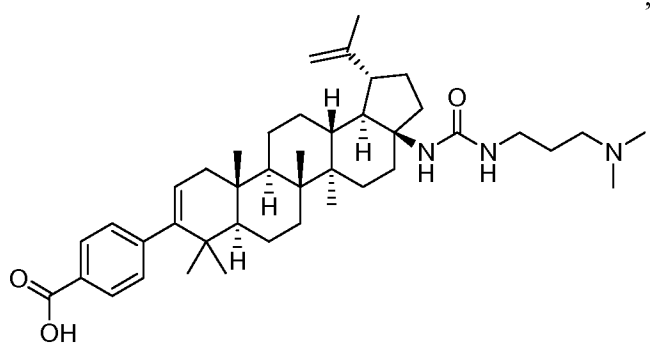
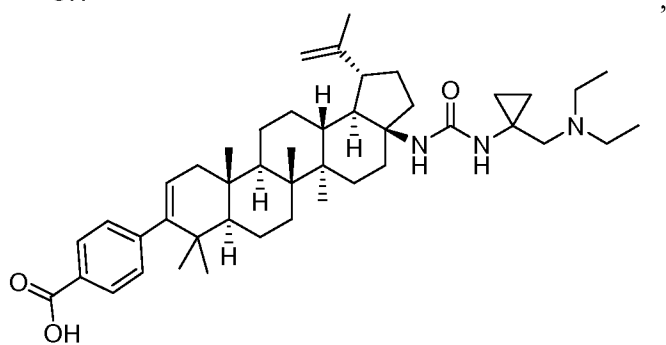
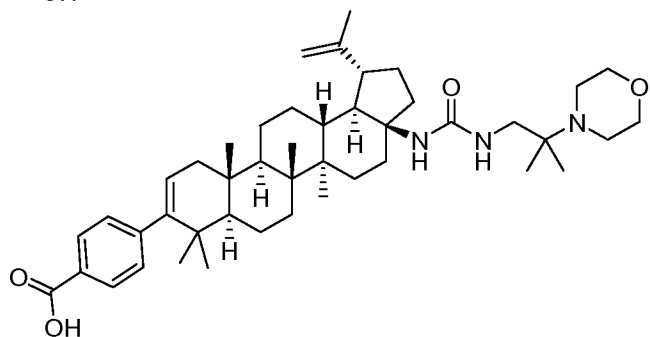
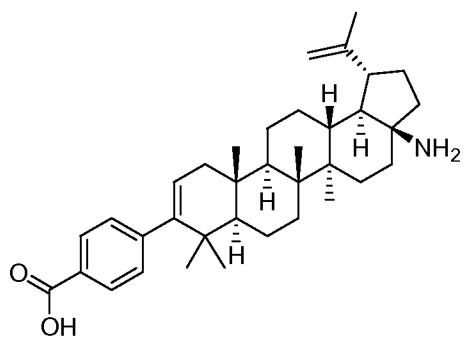
-C₁₋₆ alkyl-Q₅, -C₁₋₆ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted
heteroaryl,

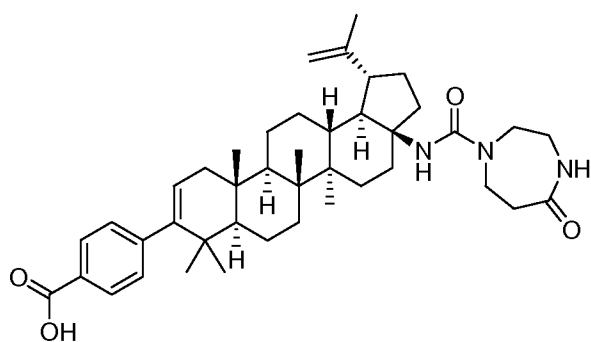
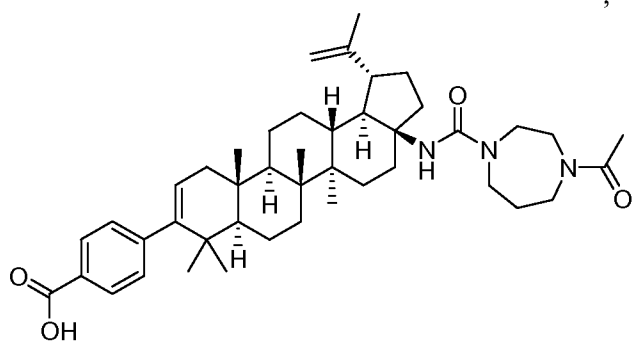
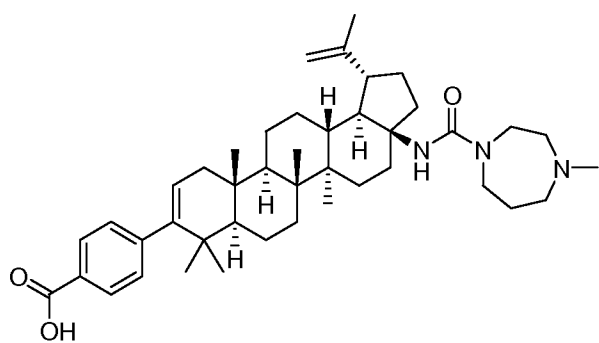
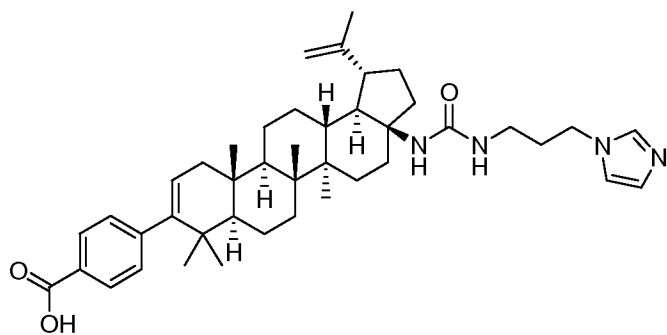
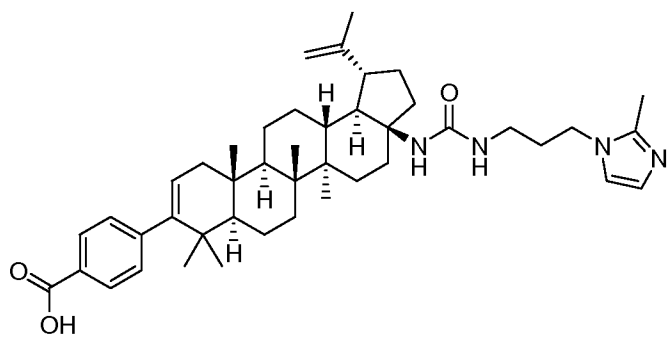
and Q₅ is selected from the group of halogen and SO₂R₃.

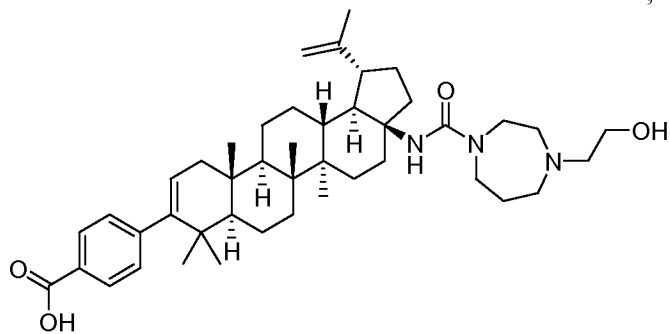
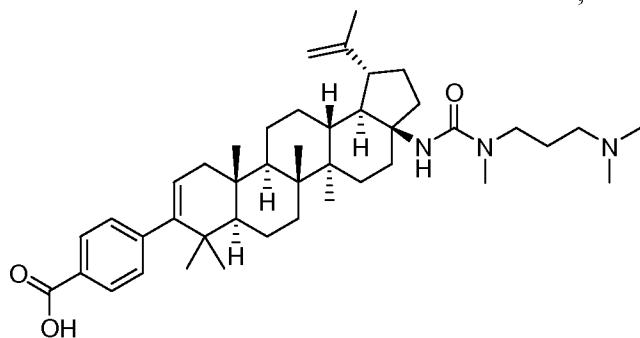
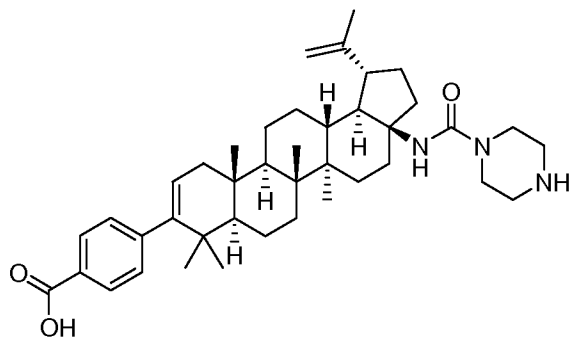
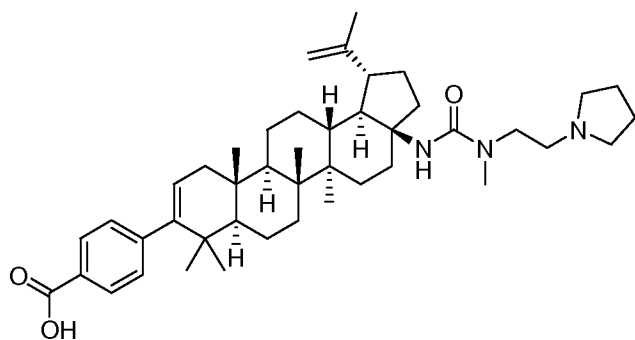
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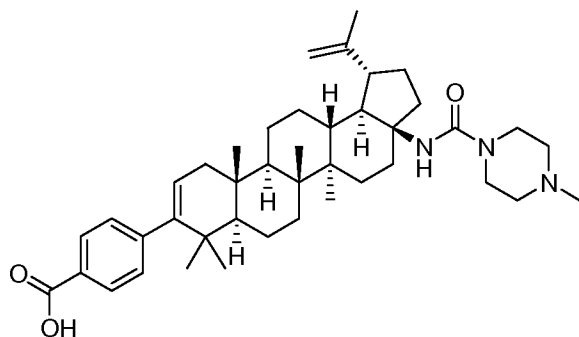
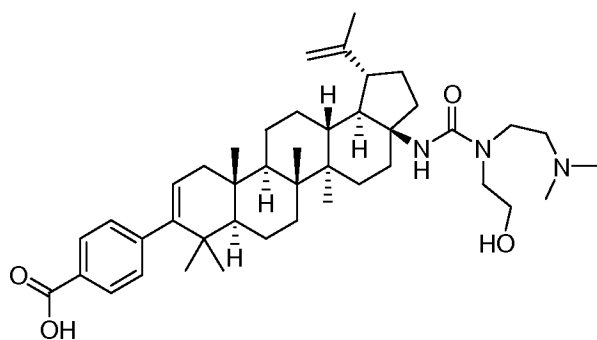
2. The compound as claimed in claim 1, wherein said compound has the
Formula I.

3. The compound as claimed in claim 1, wherein said compound has the Formula II.
4. The compound as claimed in claim 1, wherein said compound has the
5 Formula III.
5. The compound as claimed in claim 2, wherein R₁ is isopropenyl.
6. The compound as claimed in claim 5, wherein X is phenyl.
- 10 7. The compound as claimed in claim 6, wherein Y is -COOR₂.
8. The compound as claimed in claim 7, wherein Y is -COOH.
- 15 9. The compound as claimed in claim 6, wherein A is -H.
10. The compound as claimed in claim 6, wherein R₄ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-Q₁, and -COR₆.
- 20 11. The compound as claimed in claim 10, wherein R₅ is -H.
12. The compound as claimed in claim 10, wherein R₄ is -C₁₋₆ alkyl-Q₁.
13. The compound as claimed in claim 12, wherein Q₁ is -NR₈R₉.
- 25 14. The compound as claimed in claim 10, wherein R₄ is -COR₆.
15. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:
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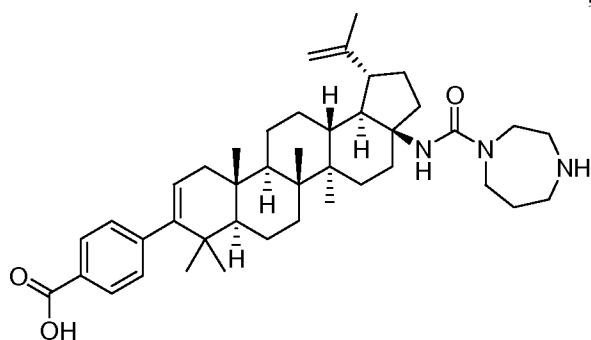




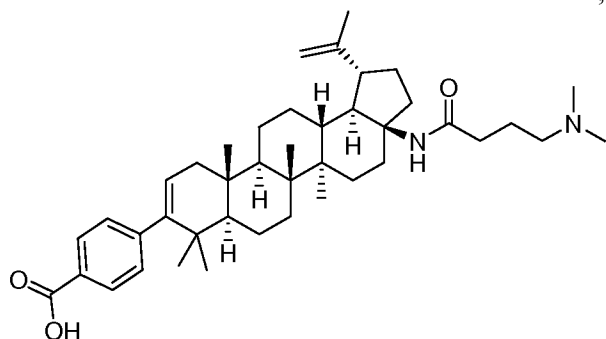




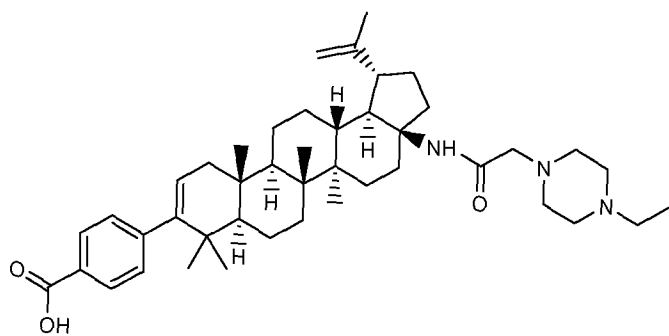
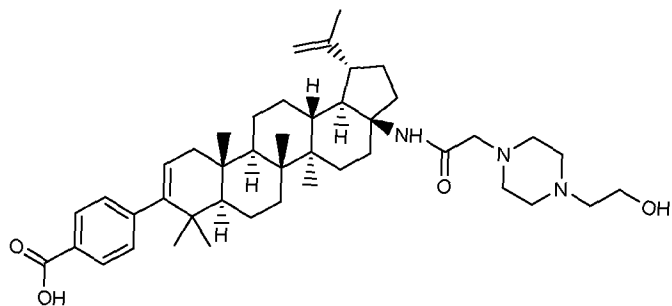
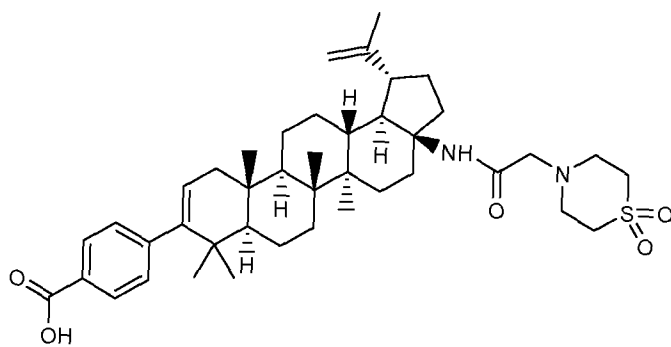
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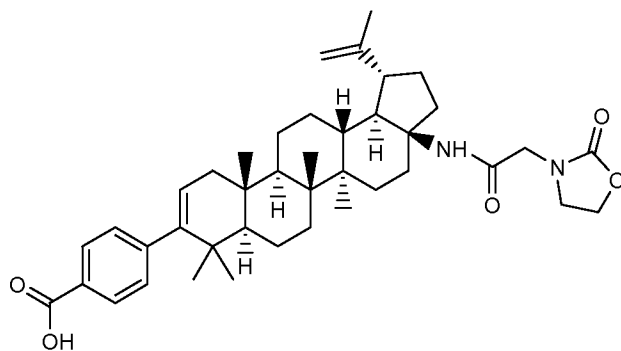
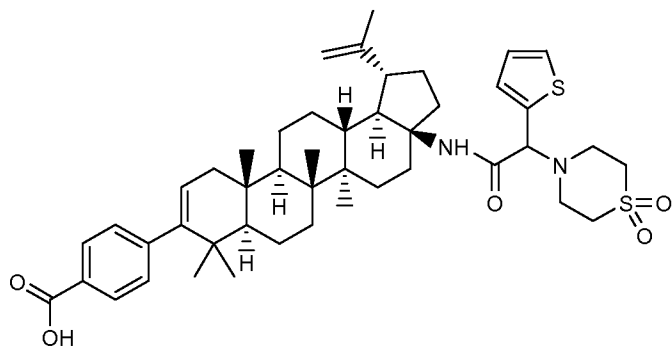
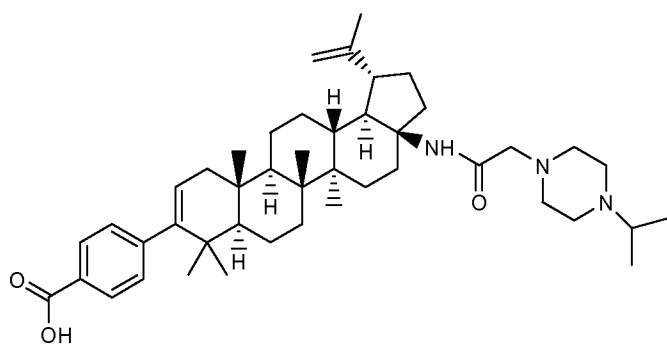
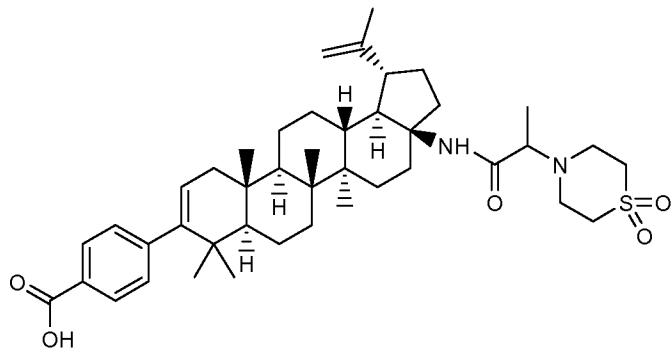
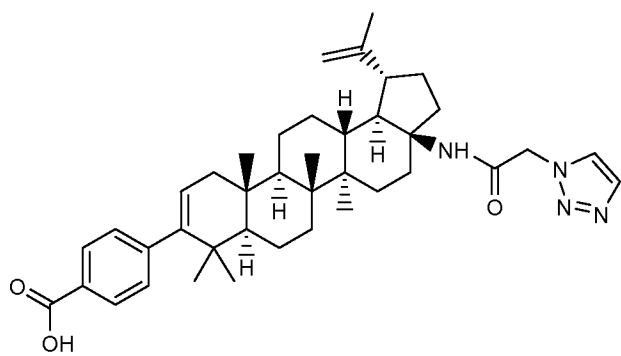


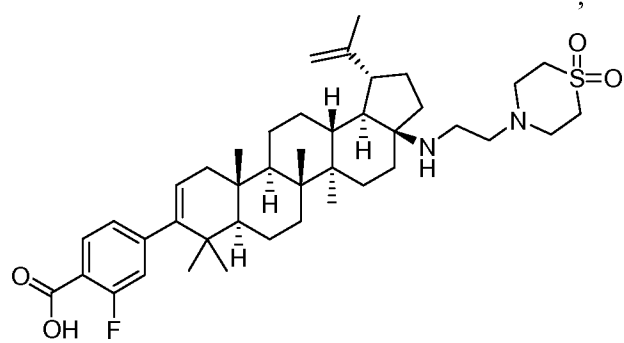
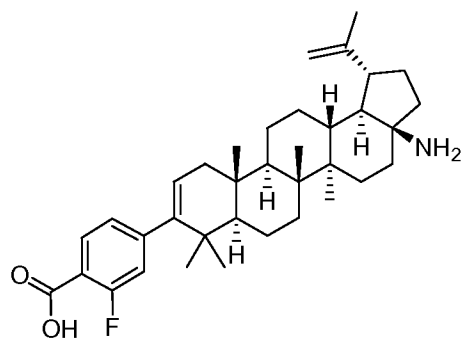
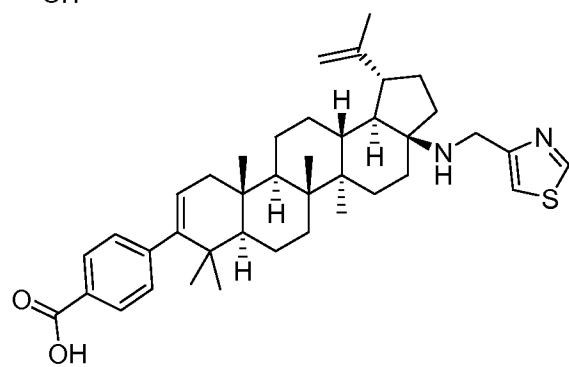
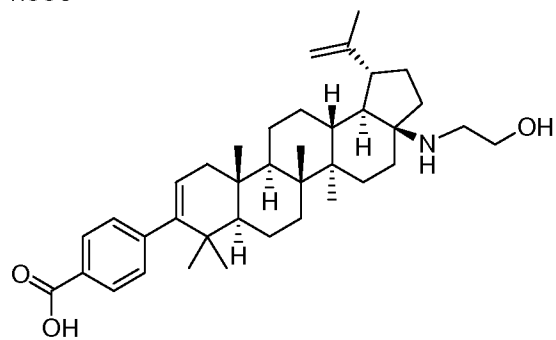
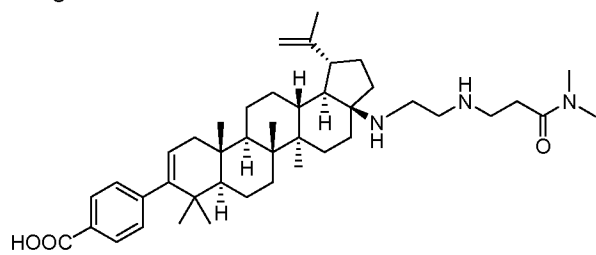
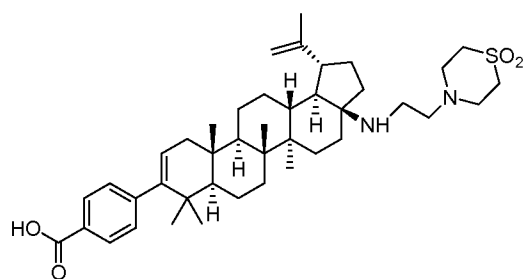
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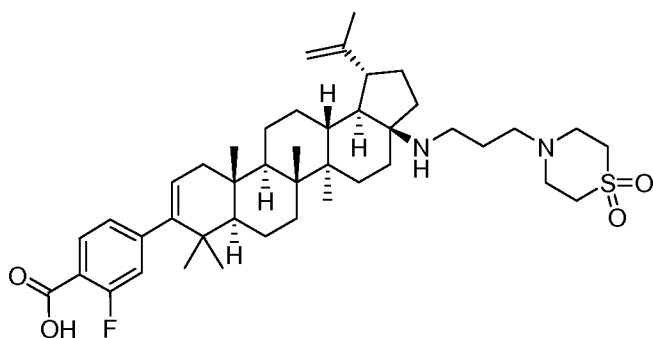






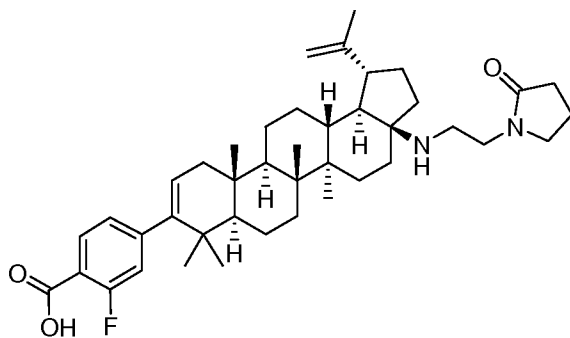
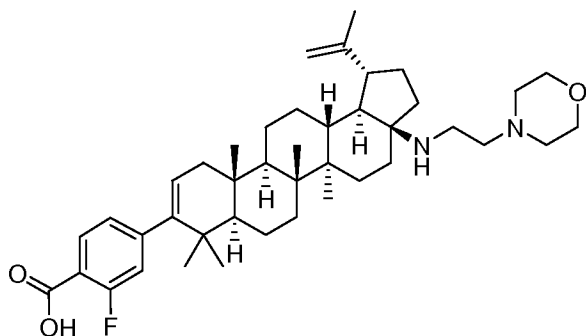
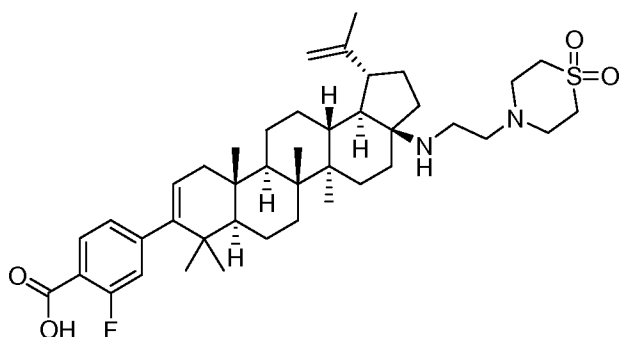
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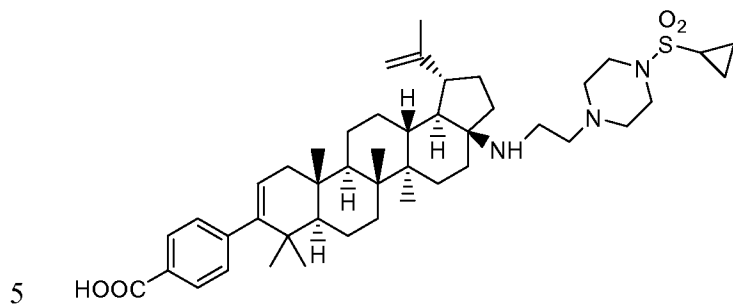
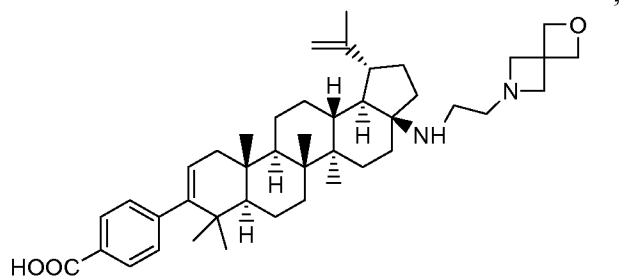
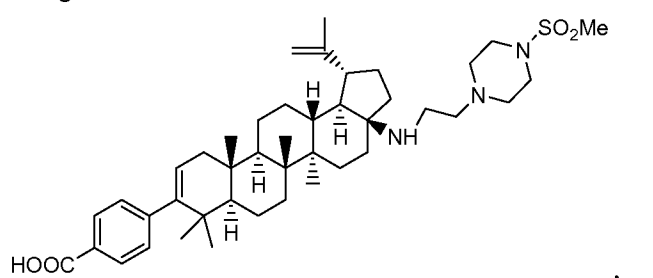
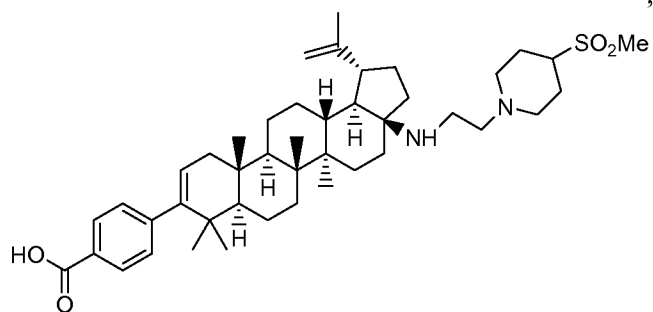
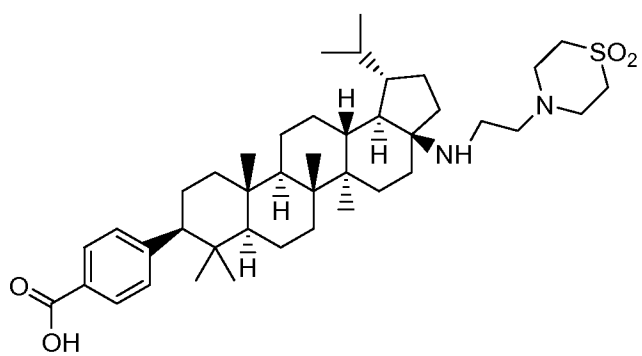
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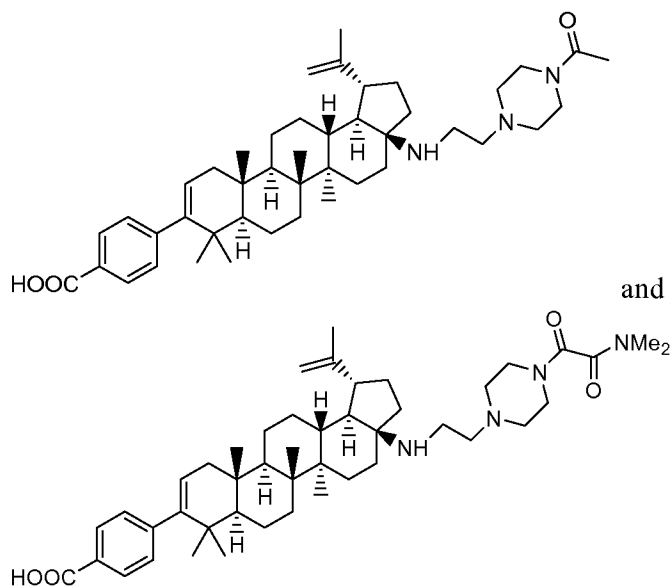


16. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:

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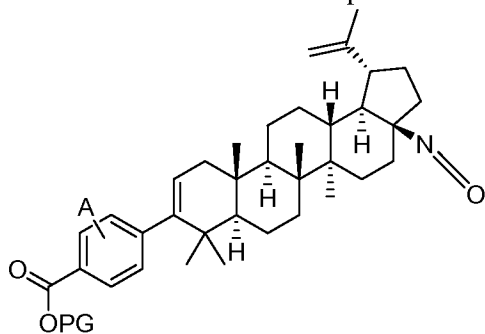


17. A pharmaceutical composition which comprises an antiviral effective amount
 5 of one or more of the compounds as claimed in claim 1, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

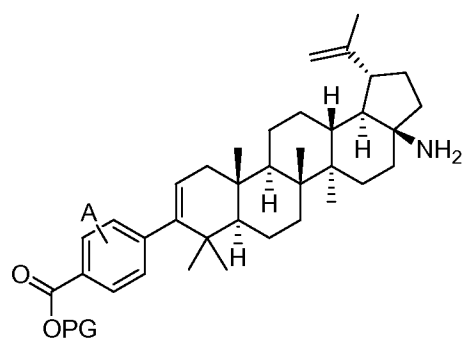
18. The pharmaceutical composition of claim 17, useful for treating infection by
 HIV, which additionally comprises an antiviral effective amount of an AIDS
 10 treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) another HIV entry inhibitor.

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

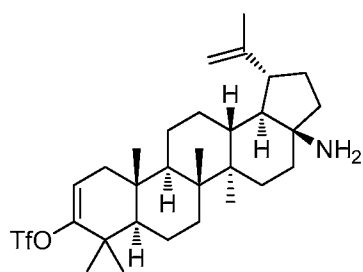
20. An intermediate compound which is selected from the group of



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, and



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