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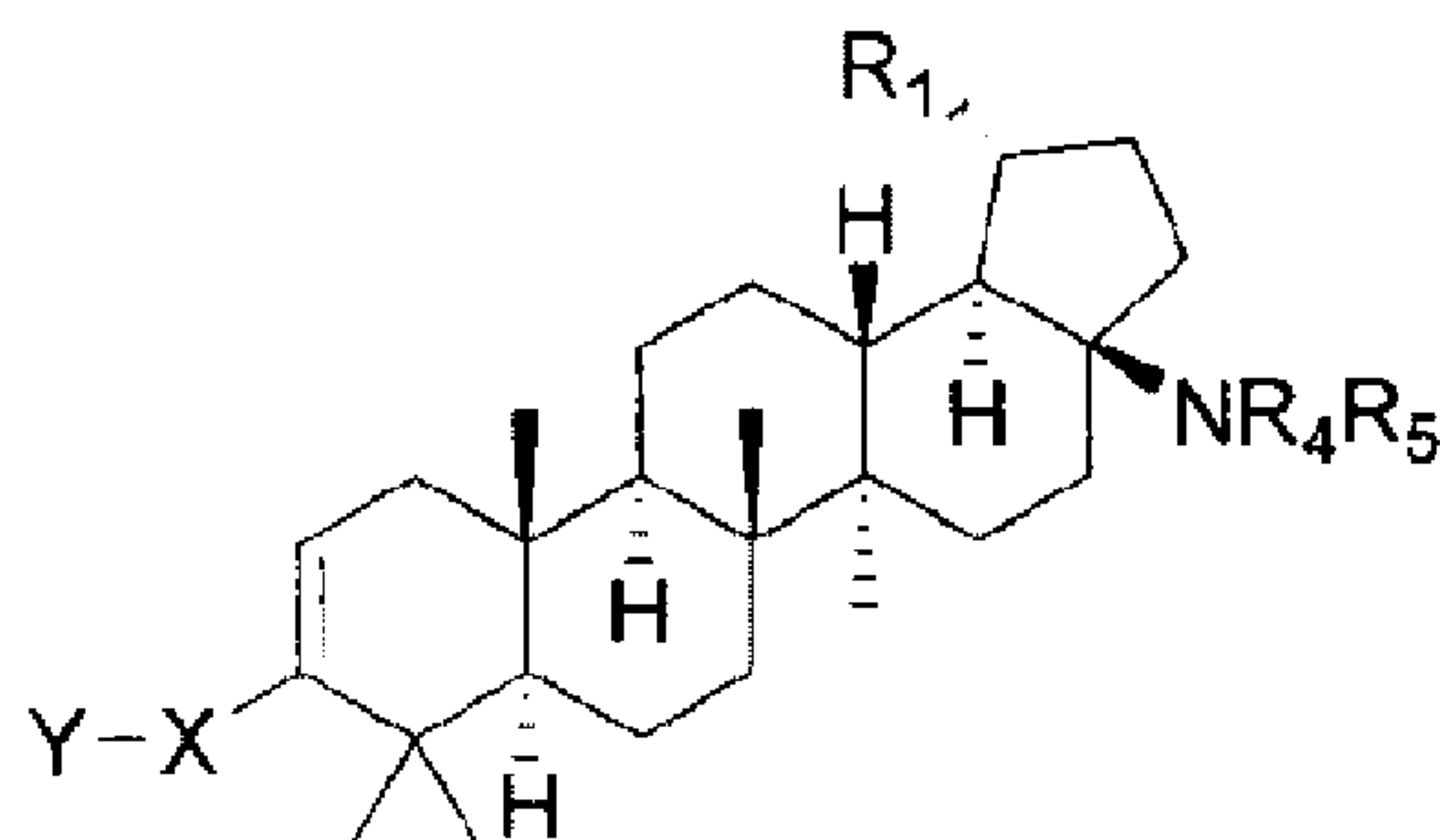
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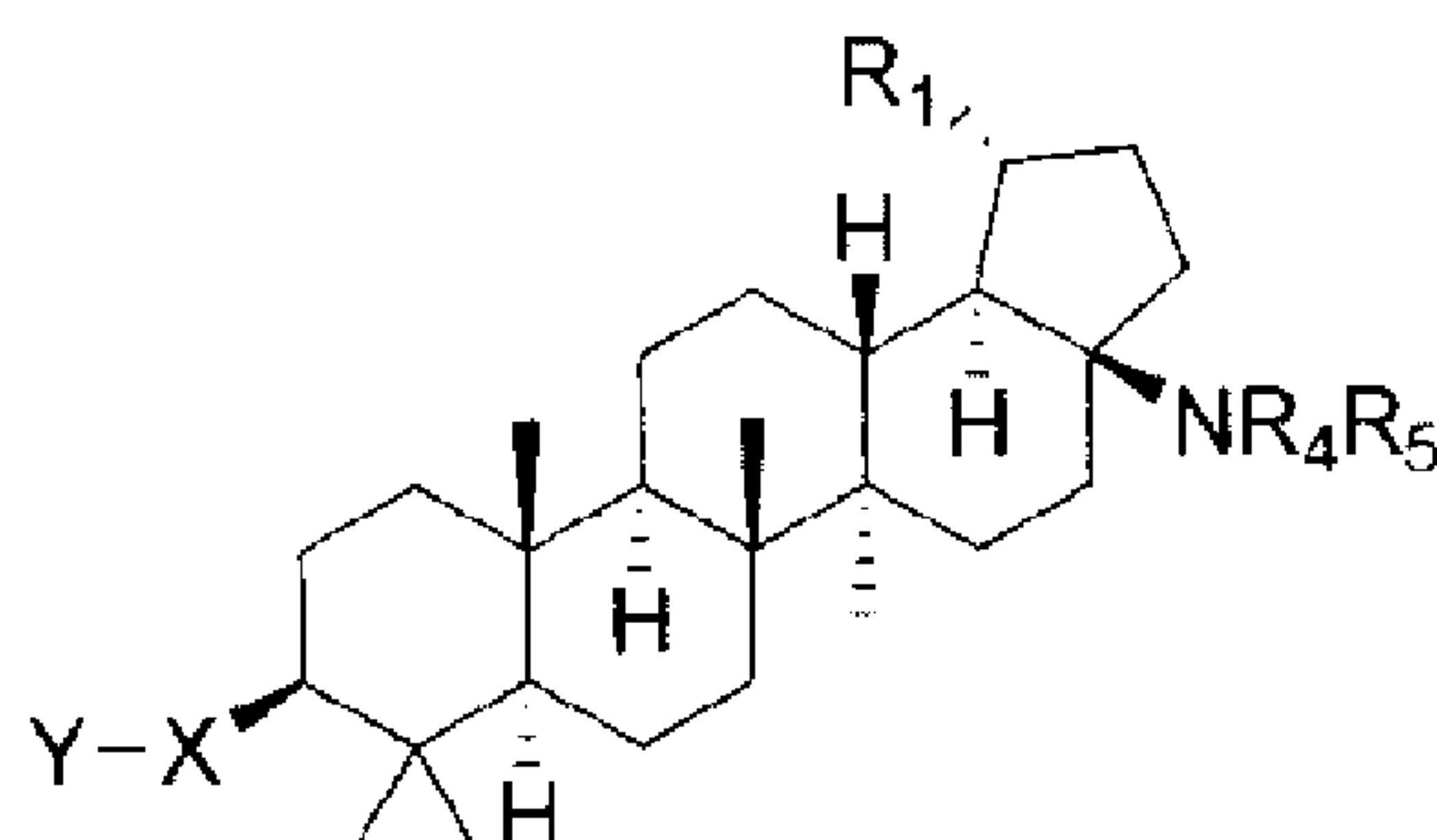
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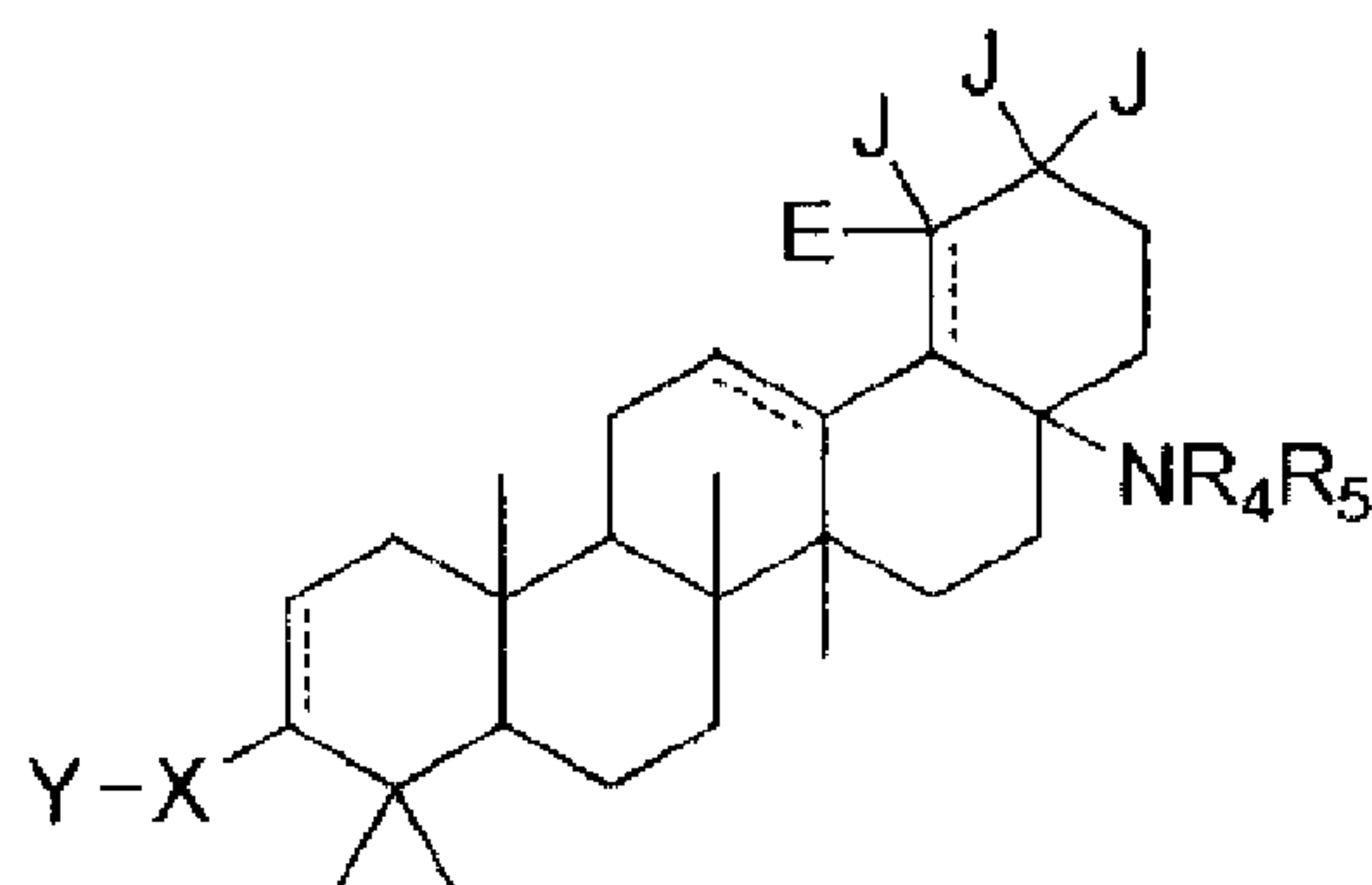
(54) **Titre : TRITERPENOIDES MODIFIES EN C-17 ET C-3 PRESENTANT UNE ACTIVITE INHIBITRICE DE LA MATURATION DU VIH**  
(54) **Title: C-17 AND C-3 MODIFIED TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY**



**Formula I**



**Formula II**



**Formula III**

(57) **Abrégé/Abstract:**

Compounds having drug and bio-affecting properties, their pharmaceutical compositions and methods of use are set forth. In particular, C-17 and C-3 modified triterpenoids that possess unique antiviral activity are provided as HIV maturation inhibitors, as represented by compounds of Formulas I, II and III. These compounds are useful for the treatment of HIV and AIDS.

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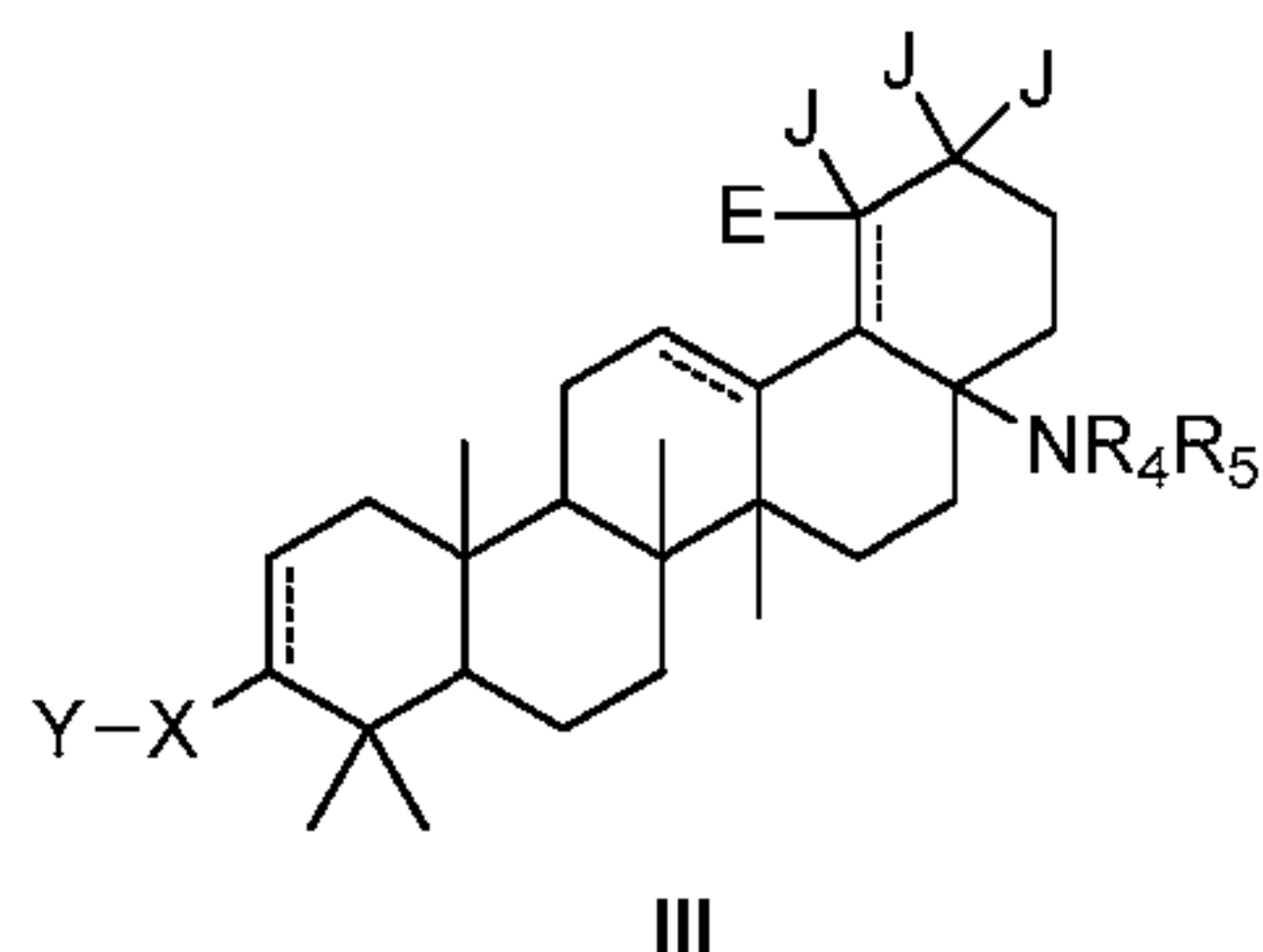
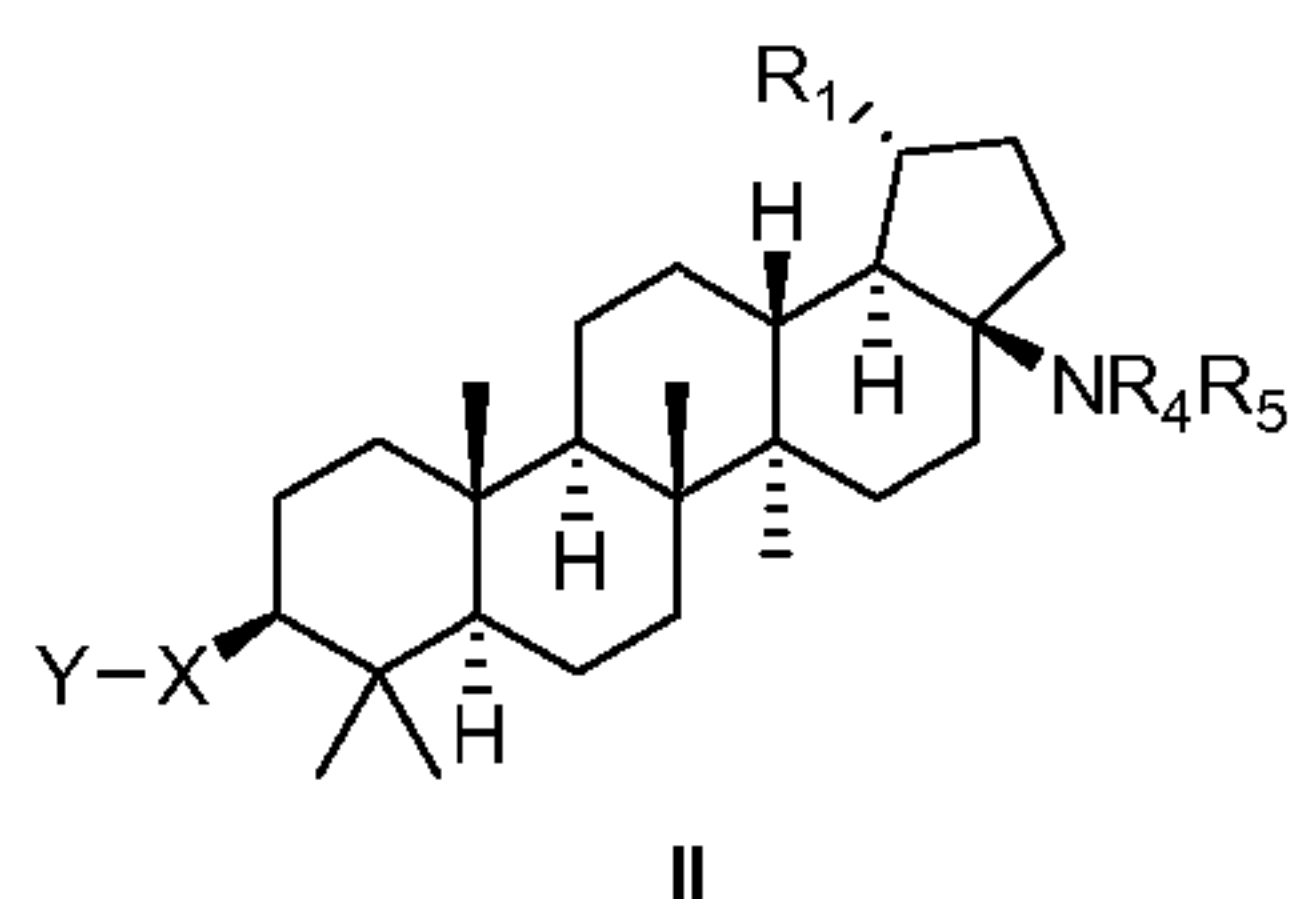
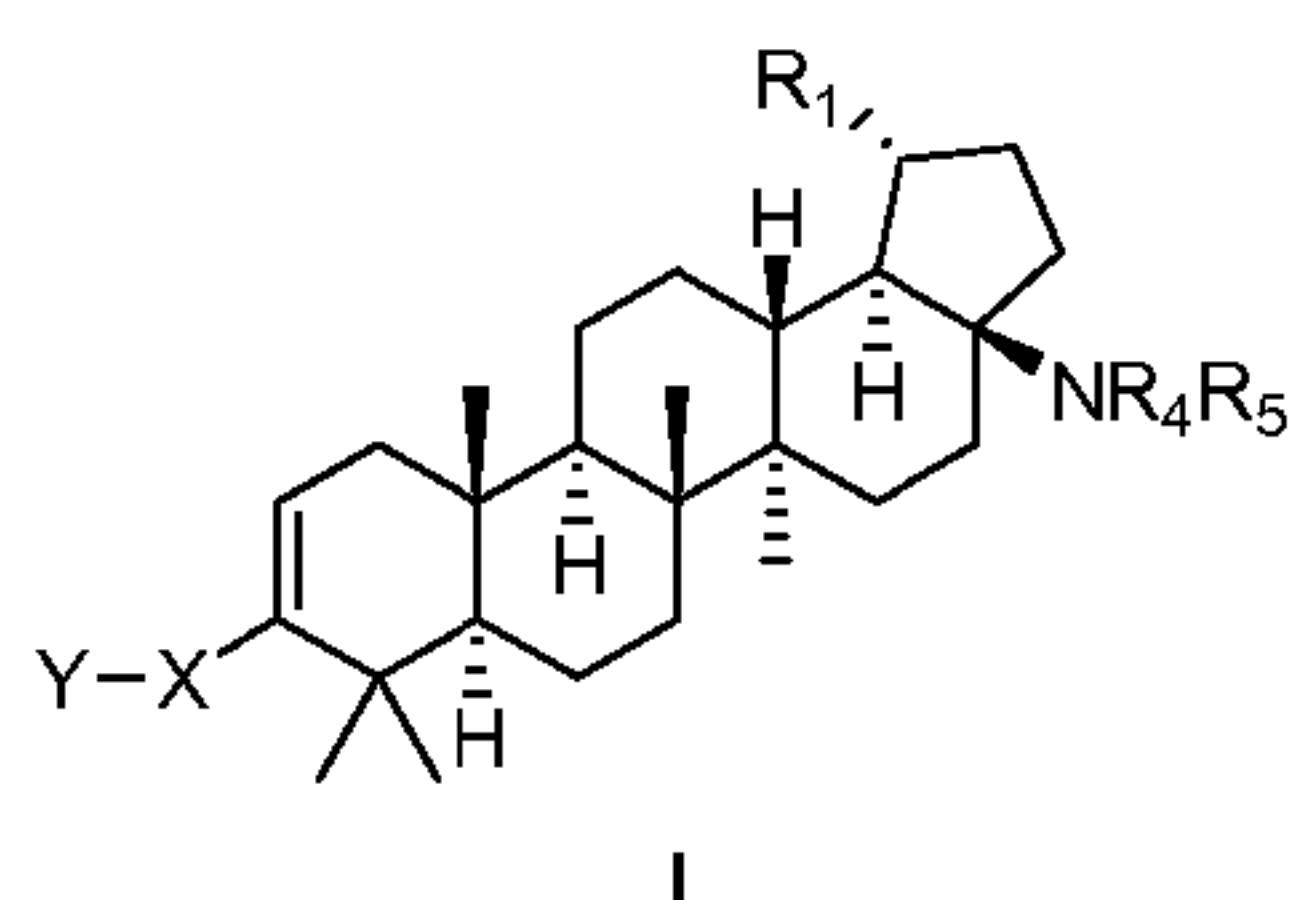
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[Continued on next page]

(54) Title: C-17 AND C-3 MODIFIED TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY



(57) Abstract: Compounds having drug and bio-affecting properties, their pharmaceutical compositions and methods of use are set forth. In particular, C-17 and C-3 modified triterpenoids that possess unique antiviral activity are provided as HIV maturation inhibitors, as represented by compounds of Formulas I, II and III. These compounds are useful for the treatment of HIV and AIDS.

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**CECI EST LE TOME \_\_1\_\_ DE \_\_2\_\_**

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

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## **JUMBO APPLICATIONS / PATENTS**

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
THAN ONE VOLUME.**

**THIS IS VOLUME \_\_1\_\_ OF \_\_2\_\_**

NOTE: For additional volumes please contact the Canadian Patent Office.

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<sup>®</sup>), didanosine (or Videx<sup>®</sup>), stavudine (or Zerit<sup>®</sup>), lamivudine (or 3TC or Epivir<sup>®</sup>), zalcitabine (or DDC or Hivid<sup>®</sup>), abacavir succinate (or Ziagen<sup>®</sup>), Tenofovir disoproxil fumarate salt (or Viread<sup>®</sup>), emtricitabine (or FTC - Emtriva<sup>®</sup>), Combivir<sup>®</sup> (contains -3TC plus AZT),  
25 Trizivir<sup>®</sup> (contains abacavir, lamivudine, and zidovudine), Epzicom<sup>®</sup> (contains abacavir and lamivudine), Truvada<sup>®</sup> (contains Viread<sup>®</sup> and Emtriva<sup>®</sup>); non-nucleoside reverse transcriptase inhibitors: nevirapine (or Viramune<sup>®</sup>), delavirdine (or Rescriptor<sup>®</sup>) and efavirenz (or Sustiva<sup>®</sup>), Atripla<sup>®</sup> (Truvada<sup>®</sup> + Sustiva<sup>®</sup>), and etravirine, and peptidomimetic protease inhibitors or approved formulations:  
30 saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra<sup>®</sup> (lopinavir and Ritonavir), darunavir, atazanavir (Reyataz<sup>®</sup>) and tipranavir (Aptivus<sup>®</sup>) and

cobicistat, and integrase inhibitors such as raltegravir (Isentress<sup>®</sup>), and entry inhibitors such as enfuvirtide (T-20) (Fuzeon<sup>®</sup>) and maraviroc (Selzentry<sup>®</sup>).

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.

30

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  $3\beta$ -(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.

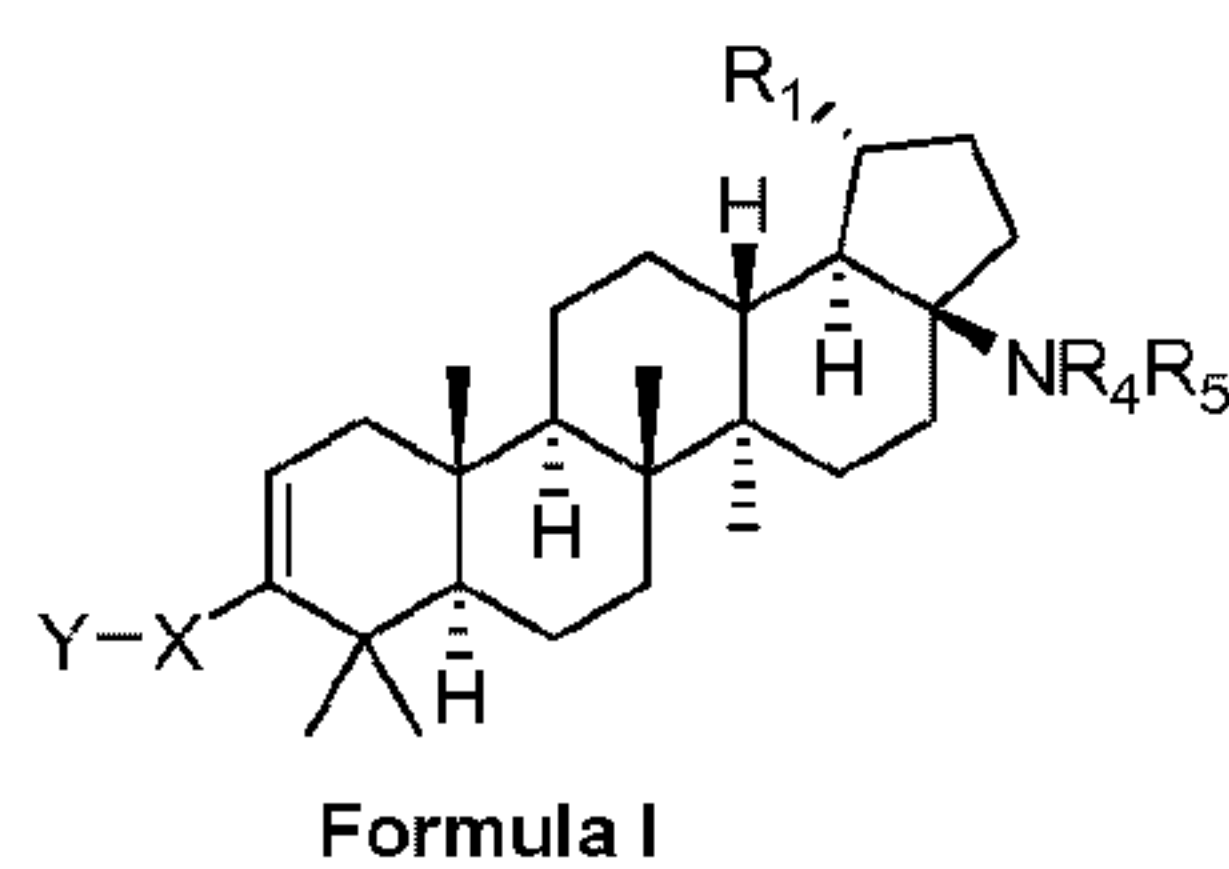
### SUMMARY OF THE INVENTION

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.

15

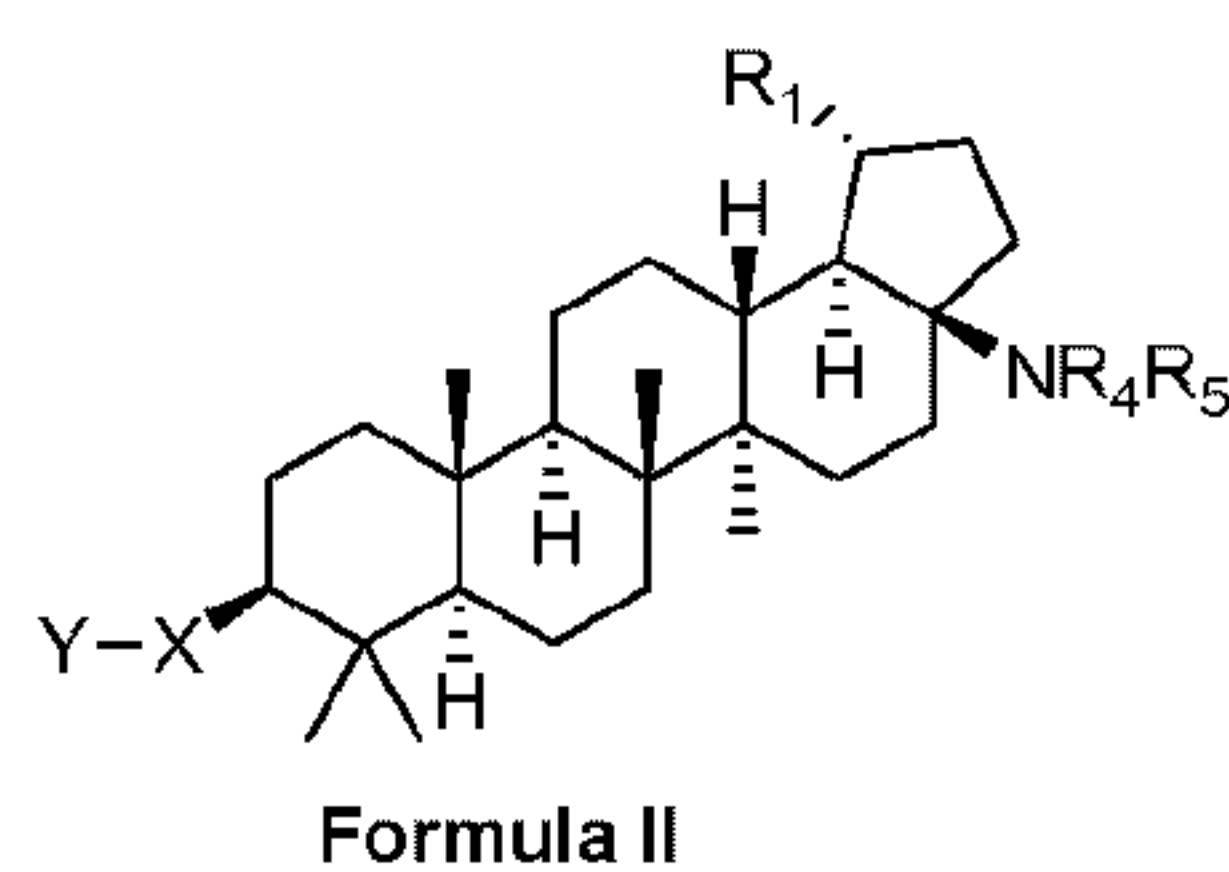
One embodiment of the present invention is directed to a compound,  
including pharmaceutically acceptable salts thereof, which is selected from the group  
of:

20 a compound of formula I



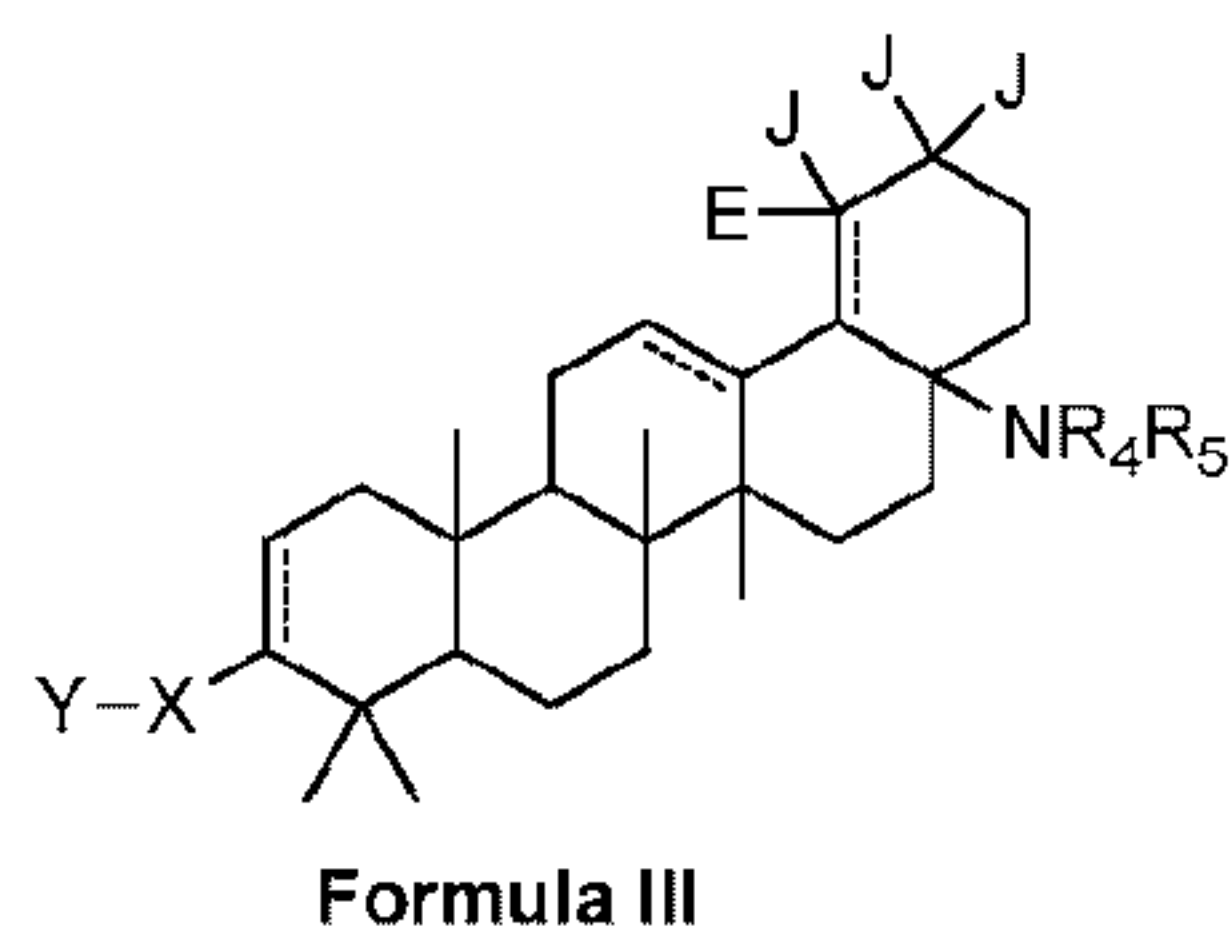
a compound of formula II

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  $-arylsubstituted\ C_{1-6}\ alkyl$ ;

15

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  $-CONHOH$ ,

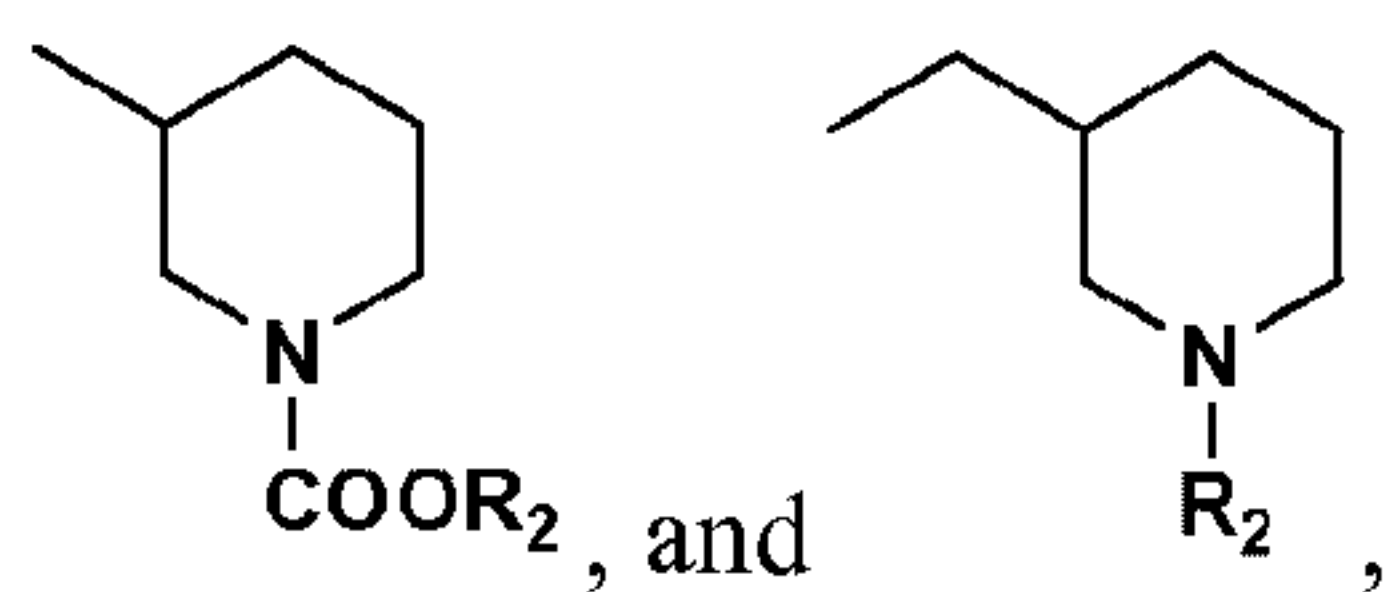
20

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,  $-C_{1-6}$  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,  $-COR_6$ ,  $-COCOR_6$ ,  $-SO_2R_7$ ,  $-SO_2NR_2R_2$ ,

25



wherein Q<sub>1</sub> is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF<sub>3</sub>, -OR<sub>2</sub>, -COOR<sub>2</sub>, -NR<sub>8</sub>R<sub>9</sub>, -CONR<sub>10</sub>R<sub>11</sub> and -SO<sub>2</sub>R<sub>7</sub>;

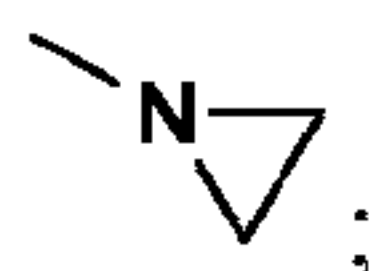
5

R<sub>5</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> alkylsubstituted alkyl, -C<sub>1-6</sub> alkyl-NR<sub>8</sub>R<sub>9</sub>, -COR<sub>10</sub>, -COR<sub>6</sub>, -COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub> and -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>;

with the proviso that only one of R<sub>4</sub> or R<sub>5</sub> can be selected from the group of -COR<sub>6</sub>, -

10 COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub> and -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>;

or R<sub>4</sub> and R<sub>5</sub> are taken together with the adjacent N to form



R<sub>6</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkyl-substitutedalkyl, -C<sub>3-6</sub>

15 cycloalkyl, -C<sub>3-6</sub> substitutedcycloalkyl-Q<sub>2</sub>, -C<sub>1-6</sub> alkyl-Q<sub>2</sub>, -C<sub>1-6</sub> alkyl-substitutedalkyl-Q<sub>2</sub>, -C<sub>3-6</sub> cycloalkyl-Q<sub>2</sub>, aryl-Q<sub>2</sub>, -NR<sub>13</sub>R<sub>14</sub>, and -OR<sub>15</sub>;

wherein Q<sub>2</sub> is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR<sub>2</sub>, -COOR<sub>2</sub>, -NR<sub>8</sub>R<sub>9</sub>, SO<sub>2</sub>R<sub>7</sub>, -CONHSO<sub>2</sub>R<sub>3</sub>, and -CONHSO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>;

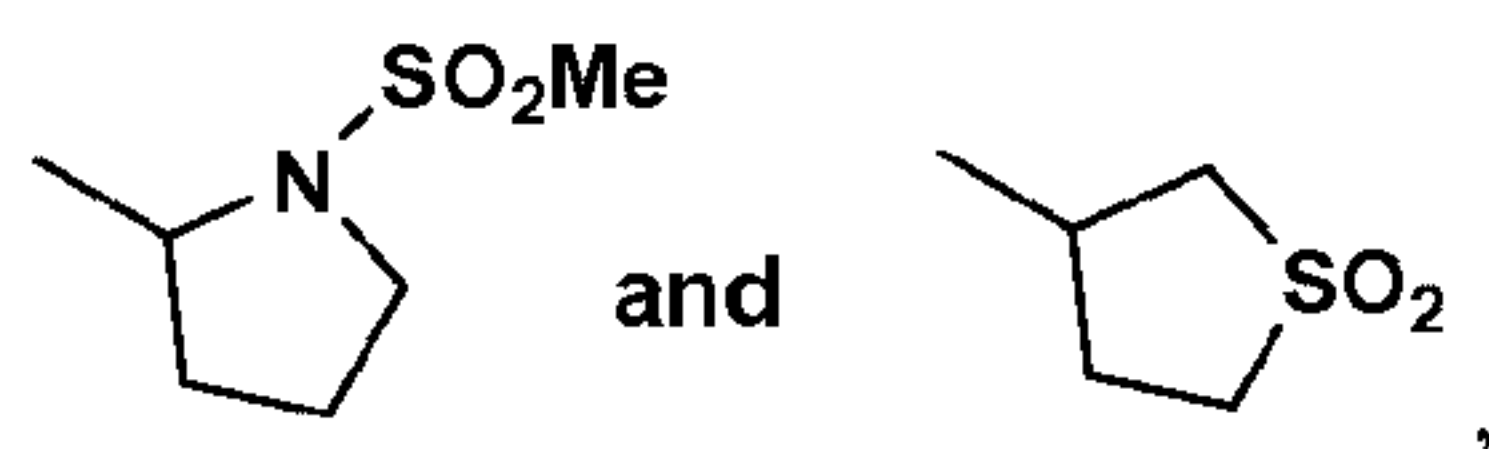
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R<sub>7</sub> is selected from the group of -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>3-6</sub> cycloalkyl, aryl, and heteroaryl;

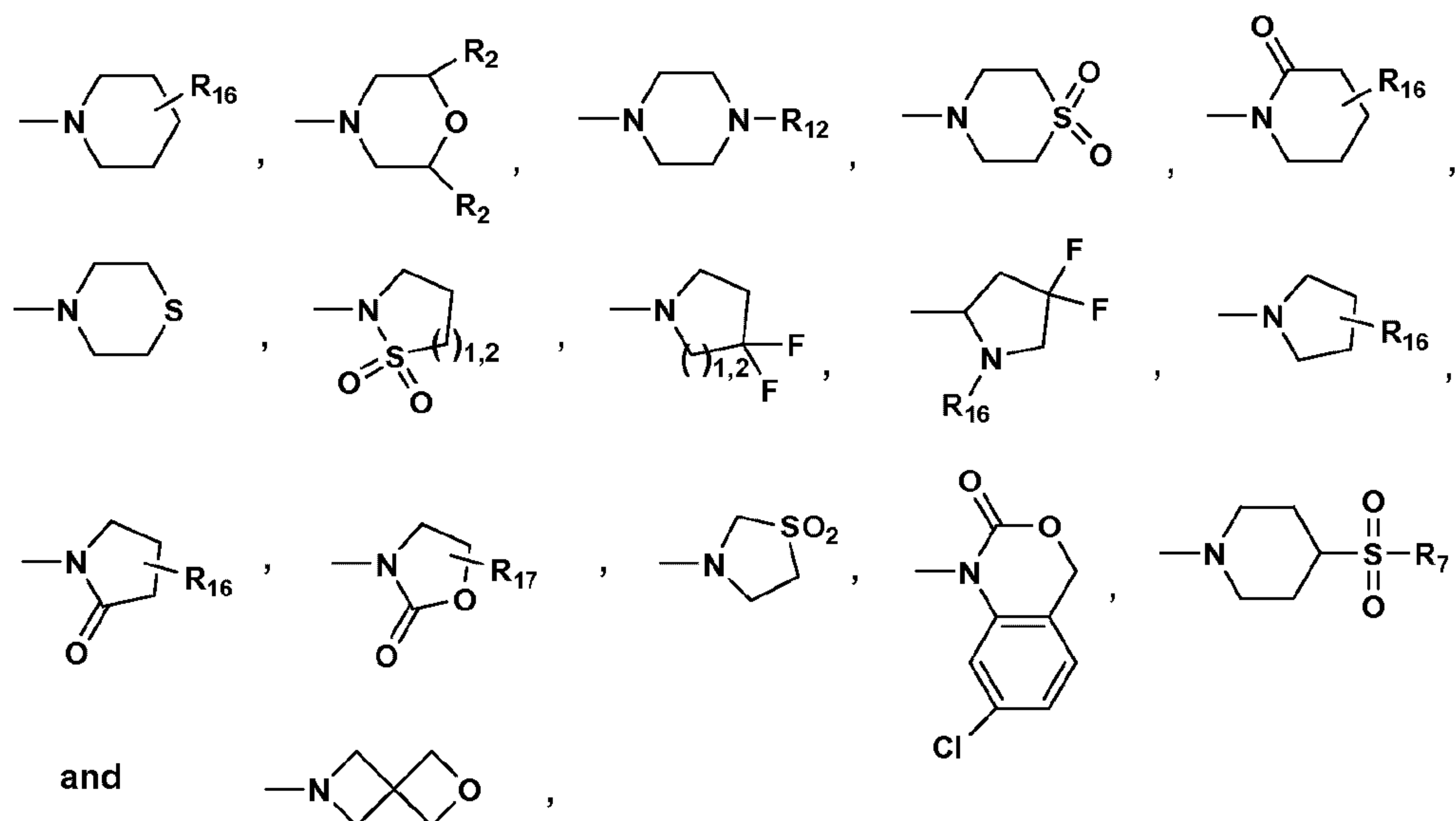
R<sub>8</sub> and R<sub>9</sub> are independently selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub>

25 substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C<sub>1-6</sub> alkyl-Q<sub>2</sub>, and -COOR<sub>3</sub>,

and R<sub>8</sub> and R<sub>9</sub> 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:



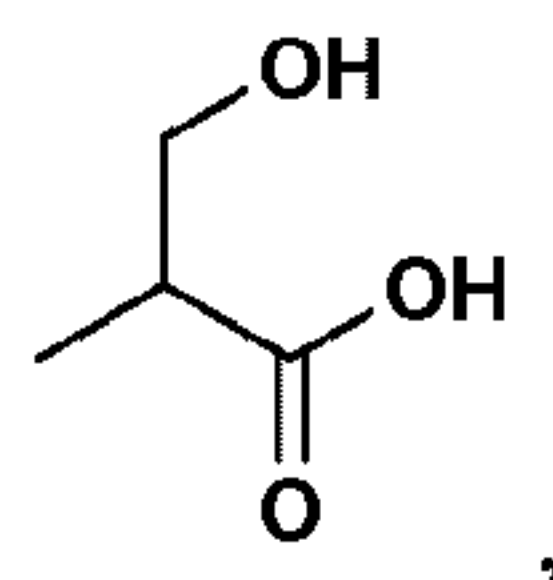
5 with the proviso that only one of R<sub>8</sub> or R<sub>9</sub> can be -COOR<sub>3</sub>;

R<sub>10</sub> and R<sub>11</sub> are independently selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl and -C<sub>3-6</sub> cycloalkyl,  
or R<sub>10</sub> and R<sub>11</sub> are taken together with the adjacent N to form a cycle such as

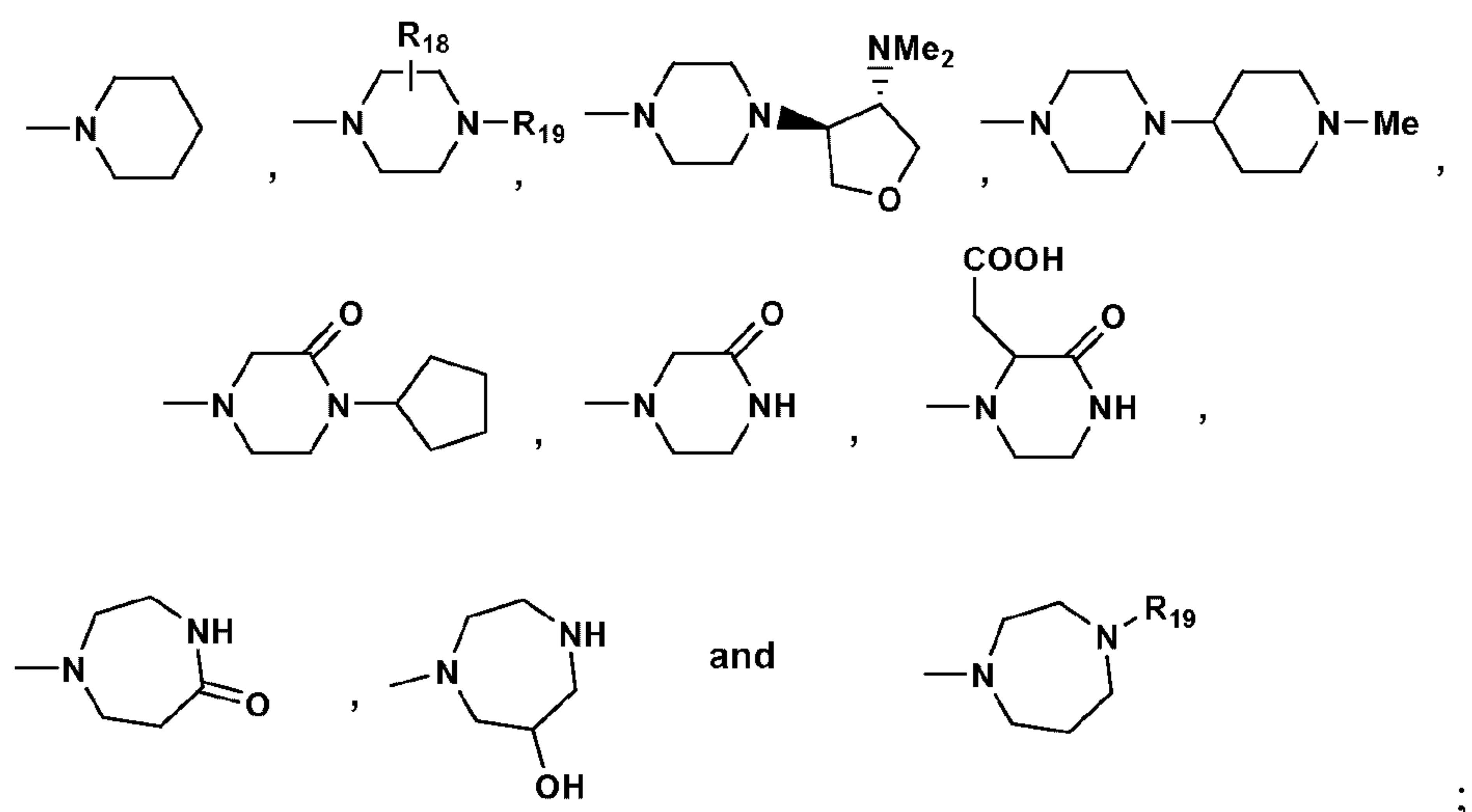
10  ;

R<sub>12</sub> is selected from the group of -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkyl-OH; -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>3-6</sub> cycloalkyl, -COR<sub>7</sub>, -COONR<sub>22</sub>R<sub>23</sub>, -SOR<sub>7</sub>, and -SONR<sub>24</sub>R<sub>25</sub>;

15 R<sub>13</sub> and R<sub>14</sub> are independently selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>1-6</sub> alkyl-Q<sub>3</sub>, -C<sub>1-6</sub> alkyl-C<sub>3-6</sub> cycloalkyl-Q<sub>3</sub>, C<sub>1-6</sub> substituted alkyl-Q<sub>3</sub> and



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



Q<sub>3</sub> is selected from the group of heteroaryl, substituted heteroaryl, -NR<sub>20</sub>R<sub>21</sub>, -CONR<sub>2</sub>R<sub>2</sub>, -COOR<sub>2</sub>, -OR<sub>2</sub>, and -SO<sub>2</sub>R<sub>3</sub>;

5

R<sub>15</sub> is selected from the group of -C<sub>1-6</sub> alkyl, -C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>1-6</sub> alkyl-Q<sub>3</sub>, -C<sub>1-6</sub> alkyl-C<sub>3-6</sub> cycloalkyl-Q<sub>3</sub> and -C<sub>1-6</sub> substituted alkyl-Q<sub>3</sub>;

R<sub>16</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -NR<sub>2</sub>R<sub>2</sub>, and -COOR<sub>3</sub>;

10

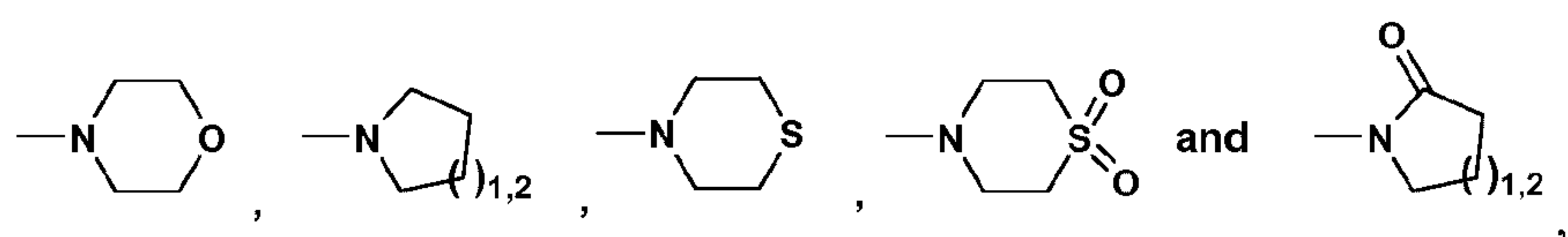
R<sub>17</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -COOR<sub>3</sub>, and aryl;

R<sub>18</sub> is selected from the group of -COOR<sub>2</sub> and -C<sub>1-6</sub> alkyl-COOR<sub>2</sub>;

15 R<sub>19</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkyl-Q<sub>4</sub>, -COR<sub>3</sub>, -COOR<sub>3</sub>, wherein Q<sub>4</sub> is selected from the group of -NR<sub>2</sub>R<sub>2</sub> and -OR<sub>2</sub>;

R<sub>20</sub> and R<sub>21</sub> are independently selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>1-6</sub> substituted alkyl-OR<sub>2</sub>, and -COR<sub>3</sub>,

20 or R<sub>20</sub> and R<sub>21</sub> are taken together with the adjacent N to form a cycle selected from the group of

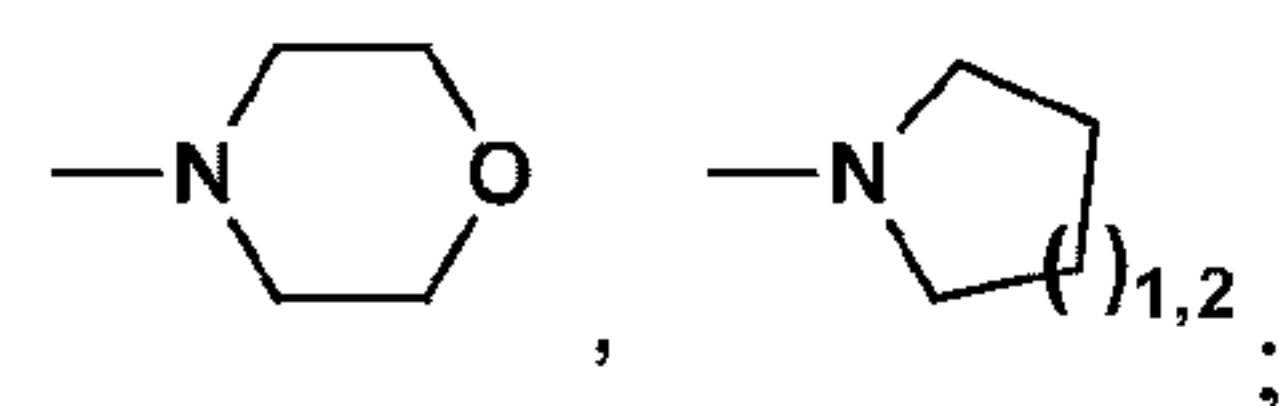


with the proviso that only one of  $R_{20}$  or  $R_{21}$  can be  $-\text{COR}_3$ ;

$R_{22}$  and  $R_{23}$  are independently selected from the group of H,  $-\text{C}_{1-6}$  alkyl,  $-\text{C}_{1-6}$

5 substituted alkyl, and  $-\text{C}_{1-6}$  cycloalkyl,

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



$R_{24}$  and  $R_{25}$  are independently from the group of H,  $-\text{C}_{1-6}$  alkyl,  $-\text{C}_{1-6}$  substituted alkyl,

10  $-\text{C}_{1-6}$  alkyl- $Q_5$ ,  $-\text{C}_{1-6}$  cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

and  $Q_5$  is selected from the group of halogen and  $\text{SO}_2\text{R}_3$ .

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 "C<sub>1-6</sub> 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

"C<sub>1</sub>–C<sub>4</sub> fluoroalkyl" refers to F-substituted C<sub>1</sub>–C<sub>4</sub> 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.

15 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, quinoliny, isoquinoliny, 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 and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane, cycloheptene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalo- methanesulfonamido, trihalomethanesulfonyl, silyl, amidino, guanidino, ureido, phosphonyl, amino and –NR<sup>x</sup>R<sup>y</sup> with R<sup>x</sup> and R<sup>y</sup> 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 two carbon atoms and at least one carbon-carbon triple bond.

20

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

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

25

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

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

30

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  $Z_3CC(=O)-$  group with said Z being a halogen.

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

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

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

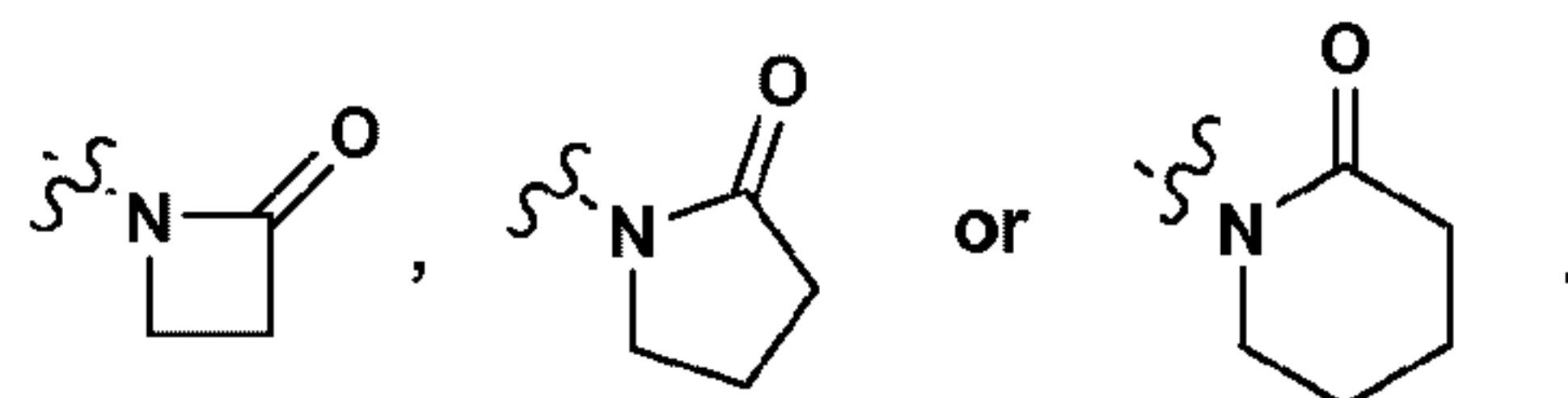
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A “silyl” group refers to a  $-Si(R'')_3$ , with  $R''$  being  $(C_{1-6})$ alkyl or phenyl.

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.

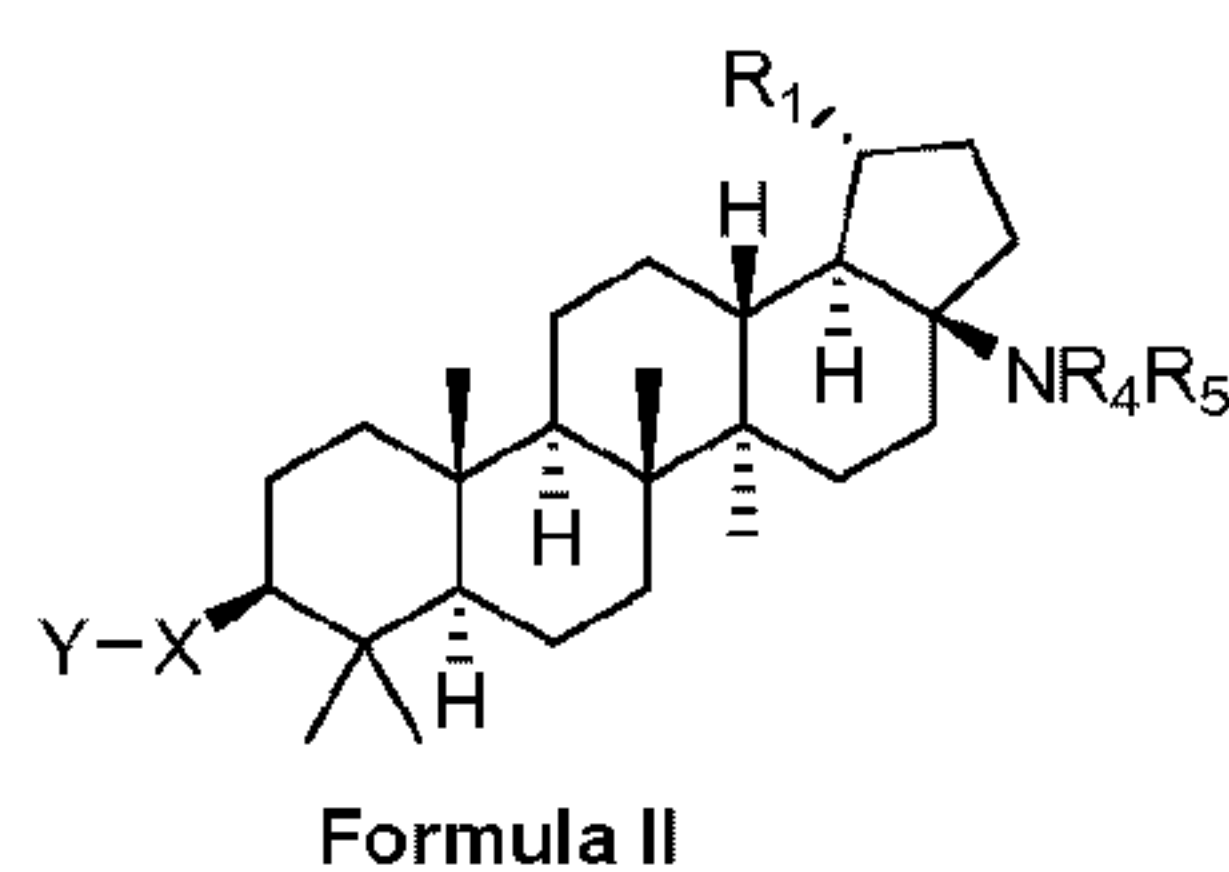
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Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of the invention. The term “pharmaceutically acceptable salt” as used herein and in the claims is intended to include nontoxic base addition salts. Suitable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

30

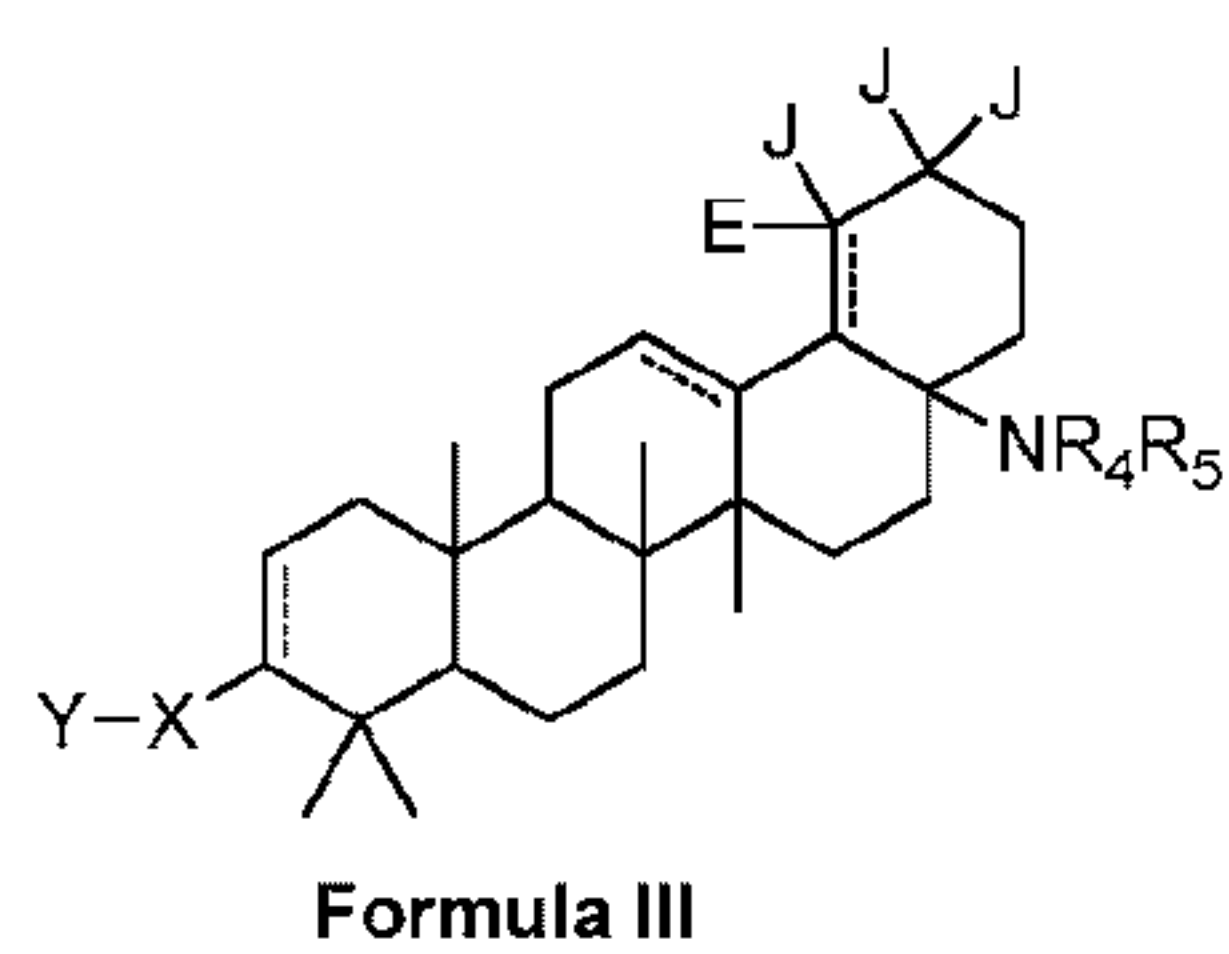


a compound of formula II



; and

5 a compound of formula III



;

wherein R<sub>1</sub> is isopropenyl or isopropyl;

10

J and E are -H or -CH<sub>3</sub>, 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, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkoxy, and

15 -COOR<sub>2</sub>;

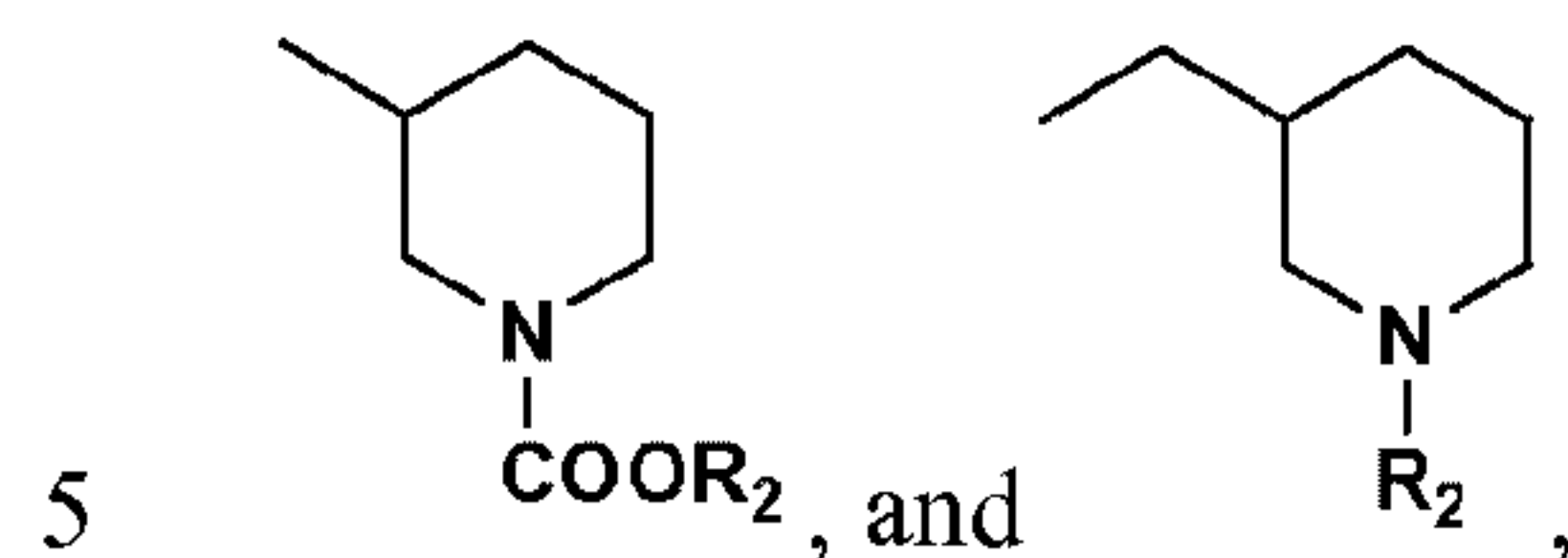
R<sub>2</sub> is -H, -C<sub>1-6</sub> alkyl, -alkylsubstituted C<sub>1-6</sub> alkyl or-arylsubstituted C<sub>1-6</sub> alkyl;

Y is selected from the group of -COOR<sub>2</sub>, -C(O)NR<sub>2</sub>SO<sub>2</sub>R<sub>3</sub>, -C(O)NHSO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>,  
 20 -NR<sub>2</sub>SO<sub>2</sub>R<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>, -C<sub>3-6</sub> cycloalkyl-COOR<sub>2</sub>, -C<sub>2-6</sub> alkenyl-COOR<sub>2</sub>, -C<sub>2-6</sub>  
 alkynyl-COOR<sub>2</sub>, -C<sub>1-6</sub> alkyl-COOR<sub>2</sub>, -NHC(O)(CH<sub>2</sub>)<sub>n</sub>-COOR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>C(O)R<sub>2</sub>,  
 -tetrazole, and -CONHOH,

wherein n=1-6;

25 R<sub>3</sub> is -C<sub>1-6</sub> alkyl or -alkylsubstituted C<sub>1-6</sub> alkyl;

R<sub>4</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkyl-C(OR<sub>3</sub>)<sub>2</sub>-C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>1-6</sub> alkyl-C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> alkyl-Q<sub>1</sub>, -C<sub>1-6</sub> alkyl-C<sub>3-6</sub> cycloalkyl-Q<sub>1</sub>, aryl, heteroaryl, substituted heteroaryl, -COR<sub>6</sub>, -COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub>, -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>,

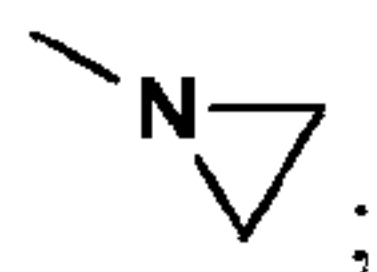


wherein Q<sub>1</sub> is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF<sub>3</sub>, -OR<sub>2</sub>, -COOR<sub>2</sub>, -NR<sub>8</sub>R<sub>9</sub>, -CONR<sub>10</sub>R<sub>11</sub> and -SO<sub>2</sub>R<sub>7</sub>;

- 10 R<sub>5</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> alkylsubstituted alkyl, -C<sub>1-6</sub> alkyl-NR<sub>8</sub>R<sub>9</sub>, -COR<sub>10</sub>, -COR<sub>6</sub>, -COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub> and -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>;

with the proviso that only one of R<sub>4</sub> or R<sub>5</sub> can be selected from the group of -COR<sub>6</sub>, -COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub> and -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>;

- 15 or R<sub>4</sub> and R<sub>5</sub> are taken together with the adjacent N to form



R<sub>6</sub> is selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkyl-substitutedalkyl, -C<sub>3-6</sub> cycloalkyl, -C<sub>3-6</sub> substitutedcycloalkyl-Q<sub>2</sub>, -C<sub>1-6</sub> alkyl-Q<sub>2</sub>, -C<sub>1-6</sub> alkyl-substitutedalkyl-Q<sub>2</sub>, -C<sub>3-6</sub> cycloalkyl-Q<sub>2</sub>, aryl-Q<sub>2</sub>, -NR<sub>13</sub>R<sub>14</sub>, and -OR<sub>15</sub>;

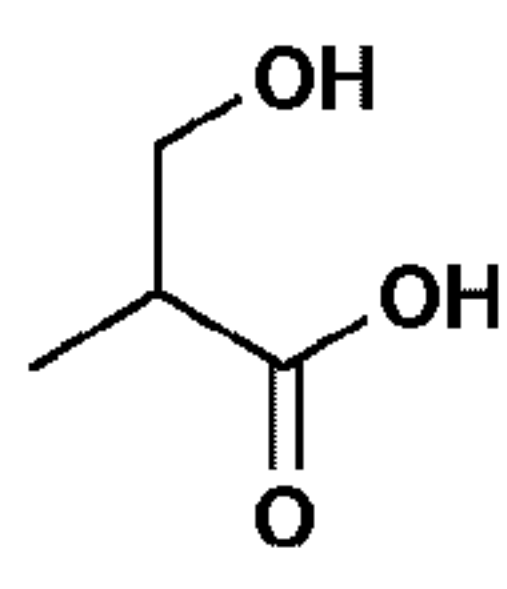
wherein Q<sub>2</sub> is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR<sub>2</sub>, -COOR<sub>2</sub>, -NR<sub>8</sub>R<sub>9</sub>, SO<sub>2</sub>R<sub>7</sub>, -CONHSO<sub>2</sub>R<sub>3</sub>, and -CONHSO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>;

- 25 R<sub>7</sub> is selected from the group of -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>3-6</sub> cycloalkyl, aryl, and heteroaryl;

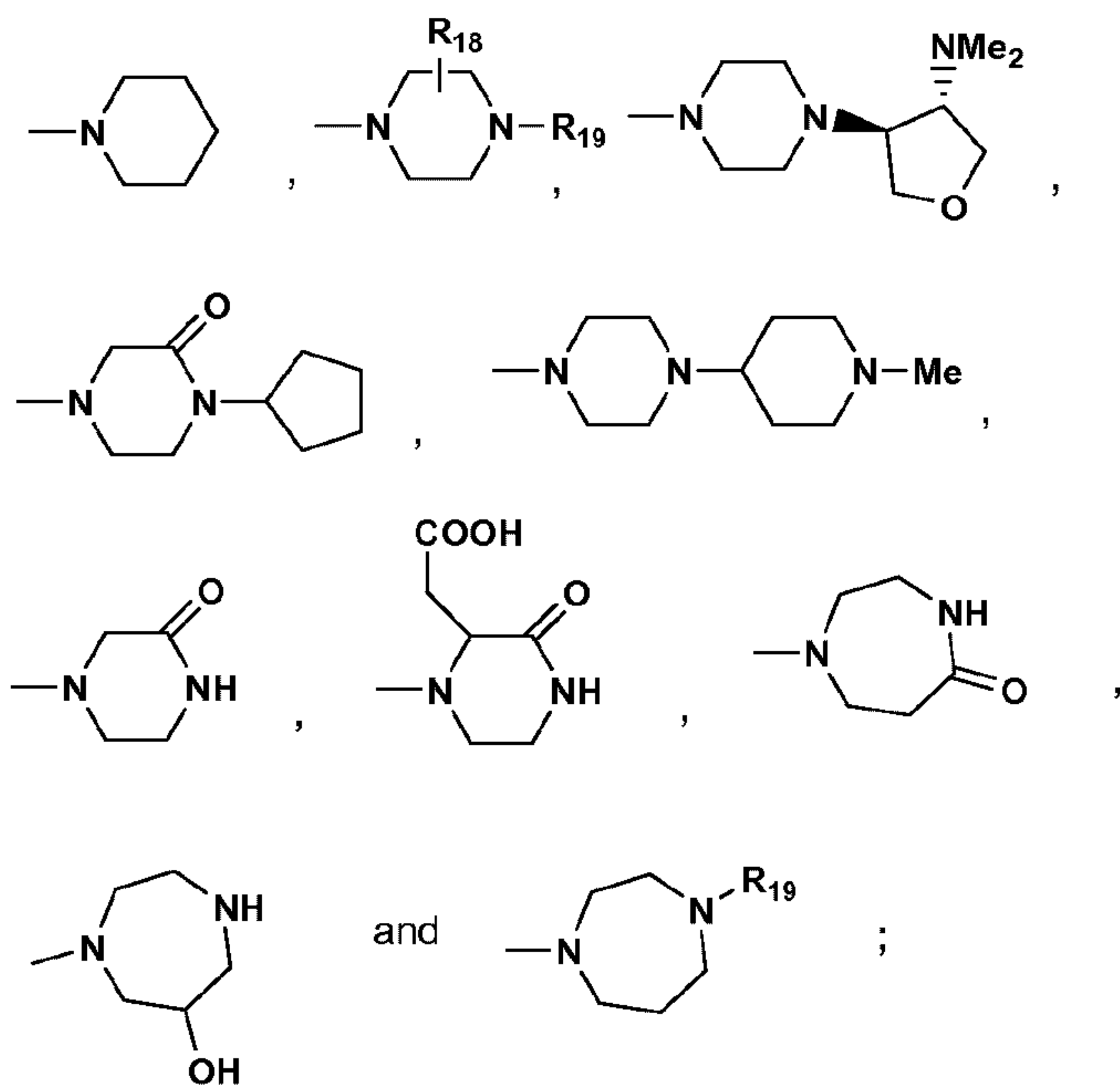
R<sub>8</sub> and R<sub>9</sub> are independently selected from the group of -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C<sub>1-6</sub> alkyl-Q<sub>2</sub>, and -COOR<sub>3</sub>,

and R<sub>8</sub> and R<sub>9</sub> can also be independently selected from the group of





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;

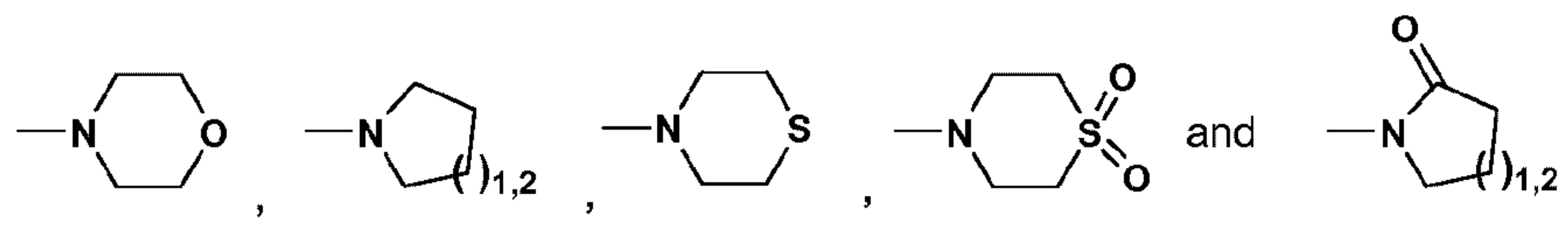
$R_{18}$  is selected from the group of  $-COOR_2$  and  $-C_{1-6}$  alkyl- $COOR_2$ ;

$R_{19}$  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

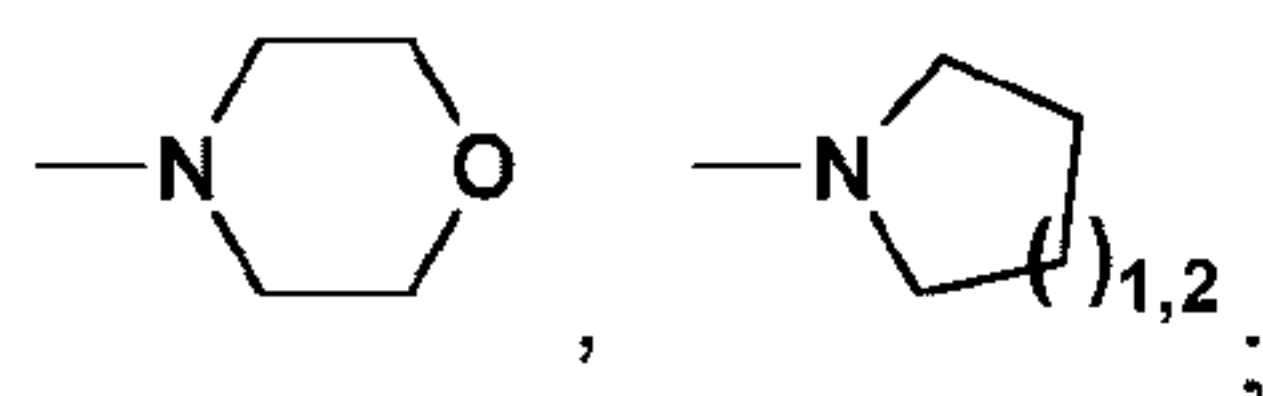


with the proviso that only one of  $R_{20}$  or  $R_{21}$  can be  $-COR_3$ ;

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

25

more preferred are compounds of Formula I wherein  $X$  is a phenyl ring and  $Y$  is in the para position.

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  $-halo$

30

is selected from the group of  $-Cl$ ,  $-F$  and  $-Br$ , with  $-F$  being more preferred. It is even more preferred that  $A$  is  $-H$ .

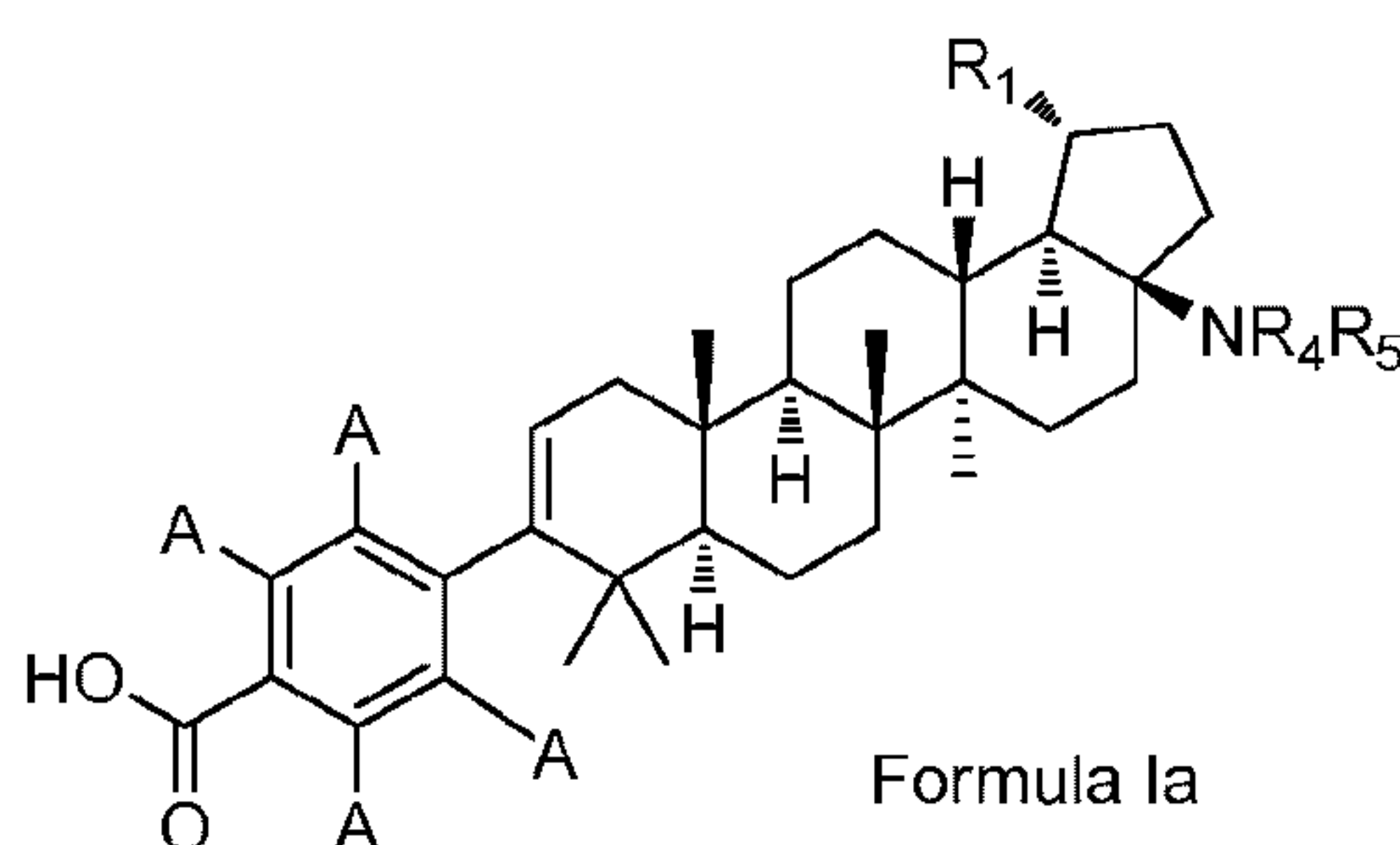
Also preferred are compounds of Formula I wherein Y is  $-\text{COOR}_2$ , and more preferably  $-\text{COOH}$ .

Also preferred are compounds wherein  $\text{R}_4$  is selected from the group of  $-\text{H}$ ,  
 5  $-\text{C}_{1-6}$  alkyl,  $-\text{C}_{1-6}$  alkyl- $\text{Q}_1$ , and  $-\text{COR}_6$ . Especially preferred are compounds wherein  $\text{R}_4$  is  $-\text{C}_{1-6}$  alkyl- $\text{Q}_1$  or  $-\text{COR}_6$ .

It is also preferred that  $\text{R}_5$  is  $-\text{H}$ .

10 In addition, it is preferred that  $\text{Q}_1$  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:

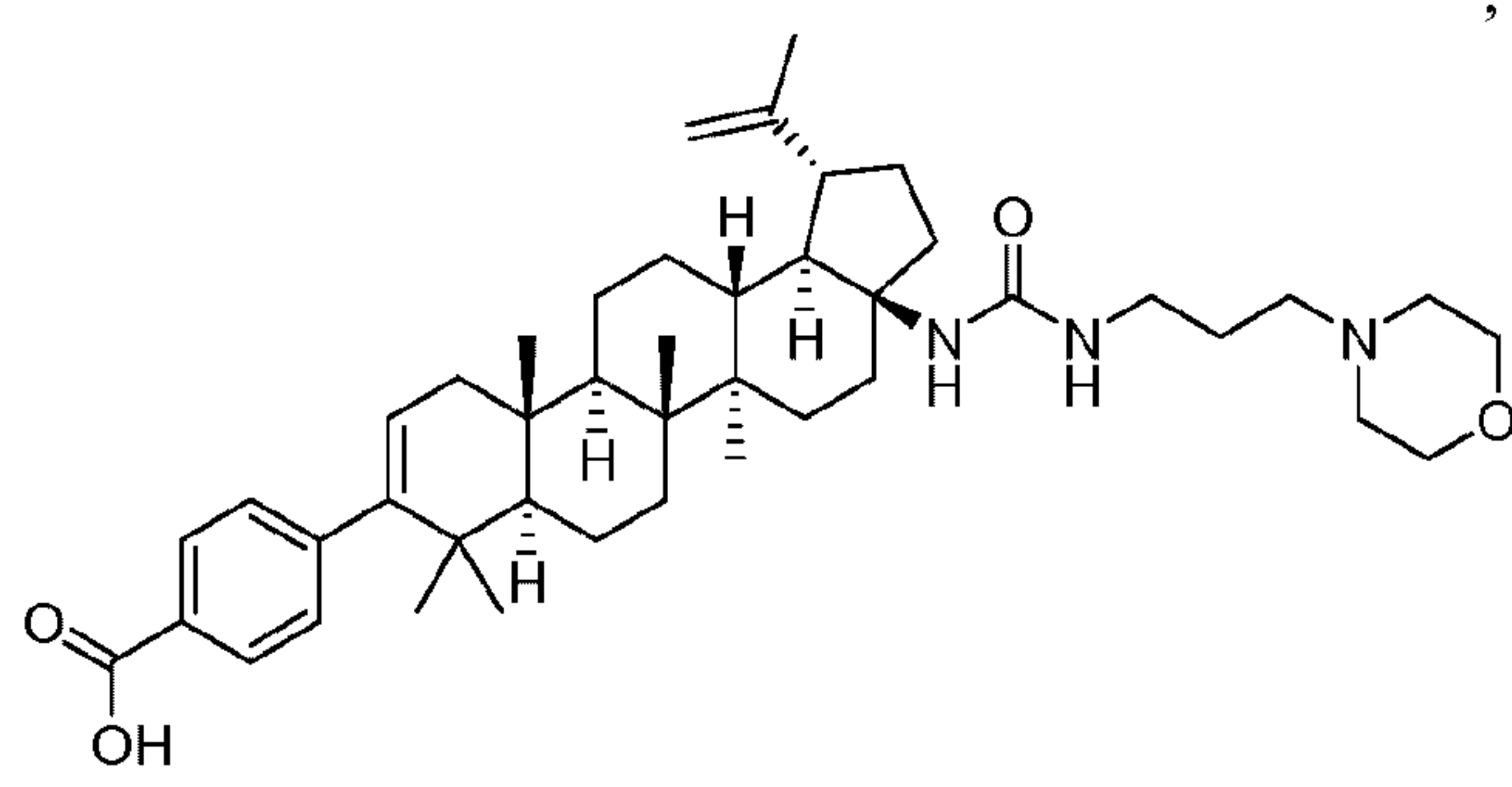
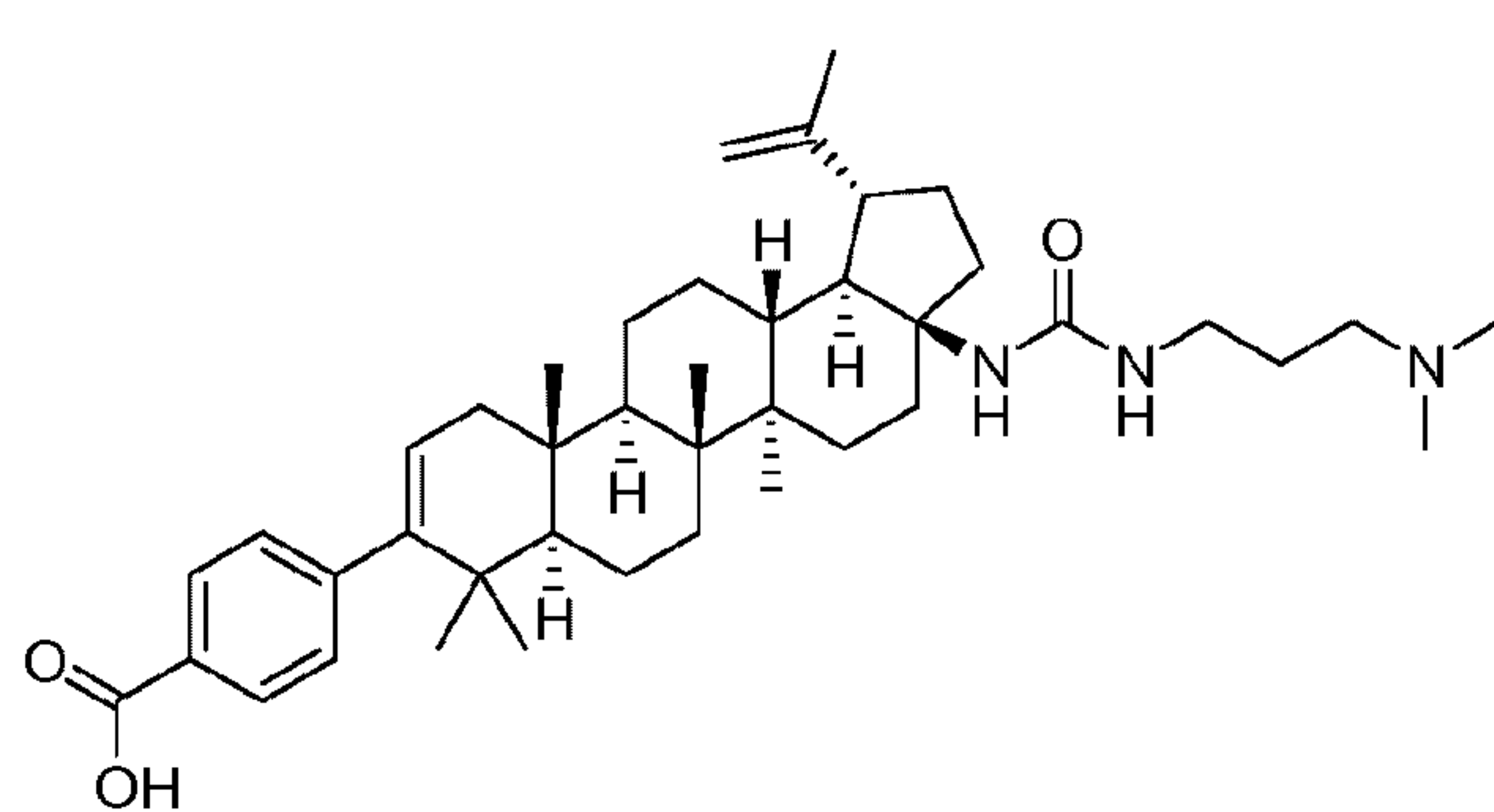
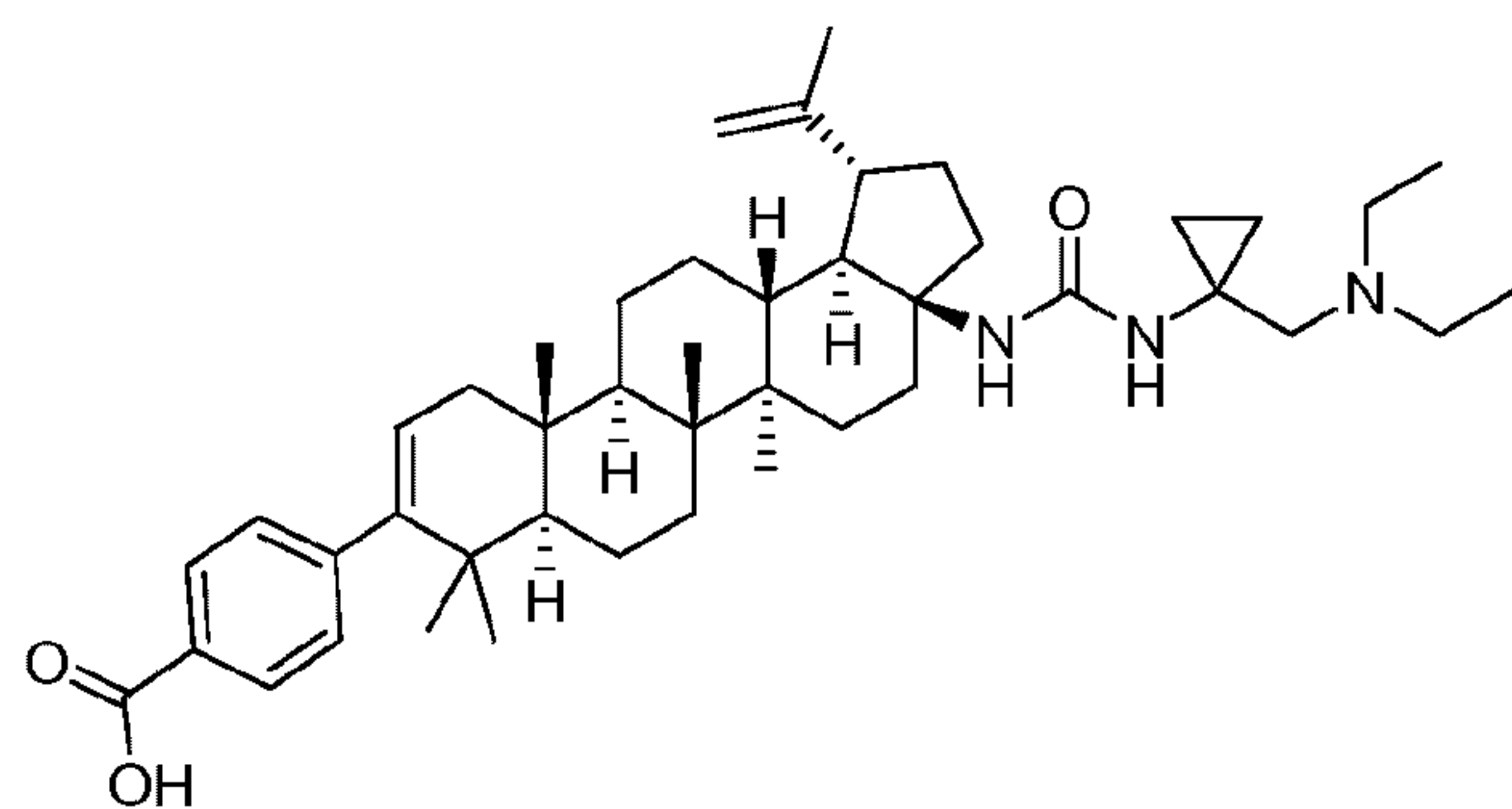
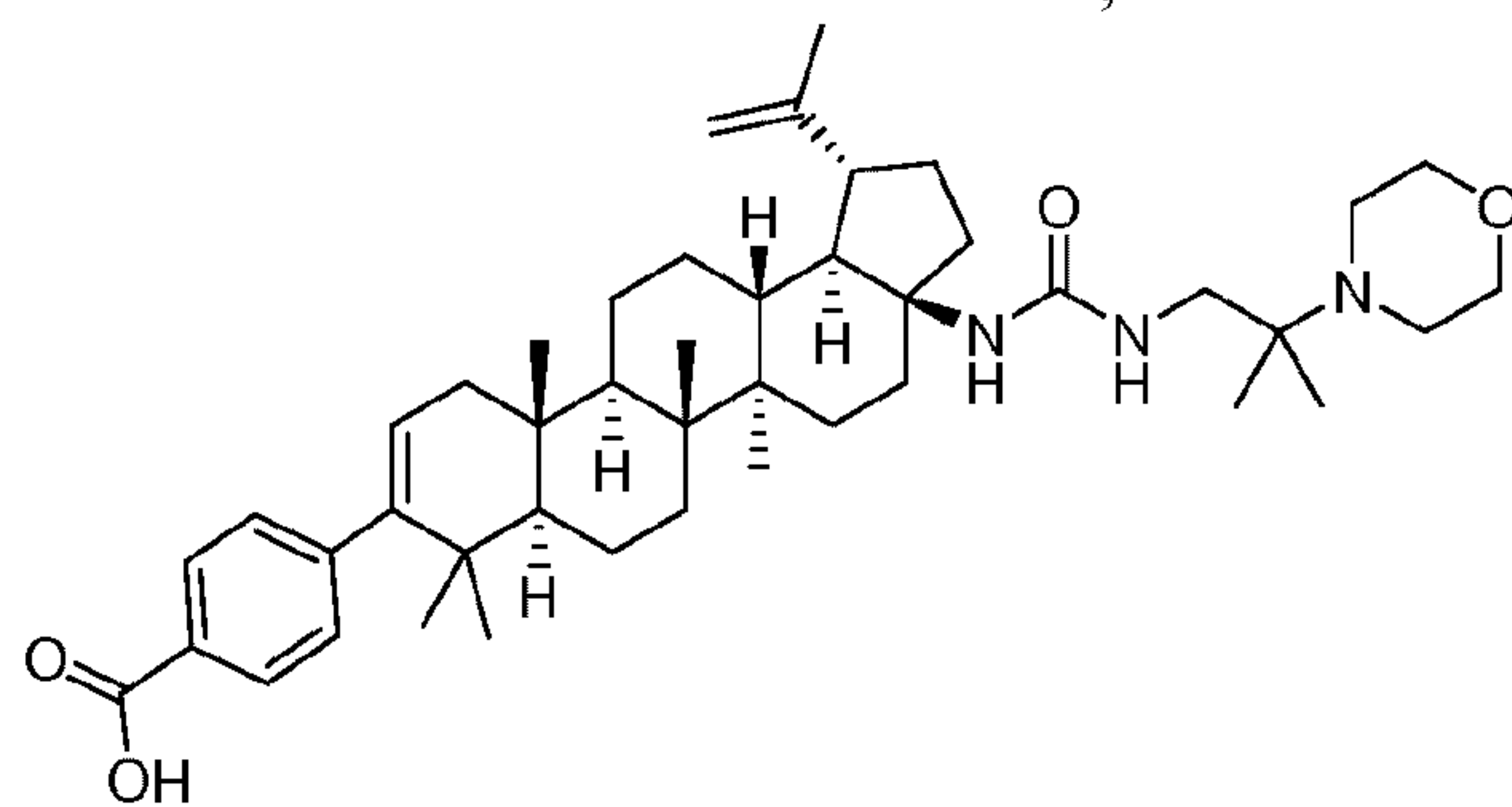
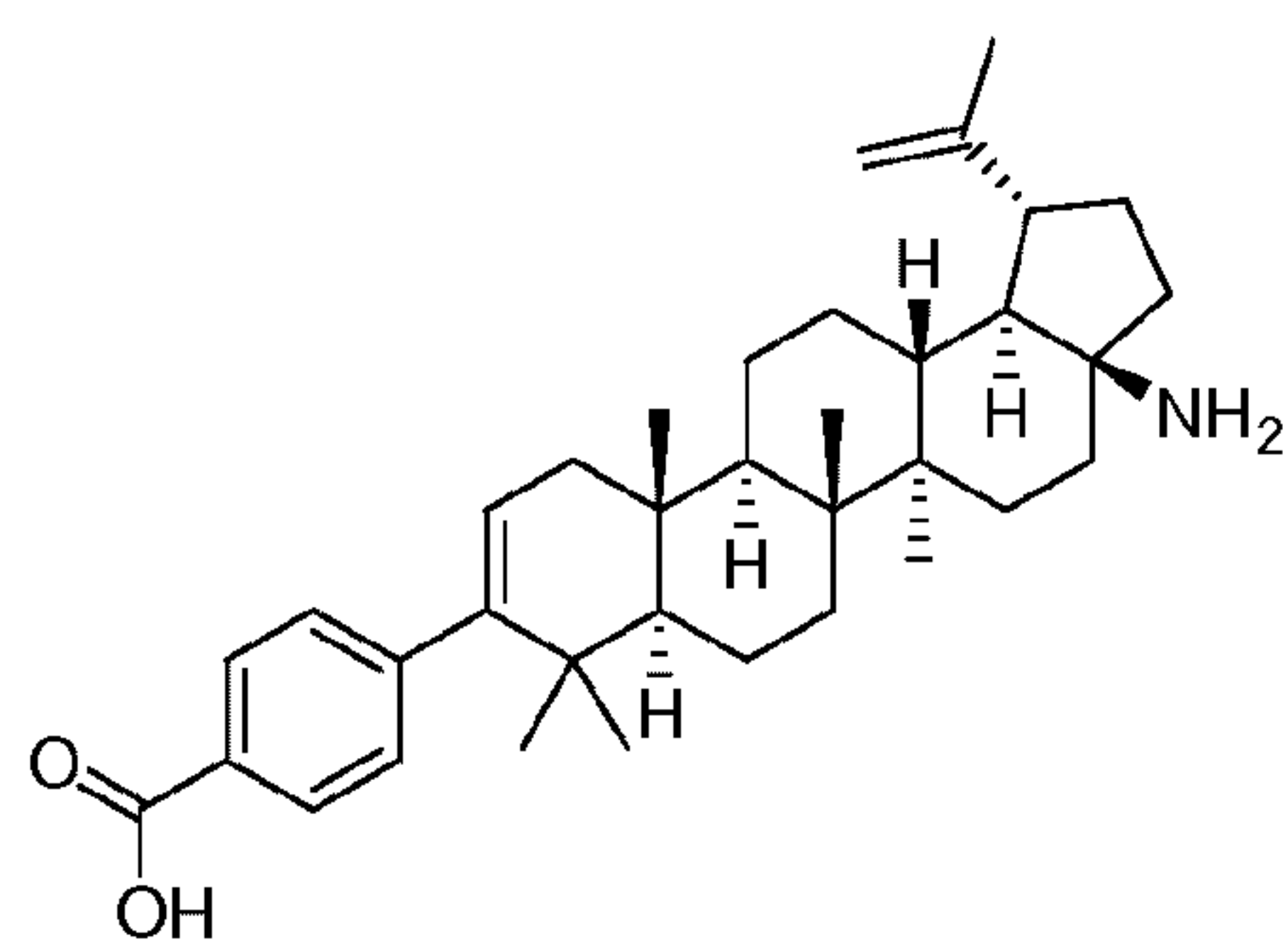


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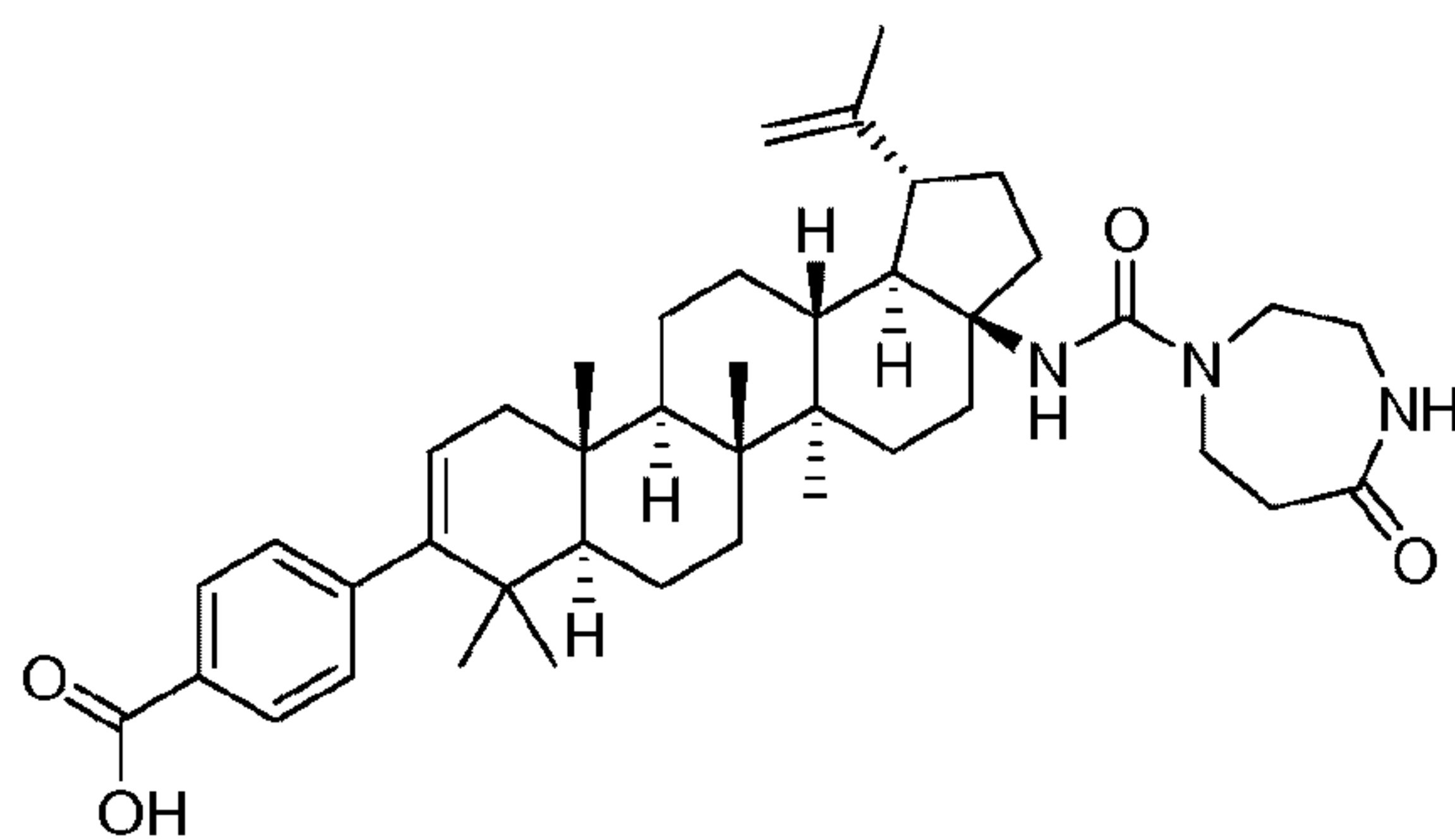
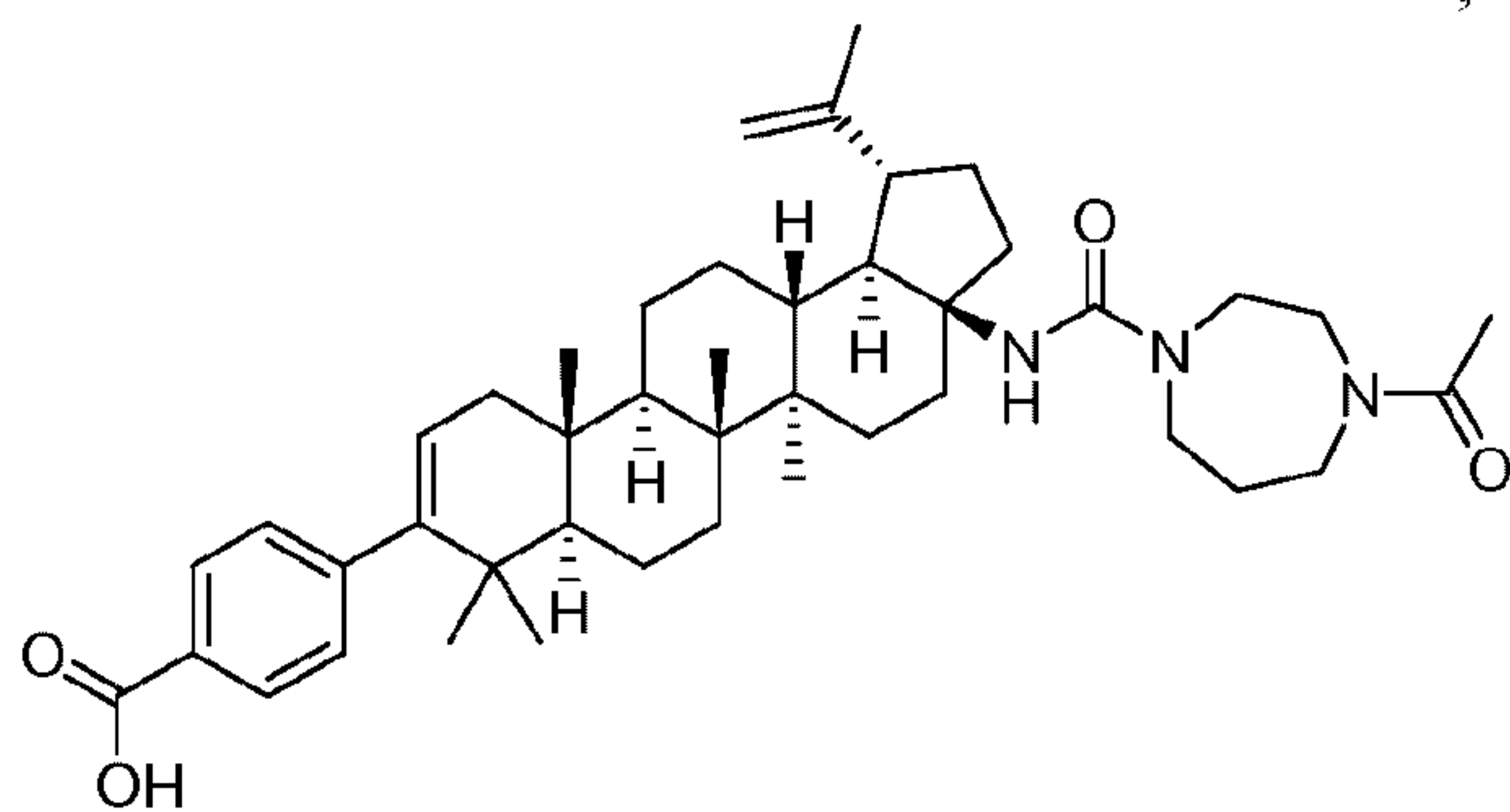
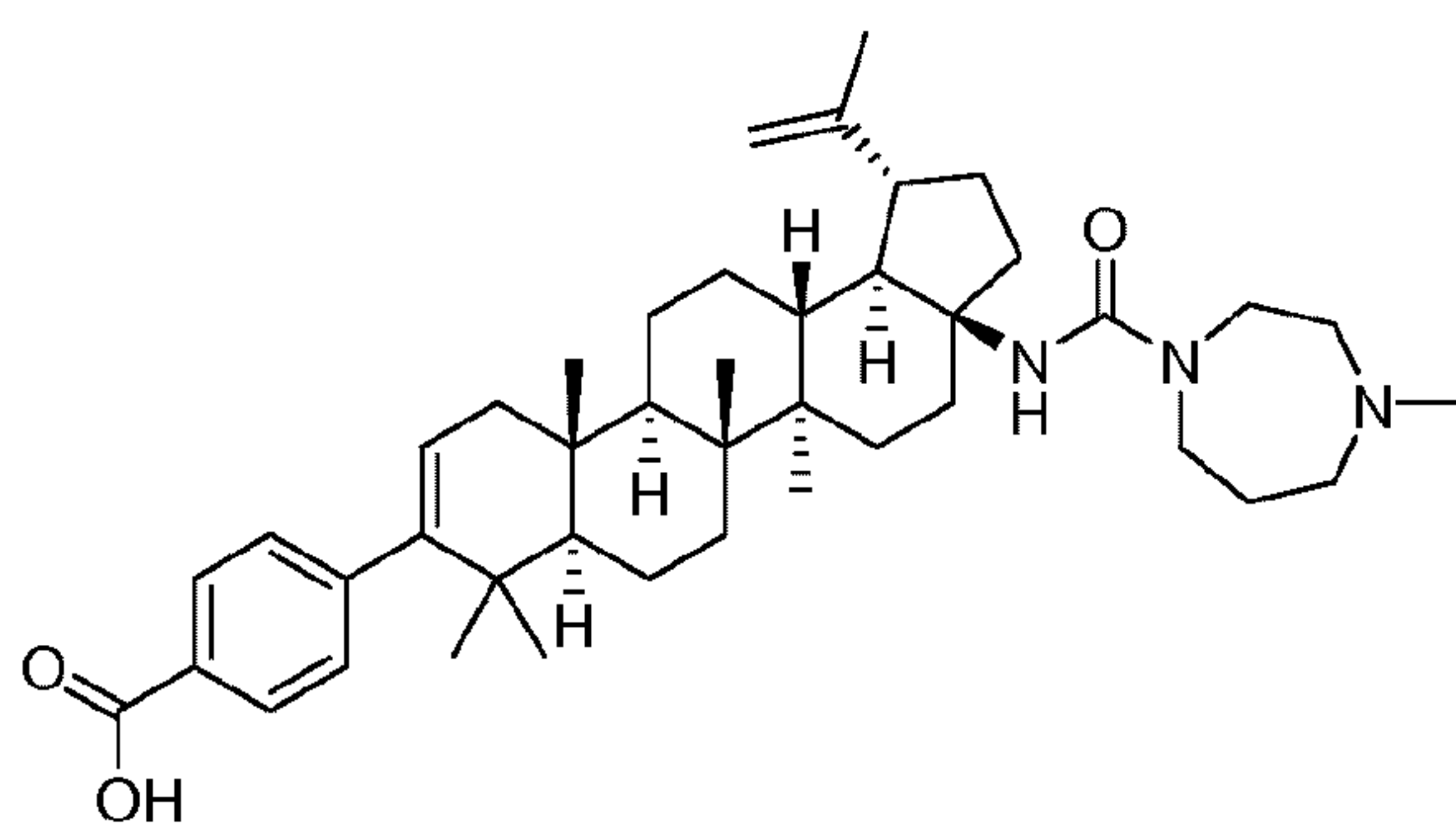
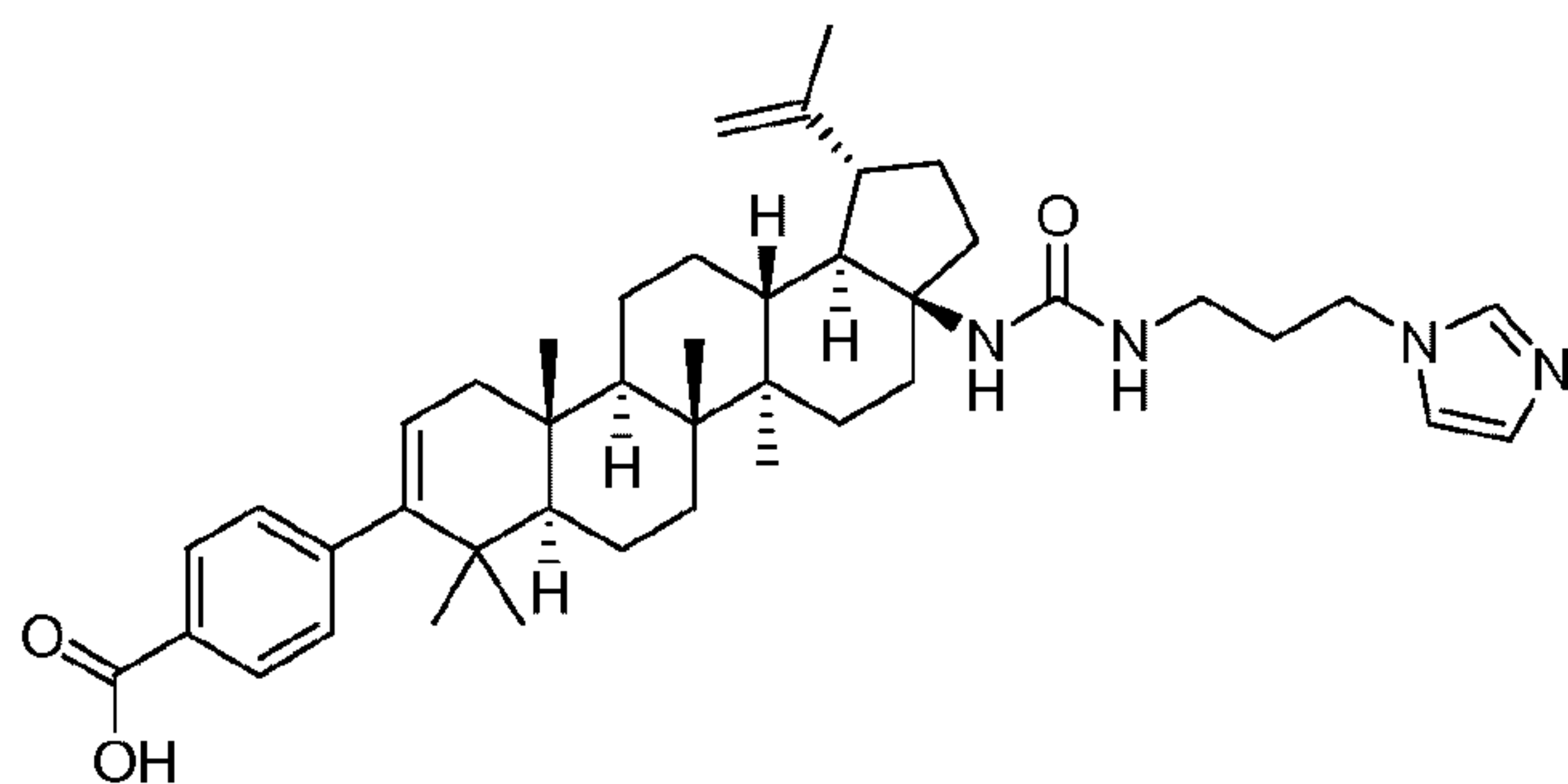
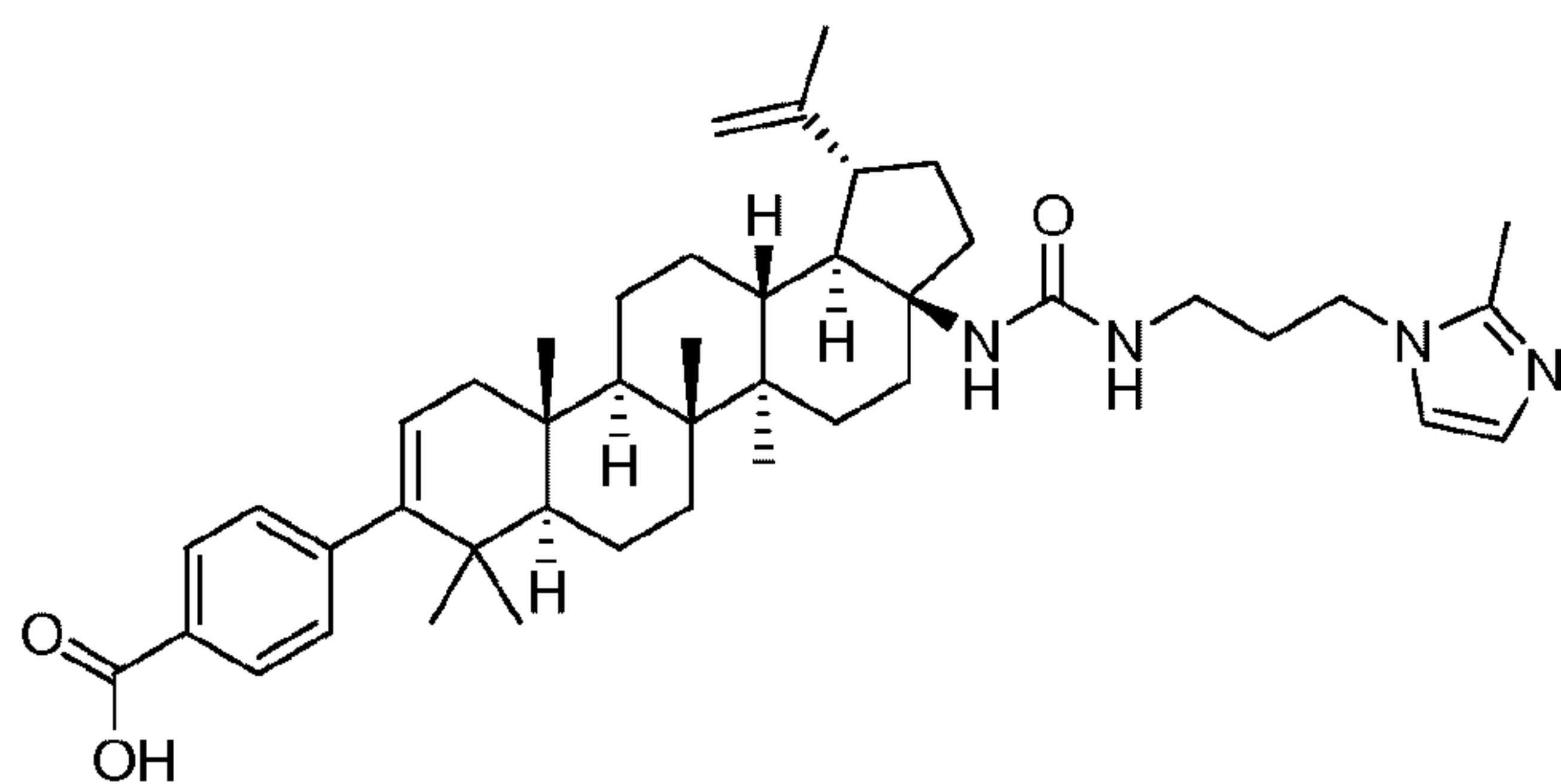
In this embodiment, it is also preferred that A is at least one member selected from the group of  $-\text{H}$ ,  $-\text{halo}$ ,  $-\text{OH}$ ,  $-\text{C}_{1-3}$  alkyl and  $-\text{C}_{1-3}$  alkoxy. It is particularly preferred that A is at least one member selected from the group of  $-\text{H}$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

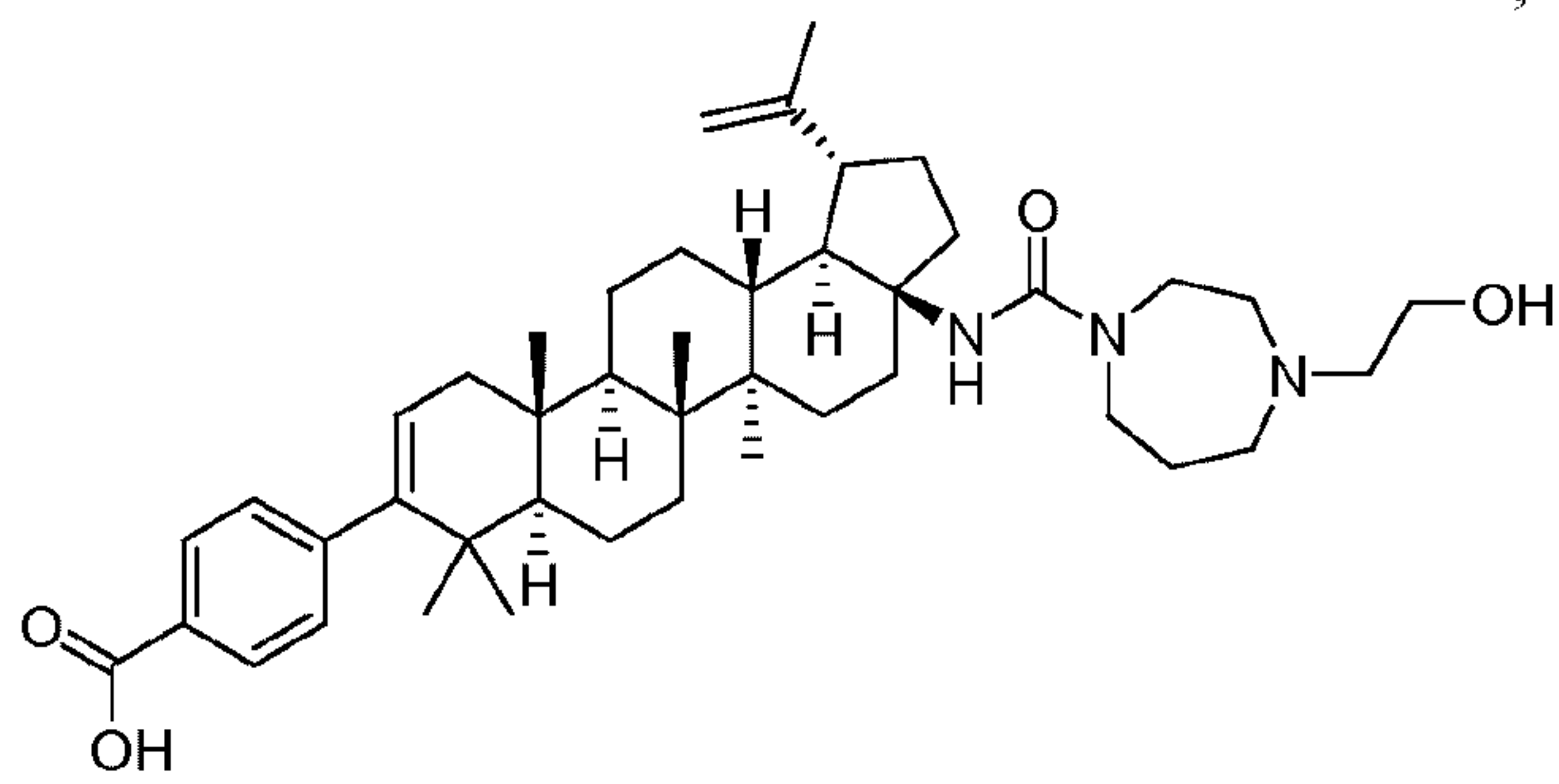
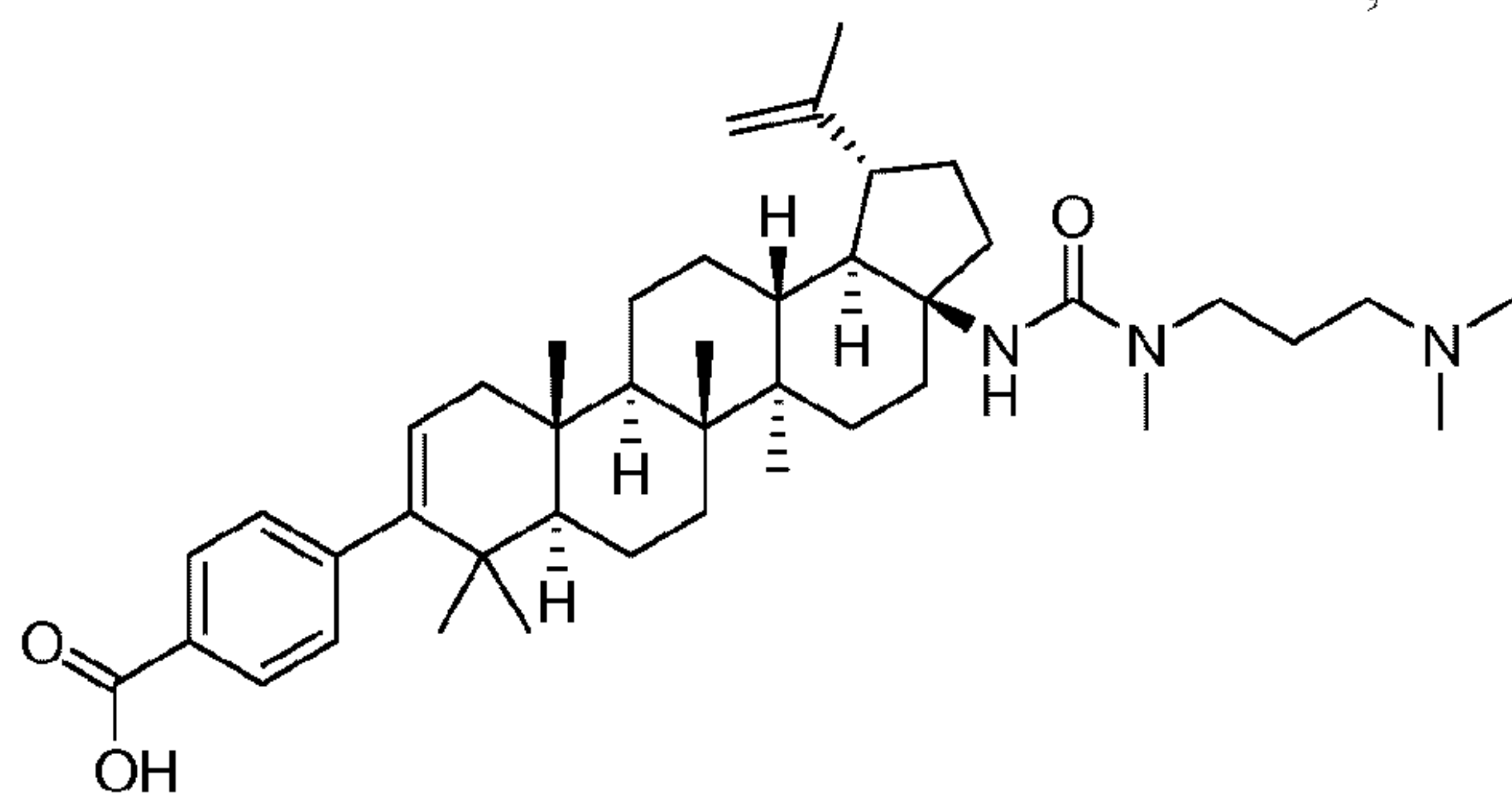
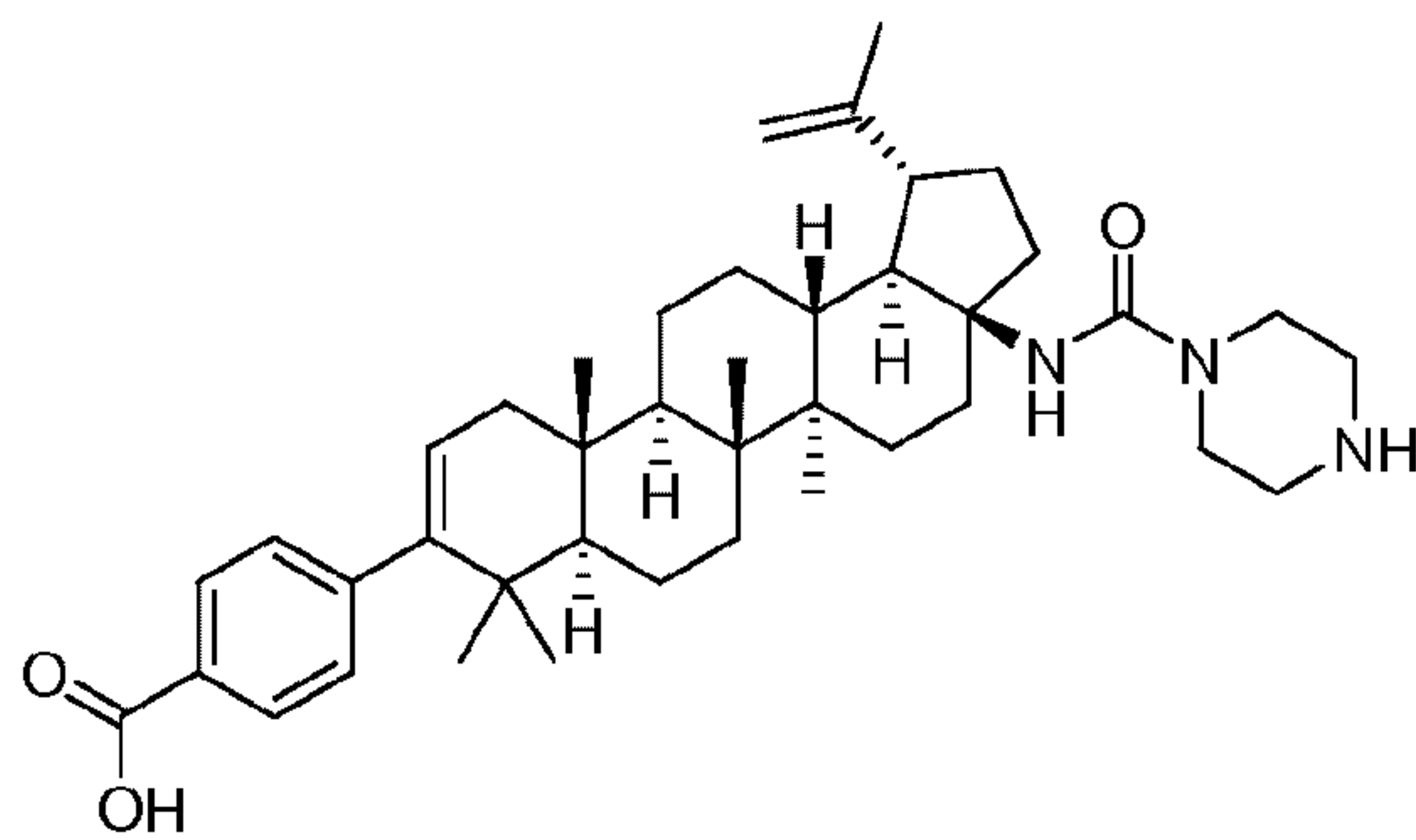
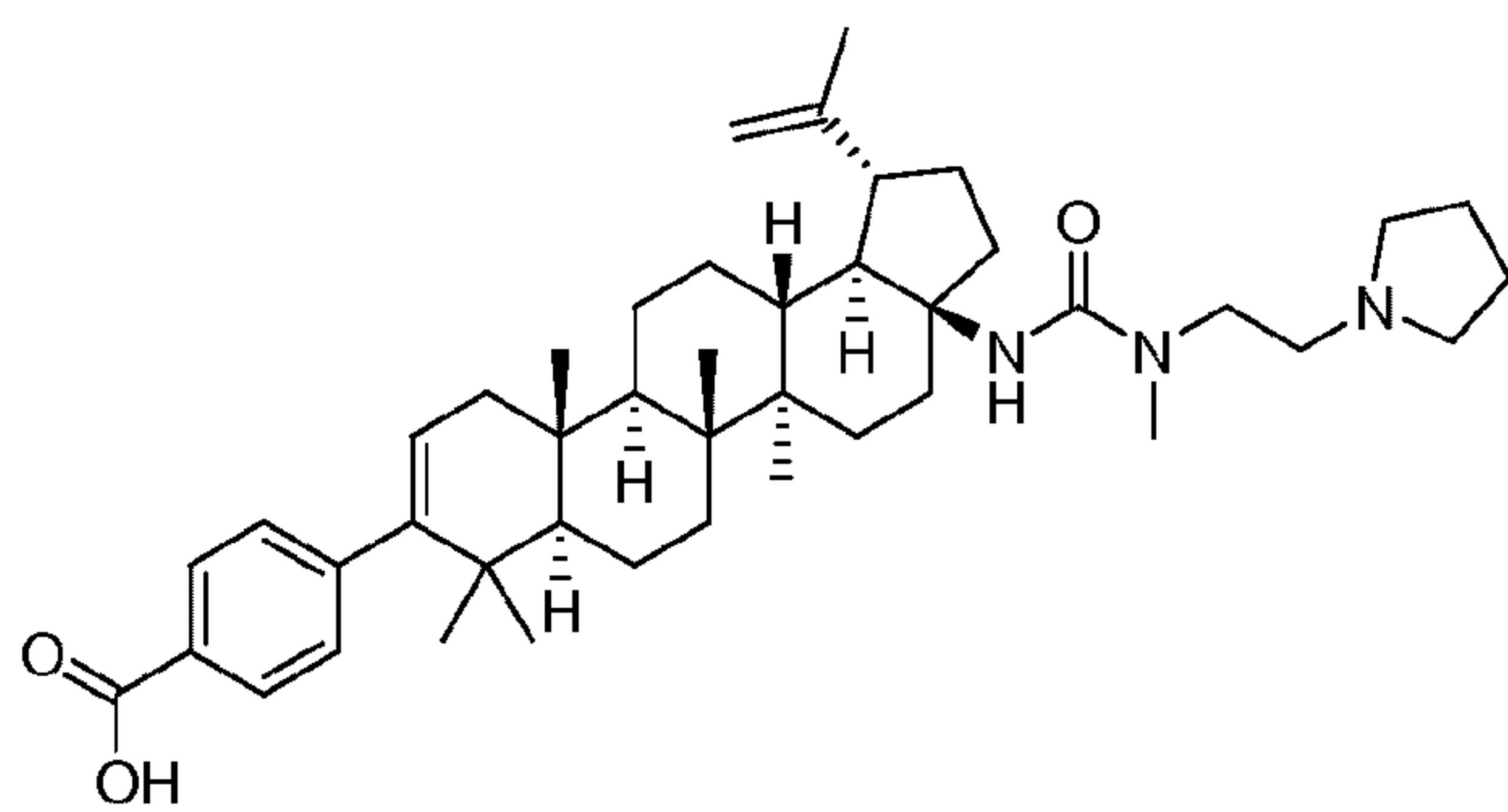
In addition, in a further embodiment of the invention compounds of Formula II are preferred, as are compounds of Formula III.

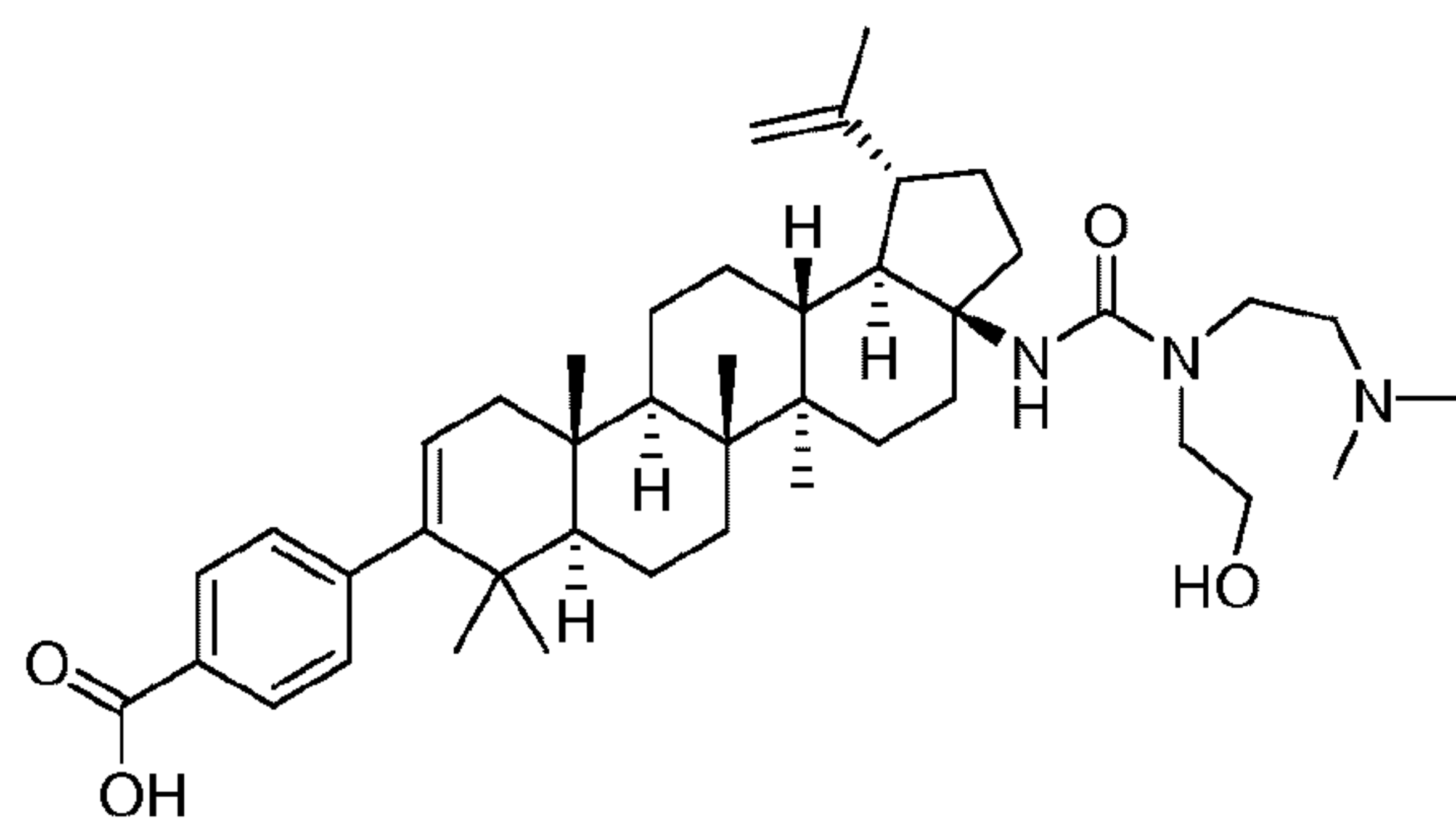
25 Other compounds, including pharmaceutically acceptable salts thereof, which are preferred as part of the invention include the following:



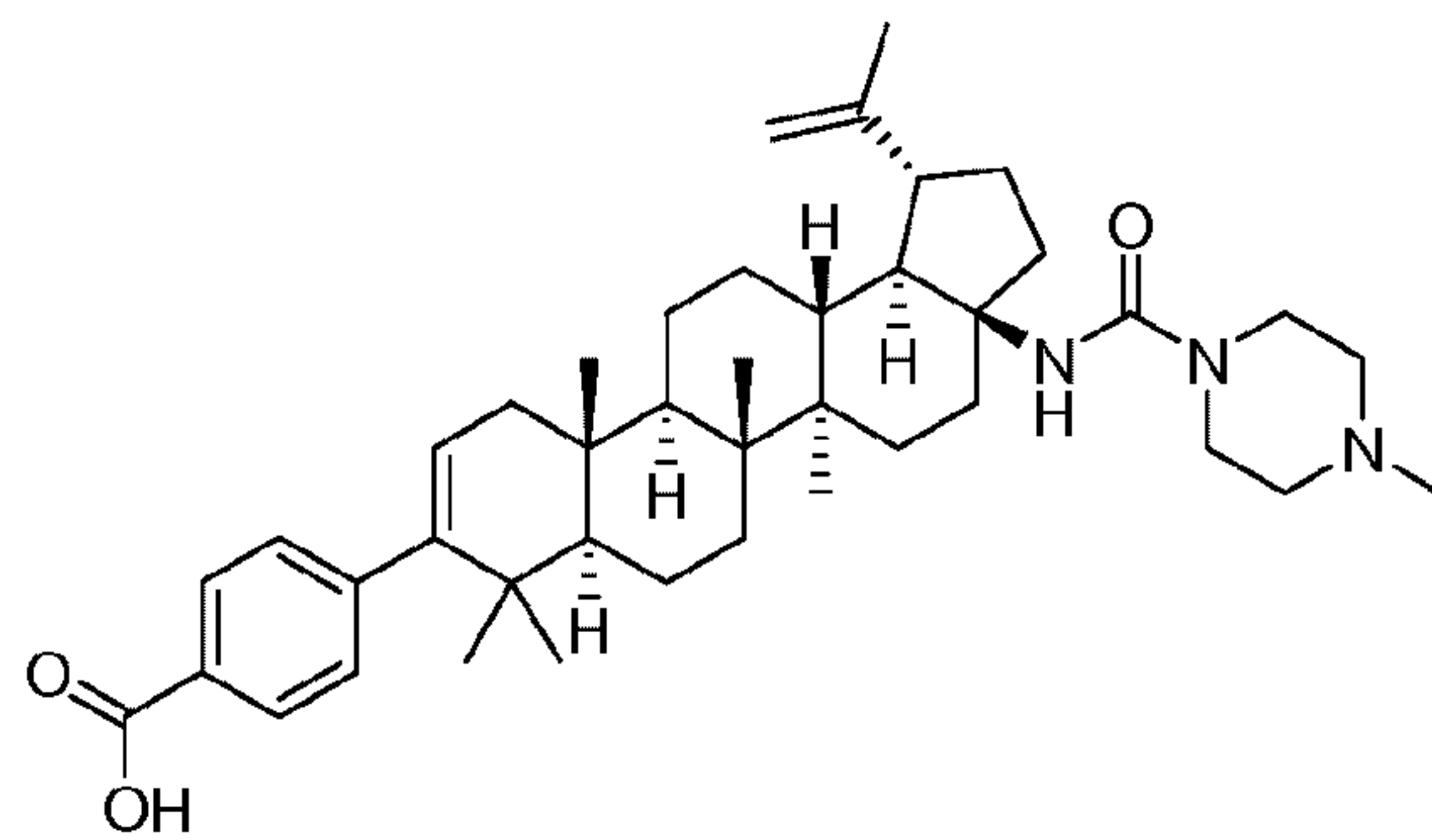
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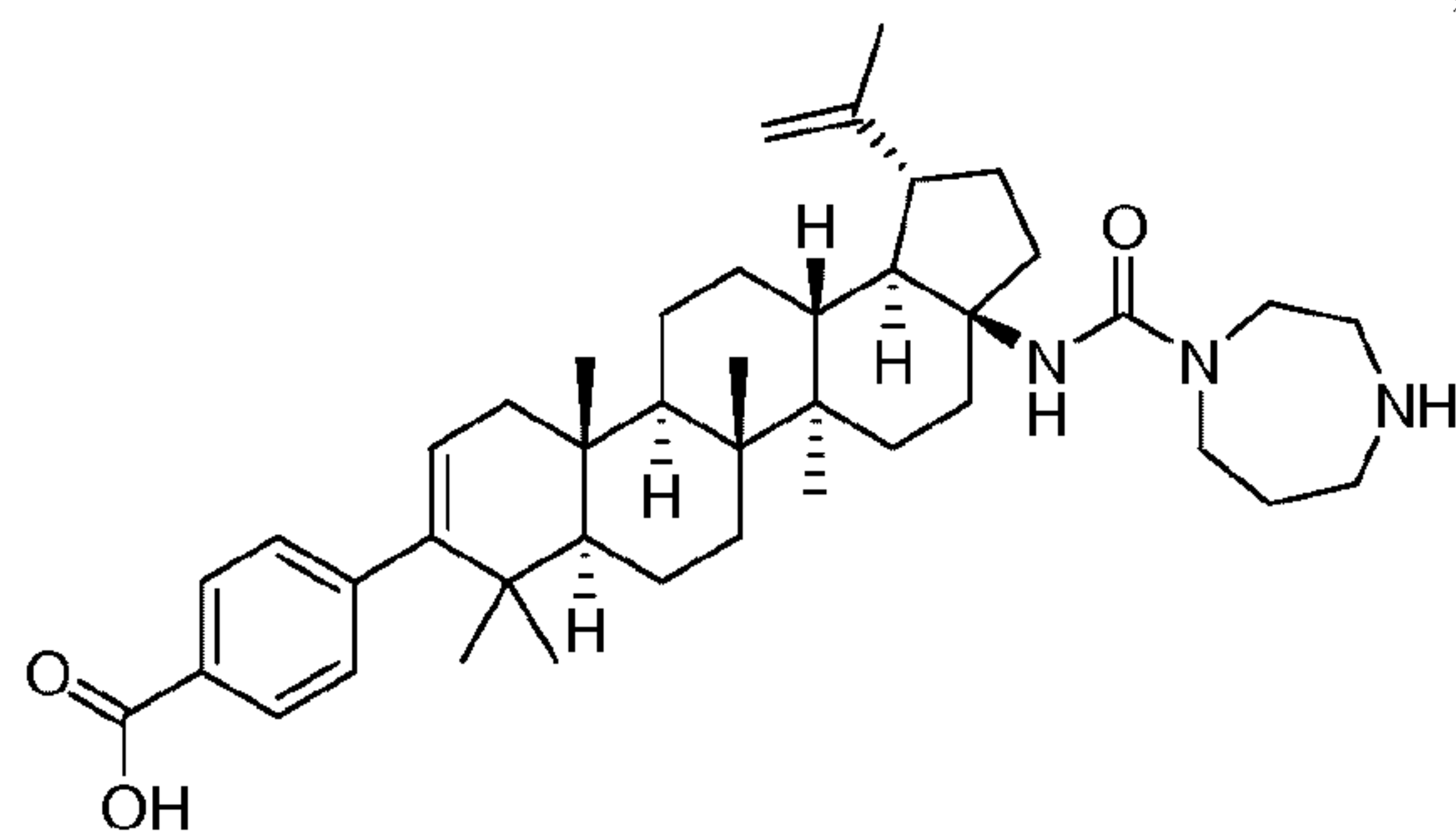




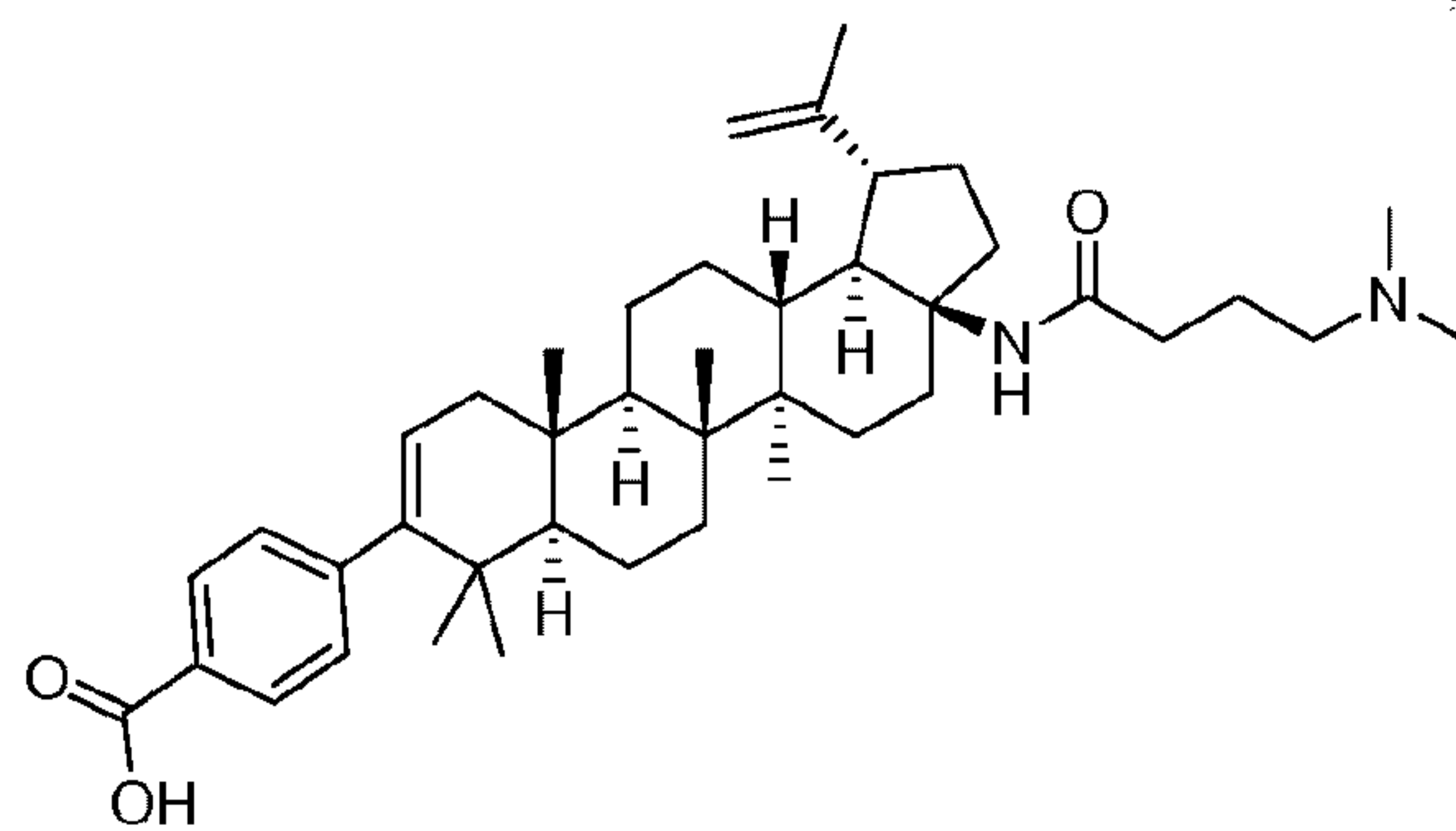
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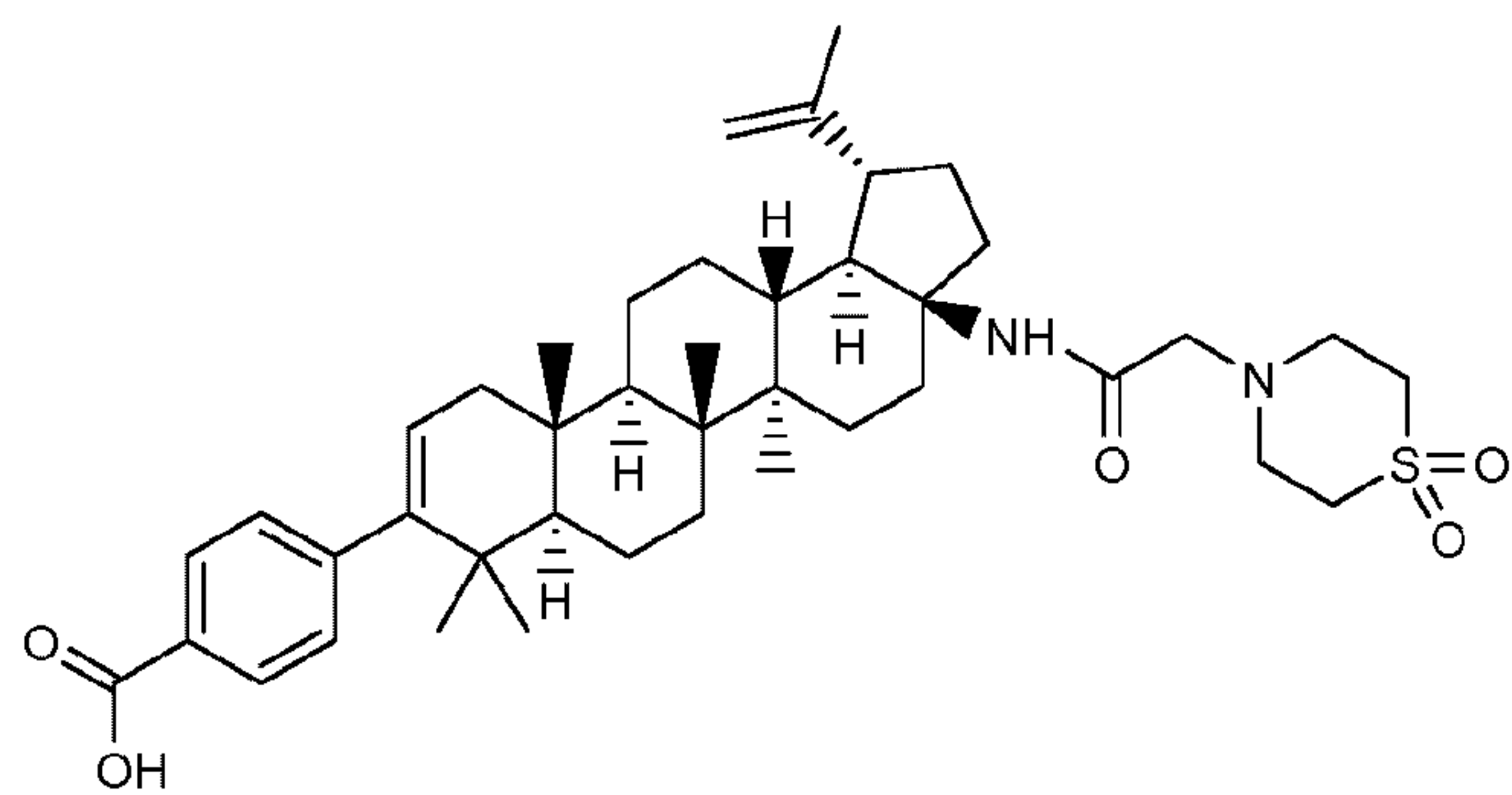
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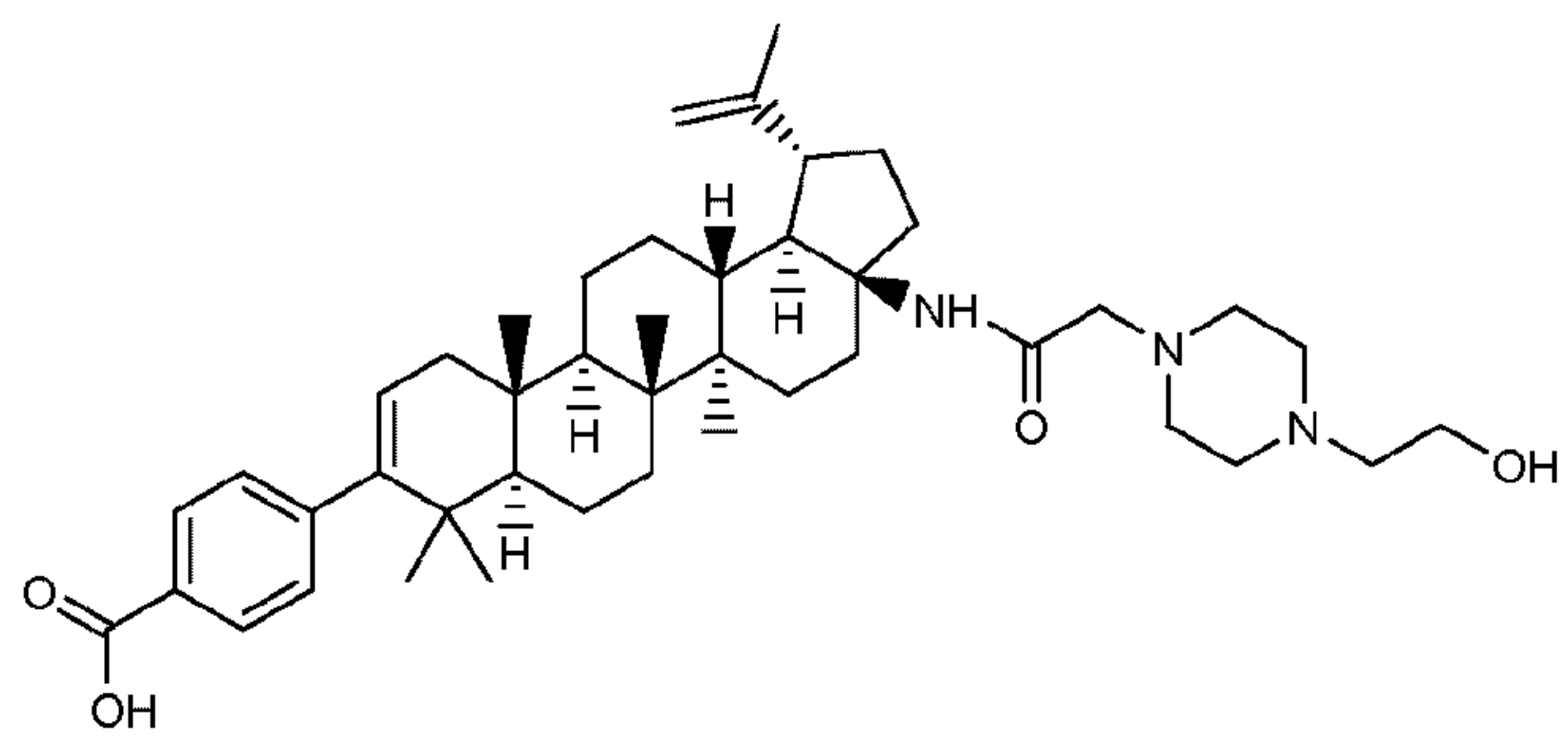
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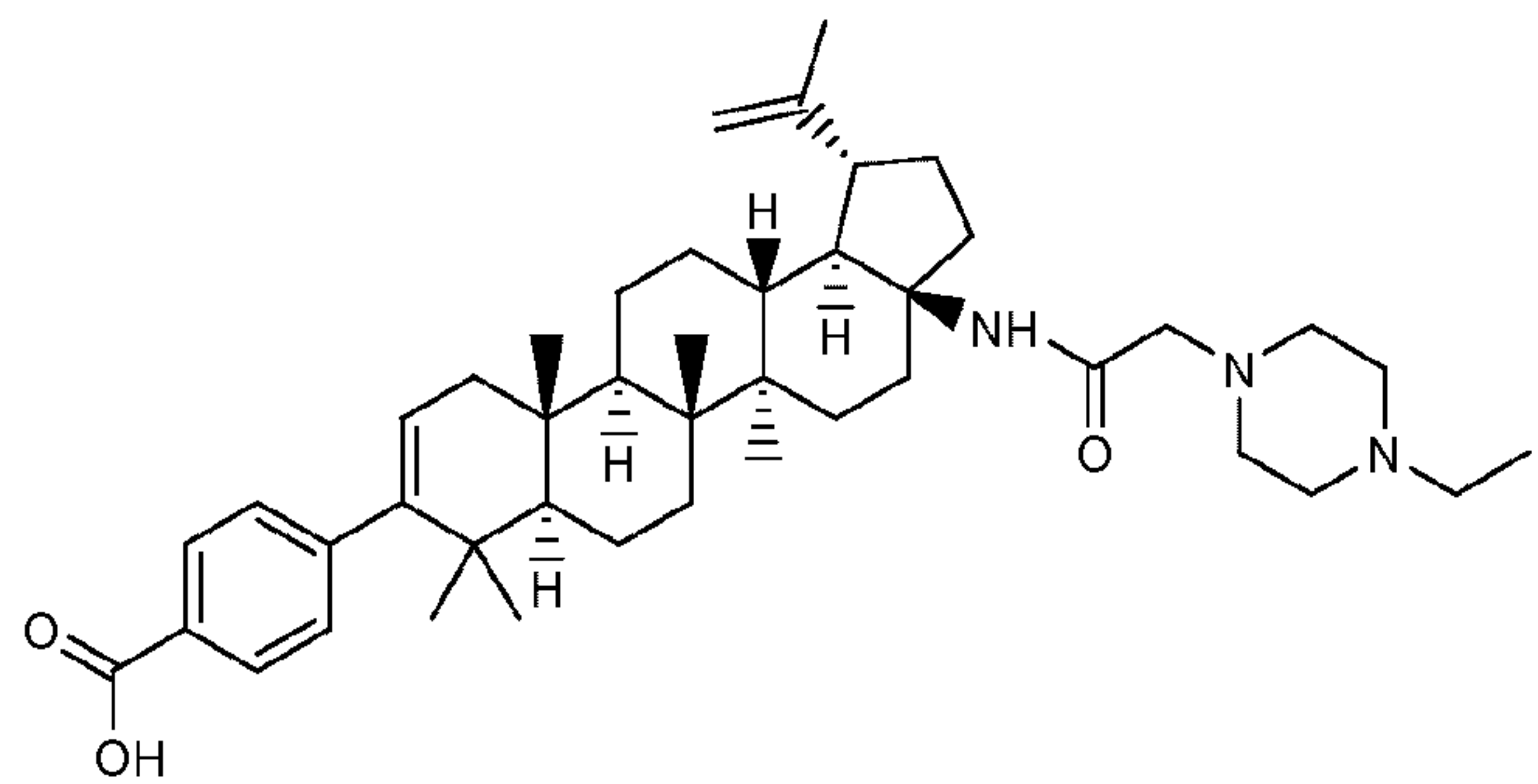
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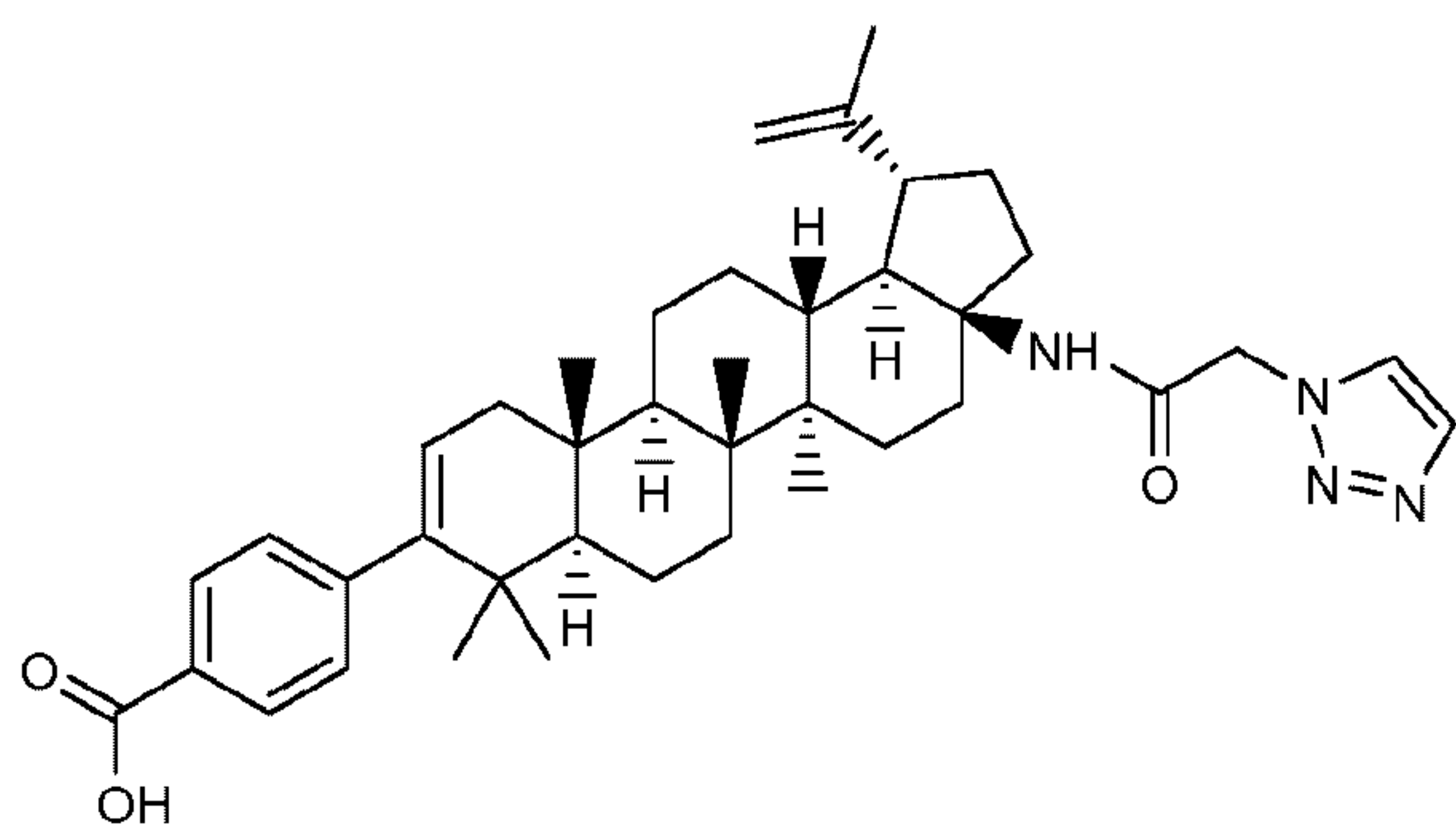


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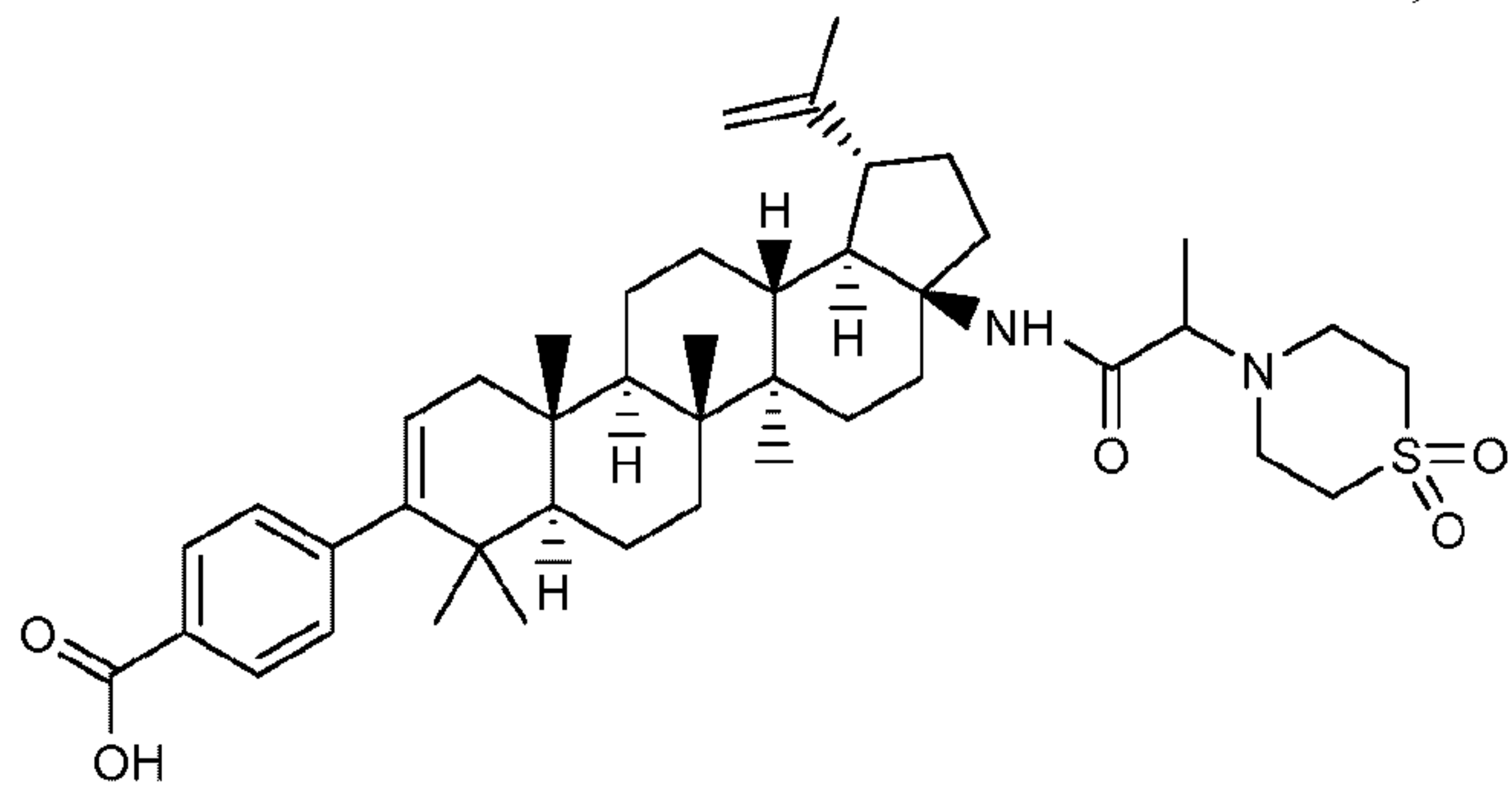


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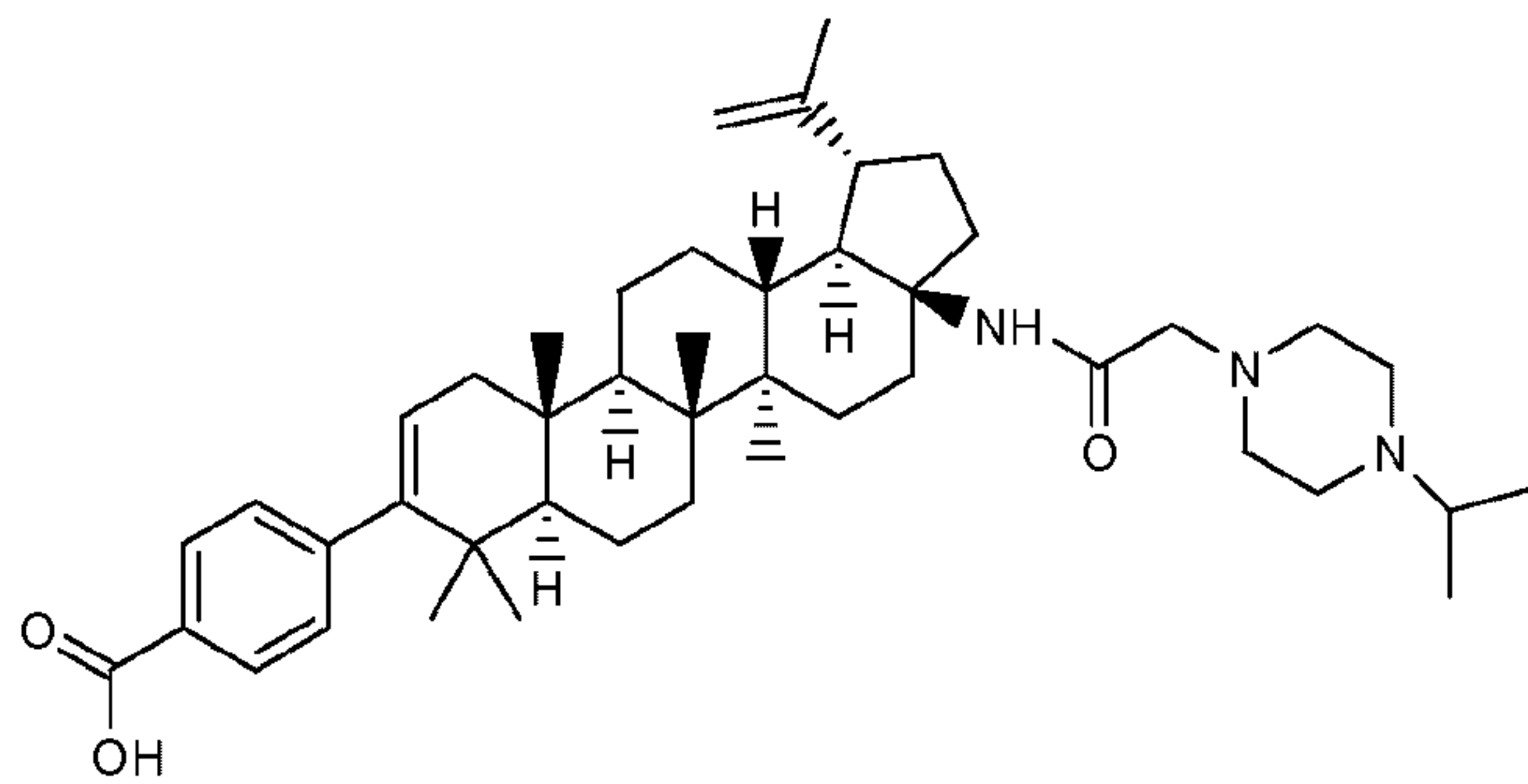
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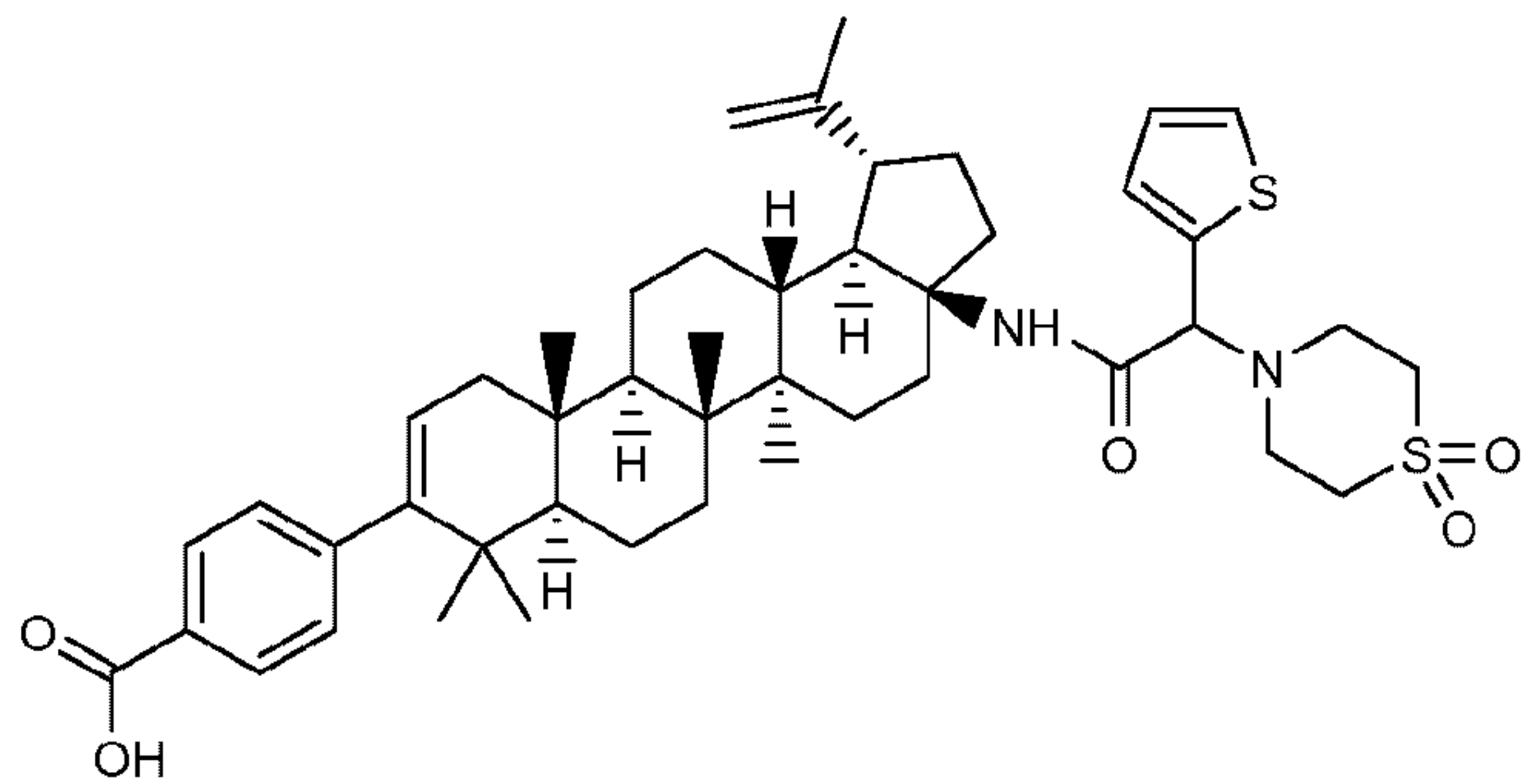
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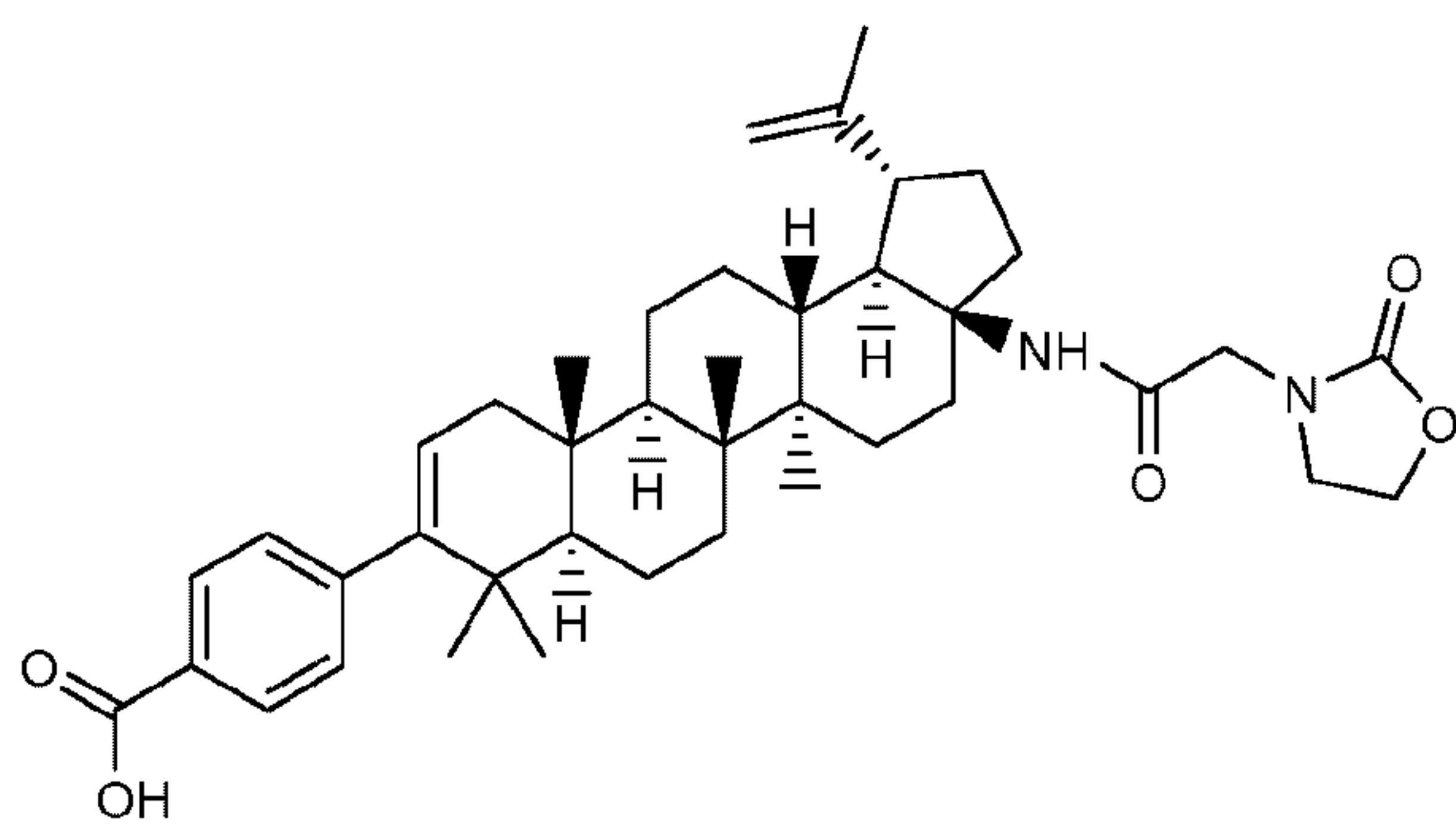
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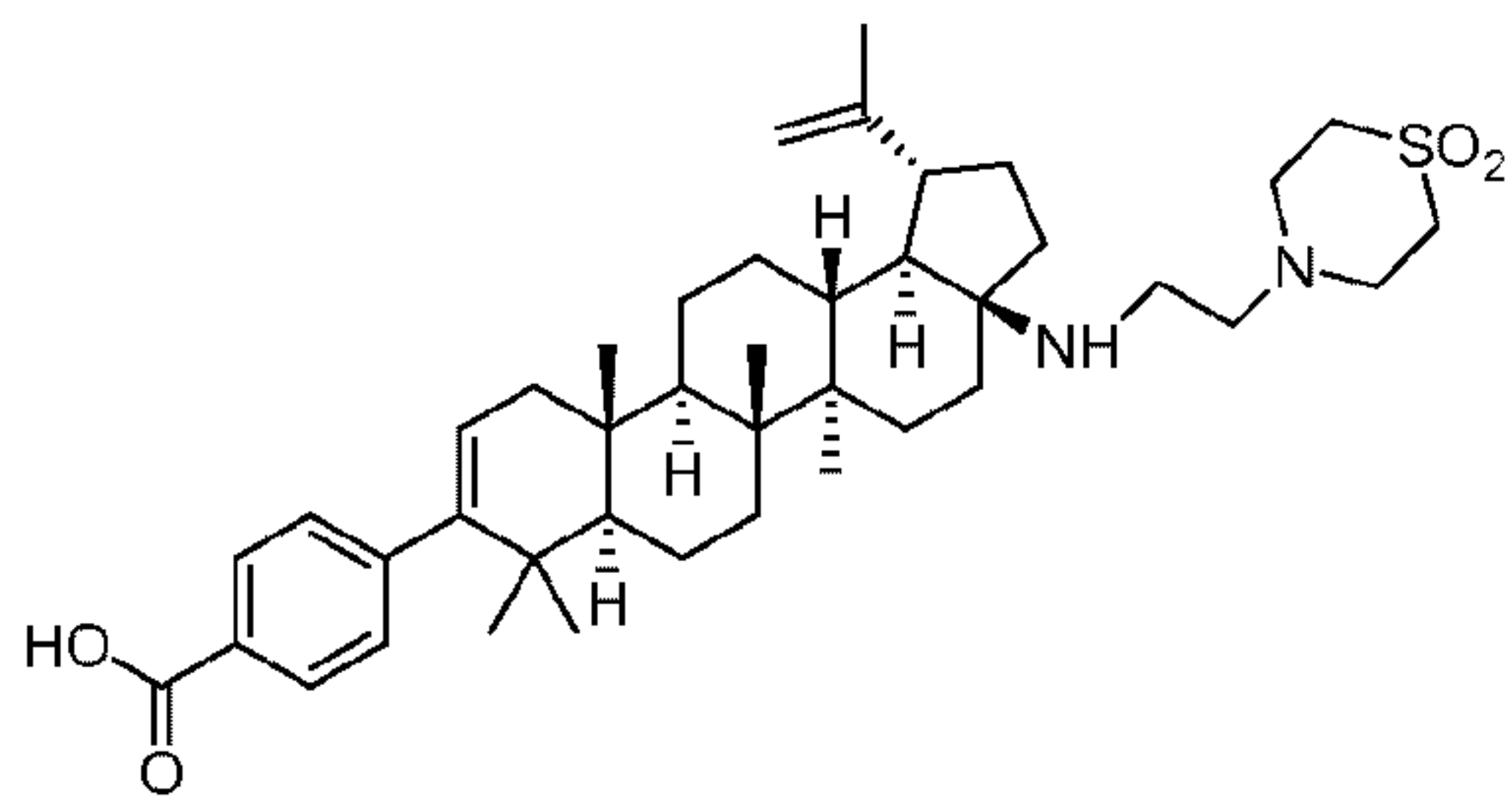
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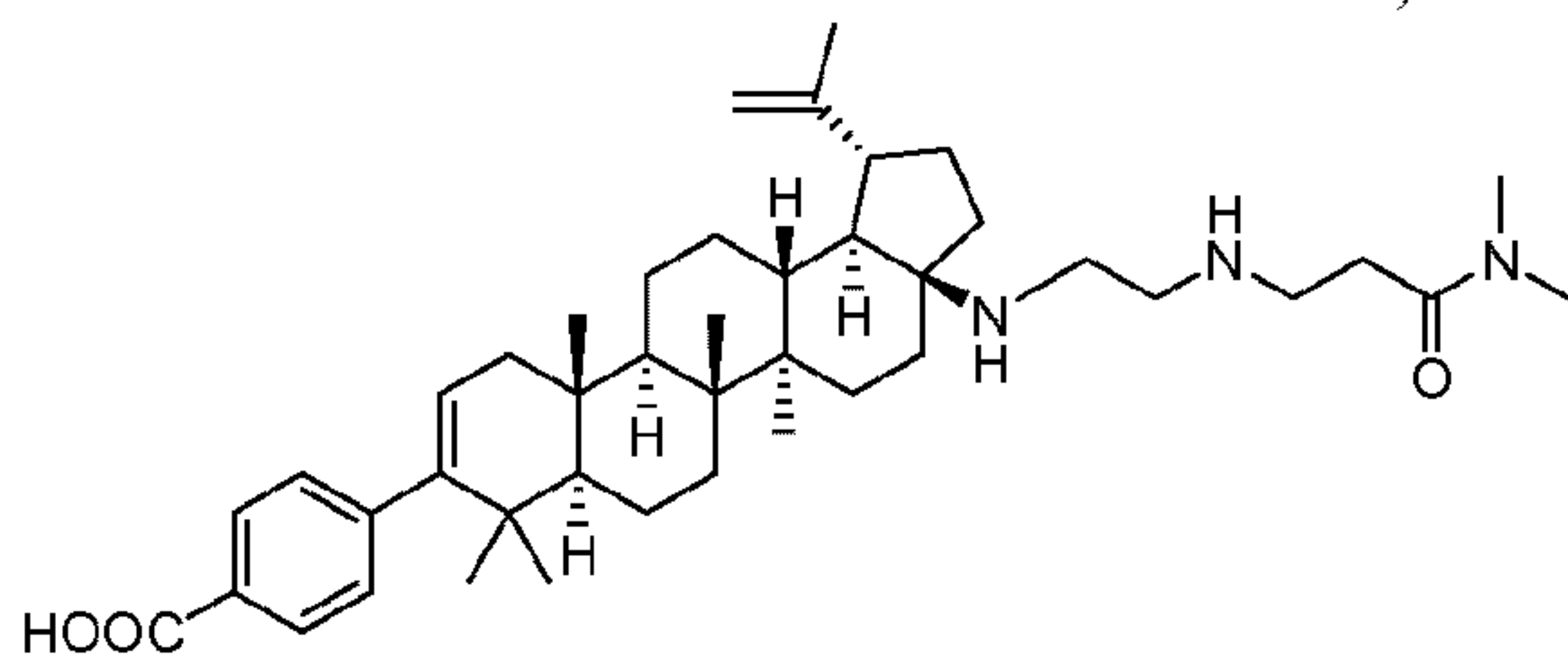
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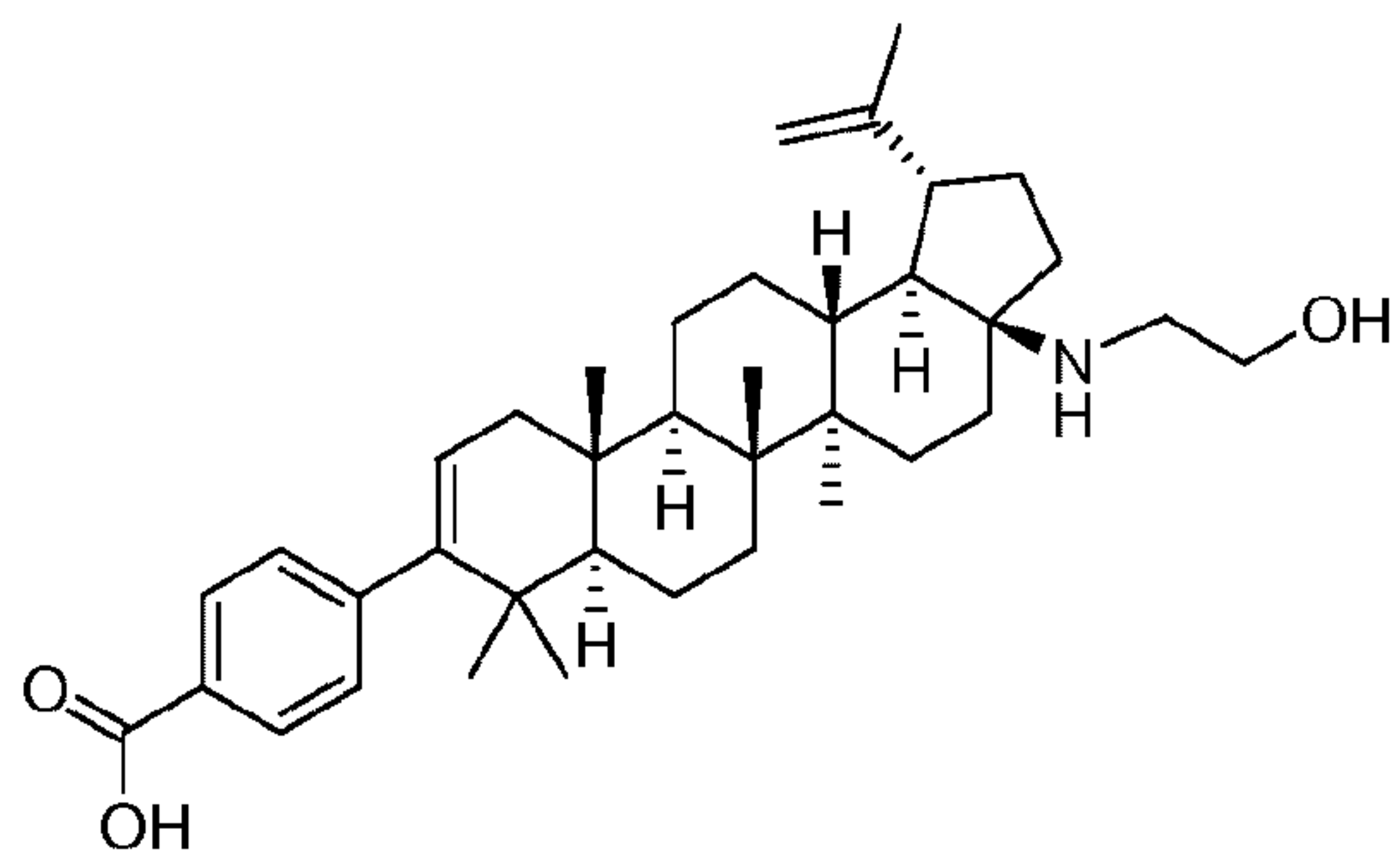
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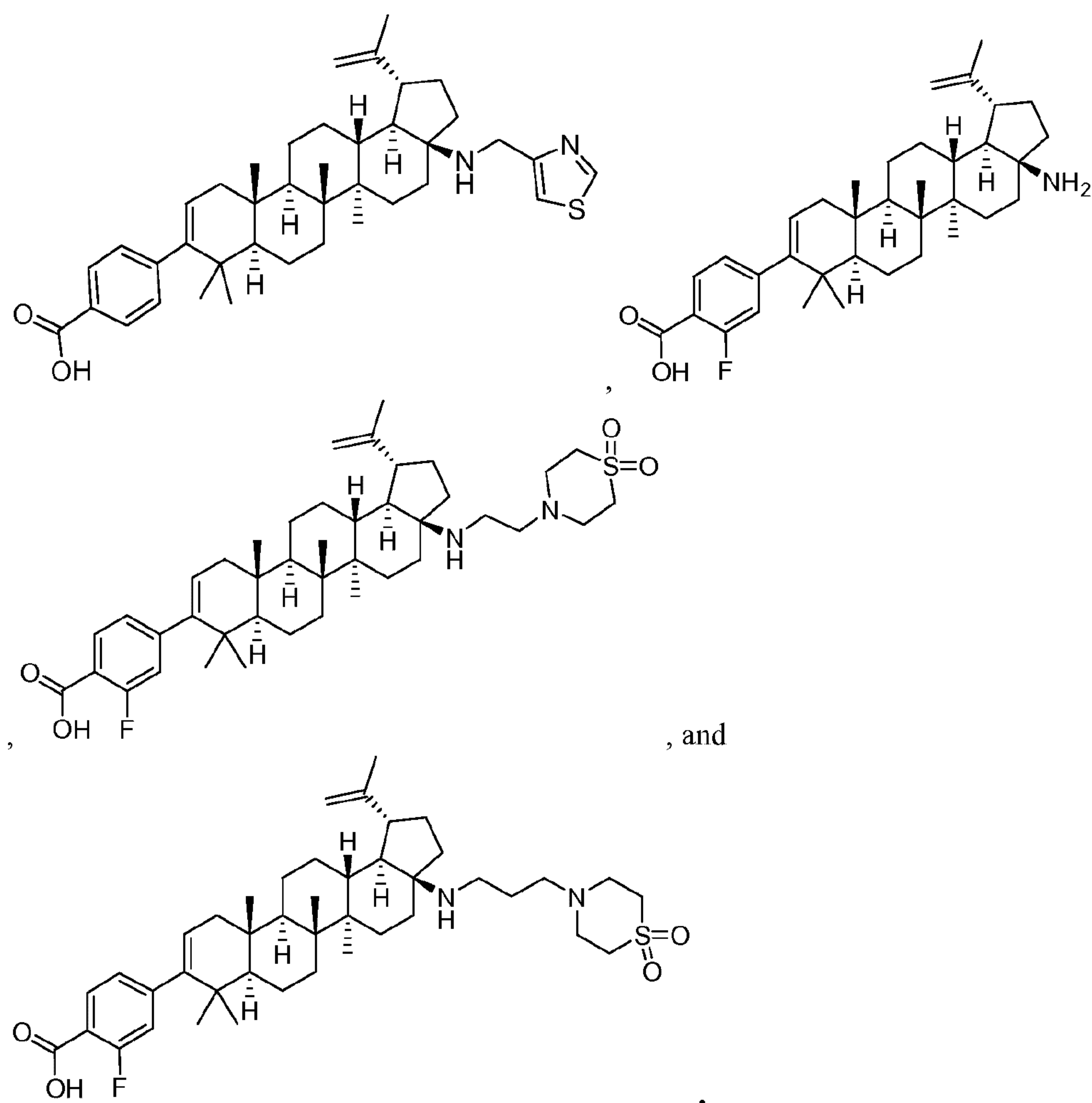
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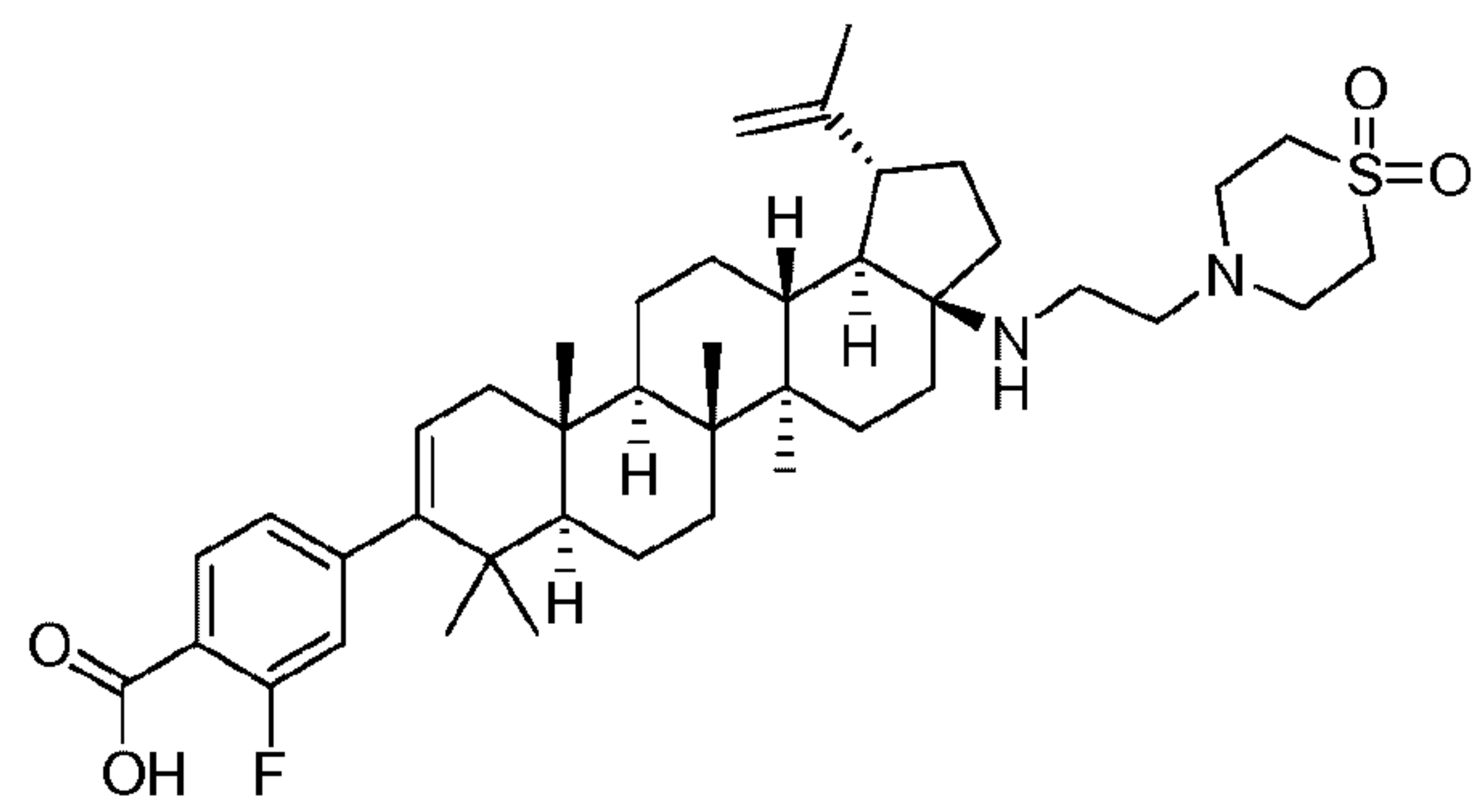
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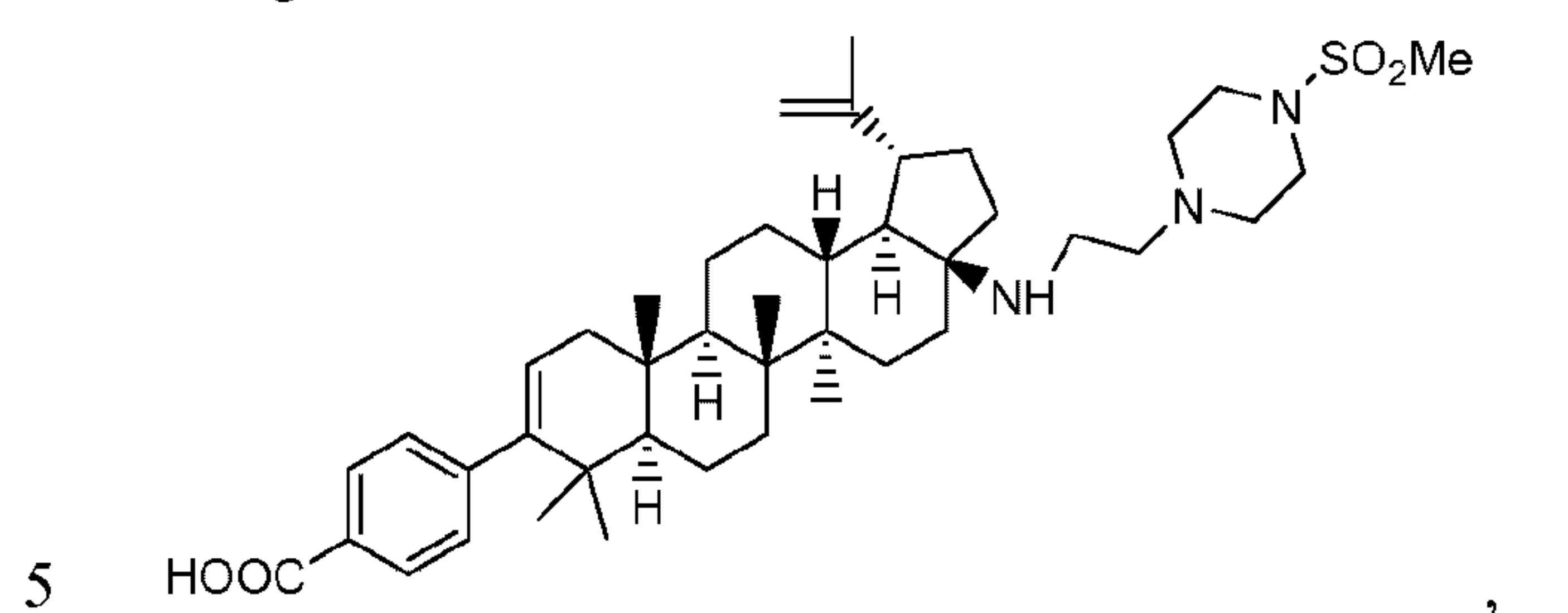
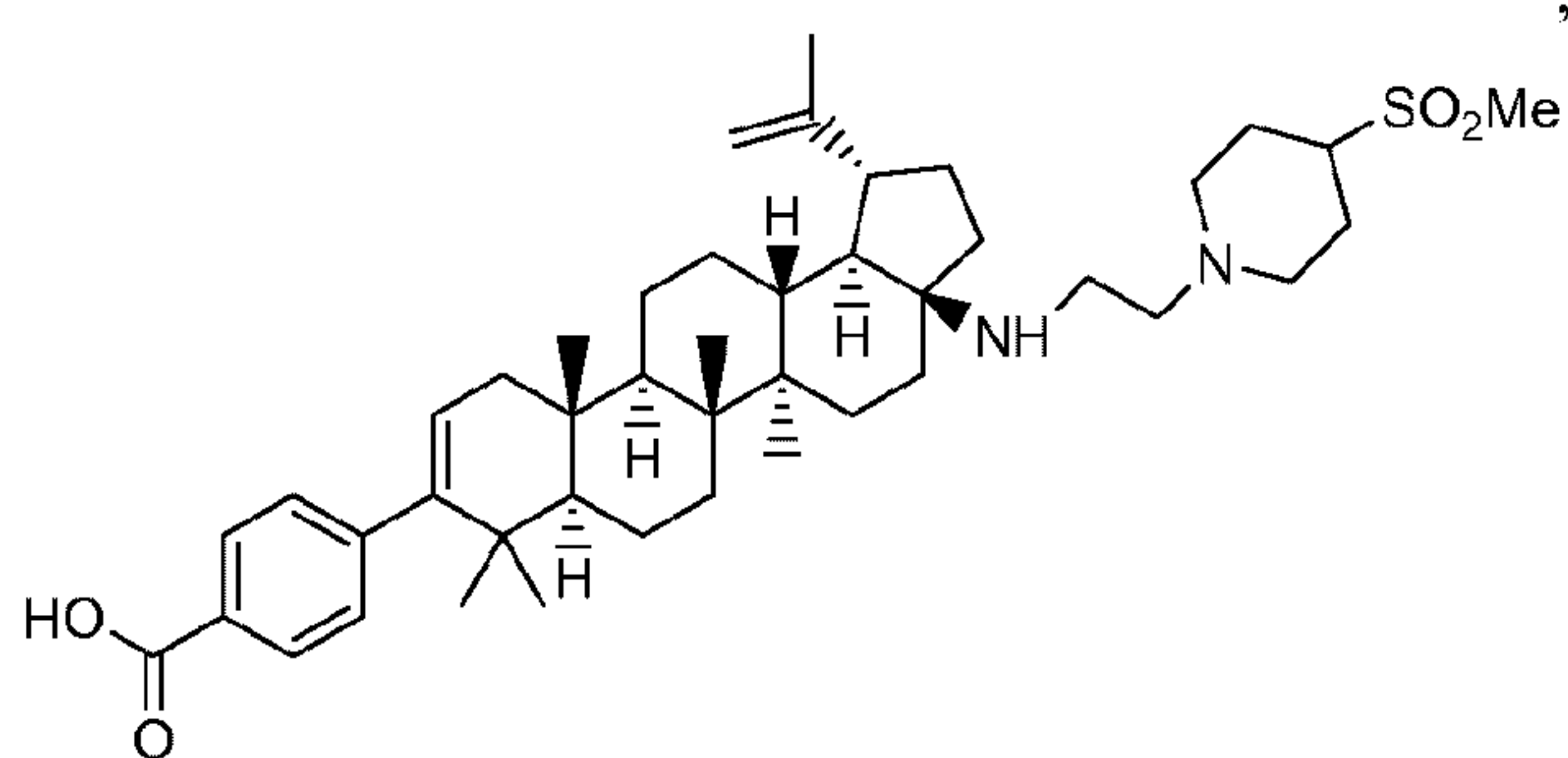
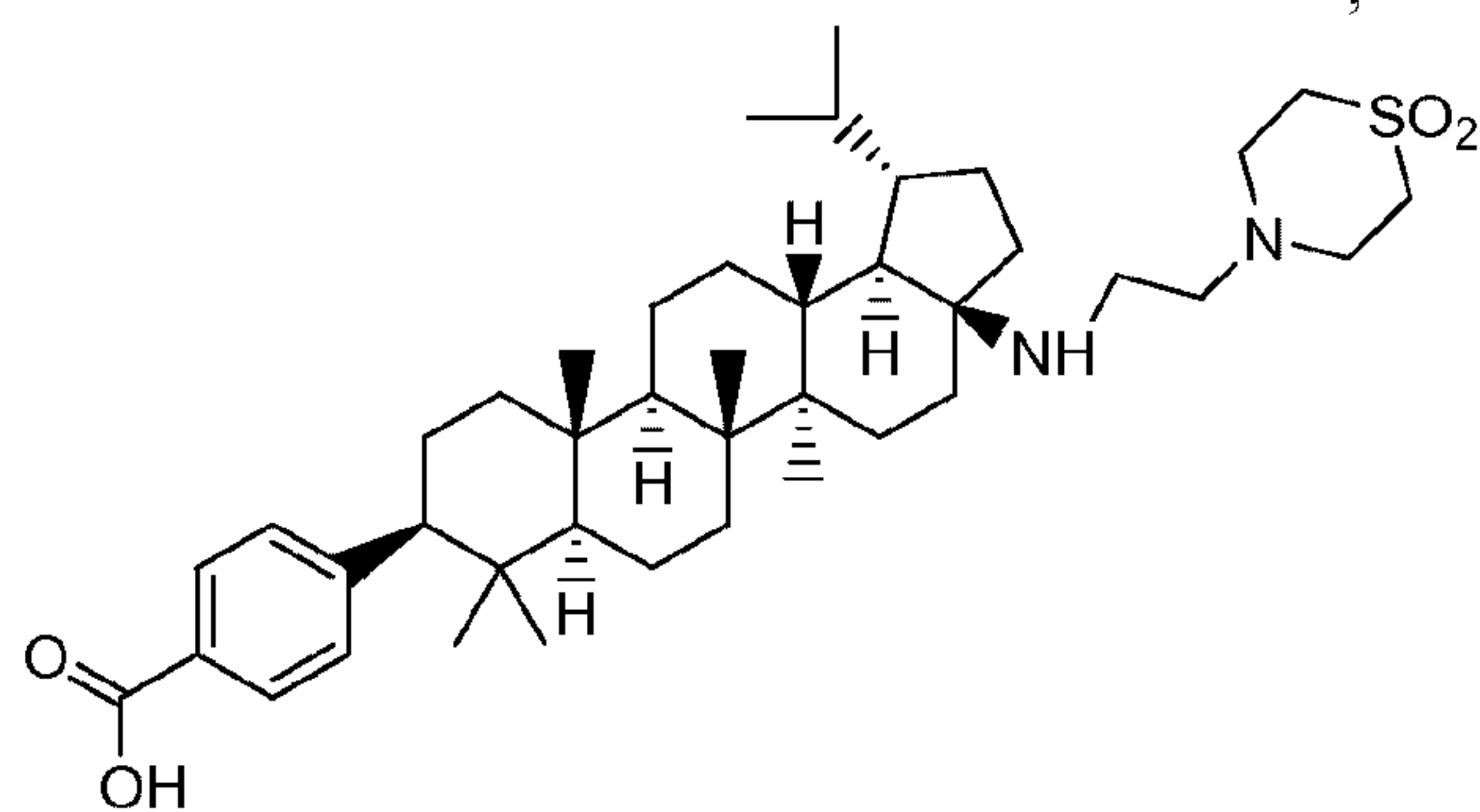
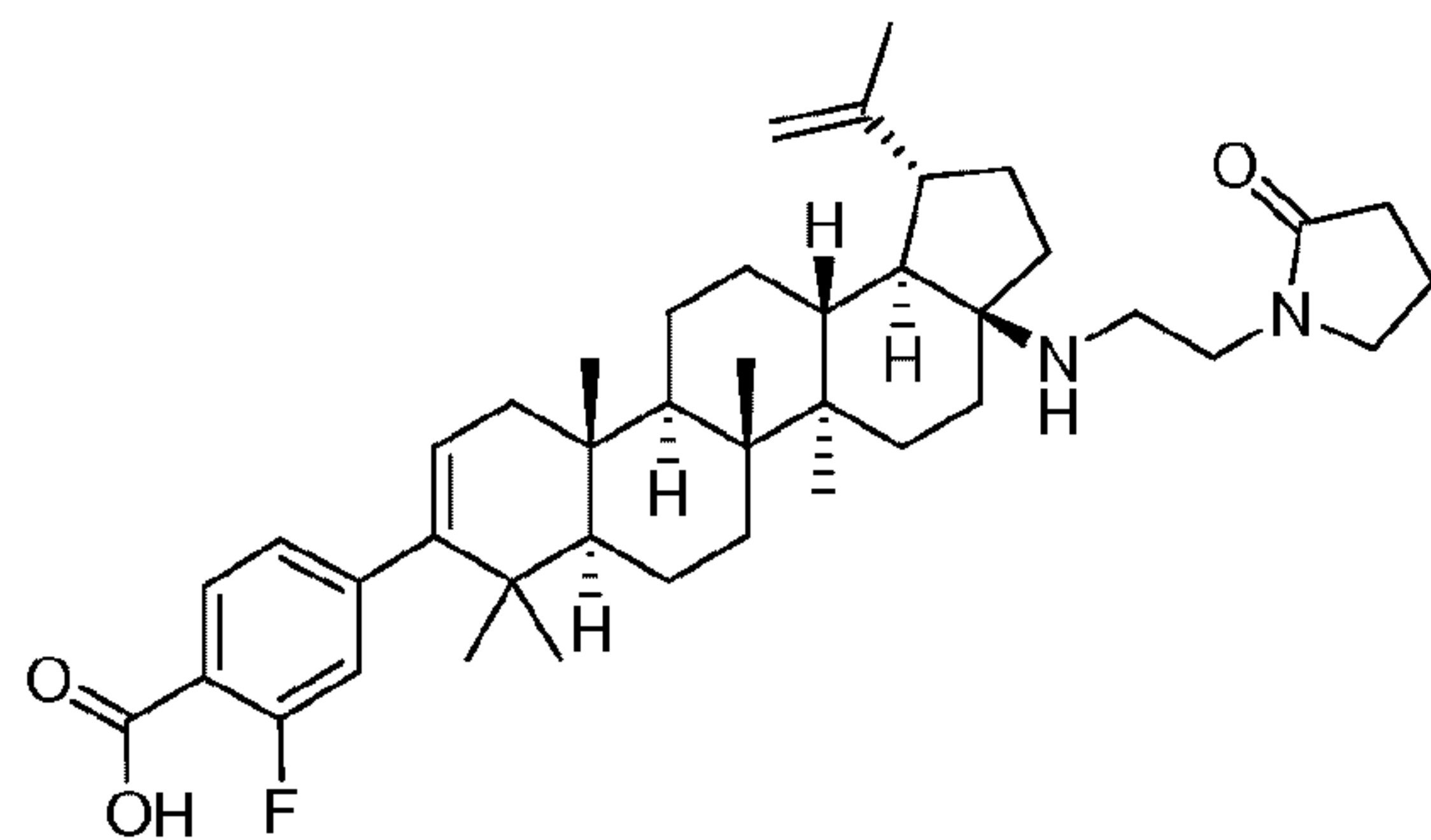
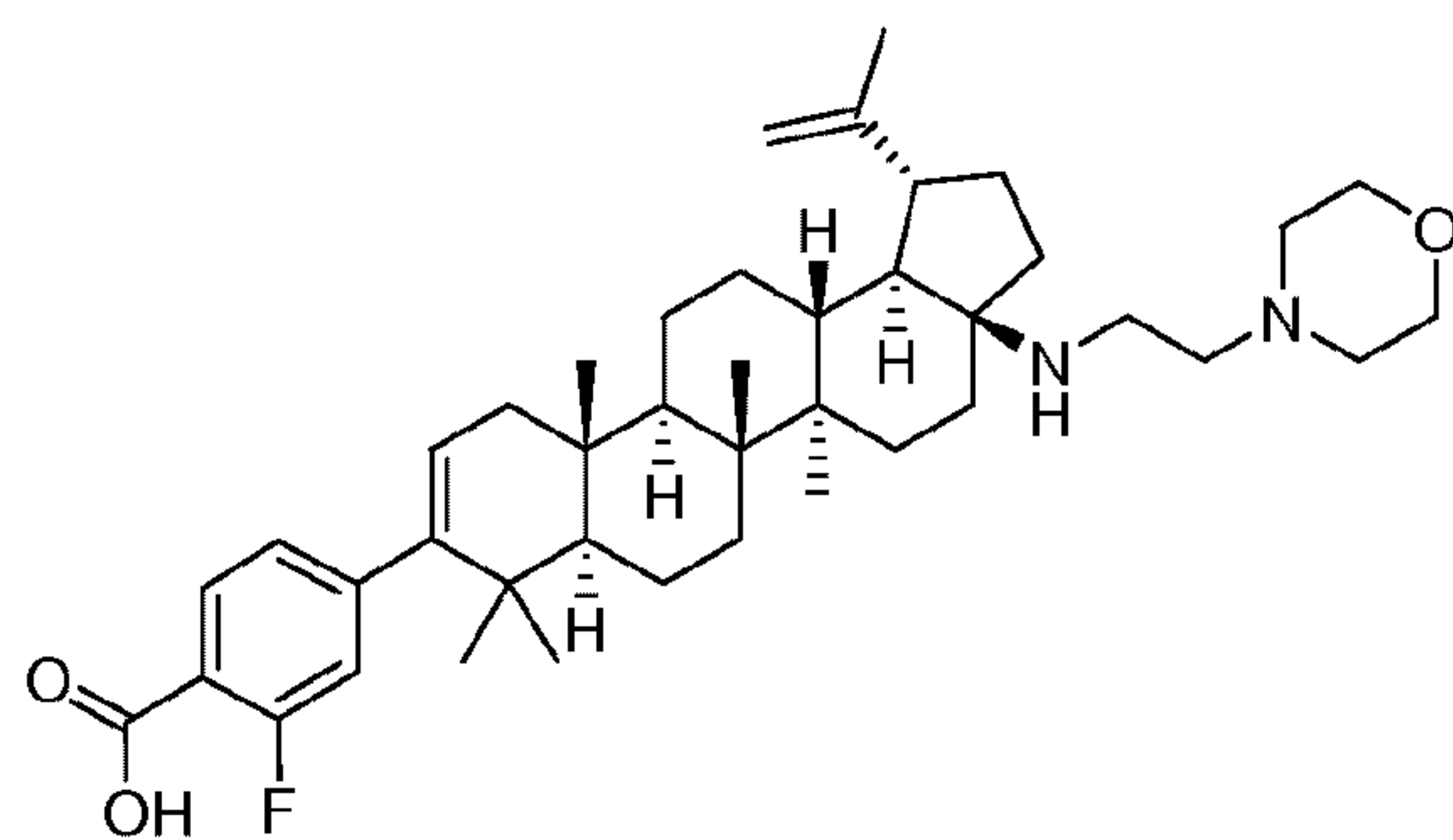


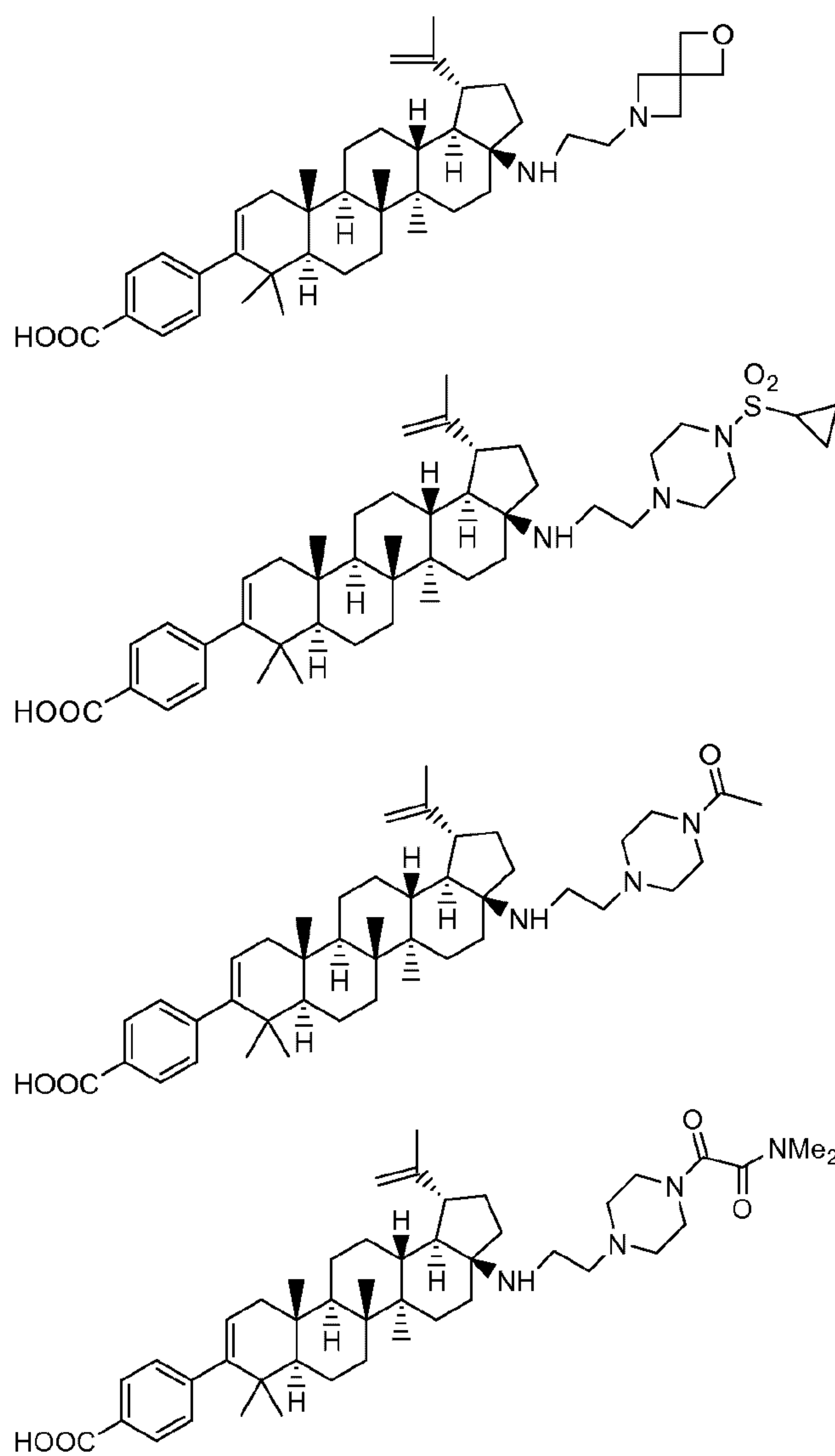
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5 Also preferred are the following compounds, including pharmaceutically acceptable salts thereof:







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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  
10 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  
20 combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following non-limiting table:

## ANTIVIRALS

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

|    |                                                                         |                                                    |                                                     |
|----|-------------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------|
| 5  | Antibody which<br>Neutralizes pH<br>Labile alpha aberrant<br>Interferon | Advanced Biotherapy<br>Concepts<br>(Rockville, MD) | AIDS, ARC                                           |
|    | AR177                                                                   | Aronex Pharm                                       | HIV infection, AIDS,<br>ARC                         |
| 10 | Beta-fluoro-ddA                                                         | Nat'l Cancer Institute                             | AIDS-associated<br>diseases                         |
| 15 | BMS-234475<br>(CGP-61755)                                               | Bristol-Myers Squibb/<br>Novartis                  | HIV infection,<br>AIDS, ARC<br>(protease inhibitor) |
|    | CI-1012                                                                 | Warner-Lambert                                     | HIV-1 infection                                     |
| 20 | Cidofovir                                                               | Gilead Science                                     | CMV retinitis,<br>herpes, papillomavirus            |
|    | Curdlan sulfate                                                         | AJI Pharma USA                                     | HIV infection                                       |
| 25 | Cytomegalovirus<br>Immune globin                                        | MedImmune                                          | CMV retinitis                                       |
|    | Cytovene                                                                | Syntex                                             | Sight threatening                                   |
| 30 | Ganciclovir                                                             |                                                    | CMV<br>peripheral CMV<br>retinitis                  |
|    | Darunavir                                                               | Tibotec- J & J                                     | HIV infection, AIDS, ARC<br>(protease inhibitor)    |
| 35 | Delaviridine                                                            | Pharmacia-Upjohn                                   | HIV infection,<br>AIDS, ARC<br>(RT inhibitor)       |
| 40 | Dextran Sulfate                                                         | Ueno Fine Chem.<br>Ind. Ltd. (Osaka,<br>Japan)     | AIDS, ARC, HIV<br>positive<br>asymptomatic          |
|    | ddC<br>Dideoxycytidine                                                  | Hoffman-La Roche                                   | HIV infection, AIDS,<br>ARC                         |

|    |                                                                                                                |                                     |                                                                                       |
|----|----------------------------------------------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------------------|
|    | ddI<br>Dideoxyinosine                                                                                          | Bristol-Myers Squibb                | HIV infection, AIDS,<br>ARC; combination<br>with AZT/d4T                              |
| 5  | DMP-450                                                                                                        | AVID<br>(Camden, NJ)                | HIV infection,<br>AIDS, ARC<br>(protease inhibitor)                                   |
| 10 | Efavirenz<br>(DMP 266, Sustiva <sup>®</sup> )<br>(-)-6-Chloro-4-(S)-<br>cyclopropylethynyl-<br>4(S)-trifluoro- | Bristol Myers Squibb                | HIV infection,<br>AIDS, ARC<br>(non-nucleoside RT<br>inhibitor)                       |
| 15 | methyl-1,4-dihydro-<br>2H-3,1-benzoxazin-<br>2-one, STOCRINE                                                   |                                     |                                                                                       |
| 20 | EL10                                                                                                           | Elan Corp, PLC<br>(Gainesville, GA) | HIV infection                                                                         |
| 25 | Etravirine                                                                                                     | Tibotec/ J & J                      | HIV infection, AIDS, ARC<br>(non-nucleoside<br>reverse transcriptase<br>inhibitor)    |
|    | Famciclovir                                                                                                    | Smith Kline                         | herpes zoster,<br>herpes simplex                                                      |
| 30 | GS 840                                                                                                         | Gilead                              | HIV infection,<br>AIDS, ARC<br>(reverse transcriptase<br>inhibitor)                   |
| 35 | HBV097                                                                                                         | Hoechst Marion<br>Roussel           | HIV infection,<br>AIDS, ARC<br>(non-nucleoside<br>reverse transcriptase<br>inhibitor) |
| 40 | Hypericin                                                                                                      | VIMRx Pharm.                        | HIV infection, AIDS,<br>ARC                                                           |
| 45 | Recombinant Human<br>Interferon Beta                                                                           | Triton Biosciences<br>(Alameda, CA) | AIDS, Kaposi's<br>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.<br>Tech (Houston, TX) | HIV infection,<br>AIDS, ARC                                                              |
|    | Ritonavir                                                     | Abbott                               | HIV infection,<br>AIDS, ARC<br>(protease inhibitor)                                      |
| 10 | Saquinavir                                                    | Hoffmann-<br>LaRoche                 | HIV infection,<br>AIDS, ARC<br>(protease inhibitor)                                      |
| 15 | Stavudine; d4T<br>Didehydrodeoxy-<br>Thymidine                | Bristol-Myers Squibb                 | HIV infection, AIDS,<br>ARC                                                              |
| 20 | Tipranavir                                                    | Boehringer Ingelheim                 | HIV infection, AIDS, ARC<br>(protease inhibitor)                                         |
|    | Valaciclovir                                                  | Glaxo Wellcome                       | Genital HSV & CMV<br>infections                                                          |
| 25 | Virazole<br>Ribavirin                                         | Viratek/ICN<br>(Costa Mesa, CA)      | asymptomatic HIV<br>positive, LAS, ARC                                                   |
|    | VX-478                                                        | Vertex                               | HIV infection, AIDS,<br>ARC                                                              |
| 30 | Zalcitabine                                                   | Hoffmann-LaRoche                     | HIV infection, AIDS,<br>ARC, with AZT                                                    |
| 35 | Zidovudine; AZT                                               | Glaxo Wellcome                       | HIV infection, AIDS,<br>ARC, Kaposi's<br>sarcoma, in combination<br>with other therapies |
| 40 | Tenofovir disoproxil,<br>fumarate salt (Viread <sup>®</sup> ) | Gilead                               | HIV infection,<br>AIDS,<br>(reverse transcriptase<br>inhibitor)                          |
| 45 | Emtriva <sup>®</sup> (Emtricitabine)<br>(FTC)                 | Gilead                               | HIV infection,<br>AIDS,<br>(reverse transcriptase<br>inhibitor)                          |

|    |                                                   |                      |                                                                 |
|----|---------------------------------------------------|----------------------|-----------------------------------------------------------------|
|    | Combivir <sup>®</sup>                             | GSK                  | HIV infection,<br>AIDS,<br>(reverse transcriptase<br>inhibitor) |
| 5  | Abacavir succinate<br>(or Ziagen <sup>®</sup> )   | GSK                  | HIV infection,<br>AIDS,<br>(reverse transcriptase<br>inhibitor) |
| 10 | Reyataz <sup>®</sup><br>(or atazanavir)           | Bristol-Myers Squibb | HIV infection<br>AIDs, protease<br>inhibitor                    |
| 15 | Fuzeon <sup>®</sup><br>(Enfuvirtide or T-20)      | Roche / Trimeris     | HIV infection<br>AIDs, viral Fusion<br>inhibitor                |
| 20 | Lexiva <sup>®</sup><br>(or Fosamprenavir calcium) | GSK/Vertex           | HIV infection<br>AIDs, viral protease<br>inhibitor              |
| 25 | Selzentry<br>Maraviroc; (UK 427857)               | Pfizer               | HIV infection<br>AIDs, (CCR5 antagonist, in<br>development)     |
| 30 | Trizivir <sup>®</sup>                             | GSK                  | HIV infection<br>AIDs, (three drug<br>combination)              |
| 35 | Sch-417690 (vicriviroc)                           | Schering-Plough      | HIV infection<br>AIDs, (CCR5 antagonist, in<br>development)     |
|    | TAK-652                                           | Takeda               | HIV infection<br>AIDs, (CCR5 antagonist, in<br>development)     |
| 40 | GSK 873140<br>(ONO-4128)                          | GSK/ONO              | HIV infection<br>AIDs, (CCR5 antagonist,<br>in development)     |
| 45 | Integrase Inhibitor<br>MK-0518<br>Raltegravir     | Merck                | HIV infection<br>AIDs                                           |

|    |                                                      |                             |                                                                                                                                                      |
|----|------------------------------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
|    | Truvada <sup>®</sup>                                 | Gilead                      | Combination of Tenofovir disoproxil fumarate salt (Viread <sup>®</sup> ) and Emtriva <sup>®</sup> (Emtricitabine)                                    |
| 5  | Integrase Inhibitor<br>GS917/JTK-303<br>Elvitegravir | Gilead/Japan Tobacco        | HIV Infection<br>AIDs<br>in development                                                                                                              |
| 10 | Triple drug combination<br>Atripla <sup>®</sup>      | Gilead/Bristol-Myers Squibb | Combination of Tenofovir disoproxil fumarate salt (Viread <sup>®</sup> ), Emtriva <sup>®</sup> (Emtricitabine), and Sustiva <sup>®</sup> (Efavirenz) |
| 15 | Festinavir <sup>®</sup><br>4'-ethynyl-d4T            | Oncolys BioPharma<br>BMS    | HIV infection<br>AIDs<br>in development                                                                                                              |
| 20 | CMX-157<br>Lipid conjugate of nucleotide tenofovir   | Chimerix                    | HIV infection<br>AIDs                                                                                                                                |
| 25 | GSK1349572<br>Integrase inhibitor                    | GSK                         | HIV infection<br>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.<br>(Irving, TX) | AIDS, ARC                         |
| 40 | CL246,738        | Wyeth<br>Lederle Labs                 | AIDS, Kaposi's sarcoma            |
|    | FP-21399         | Fuki ImmunoPharm                      | Blocks HIV fusion with CD4+ cells |

|    |                                                        |                                     |                                                         |
|----|--------------------------------------------------------|-------------------------------------|---------------------------------------------------------|
|    | Gamma Interferon                                       | Genentech                           | ARC, in combination<br>w/TNF (tumor<br>necrosis factor) |
| 5  |                                                        |                                     |                                                         |
|    | Granulocyte<br>Macrophage Colony<br>Stimulating Factor | Genetics Institute<br>Sandoz        | AIDS                                                    |
| 10 |                                                        |                                     |                                                         |
|    | Granulocyte<br>Macrophage Colony<br>Stimulating Factor | Hoechst-Roussel<br>Immunex          | AIDS                                                    |
| 15 |                                                        |                                     |                                                         |
|    | Granulocyte<br>Macrophage Colony<br>Stimulating Factor | Schering-Plough                     | AIDS,<br>combination<br>w/AZT                           |
| 20 |                                                        |                                     |                                                         |
|    | HIV Core Particle<br>Immunostimulant                   | Rorer                               | Seropositive HIV                                        |
|    | IL-2                                                   | Cetus                               | AIDS, in combination<br>w/AZT                           |
|    | Interleukin-2                                          |                                     |                                                         |
|    | IL-2                                                   | Hoffman-LaRoche                     | AIDS, ARC, HIV, in<br>combination w/AZT                 |
| 25 |                                                        |                                     |                                                         |
|    | Interleukin-2                                          | Immunex                             |                                                         |
|    | IL-2<br>Interleukin-2<br>(aldeslukin)                  | Chiron                              | AIDS, increase in<br>CD4 cell counts                    |
| 30 |                                                        |                                     |                                                         |
|    | Immune Globulin<br>Intravenous<br>(human)              | Cutter Biological<br>(Berkeley, CA) | Pediatric AIDS, in<br>combination w/AZT                 |
| 35 |                                                        |                                     |                                                         |
|    | IMREG-1                                                | Imreg<br>(New Orleans, LA)          | AIDS, Kaposi's<br>sarcoma, ARC, PGL                     |
|    | IMREG-2                                                | Imreg<br>(New Orleans, LA)          | AIDS, Kaposi's<br>sarcoma, ARC, PGL                     |
| 40 |                                                        |                                     |                                                         |
|    | Imuthiol Diethyl<br>Dithio Carbamate                   | Merieux Institute                   | AIDS, ARC                                               |
|    | Alpha-2<br>Interferon                                  | Schering Plough                     | Kaposi's sarcoma<br>w/AZT, AIDS                         |

|    |                                             |                                                        |                                                        |
|----|---------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
|    | Methionine-<br>Enkephalin                   | TNI Pharmaceutical<br>(Chicago, IL)                    | AIDS, ARC                                              |
| 5  | MTP-PE<br>Muramyl-Tripeptide                | Ciba-Geigy Corp.                                       | Kaposi's sarcoma                                       |
| 10 | Granulocyte<br>Colony Stimulating<br>Factor | Amgen                                                  | AIDS, in combination<br>w/AZT                          |
|    | Remune                                      | Immune Response<br>Corp.                               | Immunotherapeutic                                      |
| 15 | rCD4<br>Recombinant<br>Soluble Human CD4    | Genentech                                              | AIDS, ARC                                              |
| 20 | rCD4-IgG<br>hybrids                         |                                                        | AIDS, ARC                                              |
|    | Recombinant<br>Soluble Human CD4            | Biogen                                                 | AIDS, ARC                                              |
| 25 | Interferon<br>Alfa 2a                       | Hoffman-La Roche                                       | Kaposi's sarcoma<br>AIDS, ARC,<br>in combination w/AZT |
| 30 | SK&F106528<br>Soluble T4                    | Smith Kline                                            | HIV infection                                          |
|    | Thymopentin                                 | Immunobiology<br>Research Institute<br>(Annandale, NJ) | HIV infection                                          |
| 35 | Tumor Necrosis<br>Factor; TNF               | Genentech                                              | ARC, in combination<br>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<br>Nystatin Pastille             | Squibb Corp.               | Prevention of oral candidiasis              |
| 10 | Ornidyl<br>Eflornithine                   | Merrell Dow                | PCP                                         |
| 15 | Pentamidine<br>Isethionate (IM & IV)      | LyphoMed<br>(Rosemont, IL) | PCP treatment                               |
|    | Trimethoprim                              |                            | Antibacterial                               |
|    | Trimethoprim/sulfa                        |                            | Antibacterial                               |
| 20 | Piritrexim                                | Burroughs Wellcome         | PCP treatment                               |
| 25 | Pentamidine<br>Isethionate for Inhalation | Fisons Corporation         | PCP prophylaxis                             |
|    | Spiramycin                                | Rhone-Poulenc<br>diarrhea  | Cryptosporidial                             |
| 30 | Intraconazole-<br>R51211                  | Janssen-Pharm.             | Histoplasmosis;<br>cryptococcal meningitis  |
|    | Trimetrexate                              | Warner-Lambert             | PCP                                         |
| 35 | Daunorubicin                              | NeXstar, Sequus            | Kaposi's sarcoma                            |
| 40 | Recombinant Human<br>Erythropoietin       | Ortho Pharm. Corp.         | Severe anemia<br>assoc. with AZT<br>therapy |
|    | Recombinant Human                         | Serono                     | AIDS-related                                |

|    |                            |                                  |                                                  |
|----|----------------------------|----------------------------------|--------------------------------------------------|
|    | Growth Hormone             |                                  | wasting, cachexia                                |
| 5  | Megestrol Acetate          | Bristol-Myers Squibb             | Treatment of<br>anorexia assoc.<br>W/AIDS        |
|    | Testosterone               | Alza, Smith Kline                | AIDS-related wasting                             |
| 10 | Total Enteral<br>Nutrition | Norwich Eaton<br>Pharmaceuticals | Diarrhea and<br>malabsorption<br>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  
 15 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  
 20 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  
 25 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.

30 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<sup>®</sup> (active ingredient  
 35 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<sup>®</sup>. 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)-piperazinyll)-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).

#### 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:

Bz<sub>2</sub>O = benzoic anhydride

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

5

HATU = 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium  
hexafluorophosphate methanaminium

DCE = dichloroethane

10

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 Tf<sub>2</sub>NPh = (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

20

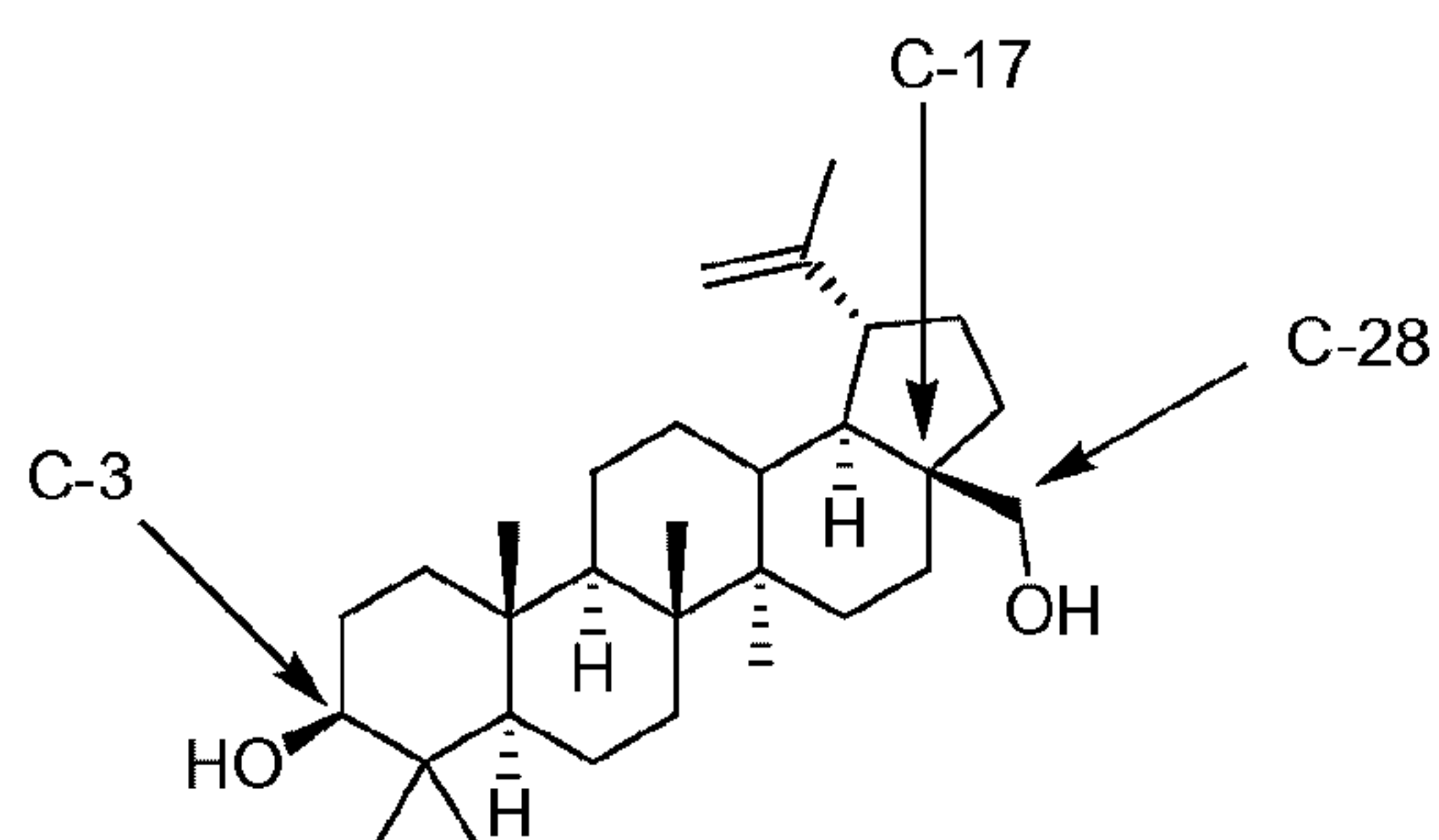
DMF= *N,N*-dimethylformamide

TBAF= tetrabutylammonium fluoride

TBDMSCl= *tert*-butyldimethylsilyl chloride

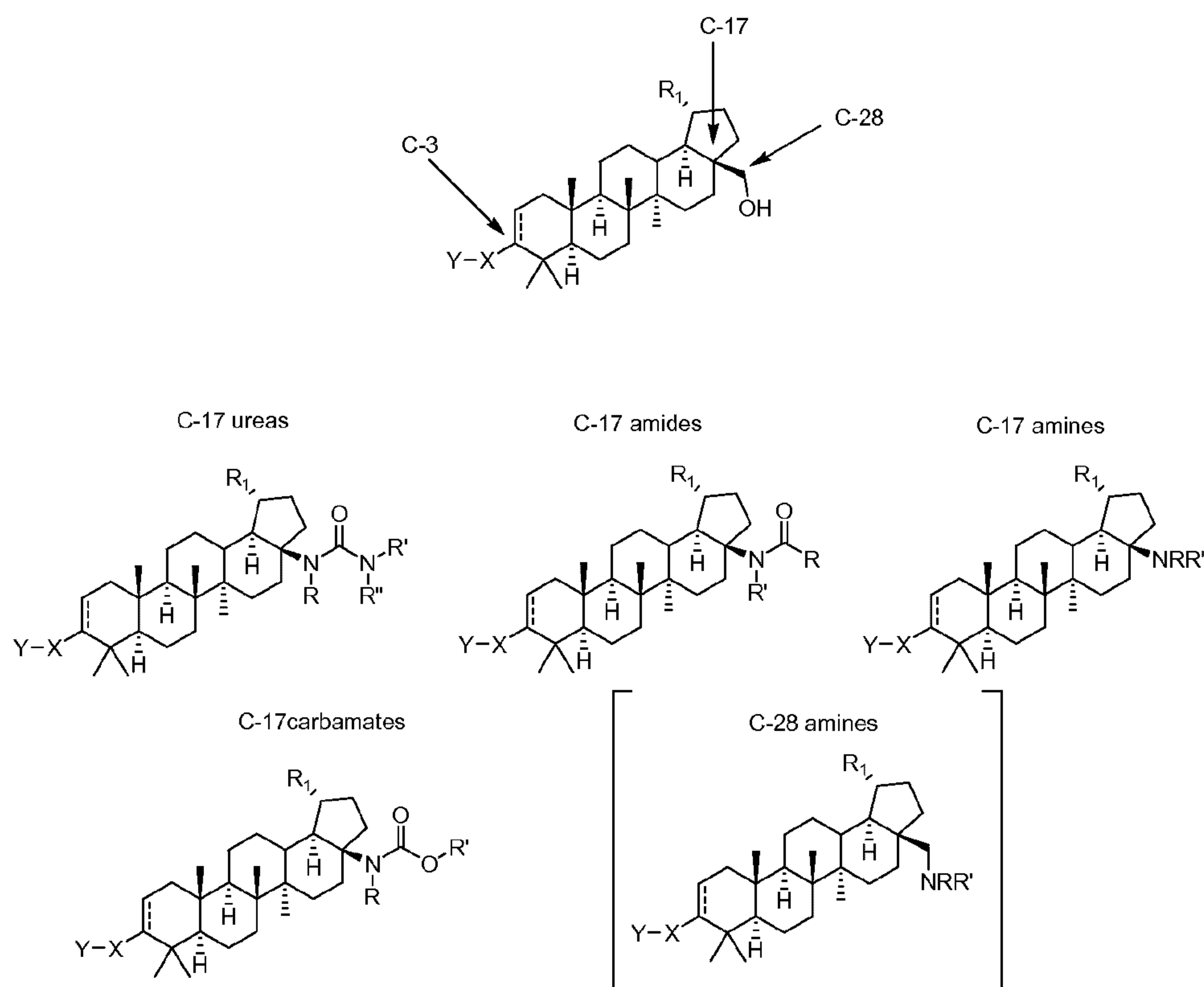
25

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):



30

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



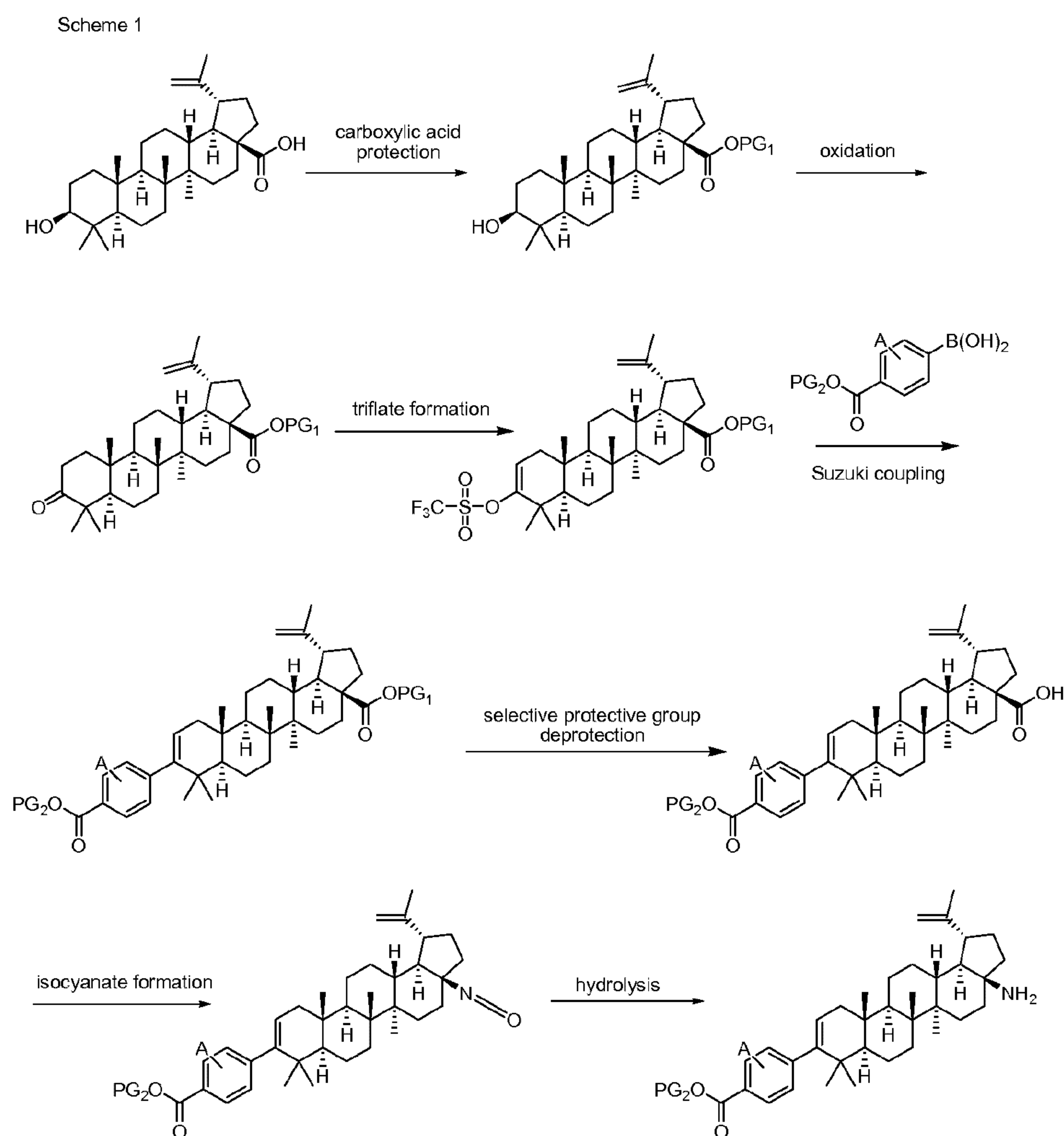
*Preparation of Compounds of Formulas I, II, and III General Chemistry Schemes:*

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

5

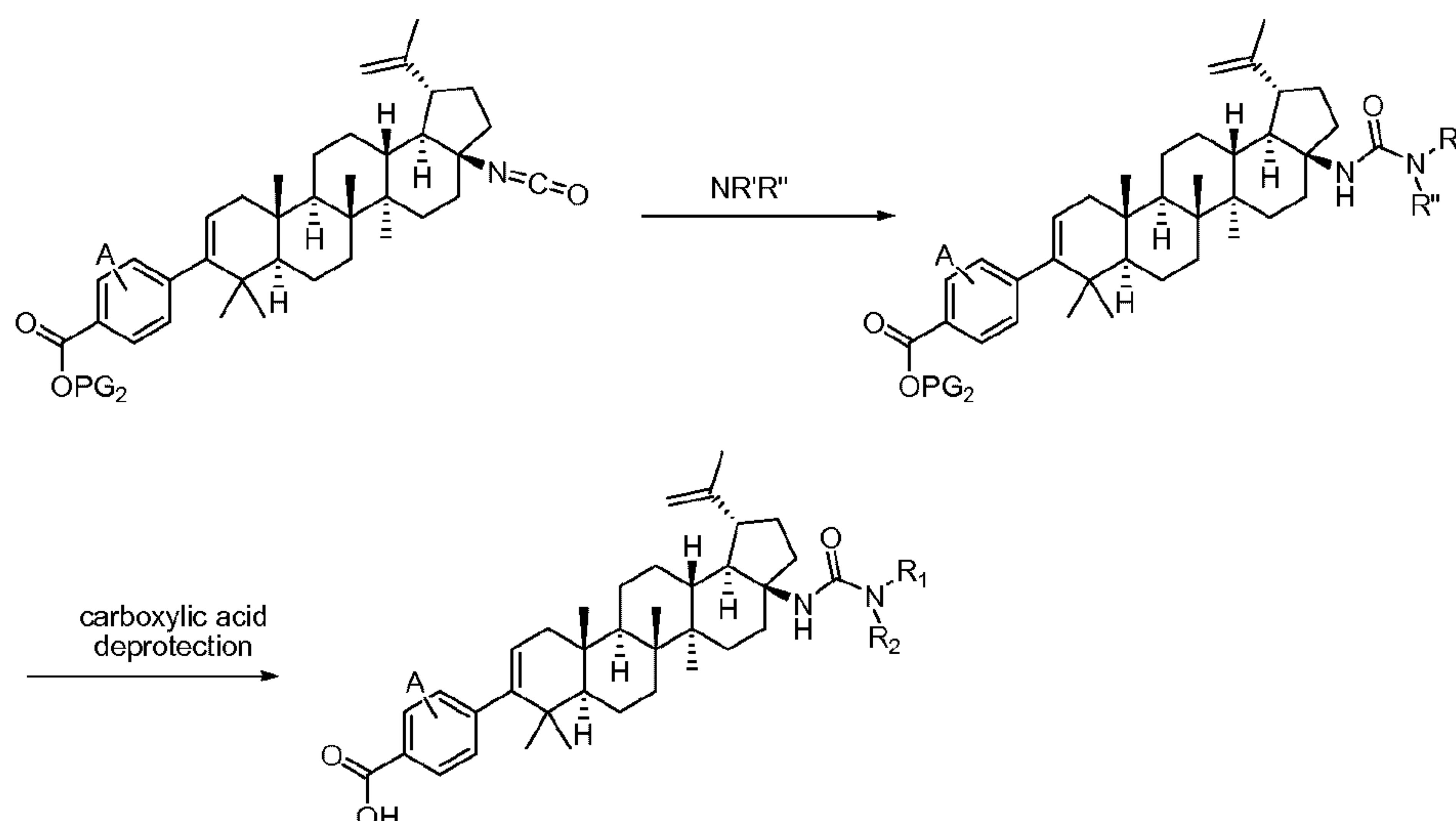
Compounds of Formula I can be prepared from commercially available (Aldrich, others) betulinic acid by chemistry described in the following schemes. Compounds of Formula II and III are described thereafter.

10 General reaction schemes are set forth as follows:



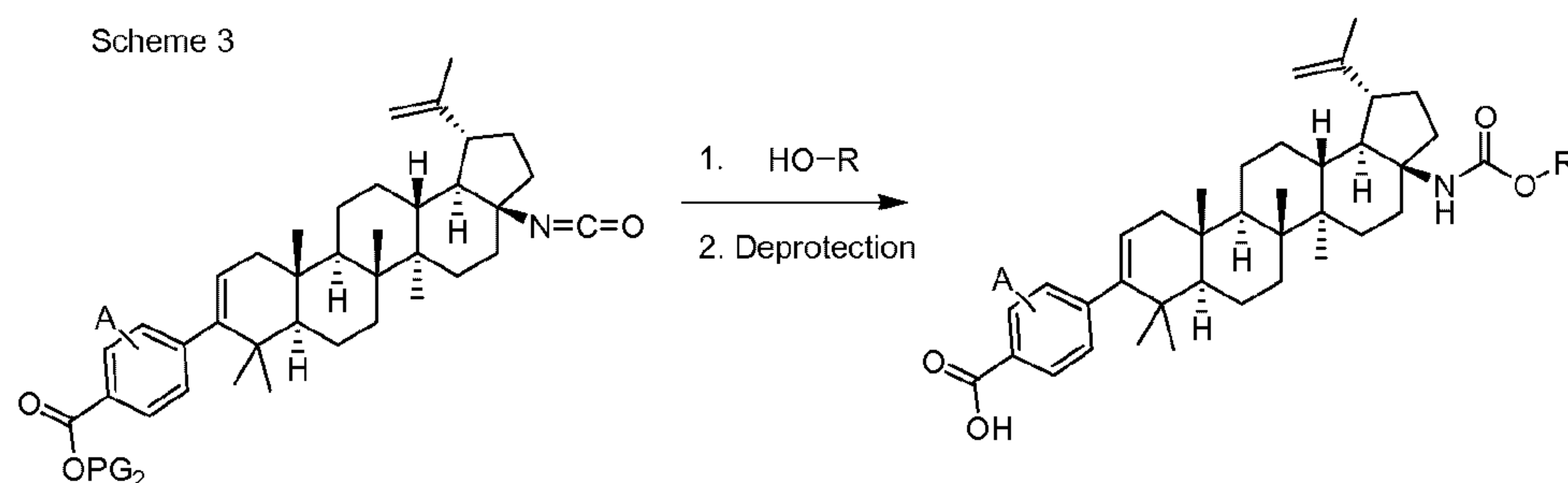
Scheme 1 describes the preparation of the key intermediate C-17 primary amine from betulinic acid. The carboxylic acid present in betulinic acid was protected with a suitable protective group. Standard oxidation (i.e. PCC, Dess-Martin) of the C-3 hydroxyl group produces the C-3 ketone which is then converted 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  
 5 necessary, affords the corresponding C-17 urea. Hydrolysis of the benzoic ester affords the benzoic acid derivative.

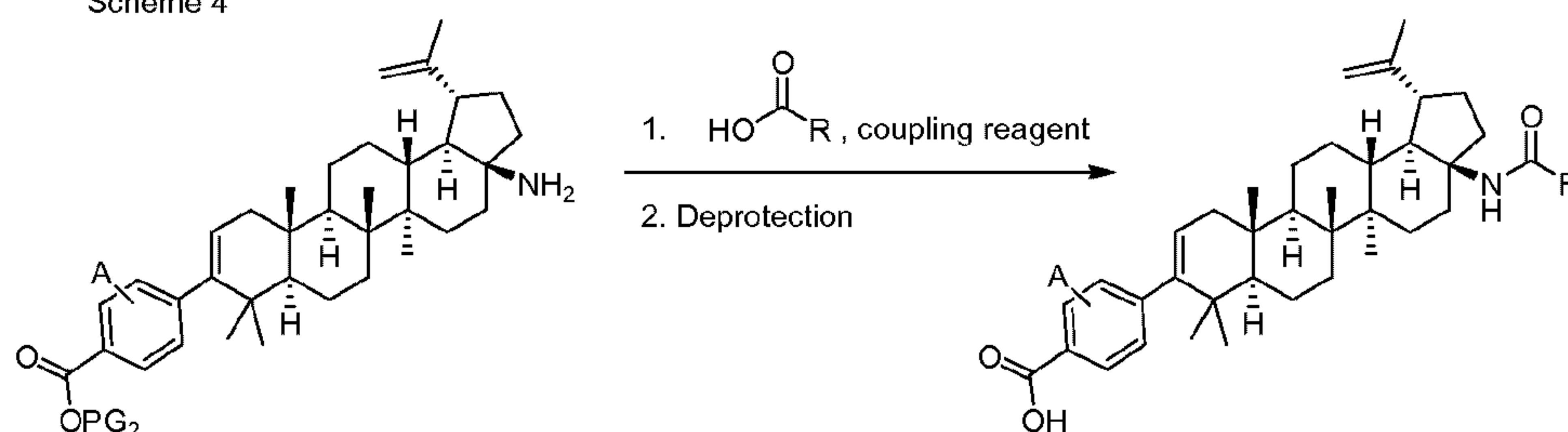
Scheme 3



Similarly, carbamates can be prepared by adding an alcohol to the isocyanate in a  
 10 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  
 15 those skill in the art. Some examples are shown in the following schemes.

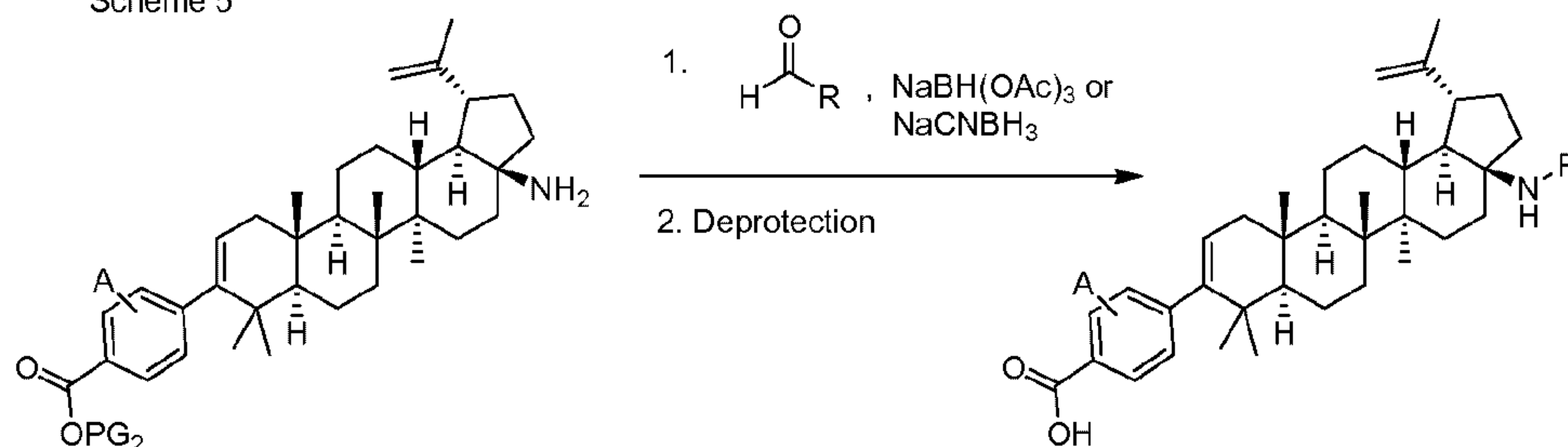
Scheme 4



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

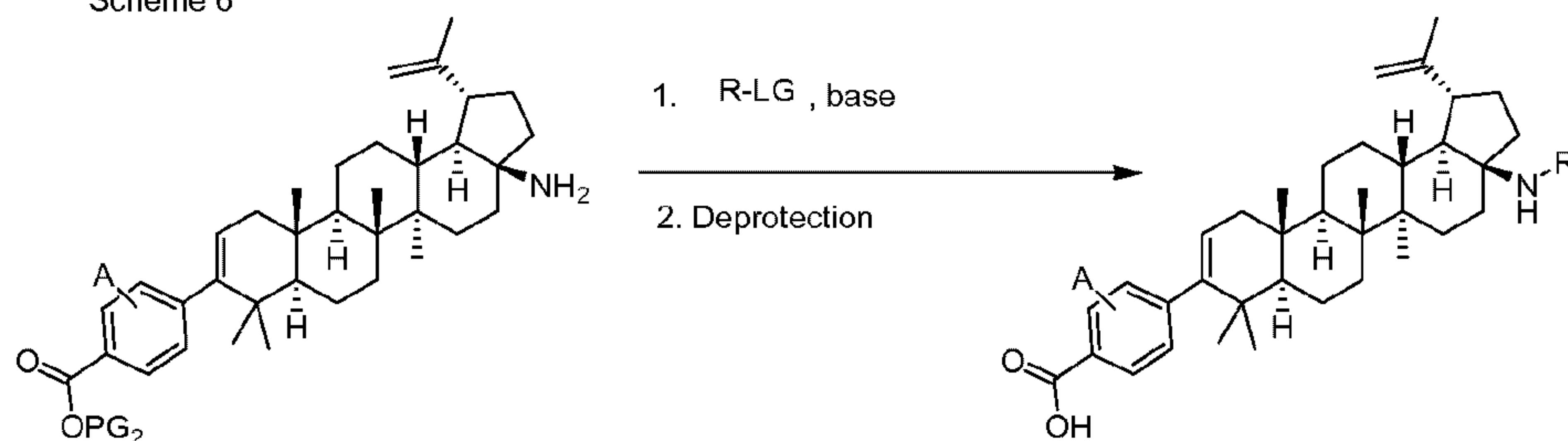
Scheme 5



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  $\text{AcOH}/\text{NaOAc}$  or  $\text{Ti}(\text{OPr})_4$  in a solvent such as THF, 1,4-dioxane, DCE or DCM) to afford C-17 secondary amines.

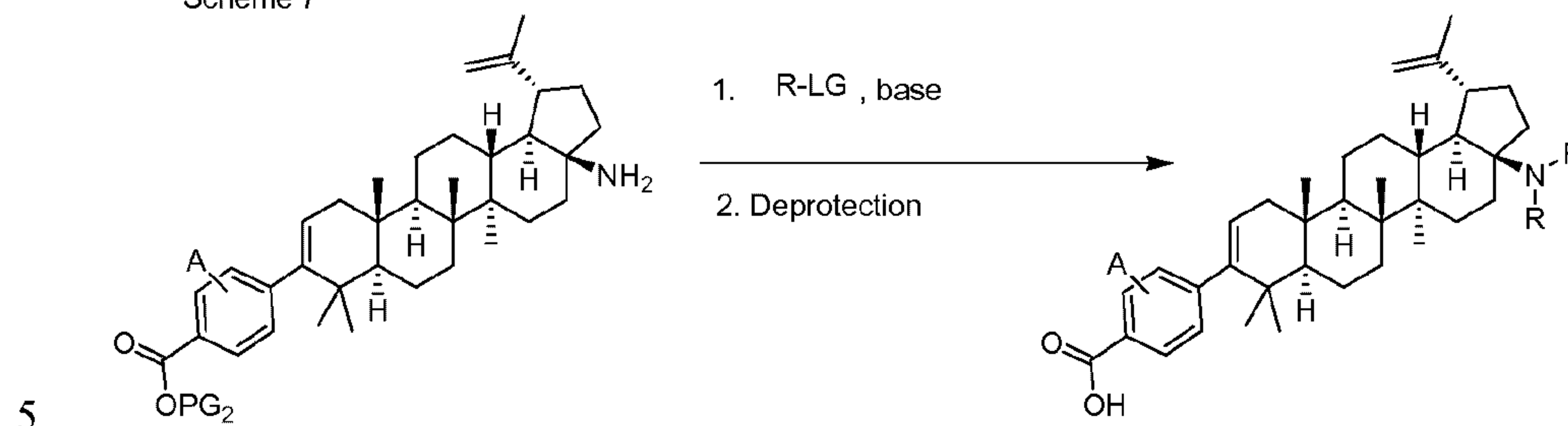
Hydrolysis of the carboxylic ester renders the benzoic acid compound.

Scheme 6



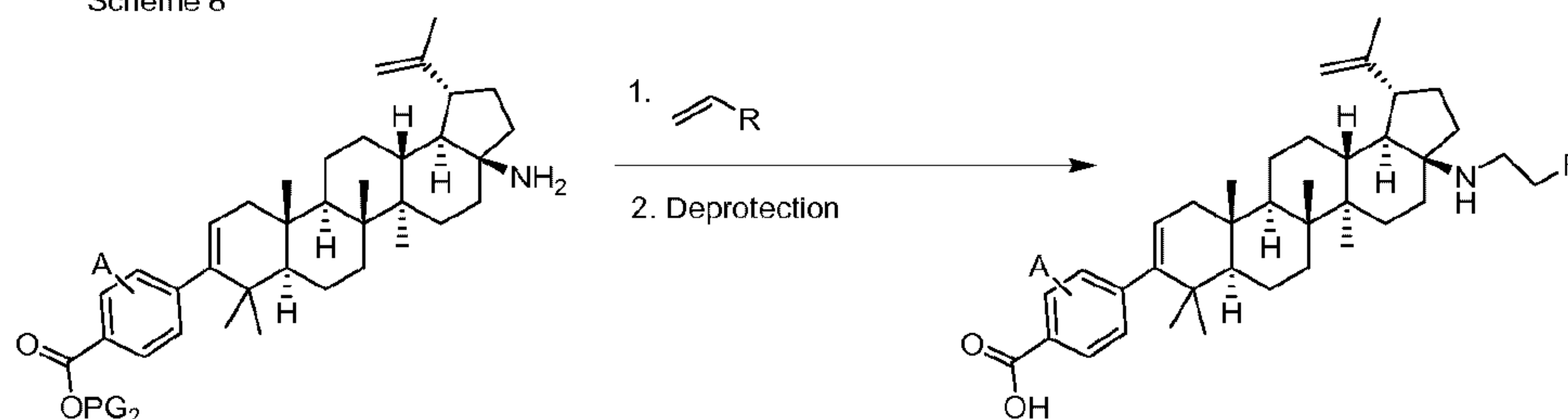
Some C-17 amines can be prepared by alkylation of the C-17 primary amine with an alkylating agent (R-LG), where LG is a leaving group such as, but not limited to Br, Cl, I, mesylate, tosylate or triflate in the presence of a base. Heating may be needed in some cases. Hydrolysis of the carboxylic ester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



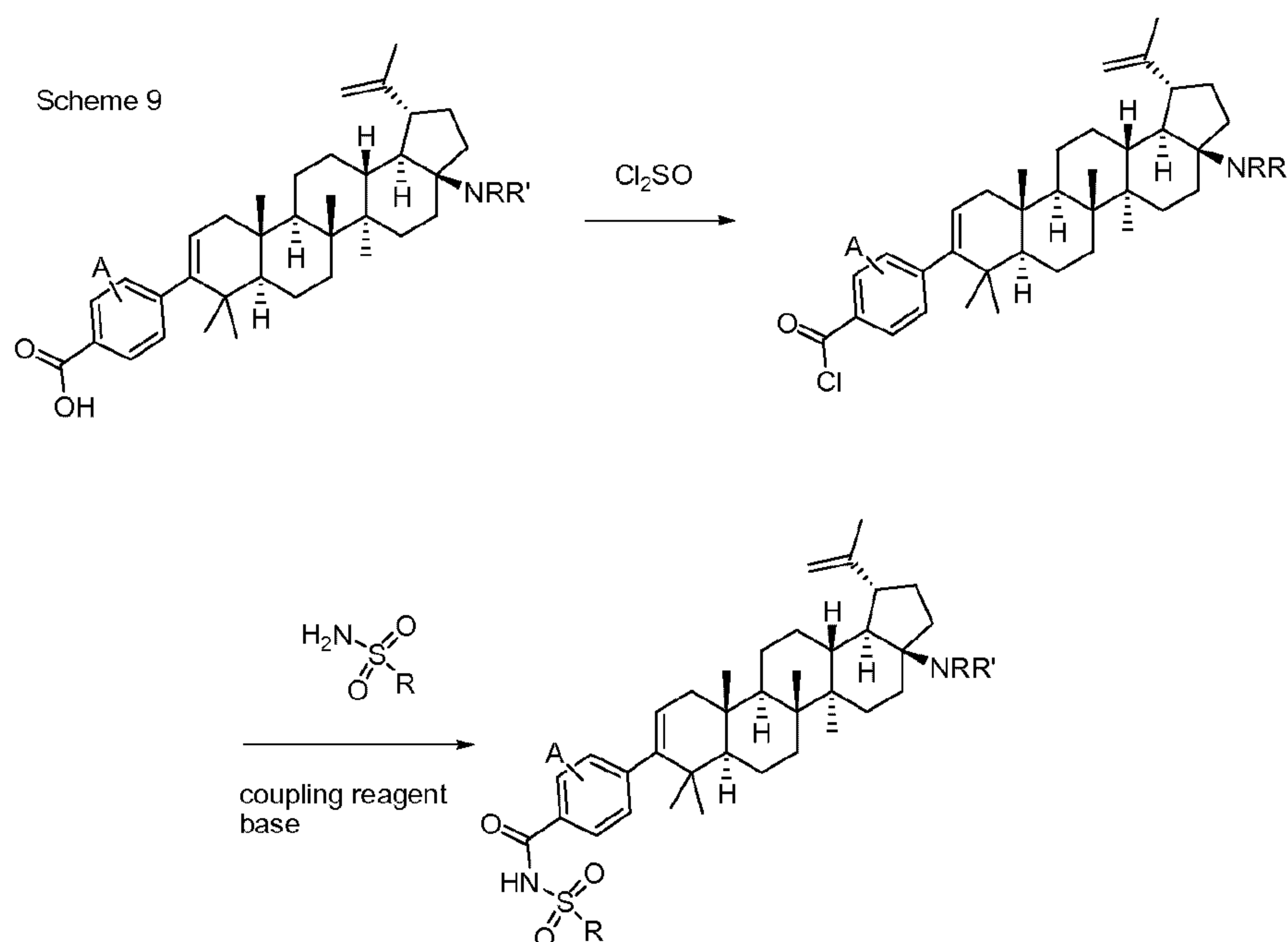
- 10 Alternatively, some C-17 amines can be prepared by 1,4-addition to Michael acceptors followed by hydrolysis of the ester.

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 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.

15

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 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.

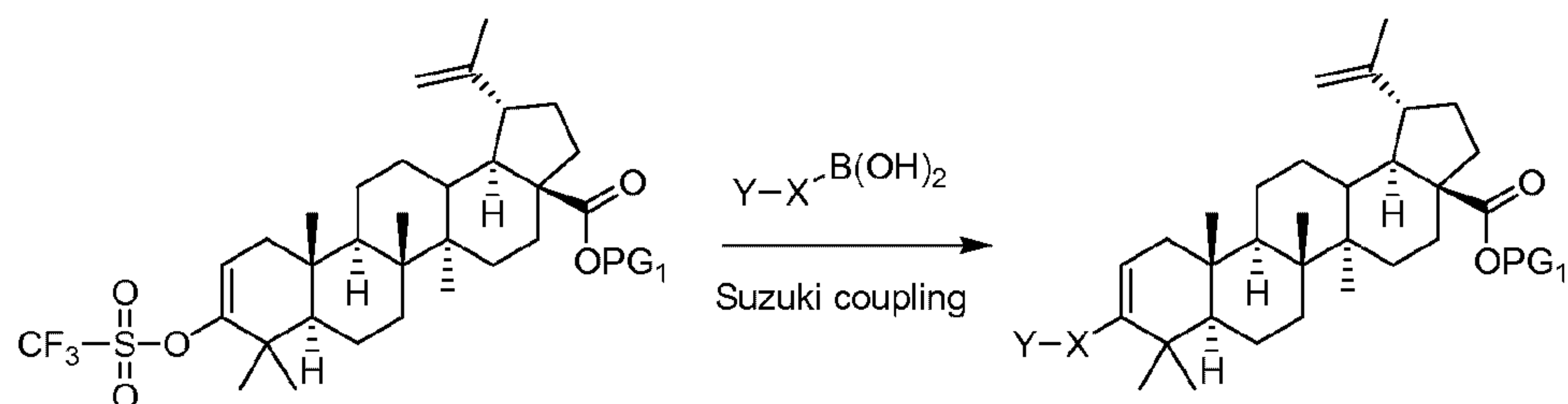
20



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



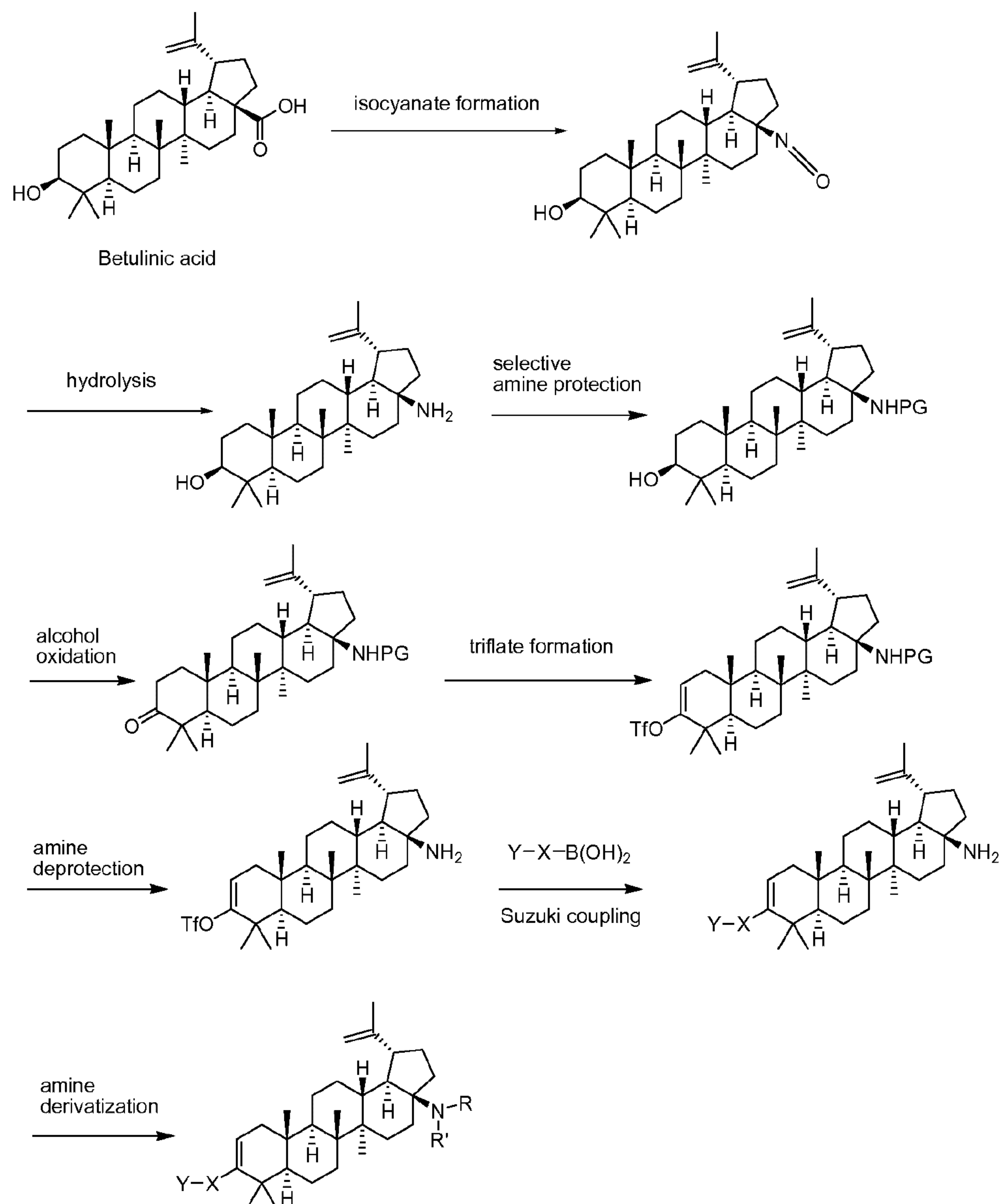
15

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

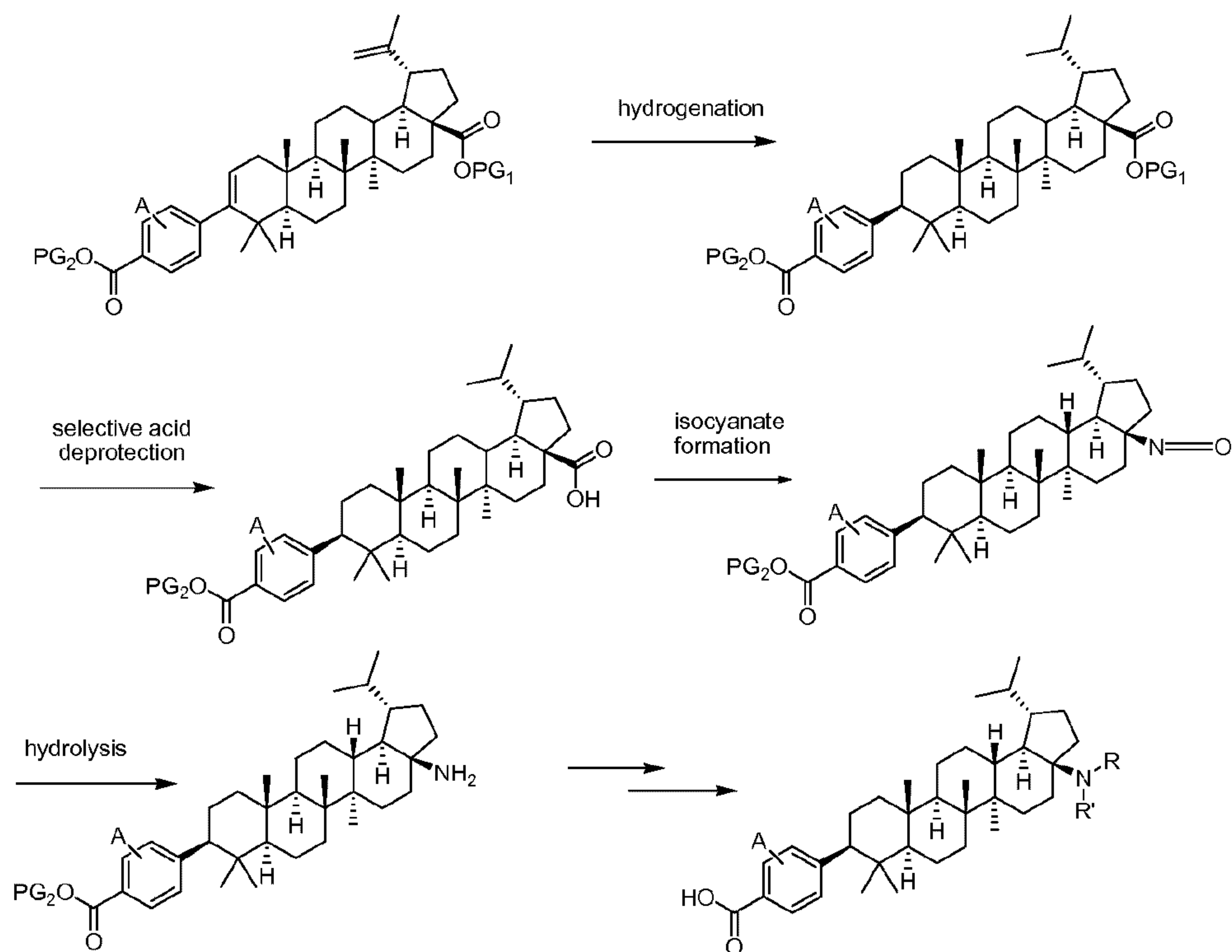
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Scheme 11



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). <sup>1</sup>H NMR spectra were recorded on Bruker DRX-500f at 500 MHz (or Bruker AV 400 MHz, Bruker DPX-300B or Varian Gemini 300 at 300 MHz as stated). The chemical shifts were reported in ppm on the  $\delta$  scale relative to  $\delta$ TMS = 0. The following internal references were used for the residual protons in the following solvents: CDCl<sub>3</sub> ( $\delta$ <sub>H</sub> 7.26), CD<sub>3</sub>OD ( $\delta$ <sub>H</sub> 3.30), Acetic-d<sub>4</sub> (*Acetic Acid d<sub>4</sub>*) ( $\delta$ <sub>H</sub> 11.6, 2.07), DMSO mix or DMSO-D<sub>6</sub>-CDCl<sub>3</sub> ( $\delta$ <sub>H</sub> 2.50 and 8.25) (ratio 75%:25%), and DMSO-D<sub>6</sub> ( $\delta$ <sub>H</sub> 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  $\mu$ 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  $\mu$ m, 2.0 x 30 mm

35

## 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ 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 $\mu$ 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

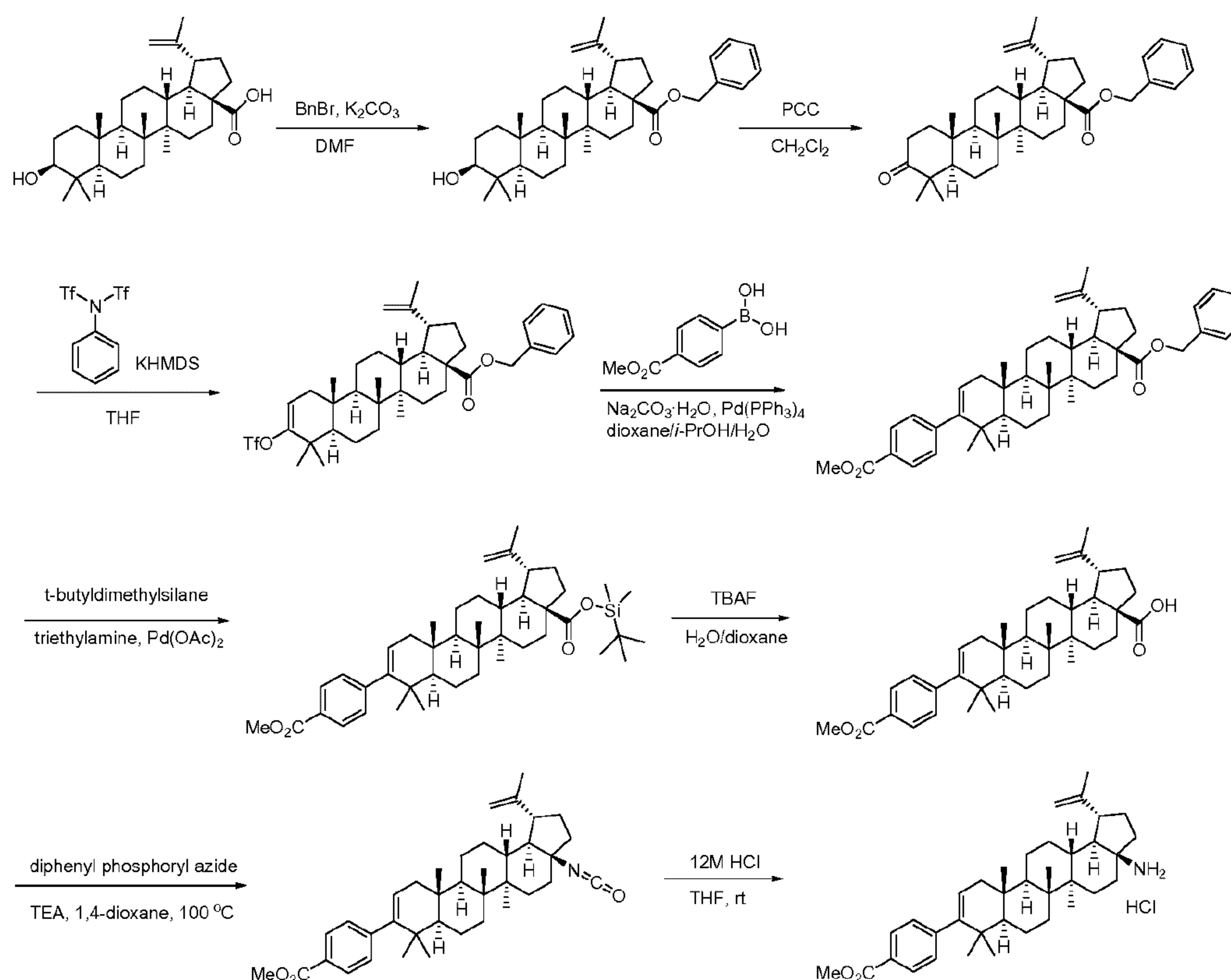
Solvent A = 0.1%TFA/95%water/5%acetonitrile

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

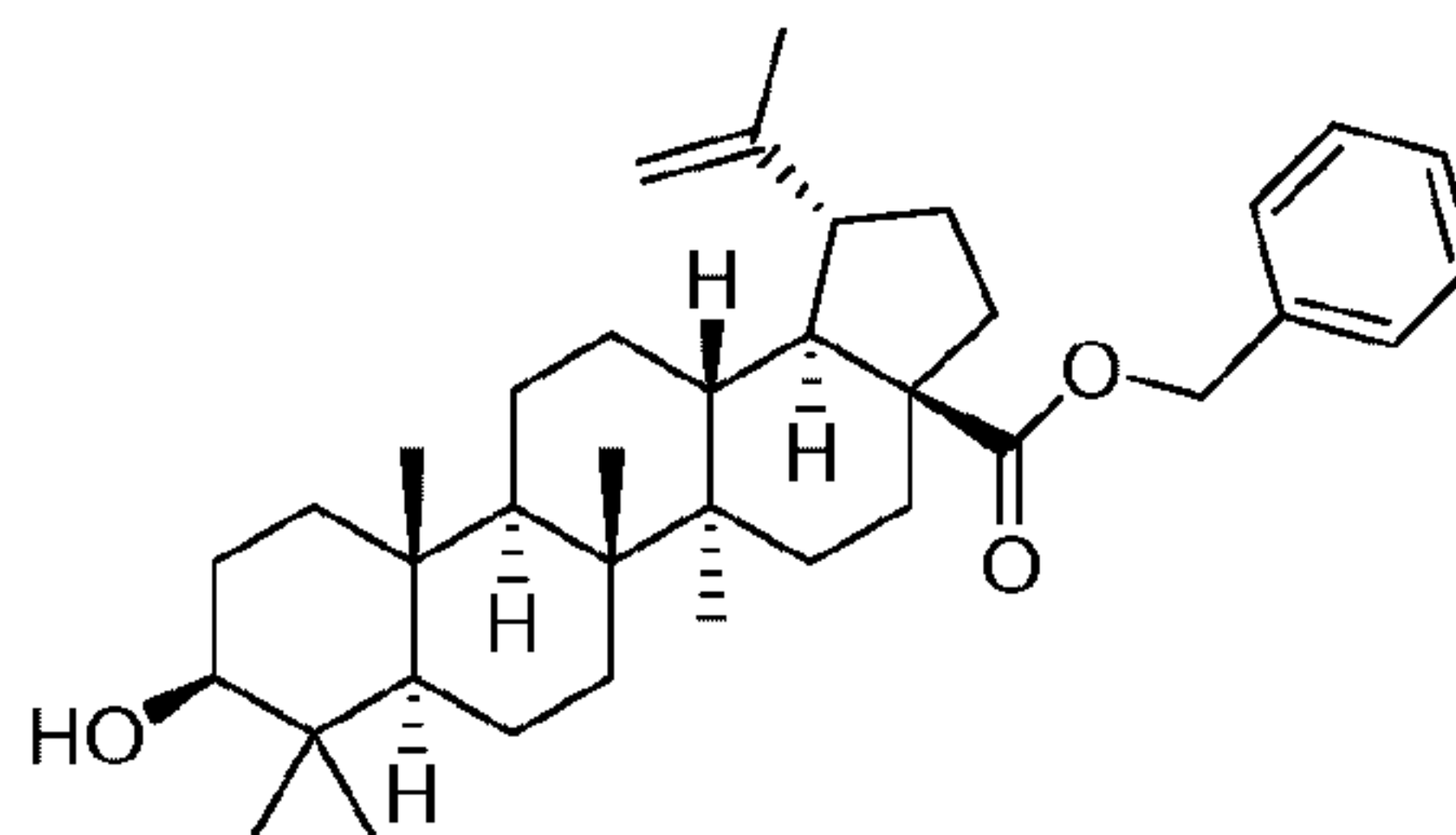
Column = Xbridge Phenyl 3.5 $\mu$ m, 3.0x150mm

Preparation of compounds:

30



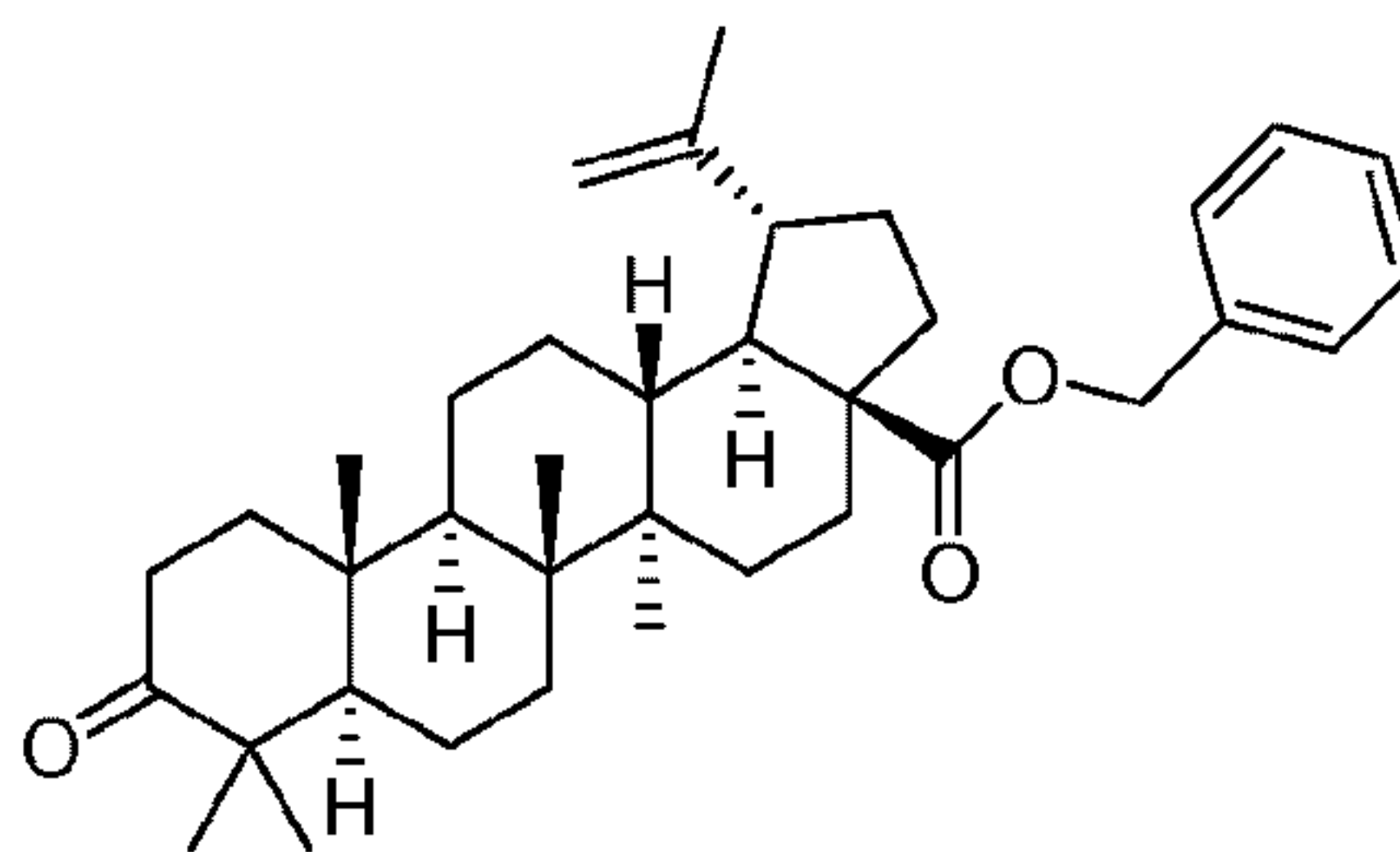
Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-benzyl 9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



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. <sup>1</sup>H NMR (500 MHz,

*CHLOROFORM-d*)  $\delta$  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.



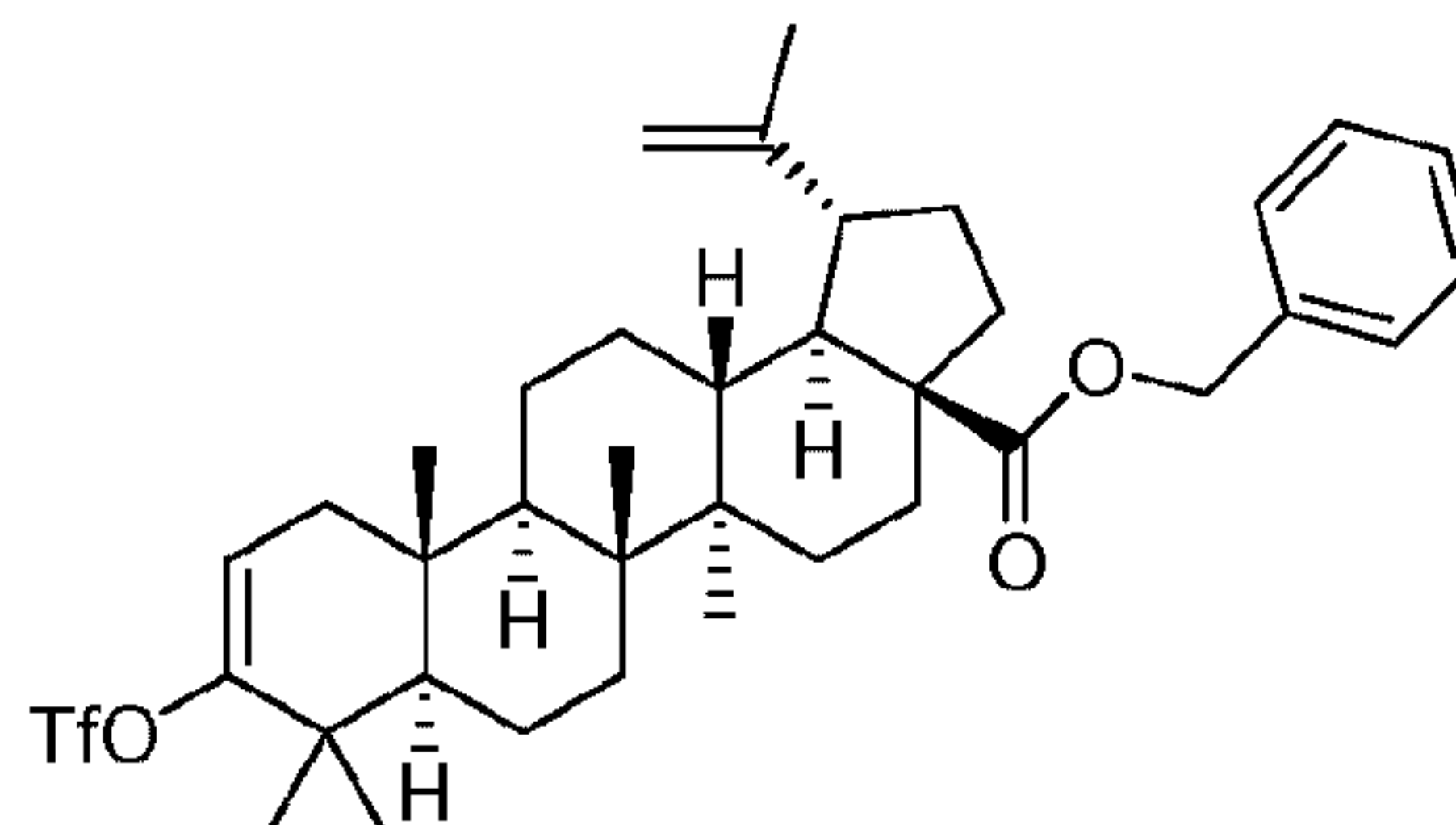
10

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.  $^1\text{H}$  NMR (500 MHz, *CHLOROFORM-d*)  $\delta$  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)-

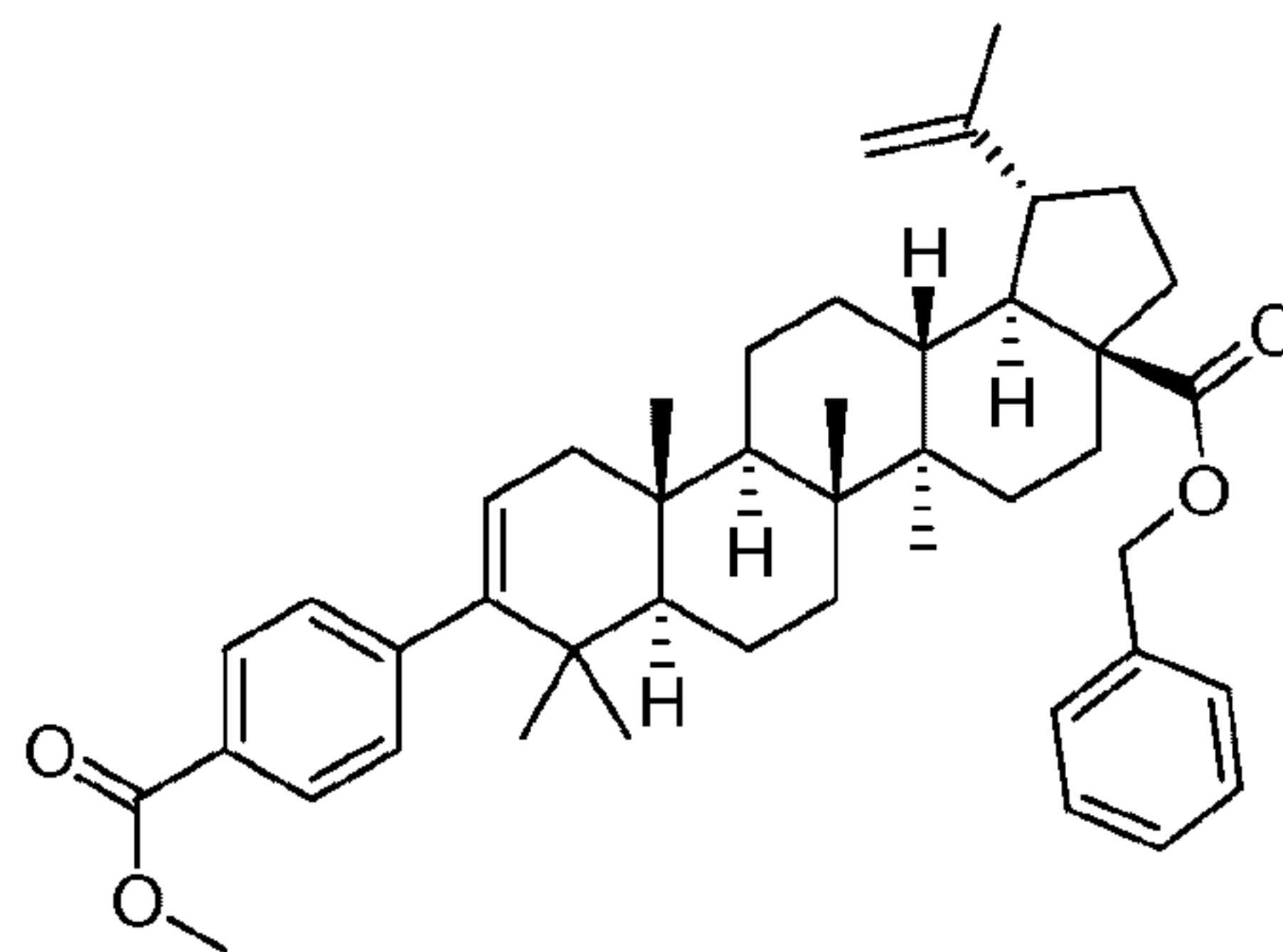
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



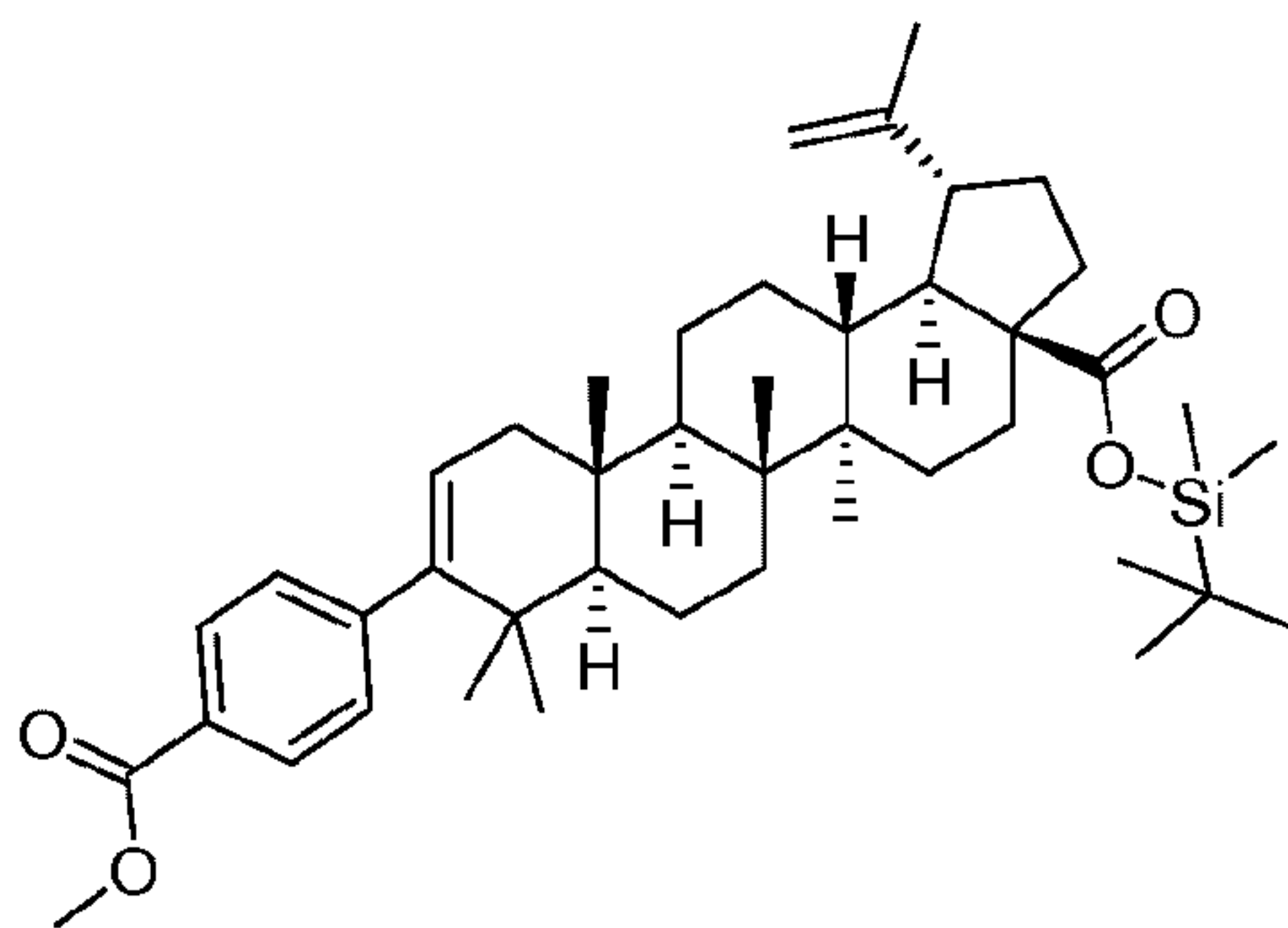
5 A solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (29.0 g, 53.2 mmol) in THF (200 mL) was cooled to -78 °C. To the solution was added KHMDS (0.5 M in toluene) (213 mL, 106 mmol). The yellow 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 MgSO<sub>4</sub>. 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<sub>f</sub> = 0.57 by silica gel TLC, 5% EtOAc in hexanes, visualized using Hanessian's stain. <sup>1</sup>H NMR (500 MHz,  
20 *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.



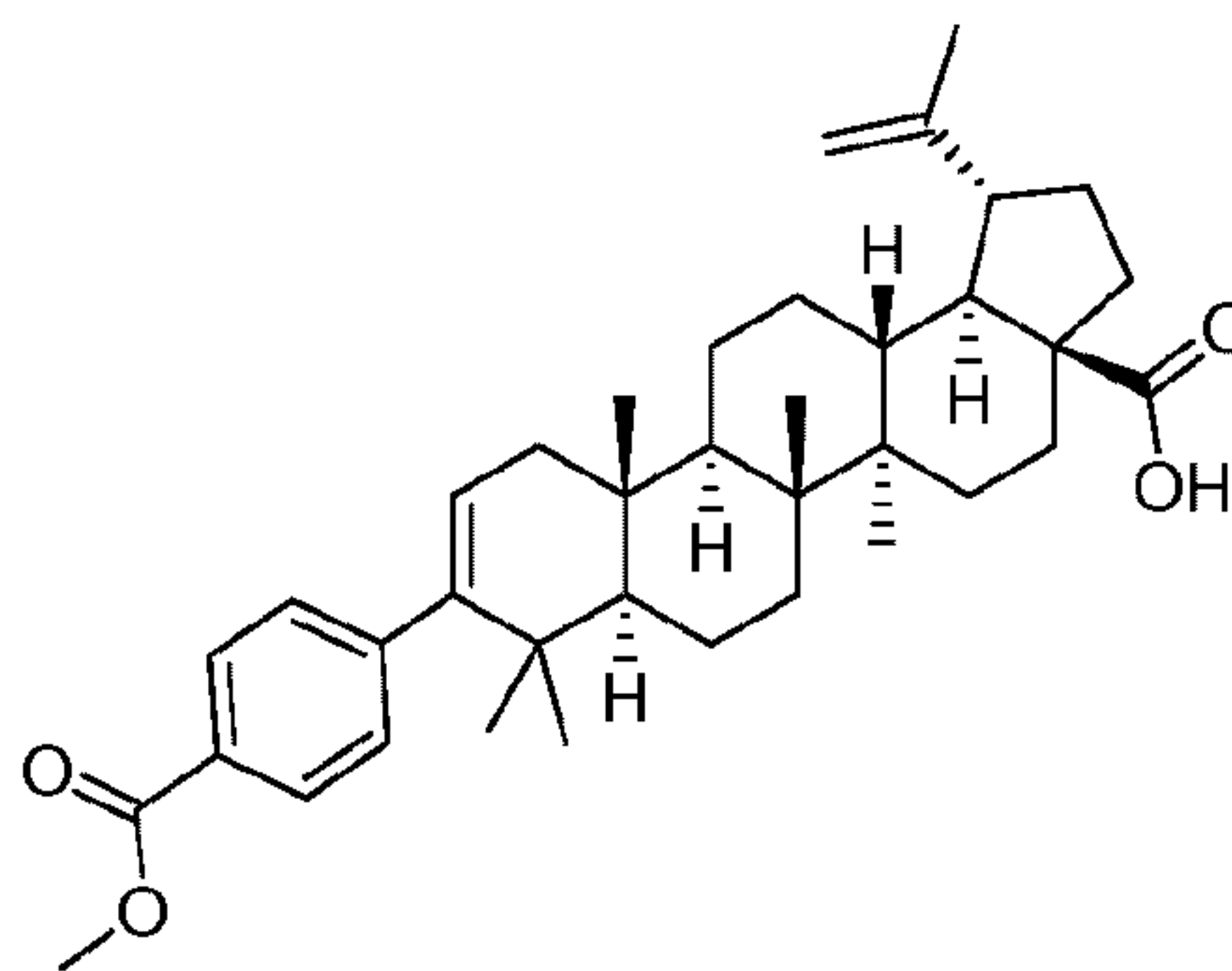
- To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(trifluoromethylsulfonyloxy)-
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (6.21 g, 9.18 mmol) in dioxane (25 mL) was added 2-propanol (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 N<sub>2</sub> 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 MgSO<sub>4</sub>, 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. <sup>1</sup>H 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 N<sub>2</sub> 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. <sup>1</sup>H 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).

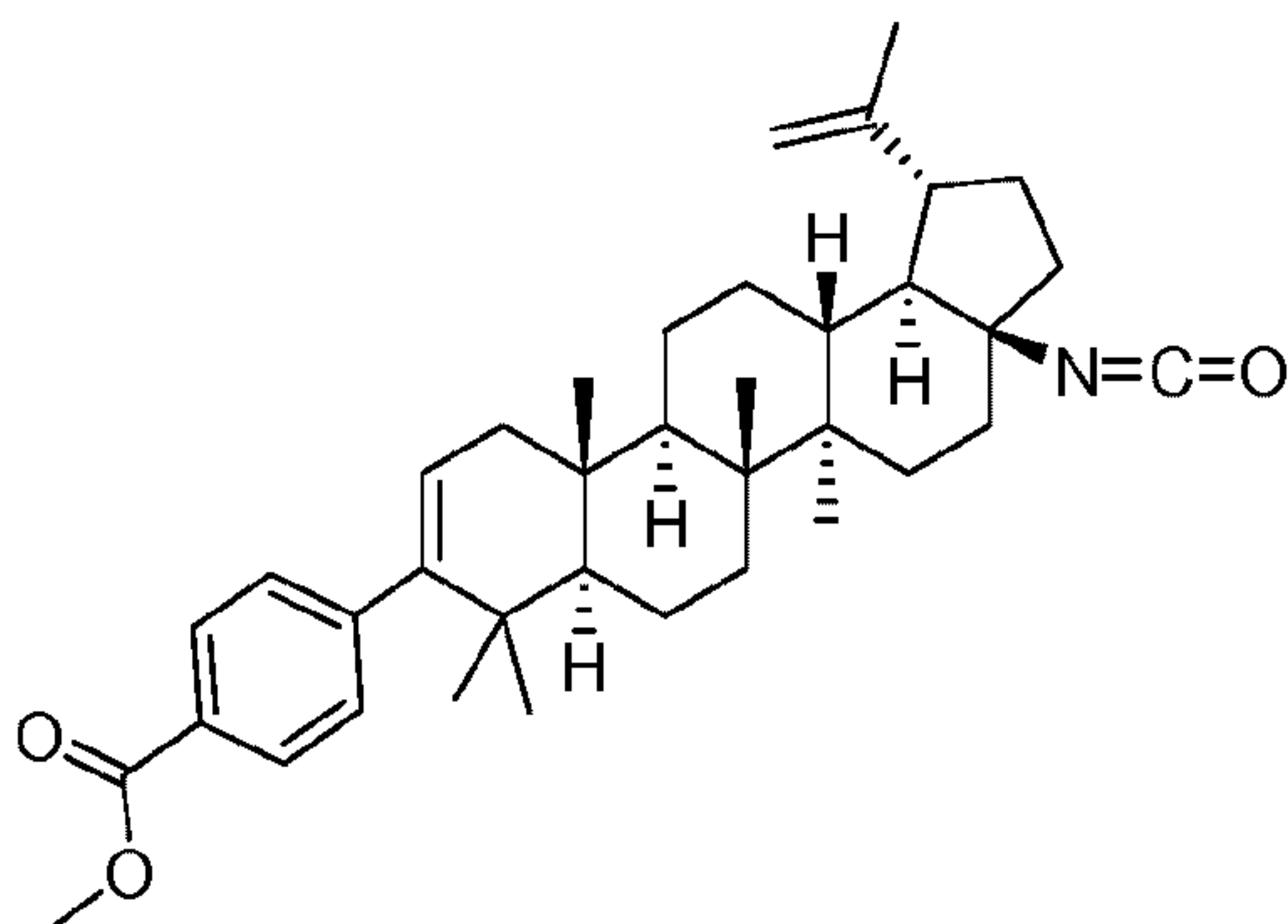
20

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-(prop-1-en-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 (3.12 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 dried over Na<sub>2</sub>SO<sub>4</sub>, 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)<sup>-</sup>, 3.60 min (method 1). <sup>1</sup>H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 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.

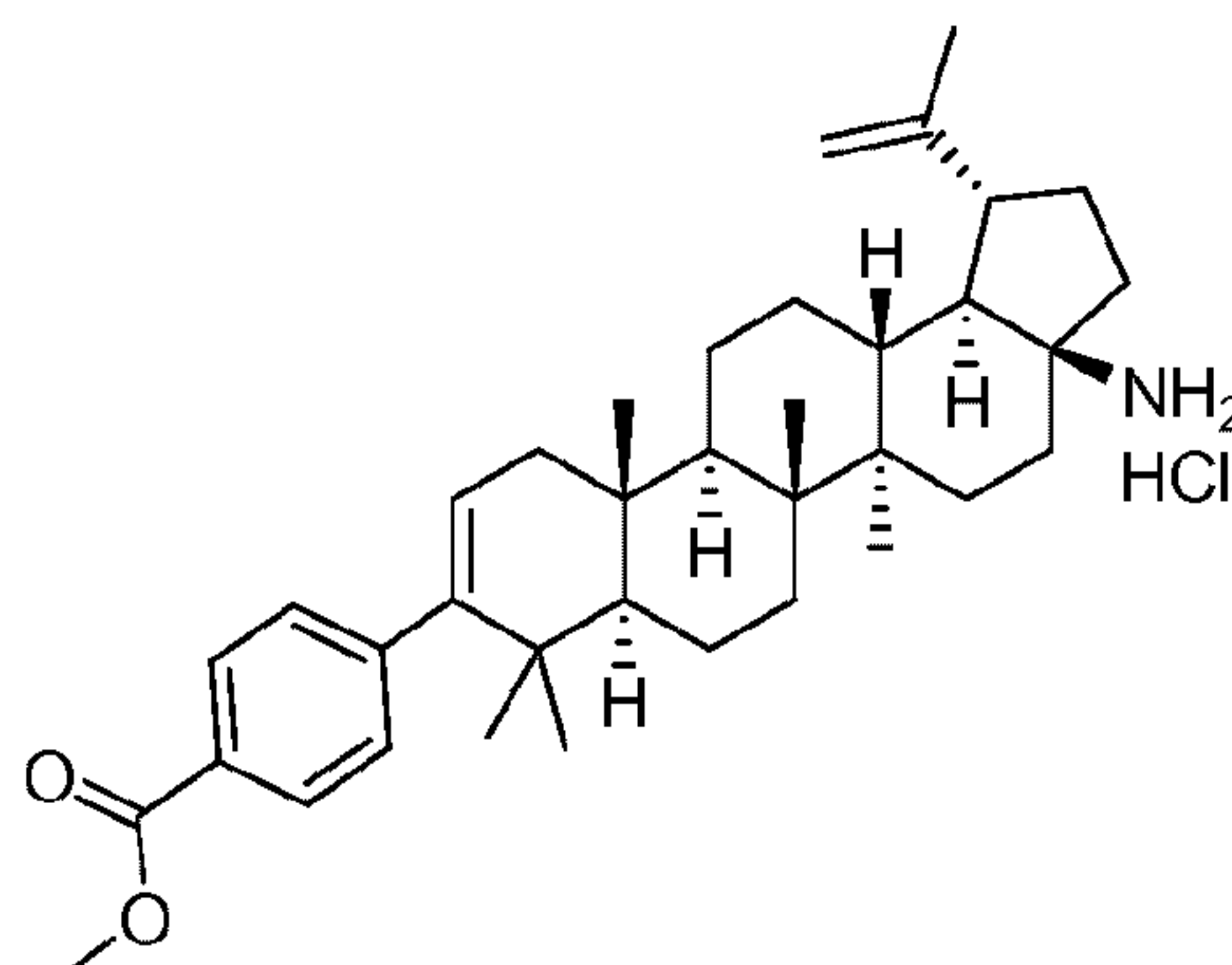


To a slurry of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (10 g, 17.46 mmol) in 1,4-dioxane (200 mL) was added triethylamine (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 Na<sub>2</sub>SO<sub>4</sub>, 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 Et<sub>2</sub>O. The liquid filtrate was concentrated to a yellow slurry which was filtered and washed with Et<sub>2</sub>O  
 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. <sup>1</sup>H 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  
 20 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.). <sup>13</sup>C 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.

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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.



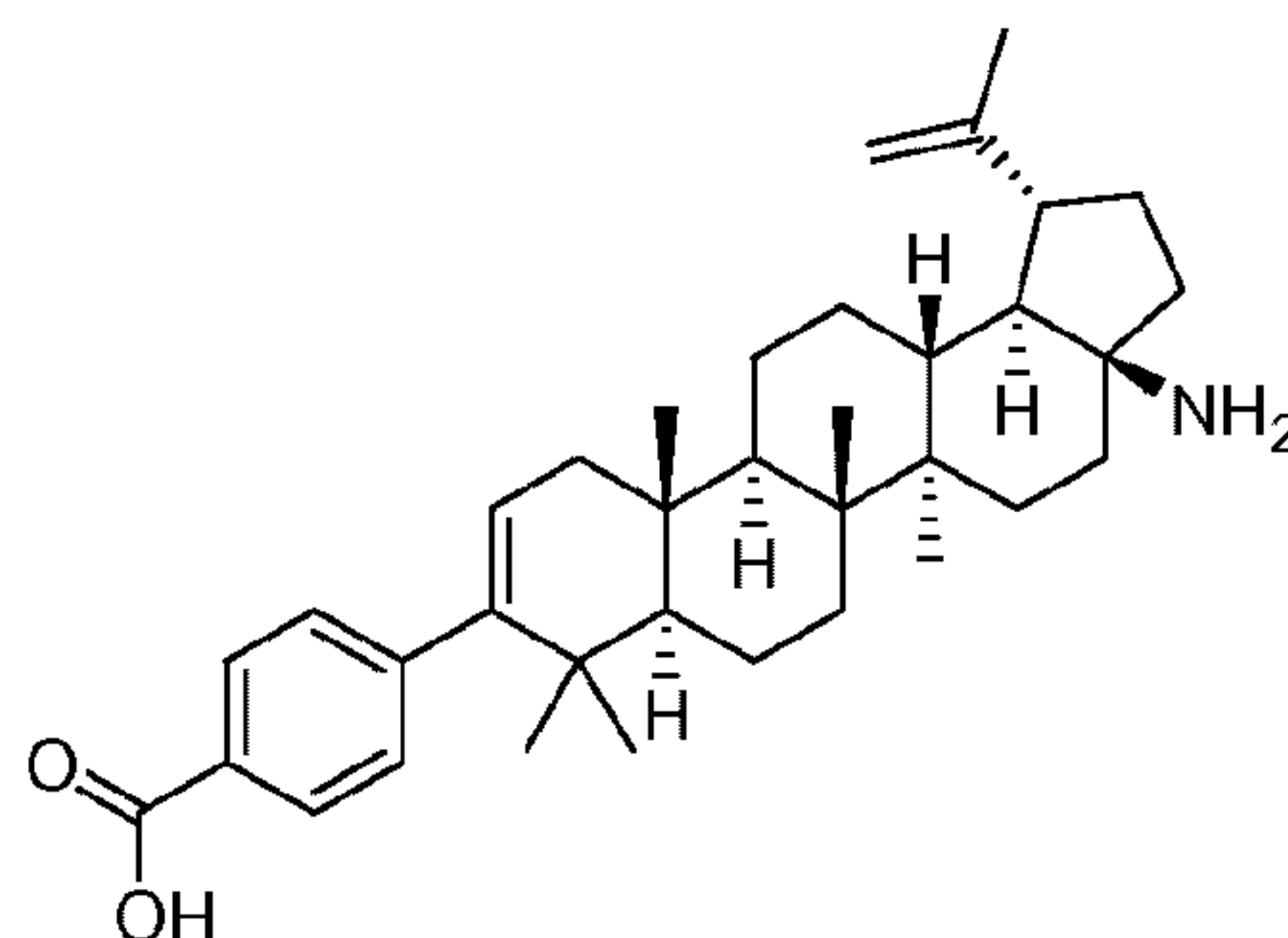
5

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 ( $M+H$ )<sup>+</sup>, 3.26 min (method 6). <sup>1</sup>H NMR (500 MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*, *MeOD* lock)  $\delta$  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).

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### 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



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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.

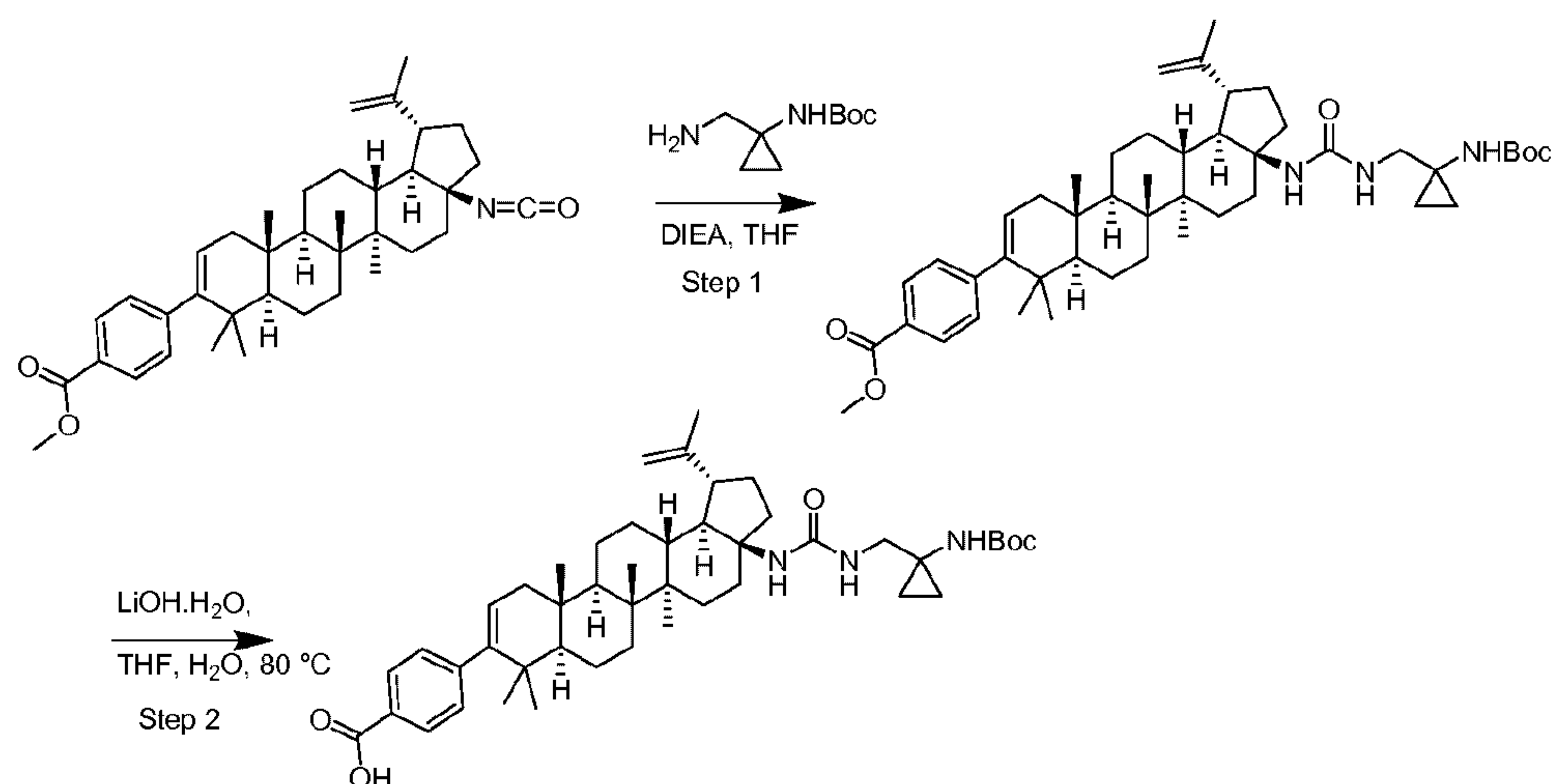
LCMS:  $m/z$  530 ( $M+H^+$ ), retention time 2.29 min (method 11).  $^1H$  NMR (500 MHz, 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  ppm 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 1.02 (s, 3 H) 1.06 (s, 3 H) 1.09 - 1.22 (m, 4 H) 1.22 - 1.30 (m, 1 H) 1.30 - 1.47 (m, 3 H) 1.49 - 1.57 (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).

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## Section 1. Ureas

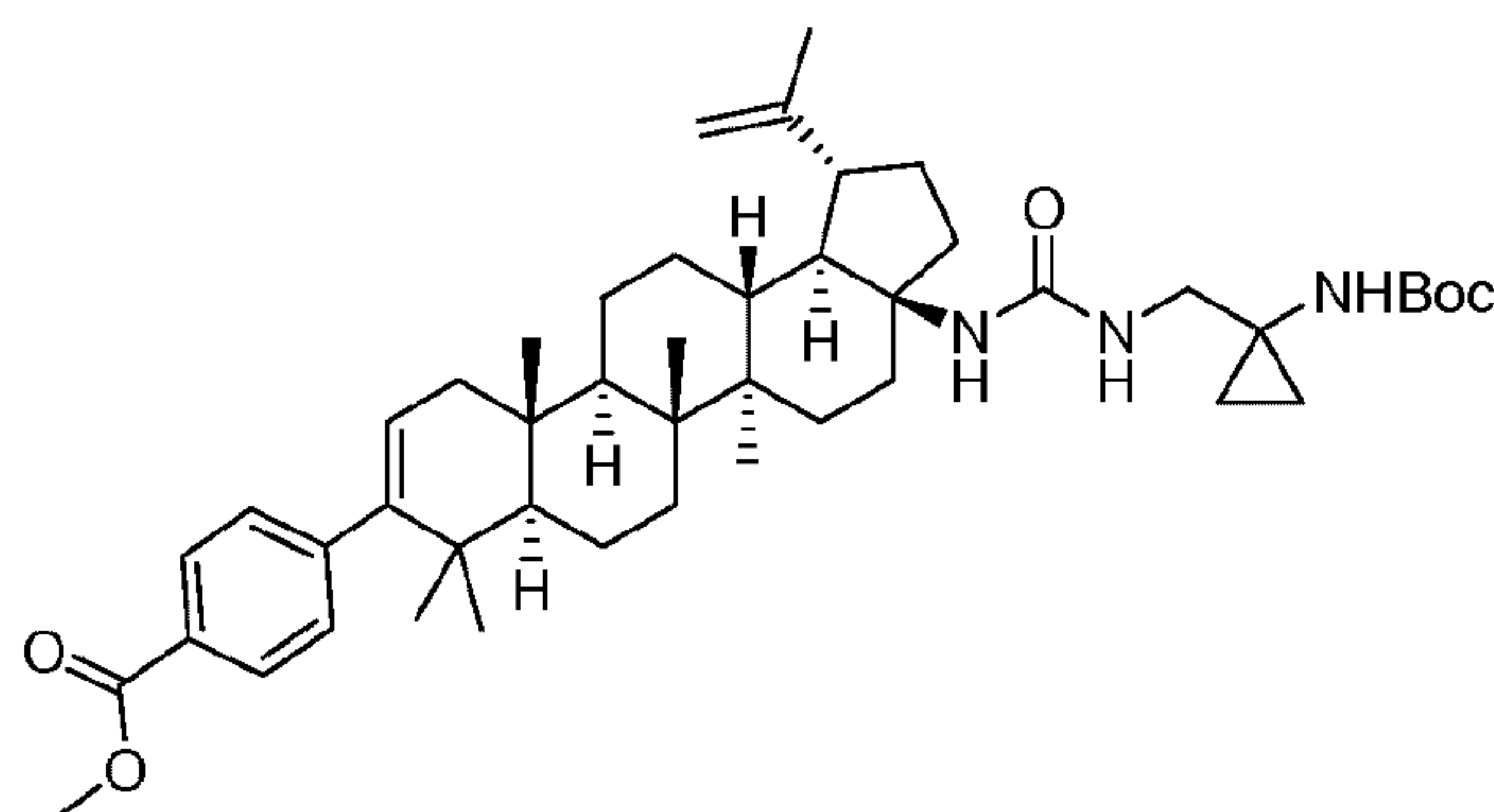
## Example 2

- 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.

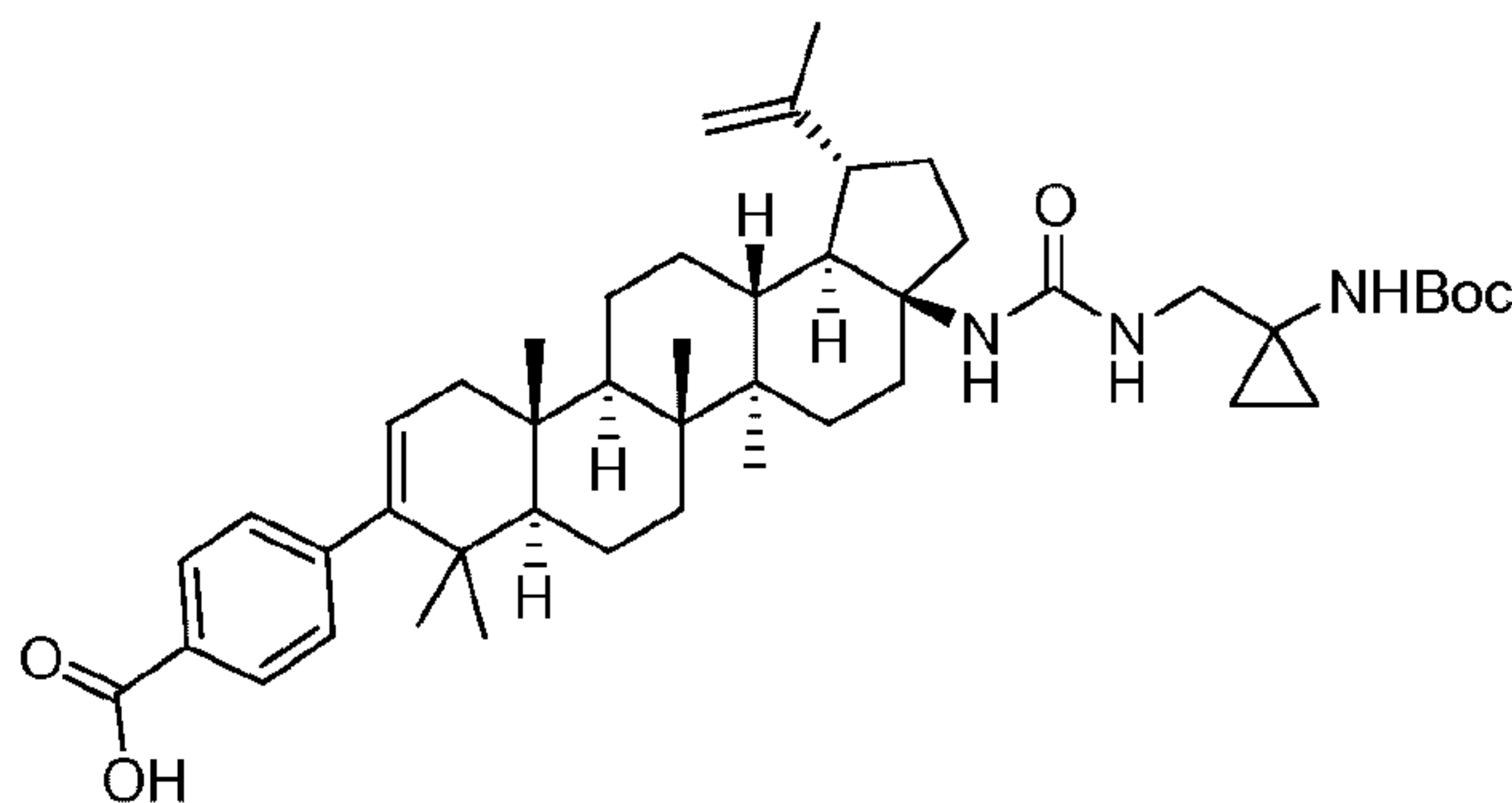


15

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 ( $M+H$ )<sup>+</sup>, 2.75 min (method 7). <sup>1</sup>H NMR (500 MHz, *CHLOROFORM-d*)  $\delta$  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). <sup>13</sup>C NMR (*CHLOROFORM-d*)  $\delta$  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.

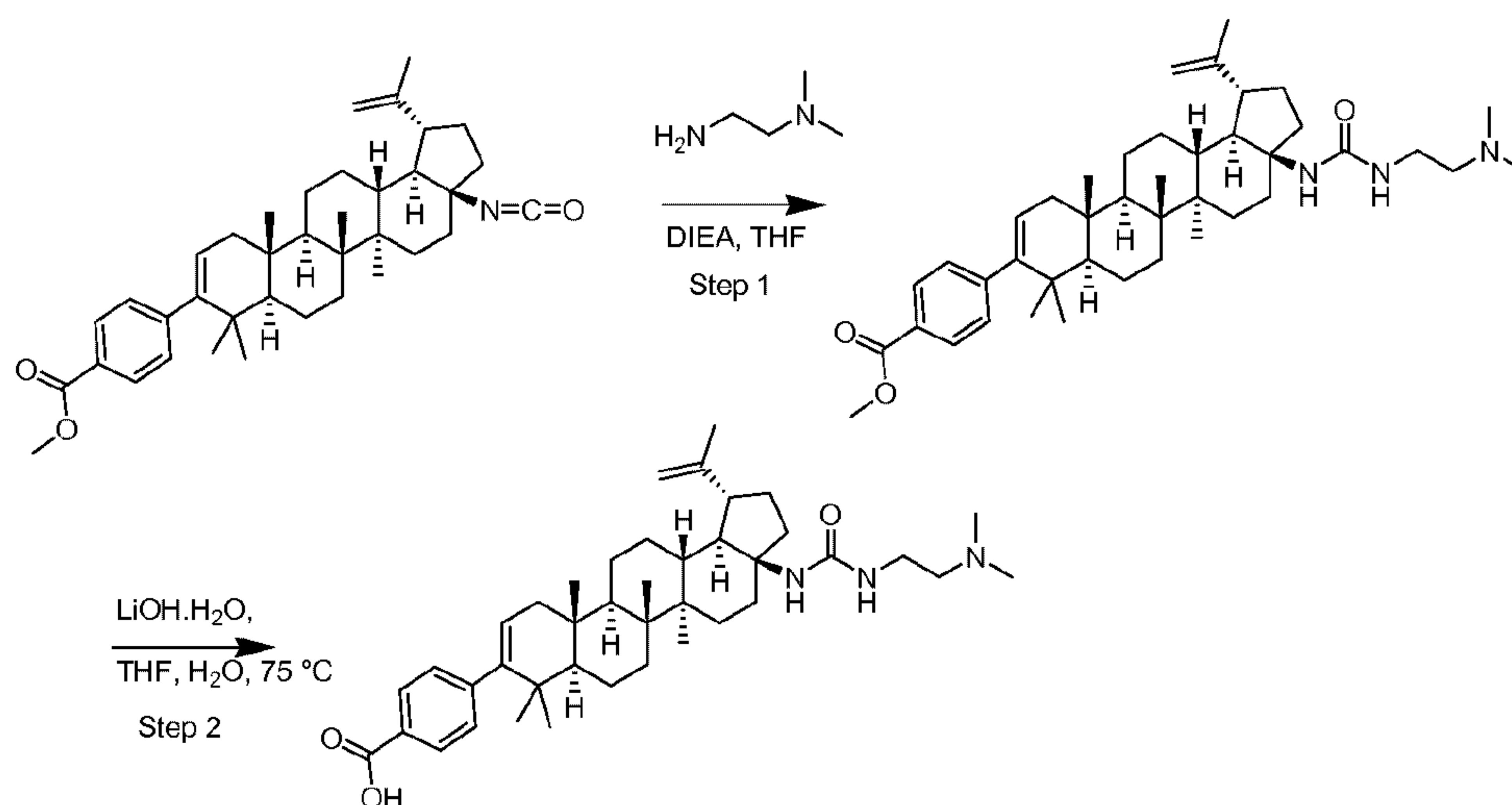


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

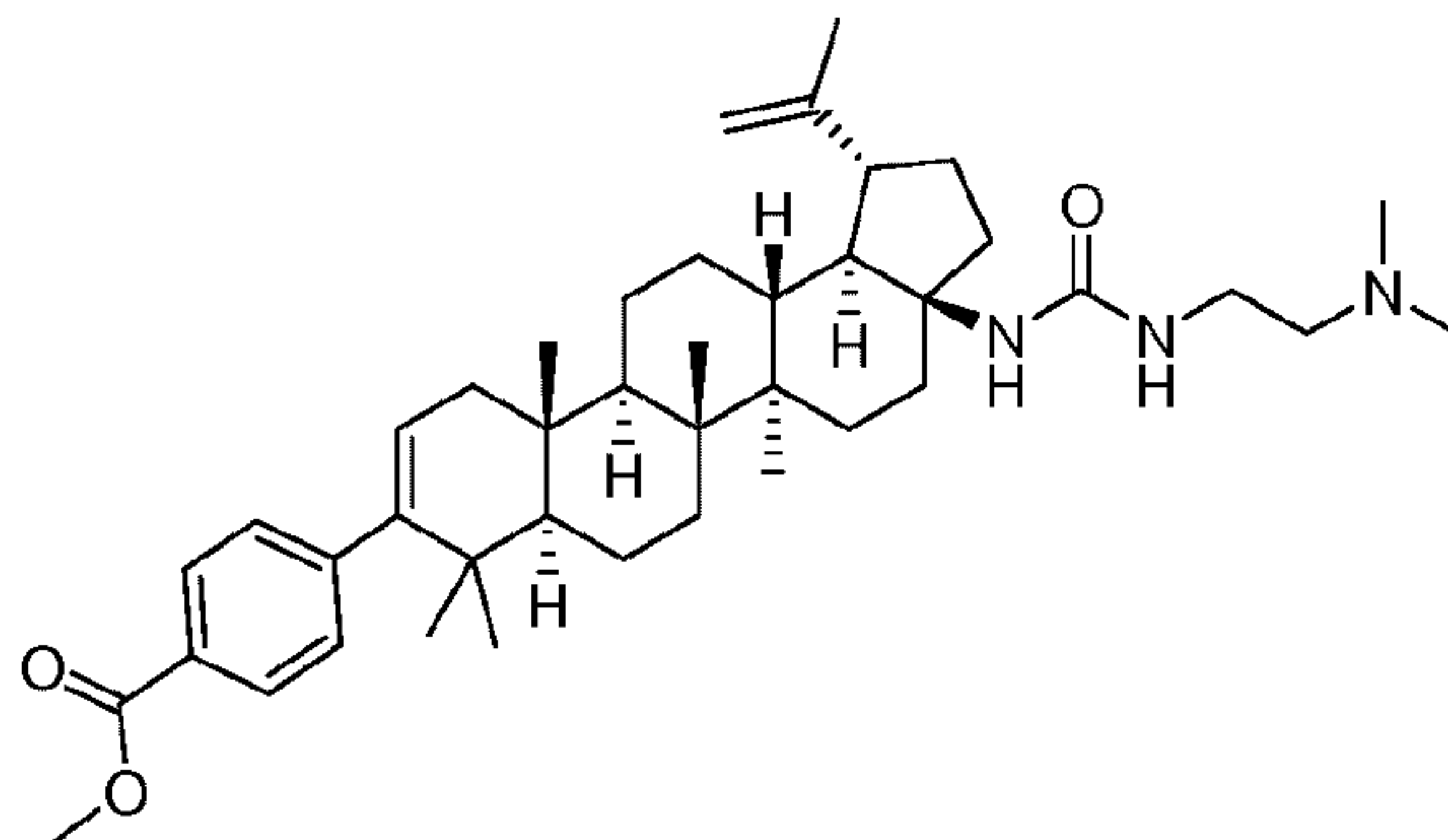
octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (91 mg, 0.12 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (20.2 mg, 0.481 mmol) in water (1.00 mL). The reaction mixture was stirred at 80 °C for 3 h. The reaction was concentrated and purified by reversed phase preparative HPLC using prep HPLC method 2. HPLC fractions containing product peaks were treated with saturated aqueous NaHCO<sub>3</sub> solution (100 mL), combined and concentrated. The resulting residue was triturated with H<sub>2</sub>O (8 mL) and extracted with a mixture of THF (30 mL) and EtOAc (50 mL). The organic layer was washed with brine, dried over MgSO<sub>4</sub>, 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)<sup>+</sup>, 2.13 min (method 6). <sup>1</sup>H 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). <sup>13</sup>C 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.



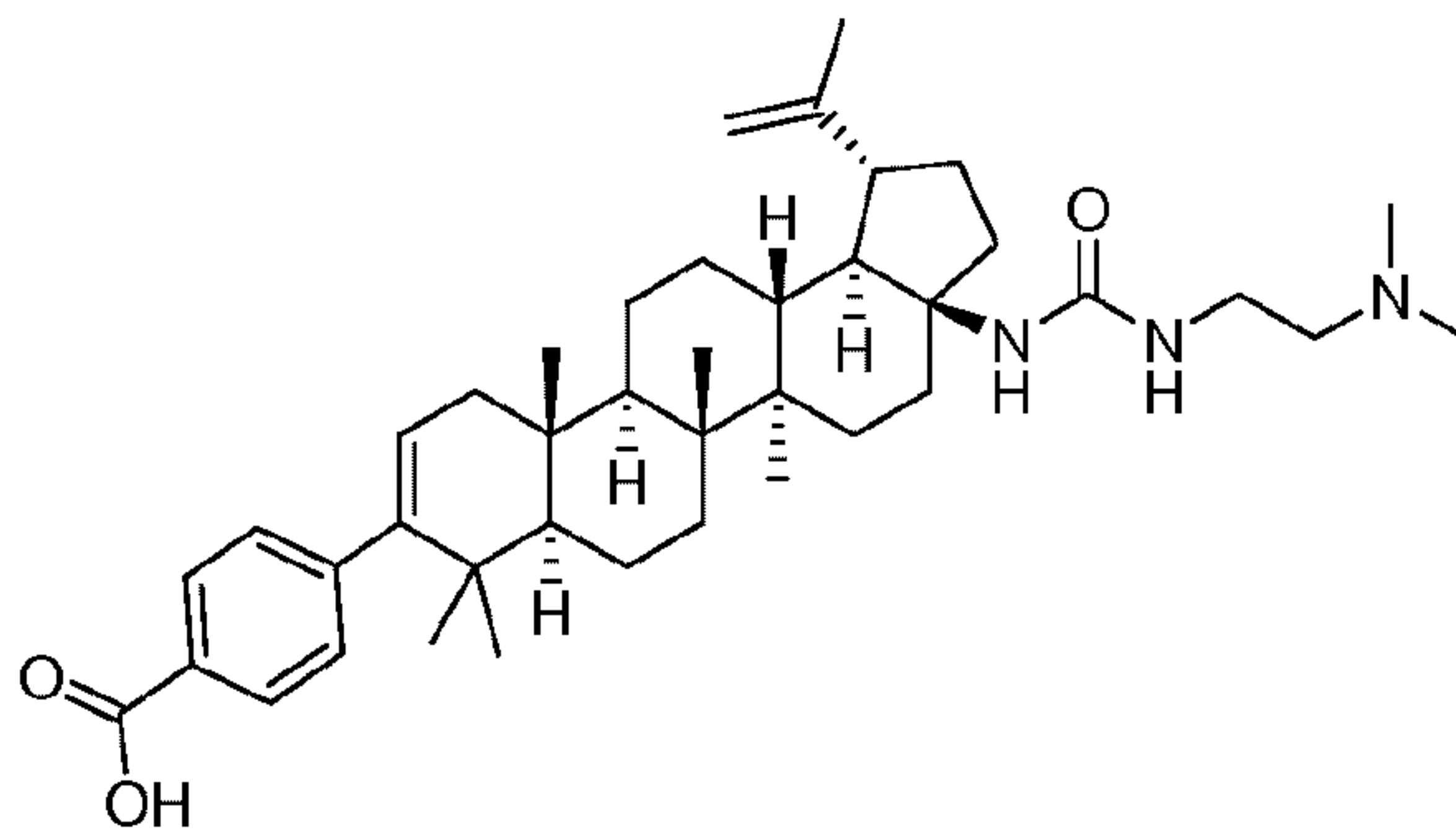
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-  
 10 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  
 15 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 Et<sub>2</sub>O. 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 ( $M+H$ )<sup>+</sup>, 4.25 min (method 8). <sup>1</sup>H NMR (500 MHz, *CHLOROFORM-d*)  $\delta$  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). <sup>13</sup>C NMR (*CHLOROFORM-d*)  $\delta$  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.



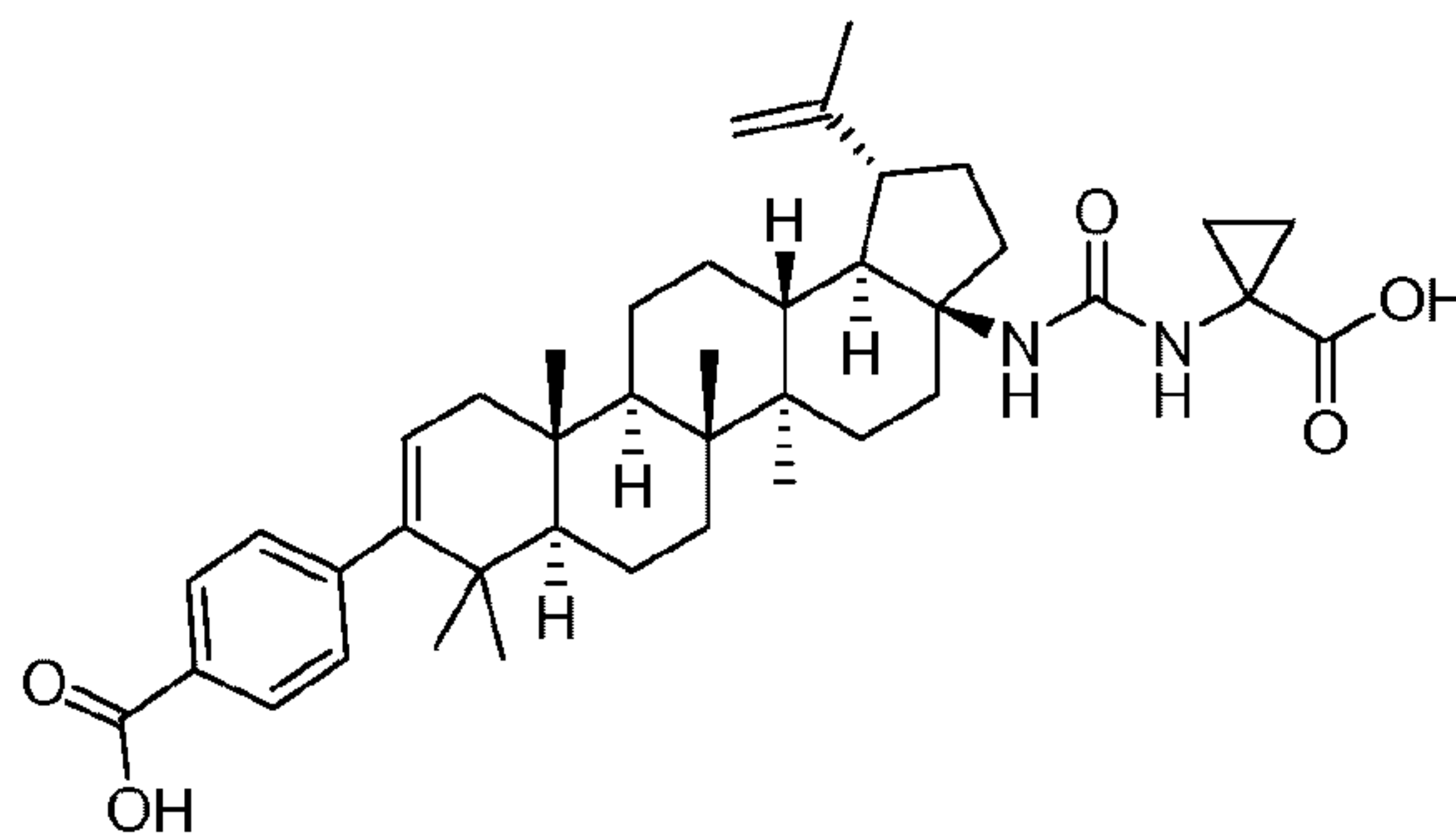
To a cloudy solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.255 g, 0.388 mmol) in THF (5 mL) was 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 ( $M+H$ )<sup>+</sup>, 3.95 min (method 8). <sup>1</sup>H NMR (500 MHz, *MeOD*)  $\delta$  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). <sup>13</sup>C NMR (*MeOD*)  $\delta$  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.

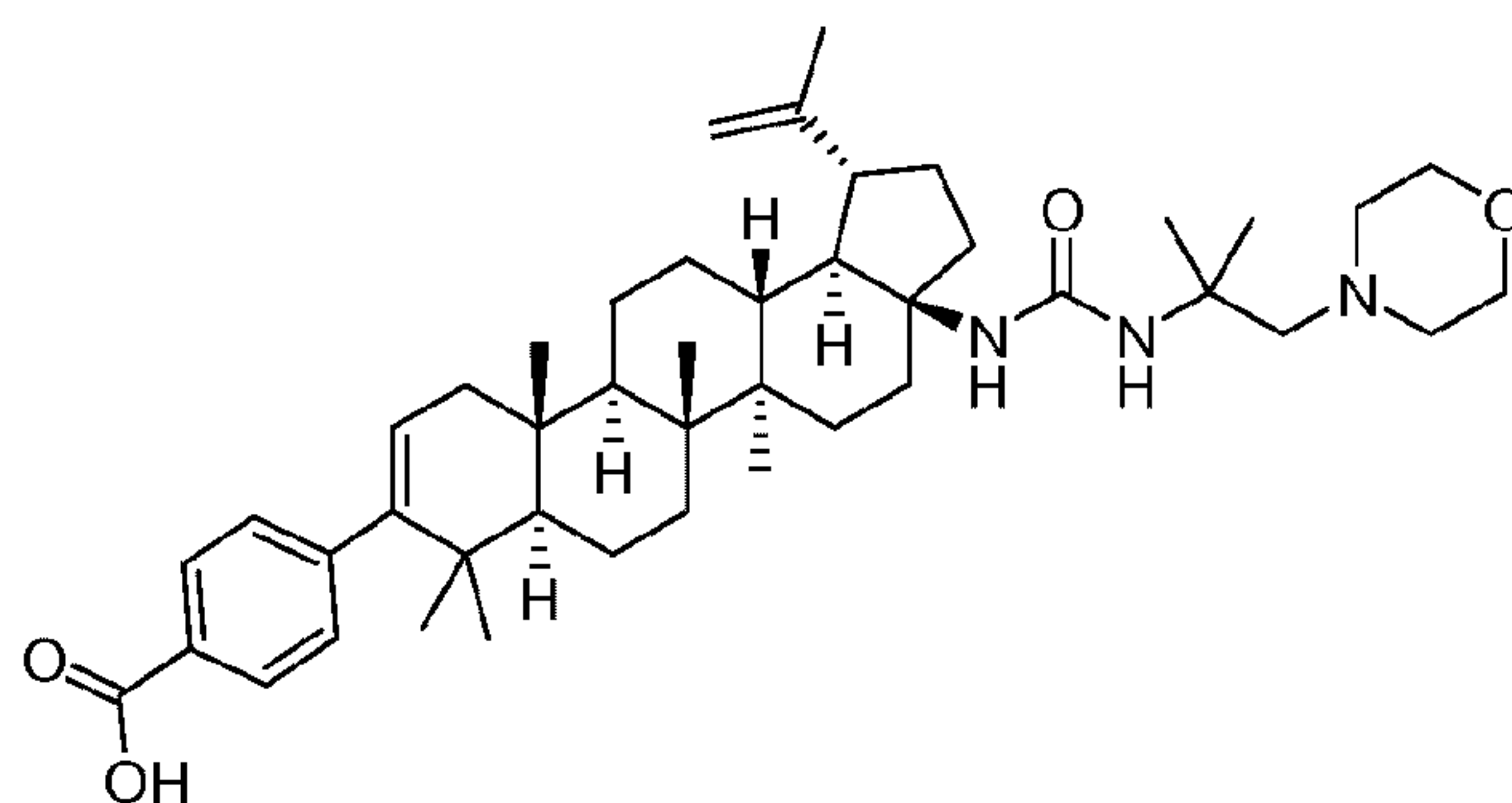


The title compound was prepared in 25% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described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

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 ( $M+H$ )<sup>+</sup>, 4.18 min (method 8). <sup>1</sup>H NMR (500 MHz,  
*MeOD*)  $\delta$  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-

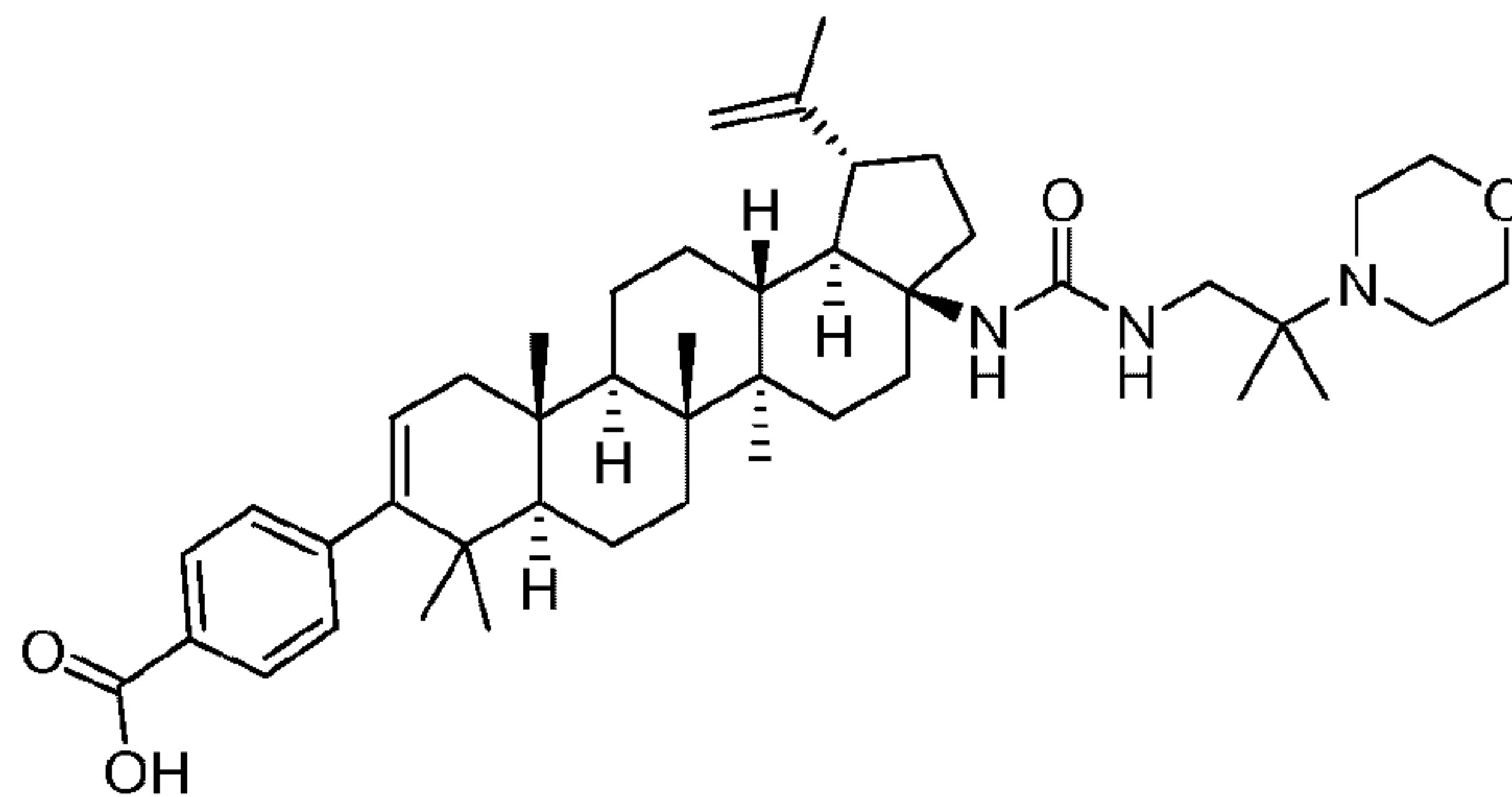
amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: *m/e* 714.3 ( $M+H$ )<sup>+</sup>, 3.97 min (method 8). <sup>1</sup>H NMR (500 MHz, *MeOD*)  $\delta$  ppm 7.9 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=4.6 Hz), 4.7 (1 H, br. s.), 2.5 - 2.7 (1 H, m), 2.2 (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),  
 5 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

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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.

15

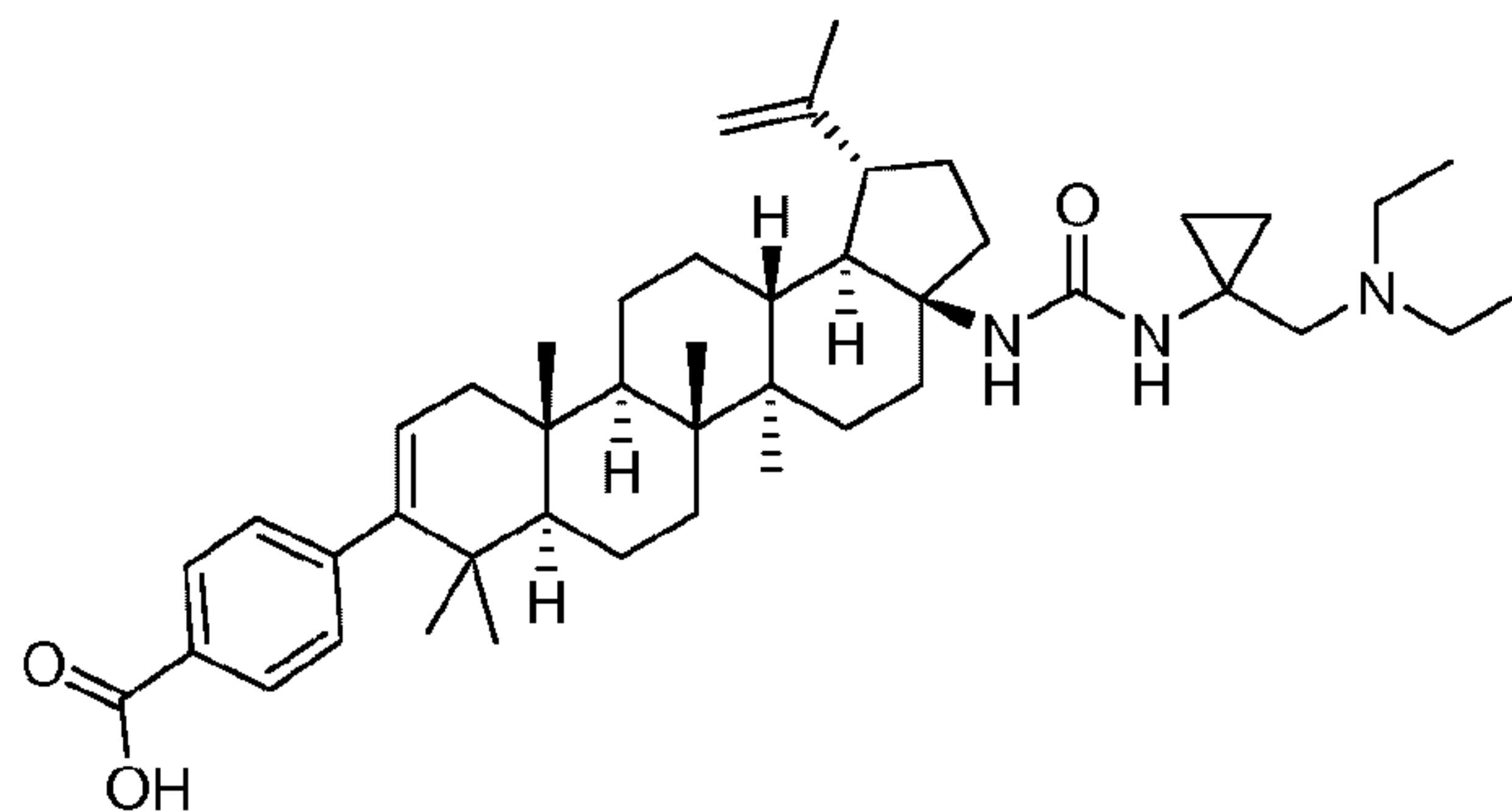


The title compound was prepared in 20% yield from methyl 4-((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,11*aS*,11*bR*,13*aR*,13*bR*)-3*a*-isocyanato-5*a*,5*b*,8,8,11*a*-pentamethyl-1-(prop-1-en-2-yl)-2,3,3*a*,4,5,5*a*,5*b*,6,7,7*a*,8,11,11*a*,11*b*,12,13,13*a*,13*b*-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl)benzoate 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-  
 20 amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: *m/e* 714.3 ( $M+H$ )<sup>+</sup>, 3.95 min (method 8). <sup>1</sup>H NMR (500 MHz, *MeOD*)  $\delta$  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,  
 25

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.



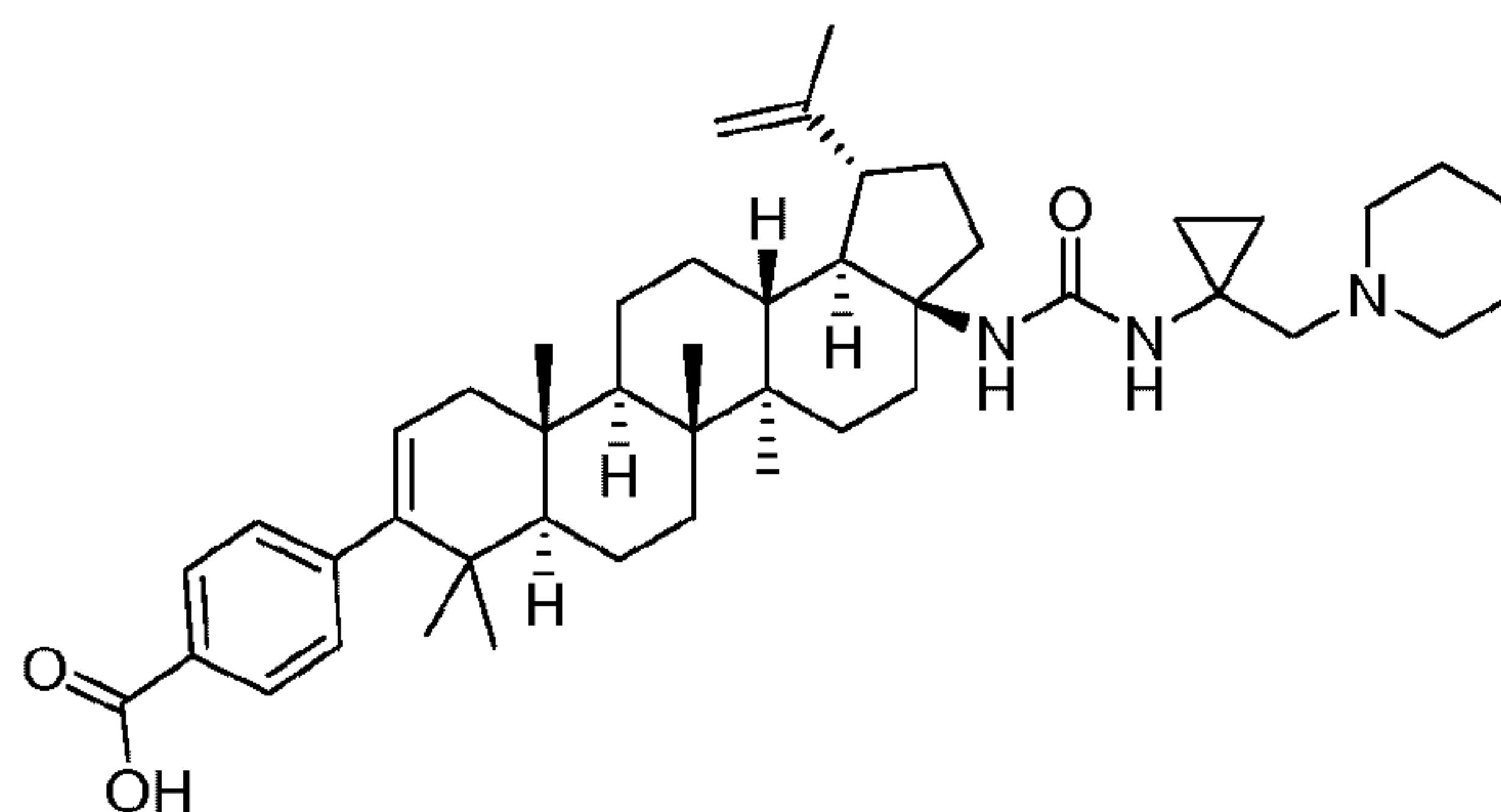
15 The title compound was prepared in 25% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described 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 ( $M+H$ )<sup>+</sup>, 3.97 min (method 8).  
 25 <sup>1</sup>H NMR (500 MHz, *MeOD*)  $\delta$  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

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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.



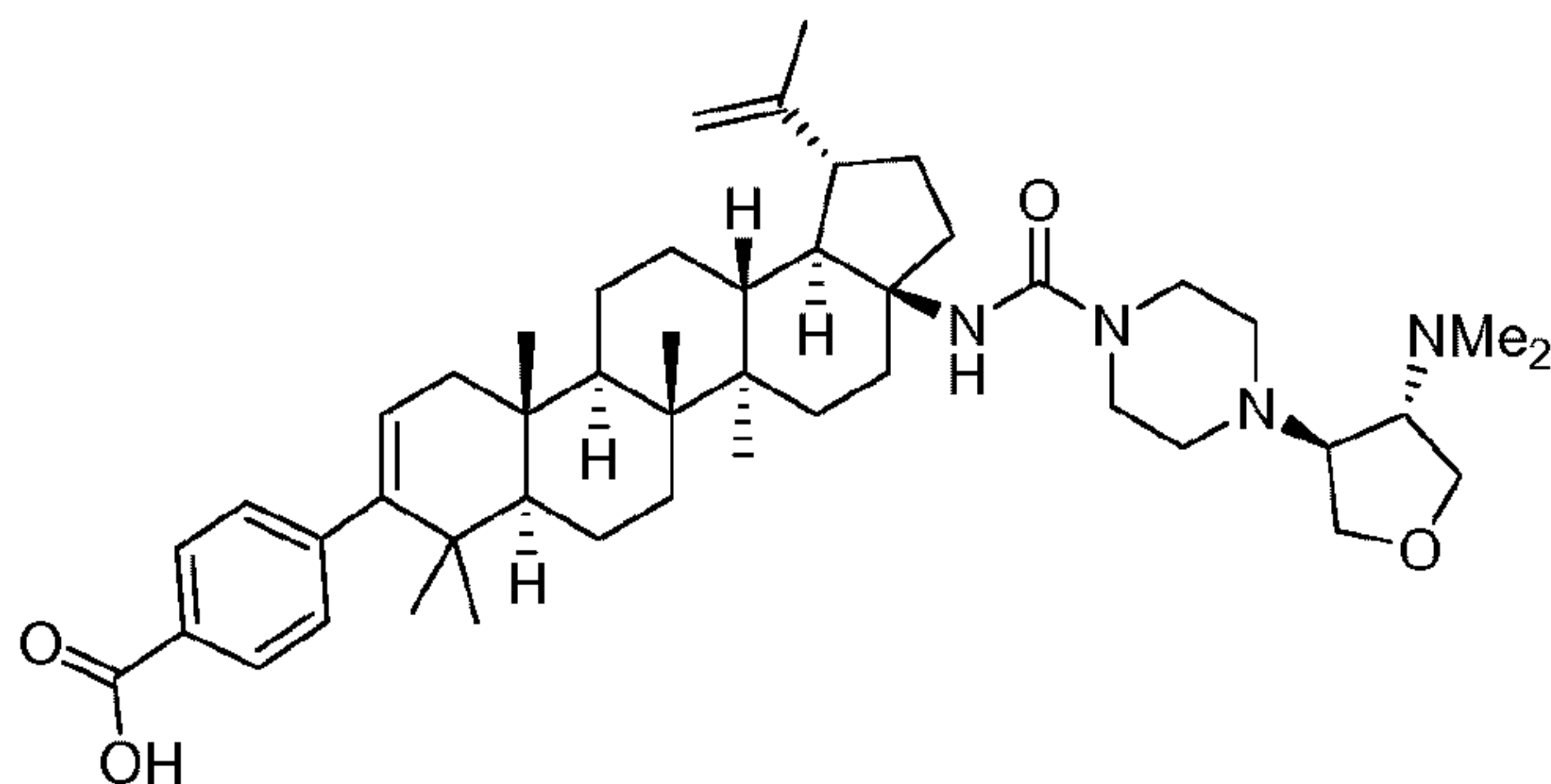
10

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 ( $M+H$ )<sup>+</sup>, 2.00 min (method 6). <sup>1</sup>H NMR (500 MHz, *MeOD*)  $\delta$  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

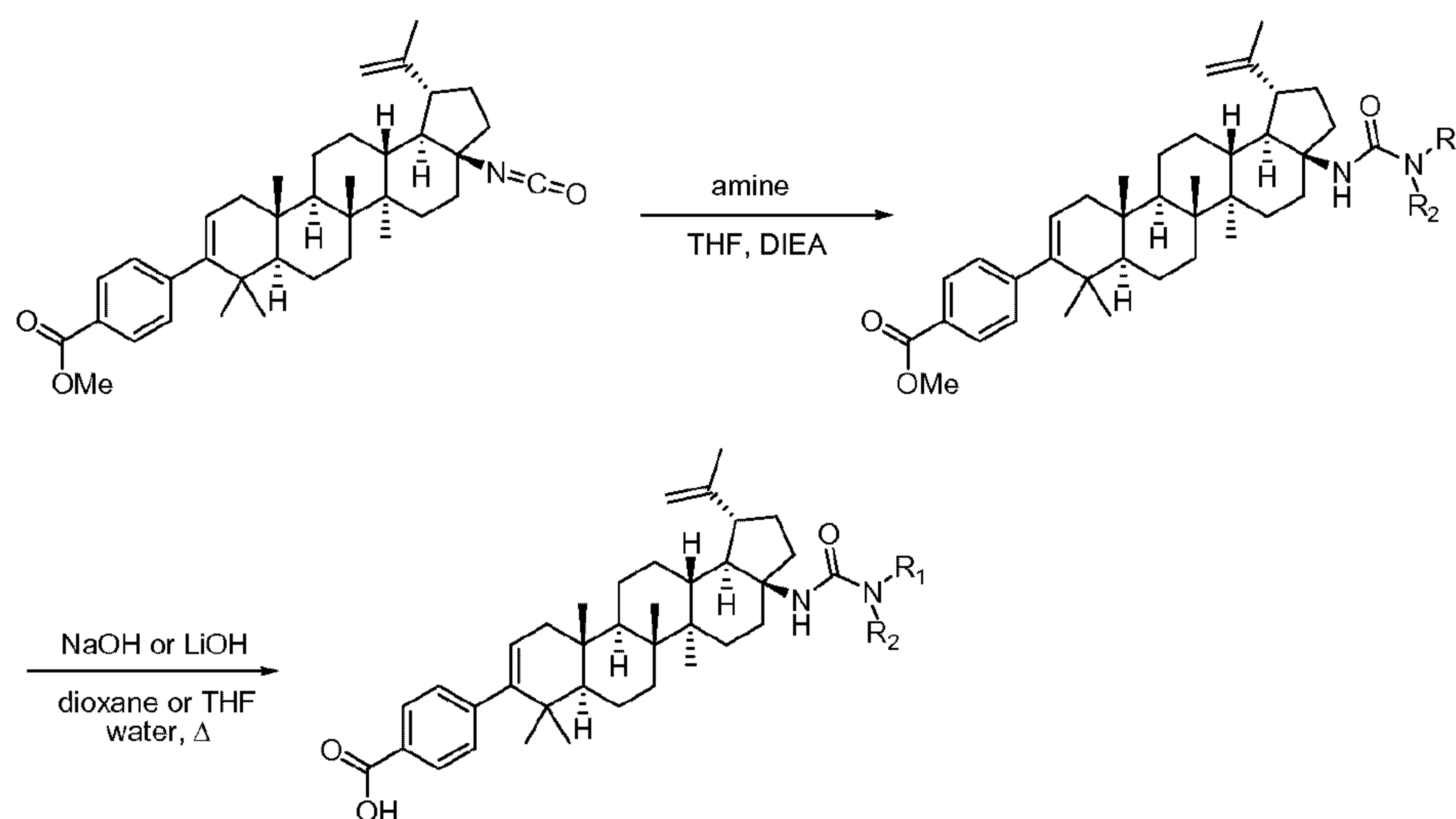
### Example 9

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



10 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)-  
15 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)<sup>+</sup>, 1.85 min (method 6). <sup>1</sup>H NMR (500MHz,   
20 *METHANOL-d<sub>4</sub>*) 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  
25 (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·H<sub>2</sub>O.

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.

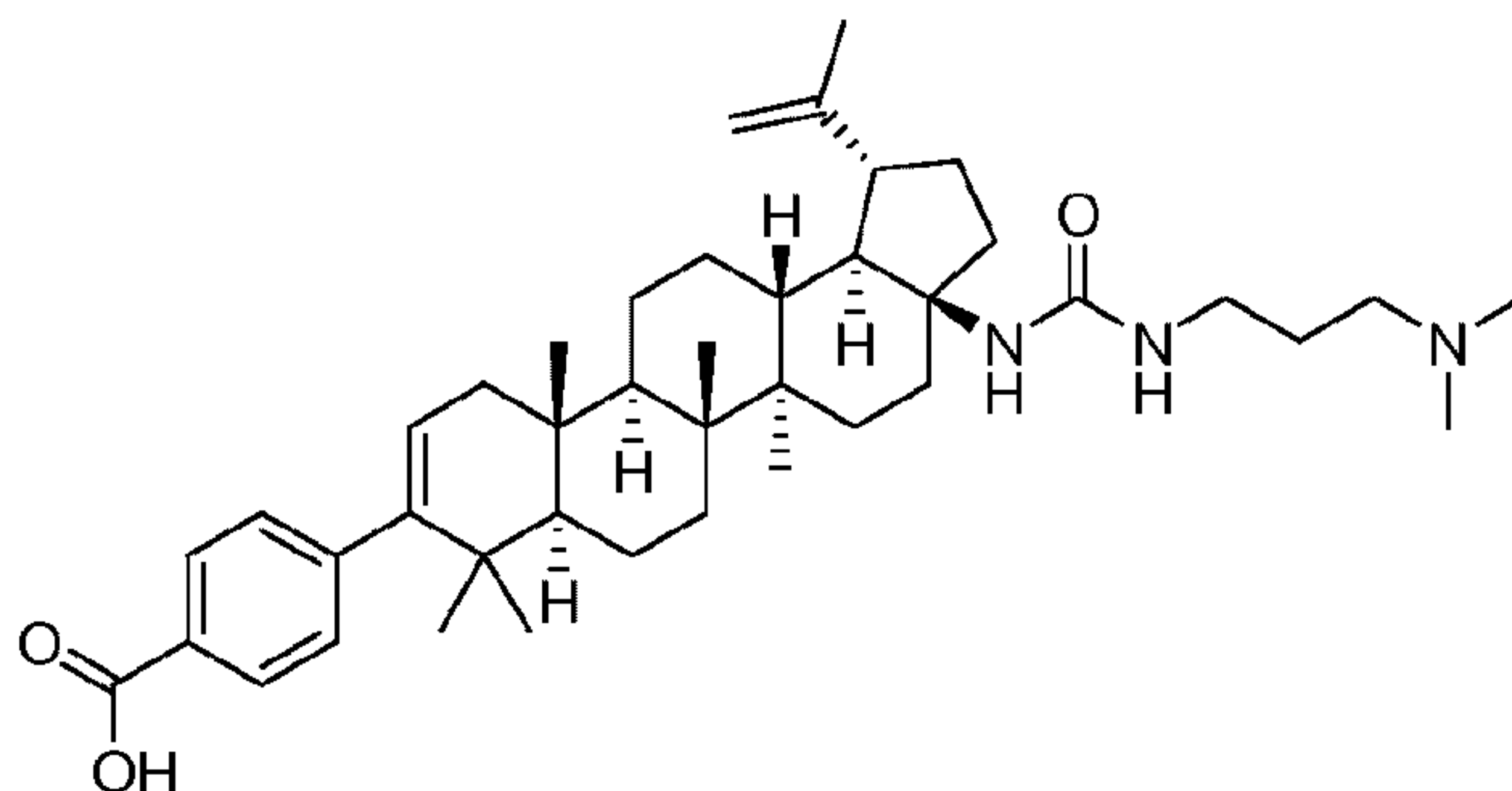
Alternatively, the ester hydrolysis can be carried out as follows: The C-17 urea formed in Step 1 above was dissolved in either 1,4-dioxane or THF to give approximately a 0.1M solution. To the solution was added water (ratio 4:1 or 5:1

organic 1,4-dioxane or THF: water) followed by LiOH·H<sub>2</sub>O (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

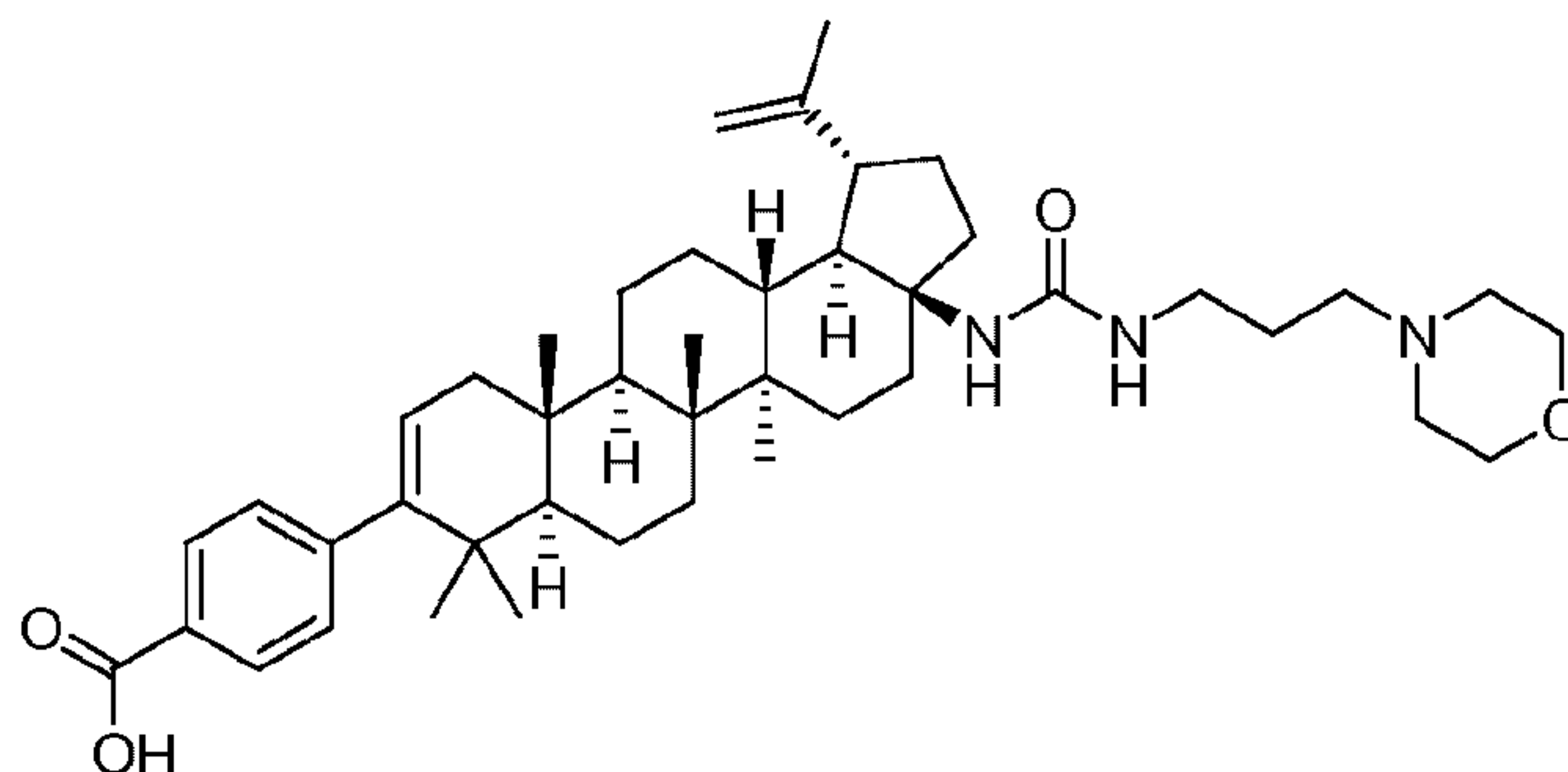
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(dimethylamino)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 10 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



15 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1*-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<sup>+</sup>), retention time 1.86 min (method 2). <sup>1</sup>H  
 20 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  
 25 (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).

### Example 11

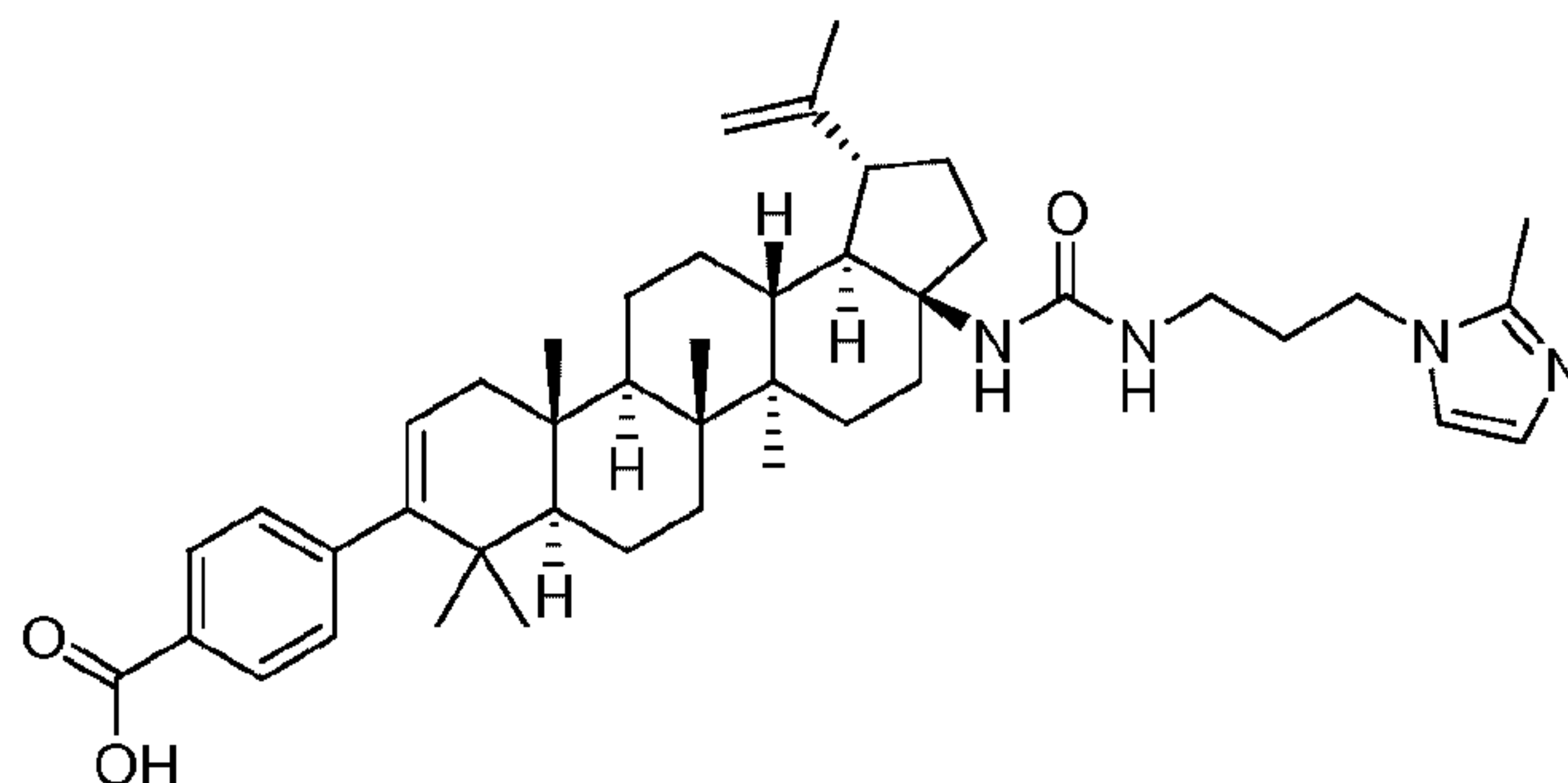
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-morpholinopropyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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*)  $\delta$  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

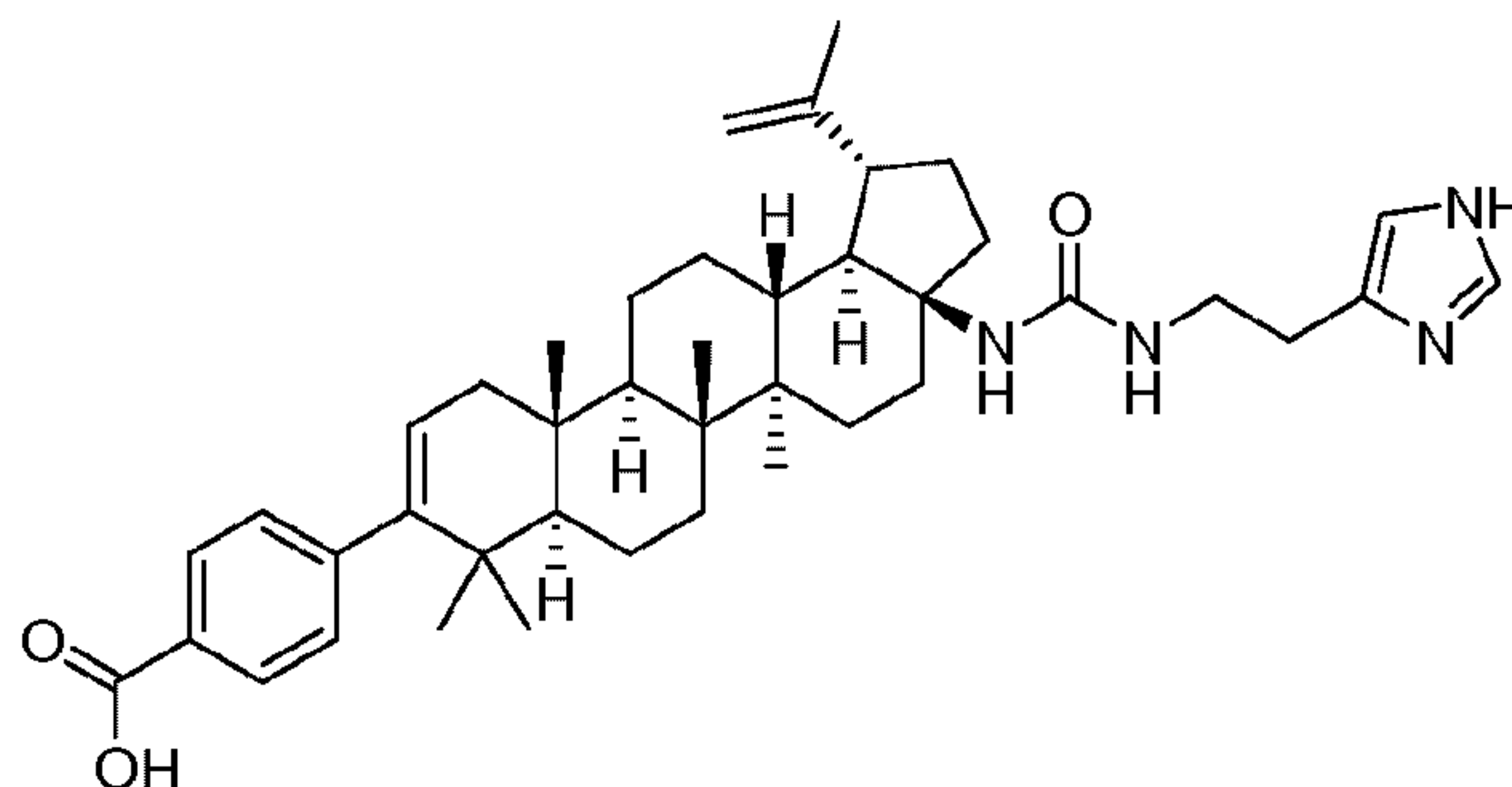
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(2-methyl-1H-imidazol-1-yl)propyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 3-(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  
 15 (method 2).  $^1H$  NMR (500 MHz, *MeOD*)  $\delta$  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).  
 20

### Example 13

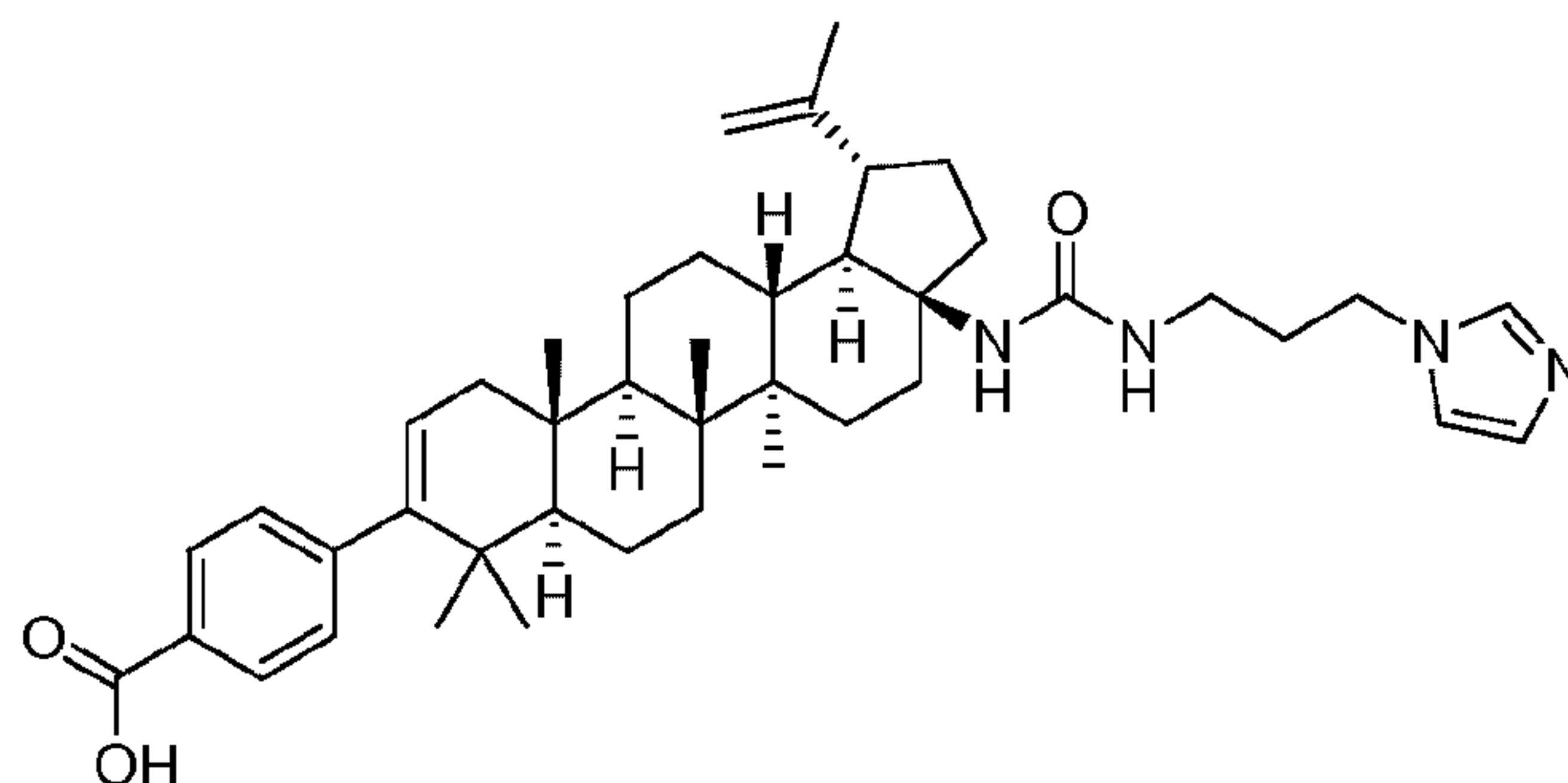
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-4-yl)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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*)  $\delta$  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

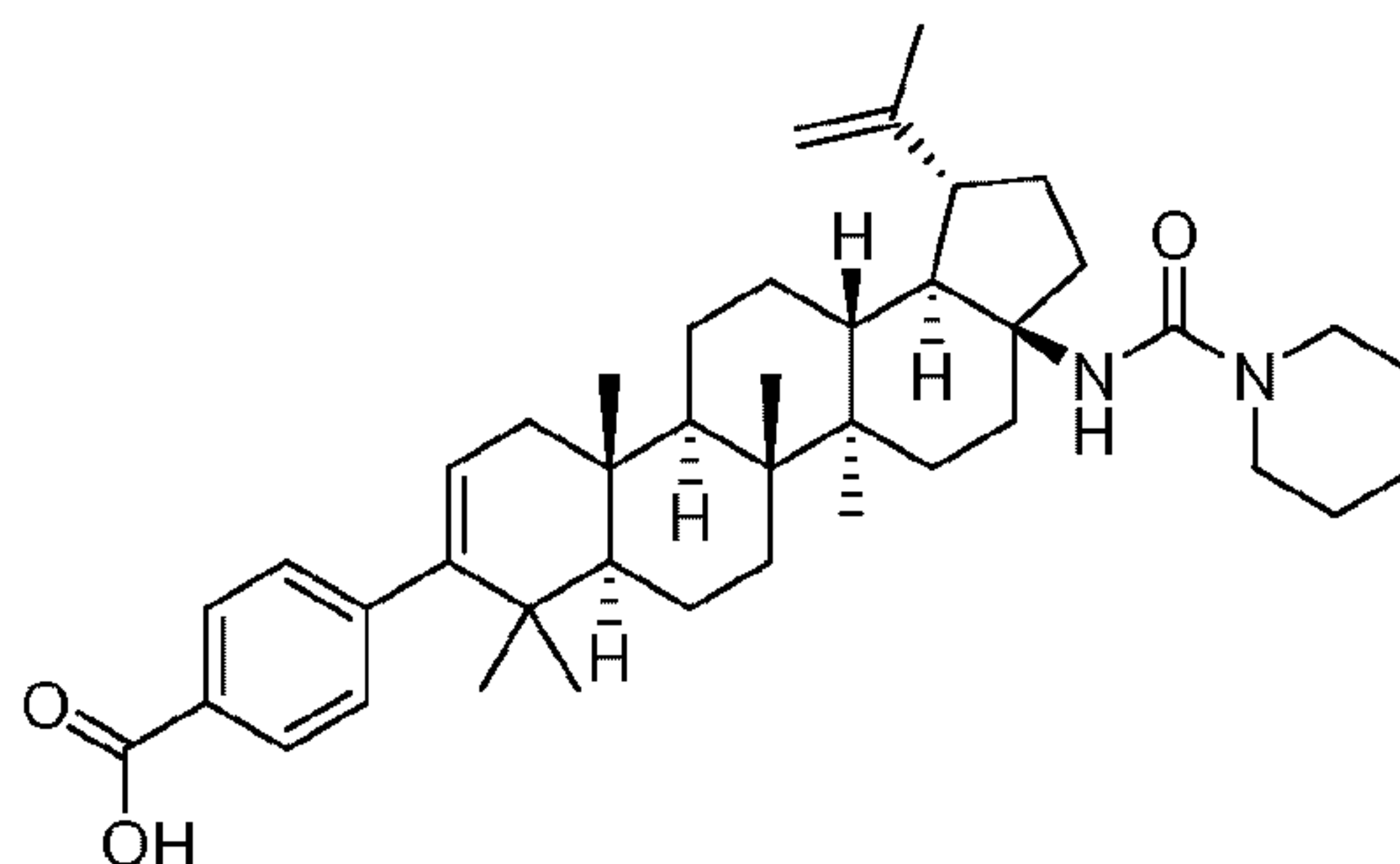
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(1H-imidazol-1-yl)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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*)  $\delta$  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).

### Example 15

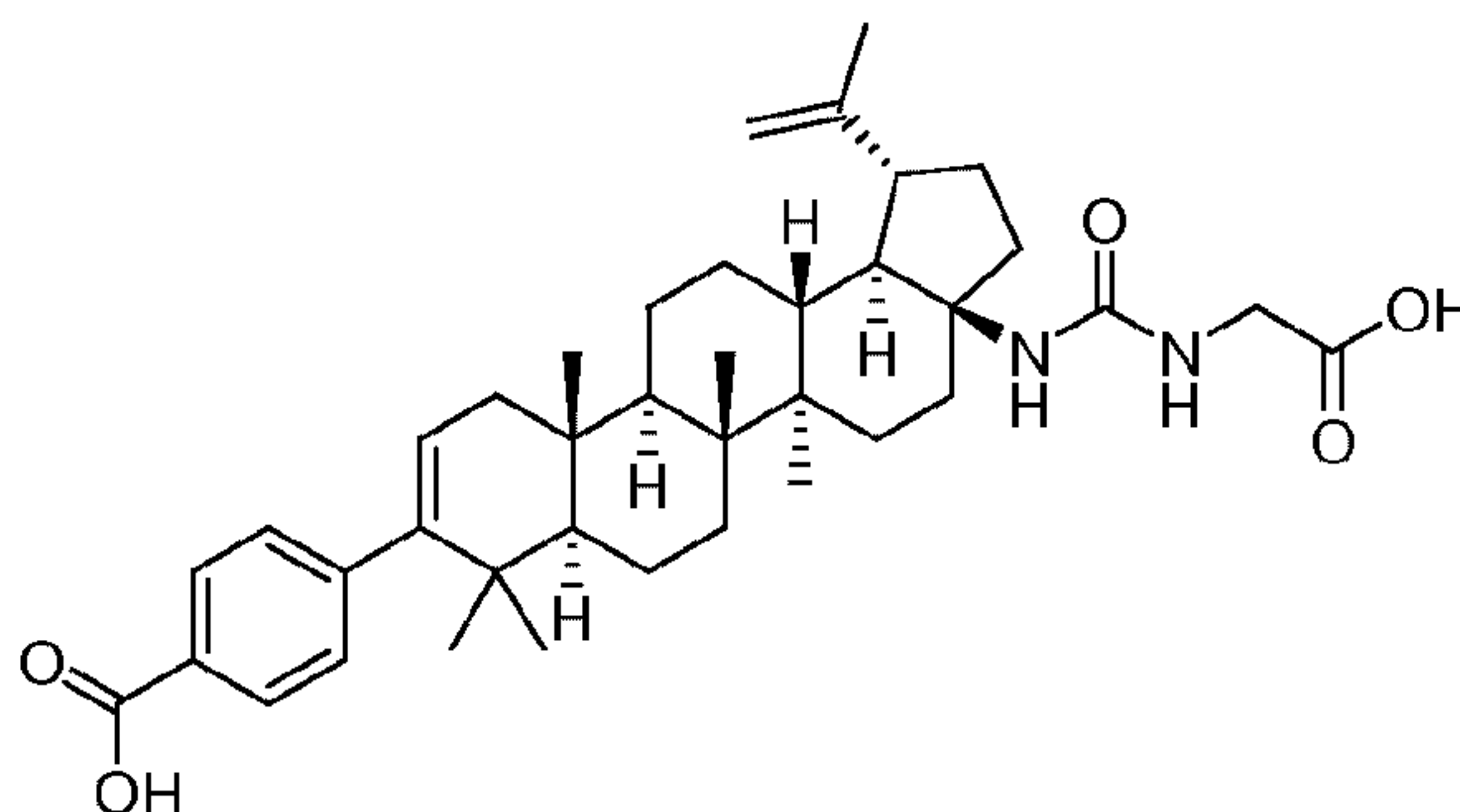
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidine-1-carboxamido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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  
 15 time 2.67 min (method 2).  $^1H$  NMR (500 MHz, *MeOD*)  $\delta$  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,  $J=8.24$   
 20 Hz, 2 H).

### Example 16

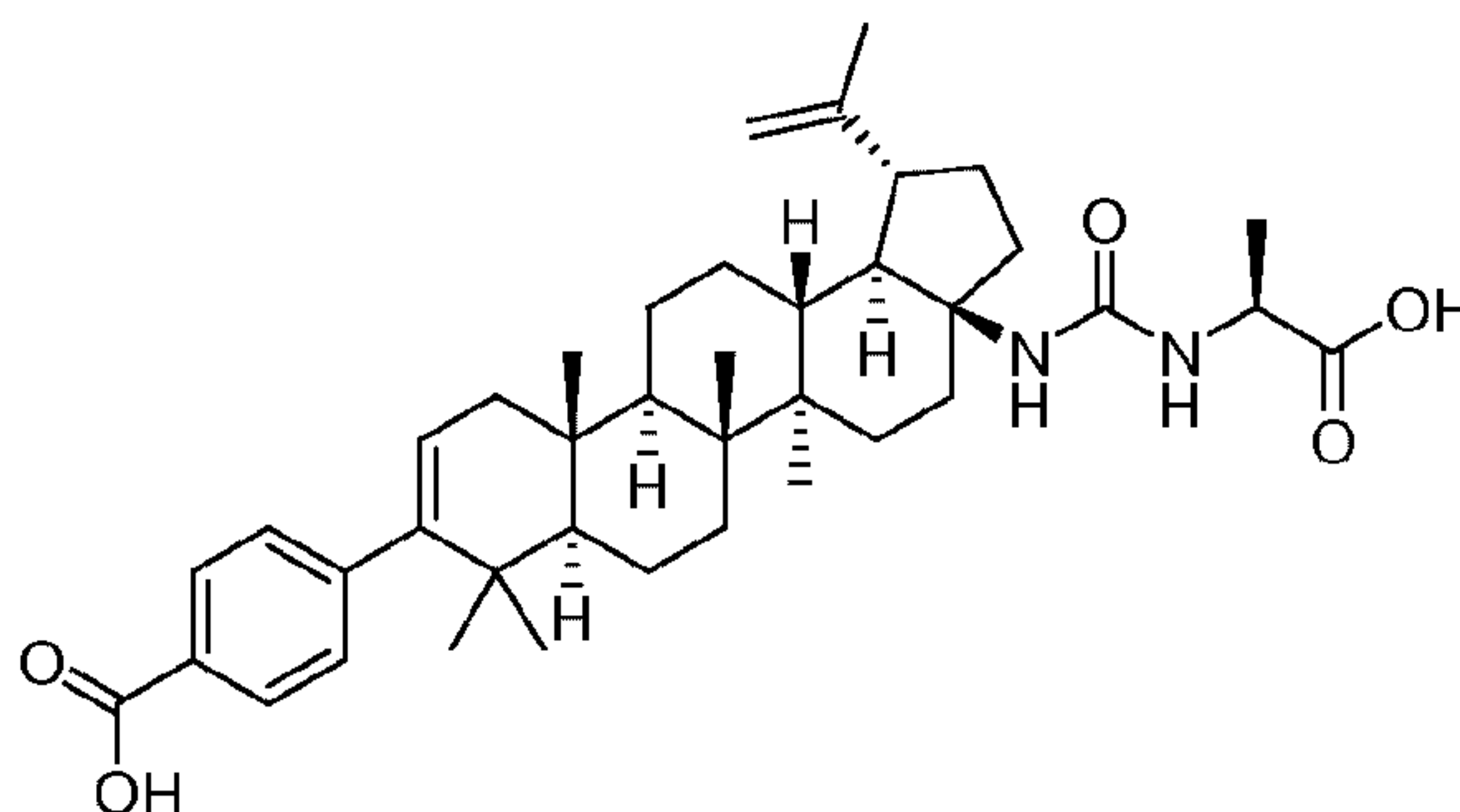
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(carboxymethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 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,  
 15 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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,  $J=1.83$   
 20 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

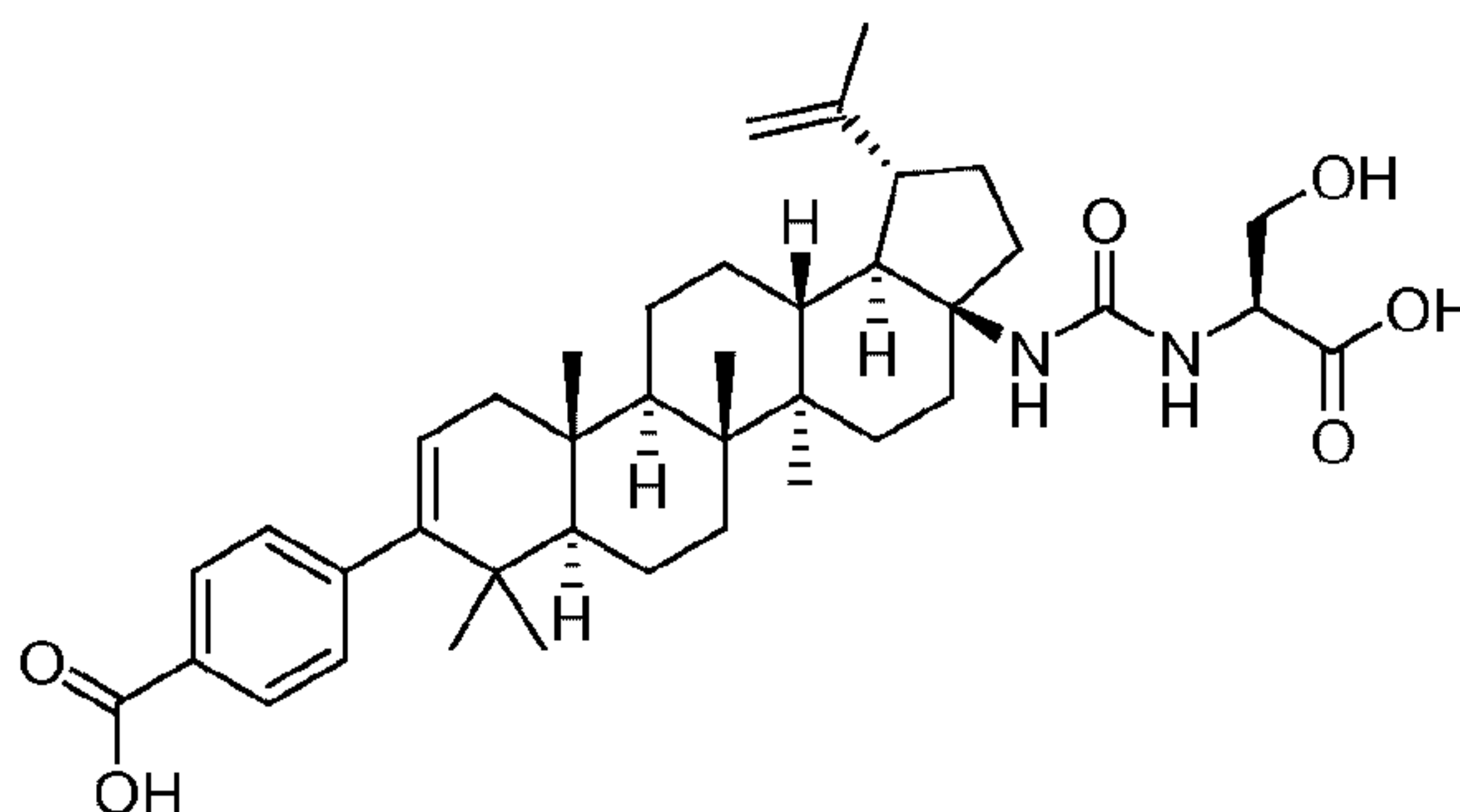
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 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,  
 15 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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  
 20 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

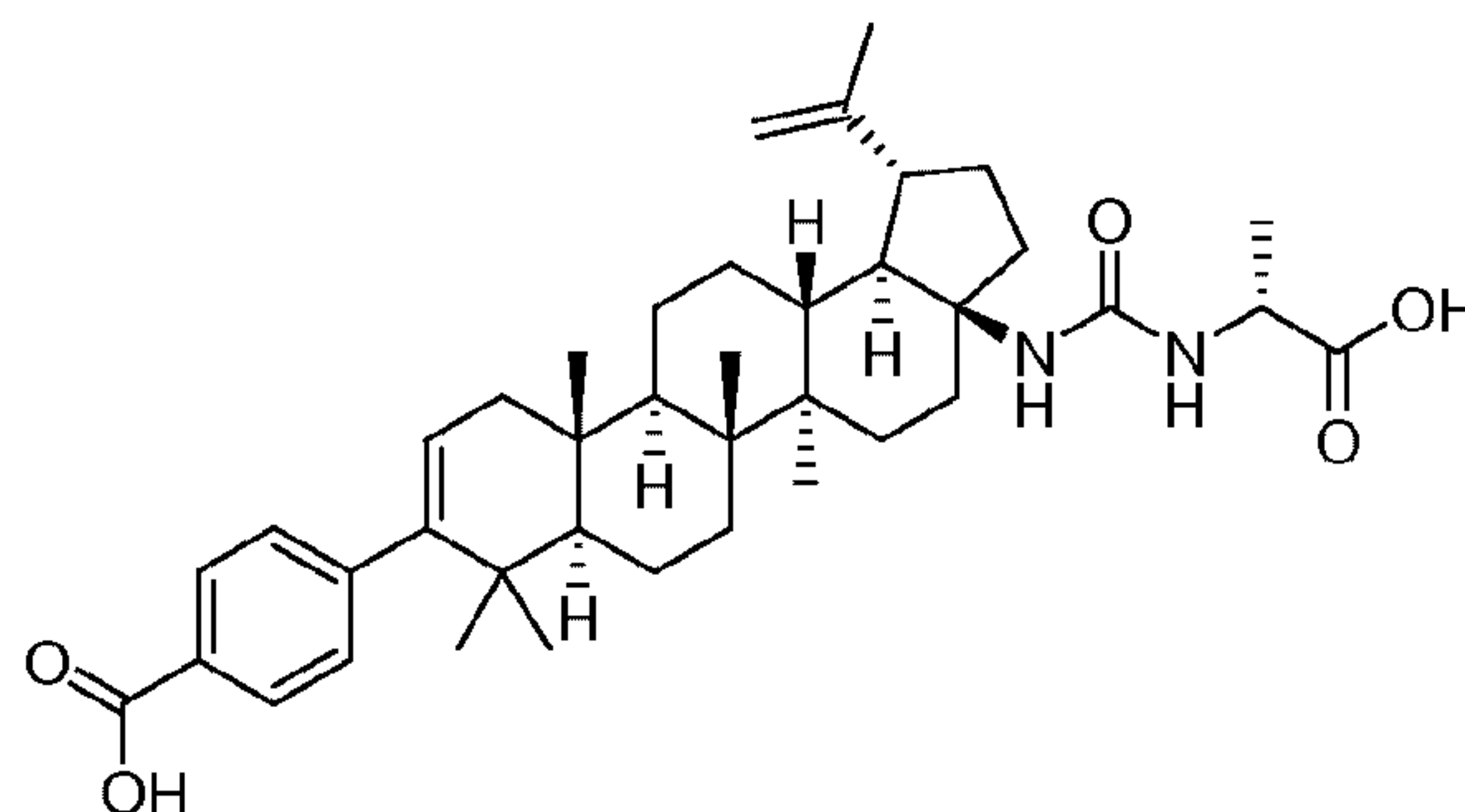
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxy-2-hydroxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 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,  
 15 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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),  
 20 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).

## Example 19

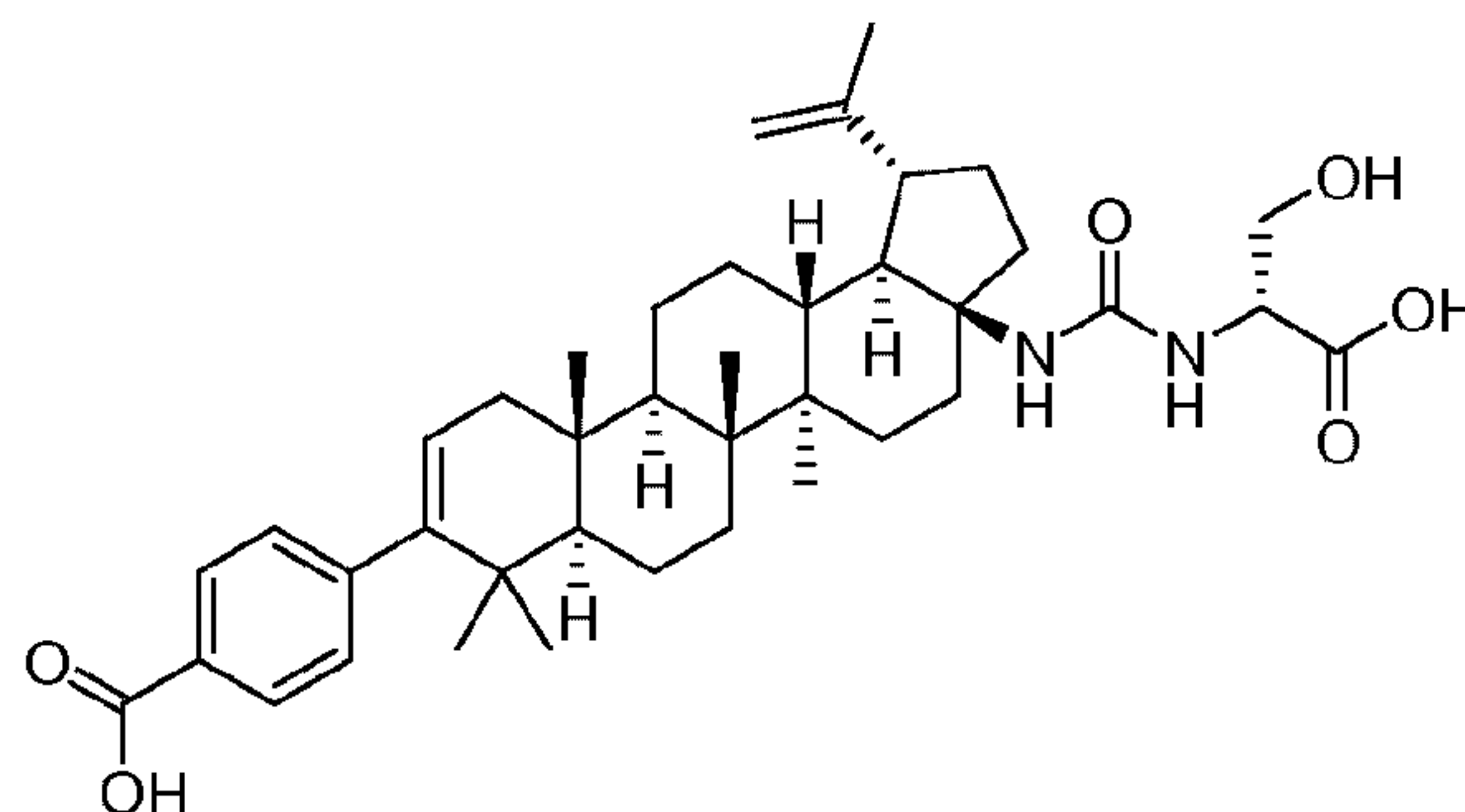
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *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,  
 15 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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,  $J=1.53$   
 20 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

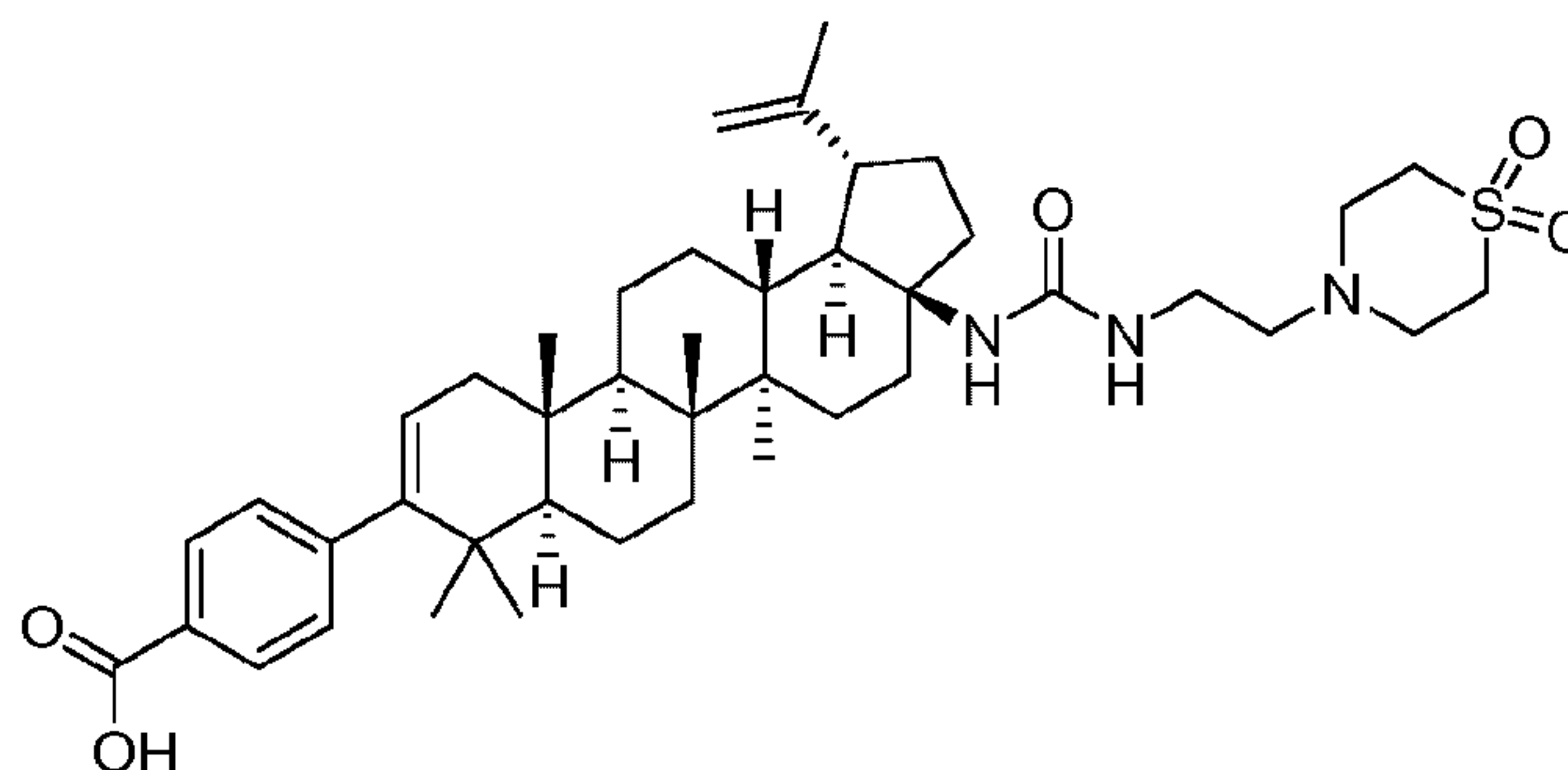
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxy-2-hydroxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *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,  
 15 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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  
 20 (m,  $J=7.32$  Hz, 2 H), 7.92 (m,  $J=7.63$  Hz, 2 H).

### Example 21

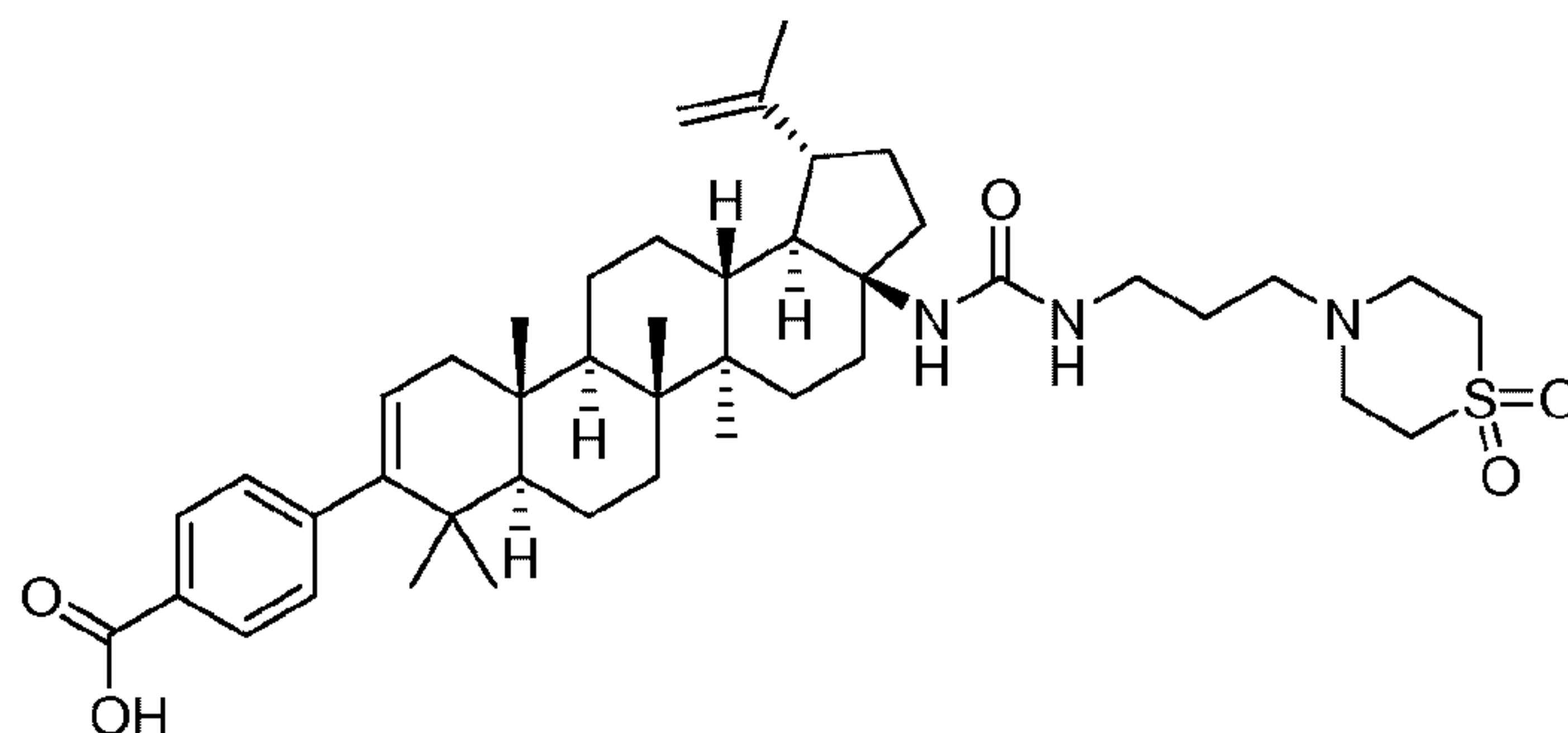
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 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)  $\delta$  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

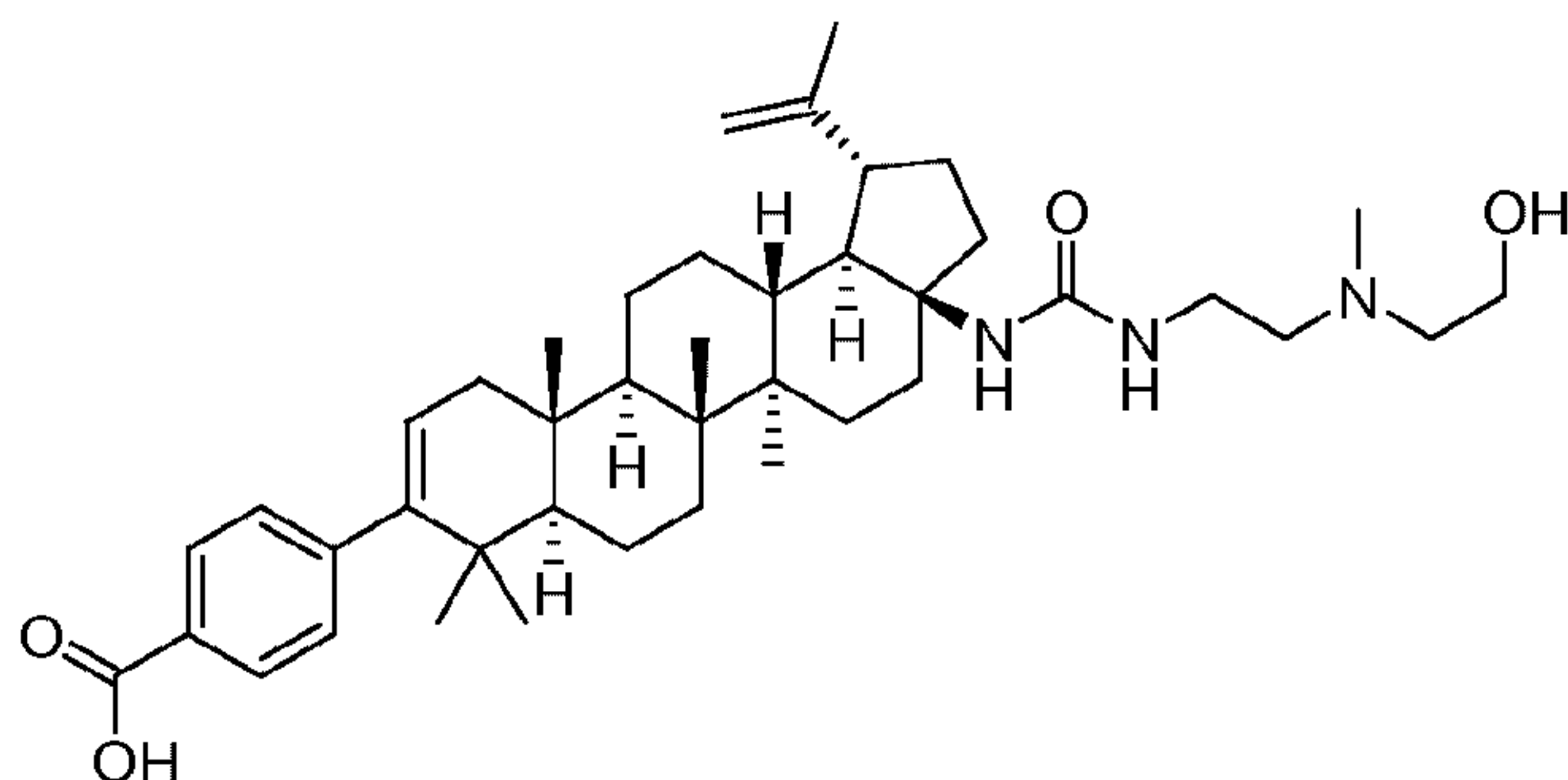
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxido-4-thiomorpholinyl)propyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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 (method 11).  $^1H$  NMR (500 MHz, 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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,  $J=4.58$  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

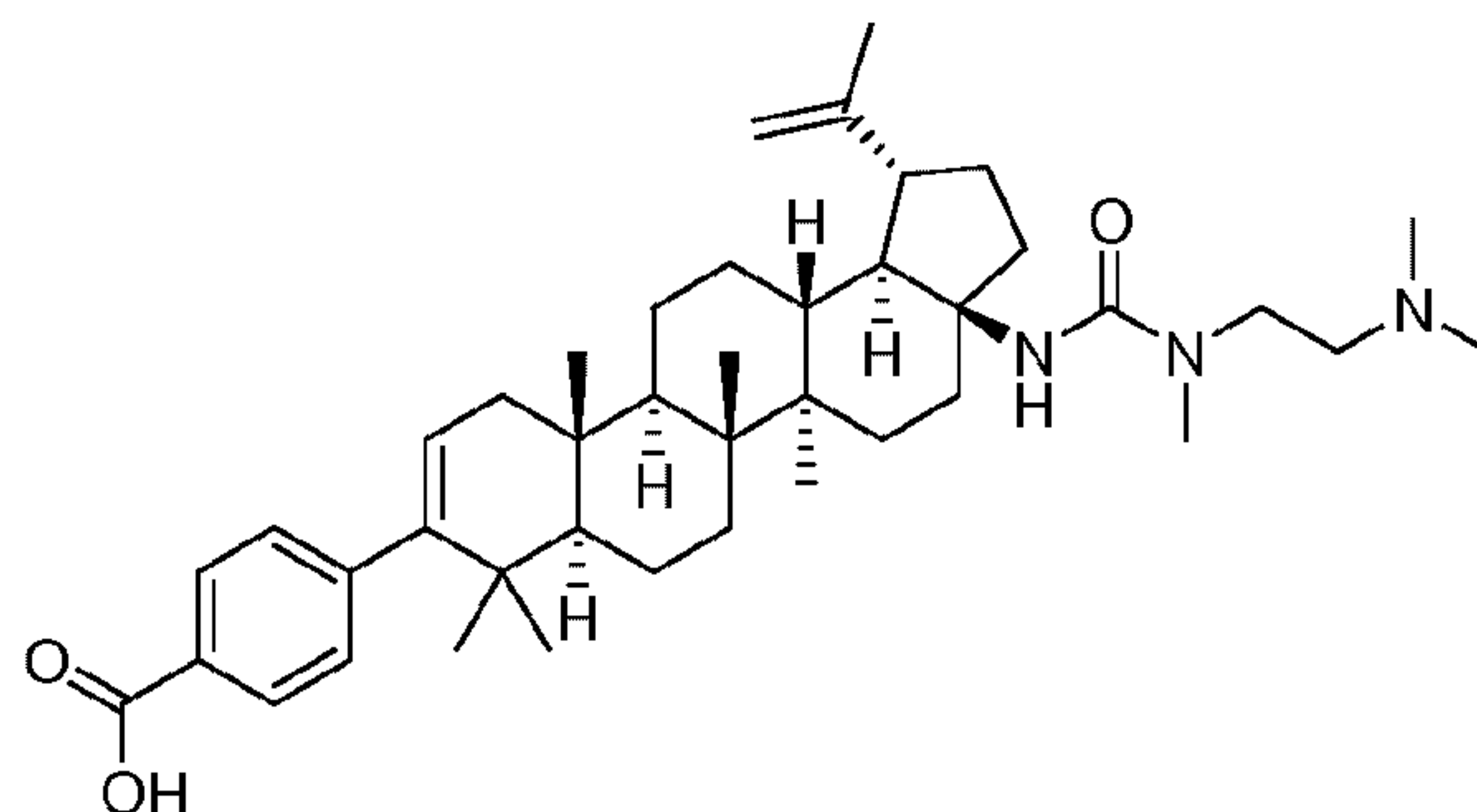
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-  
hydroxyethyl)(methyl)amino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-  
5 2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

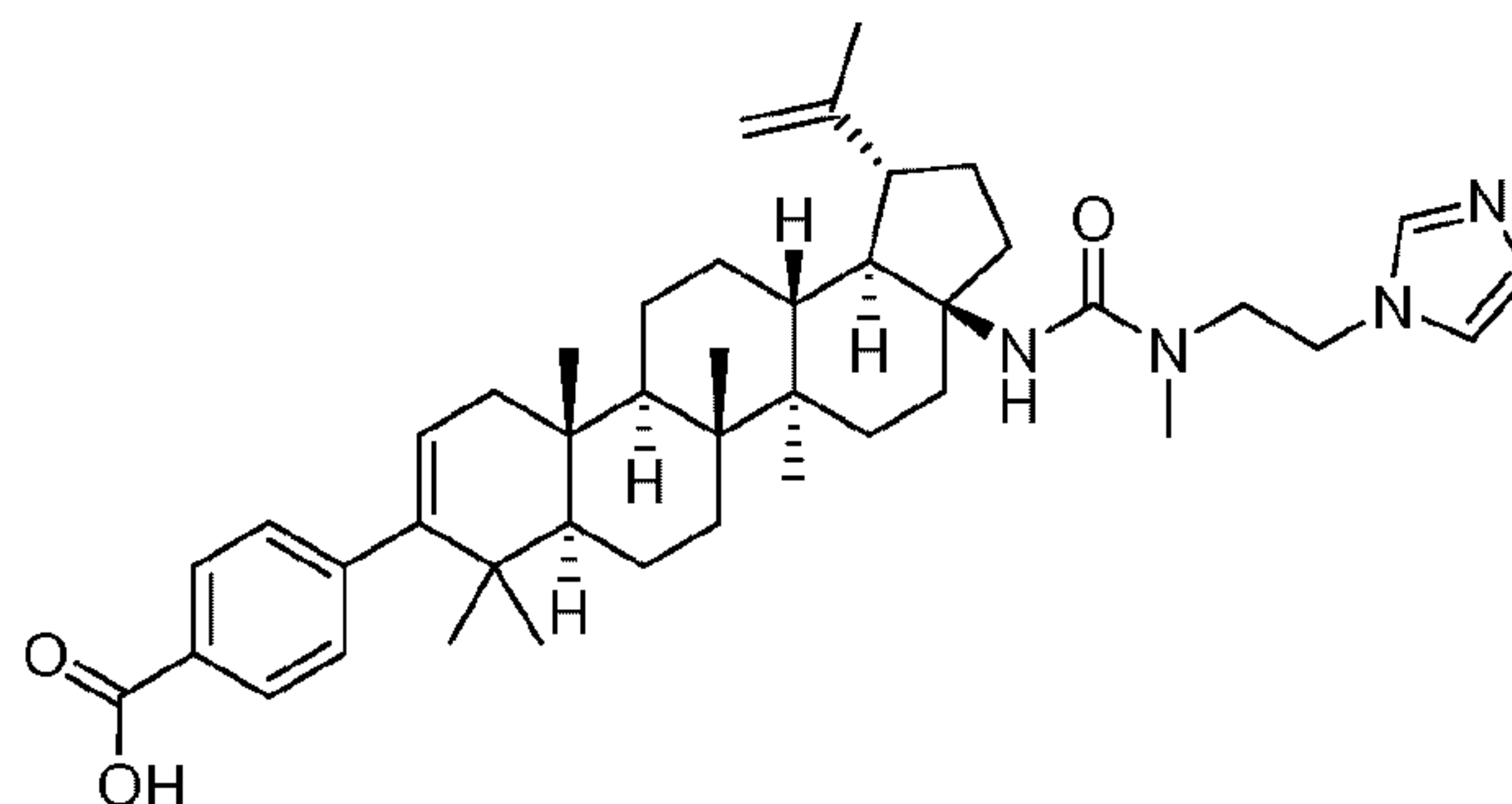
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(  
 (dimethylamino)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-  
 5 yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described  
 above for the C-17 urea formation and subsequent ester hydrolysis using *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  
 15 (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock)  $\delta$  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 -  
 20 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

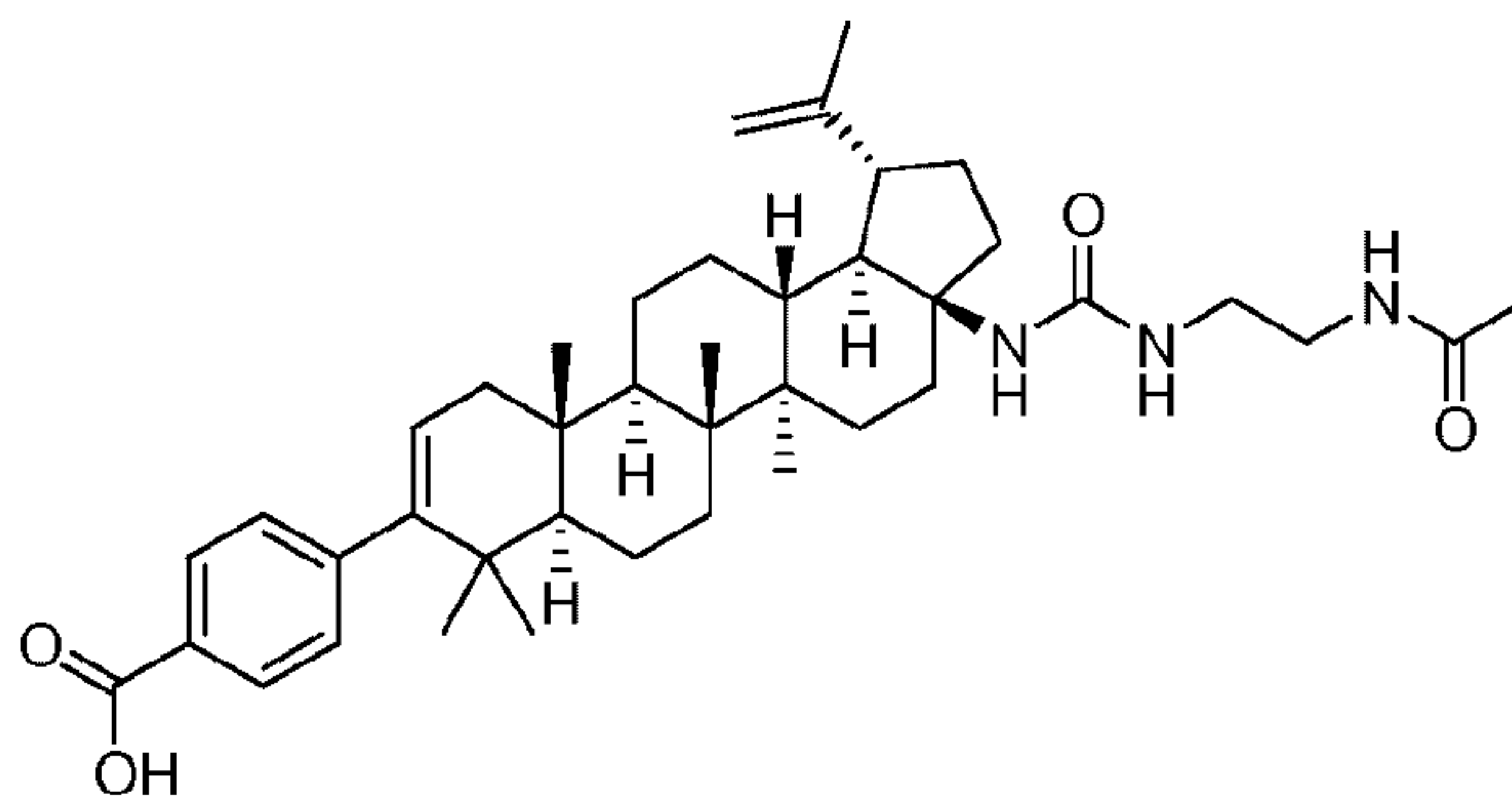
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-1-yl)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

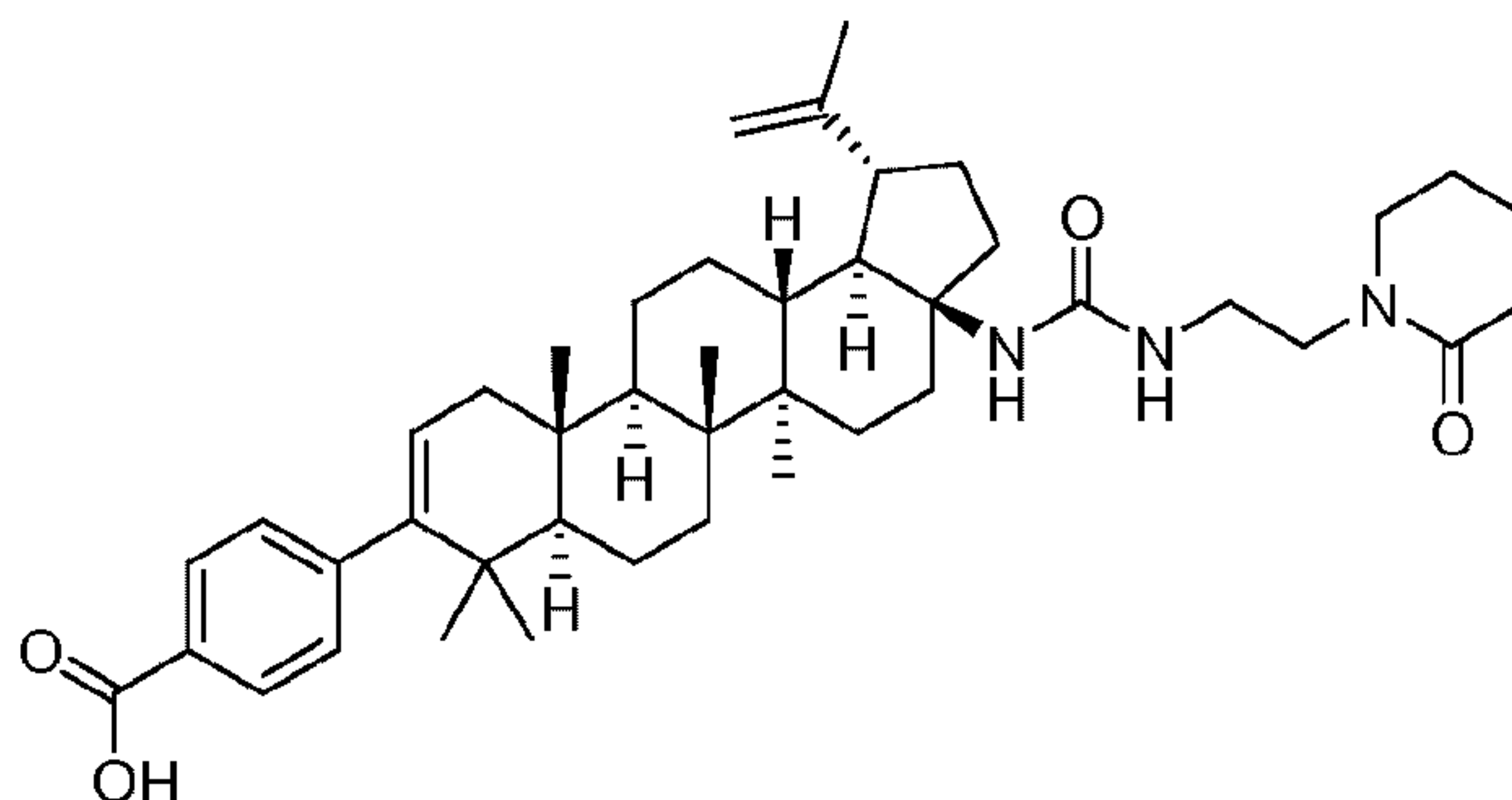
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-  
acetamidoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

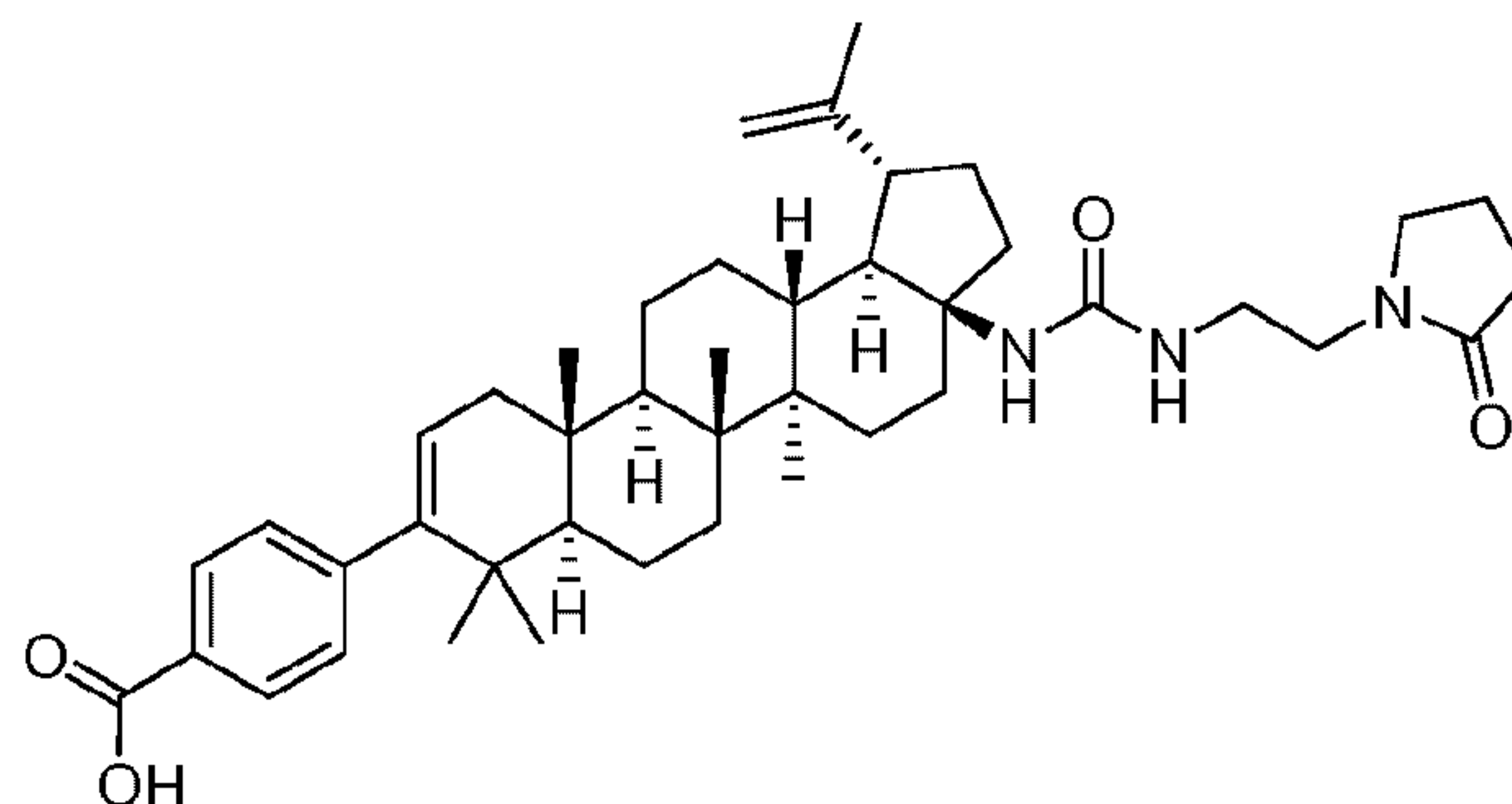
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(2-oxopiperidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

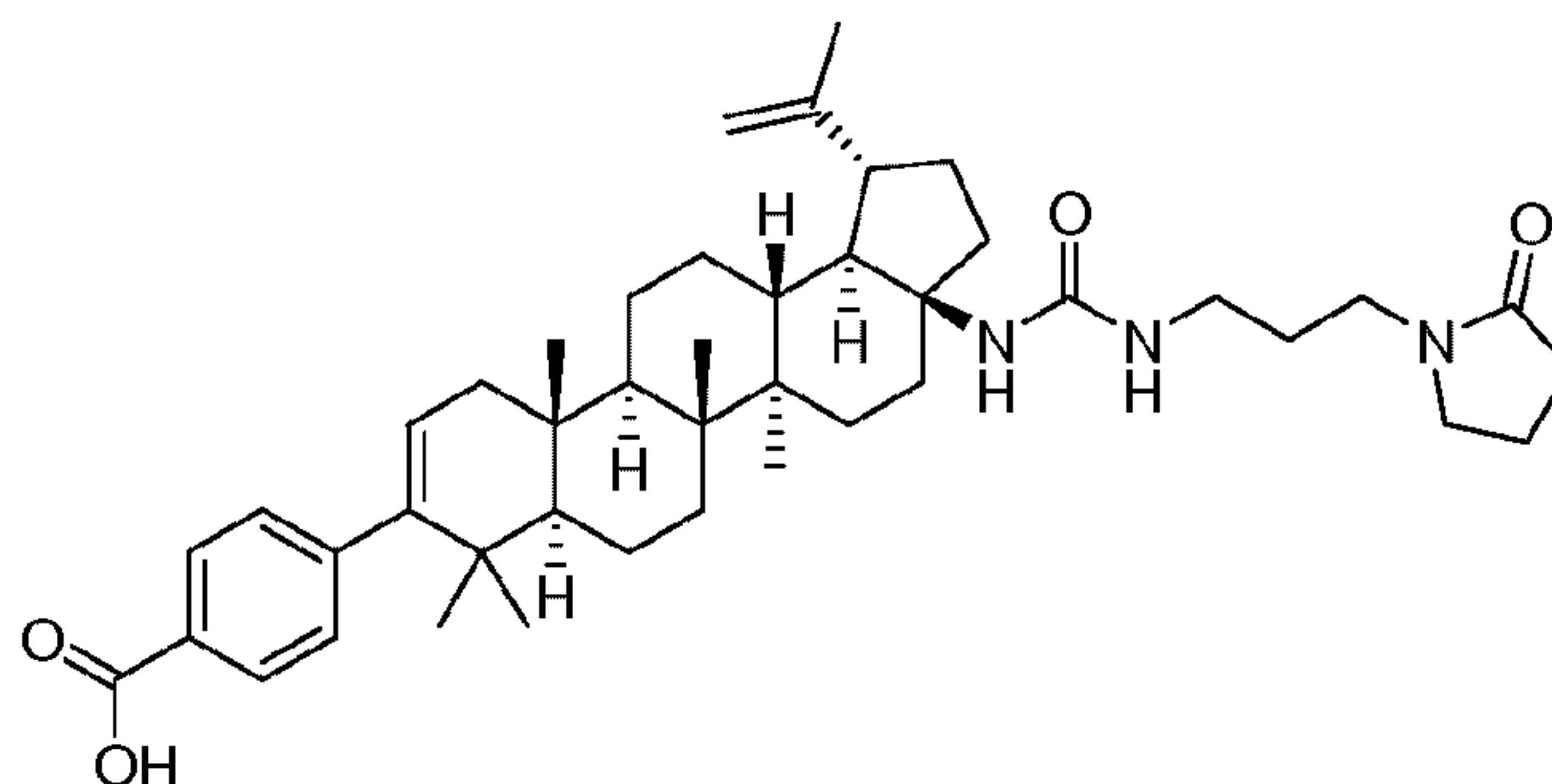
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(2-oxopyrrolidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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, 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).  
 20

## Example 29

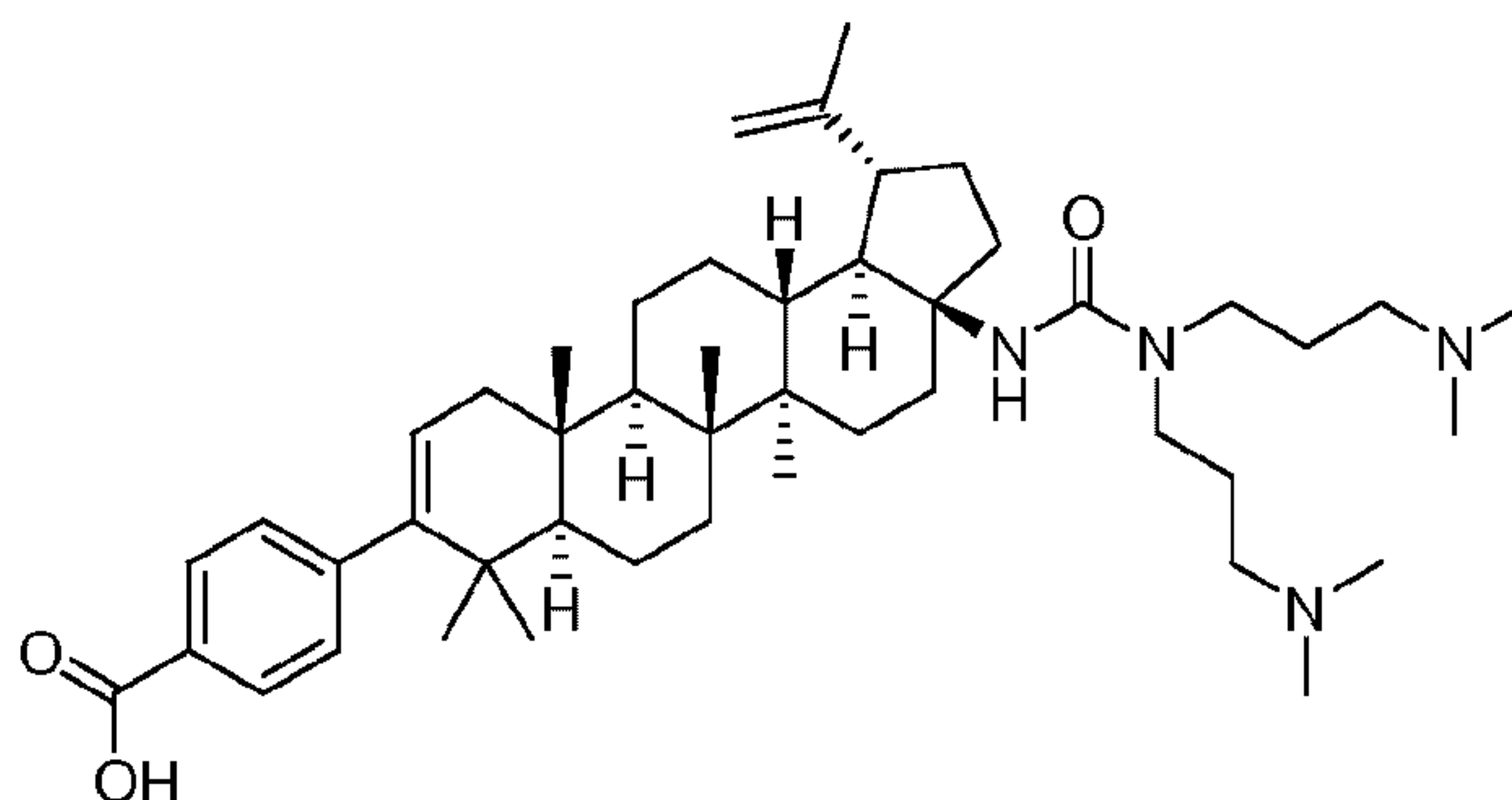
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(2-oxopyrrolidin-1-yl)propyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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,  
 15 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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,  $J=7.17$   
 20 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

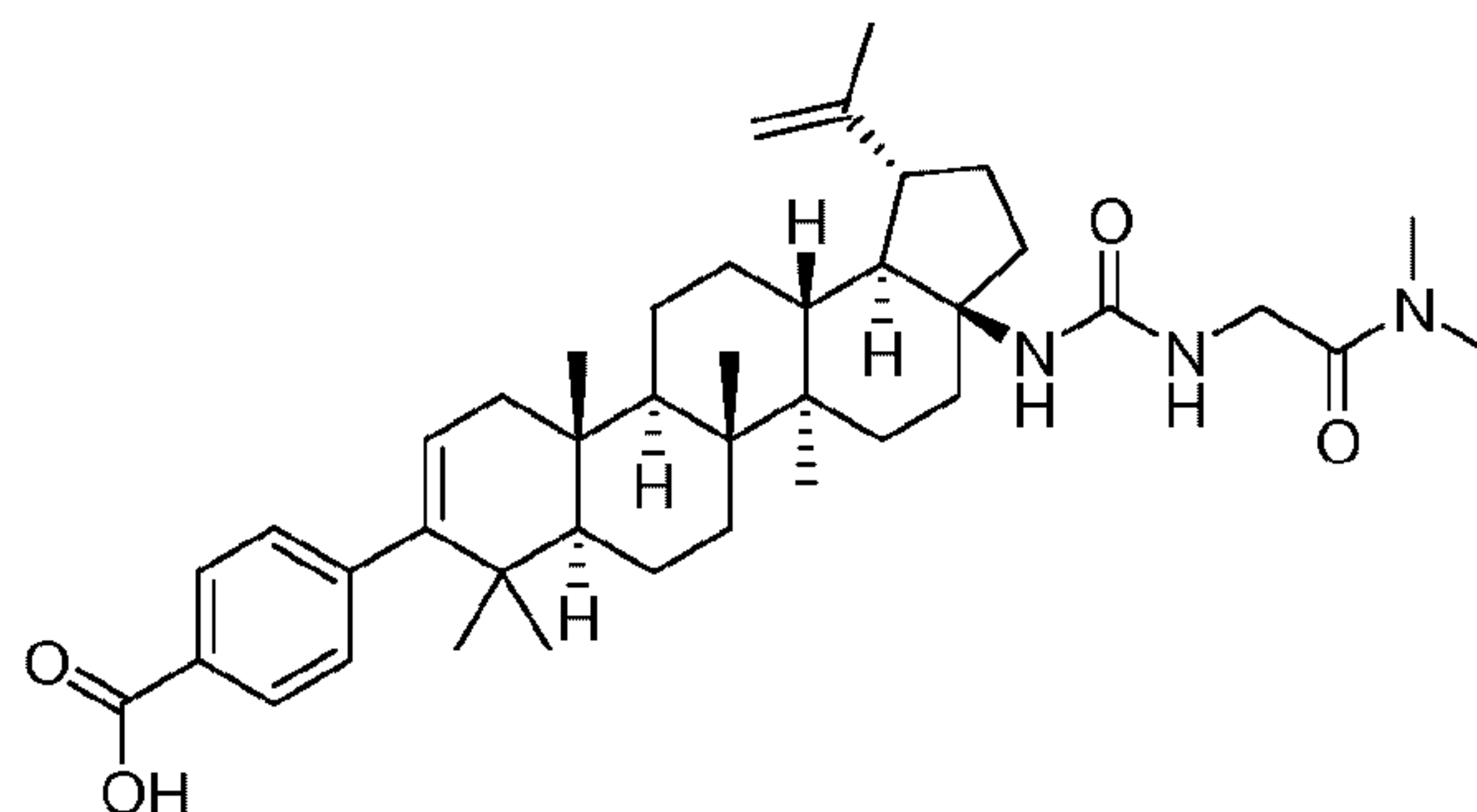
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-bis(3-(dimethylamino)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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, 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  
 20 (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

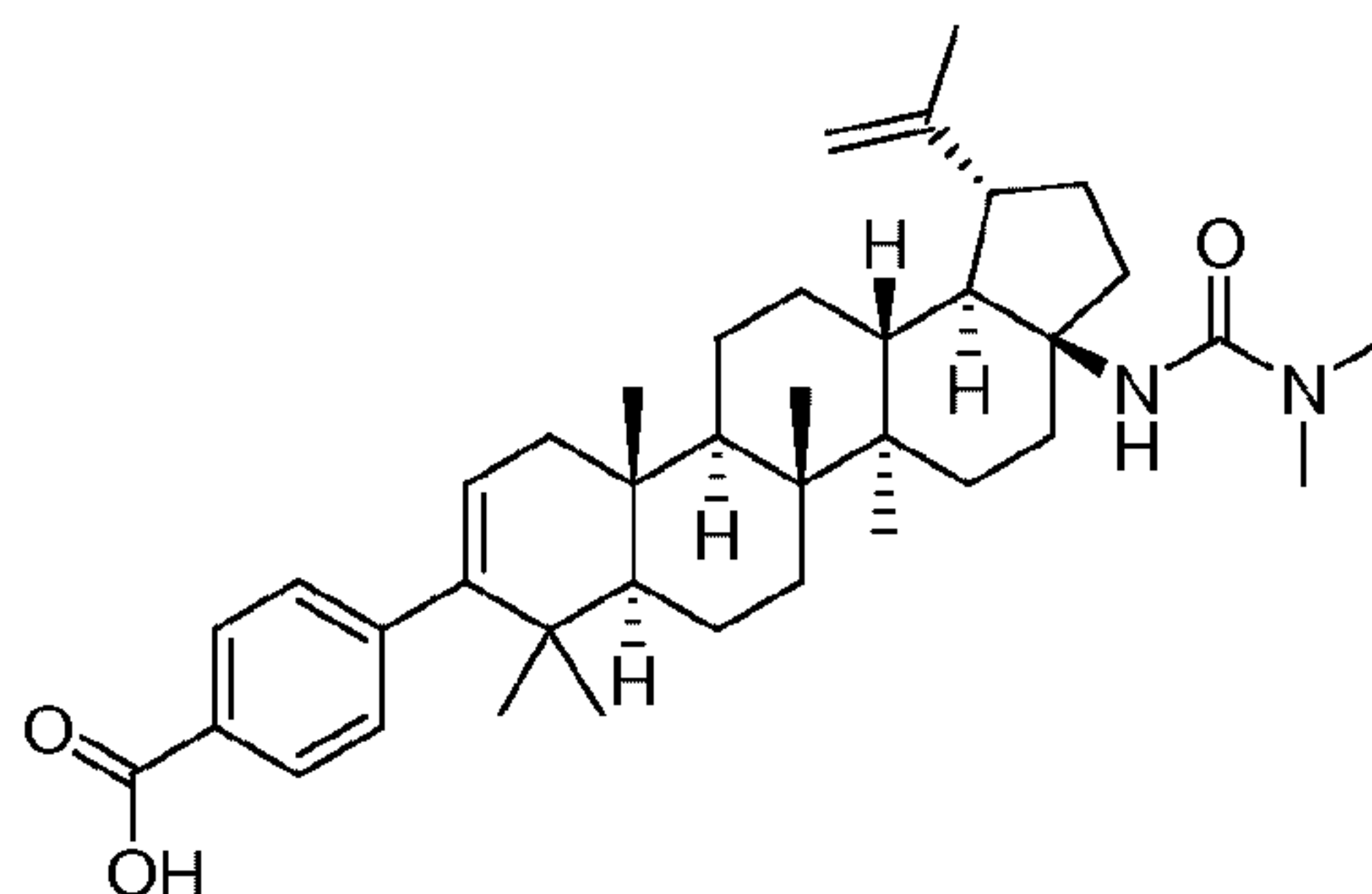
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)-2-oxoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-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  
 15 of *CDCl3* and *MeOD*, *MeOD* lock)  $\delta$  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,  
 20  $J=6.10$ , 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

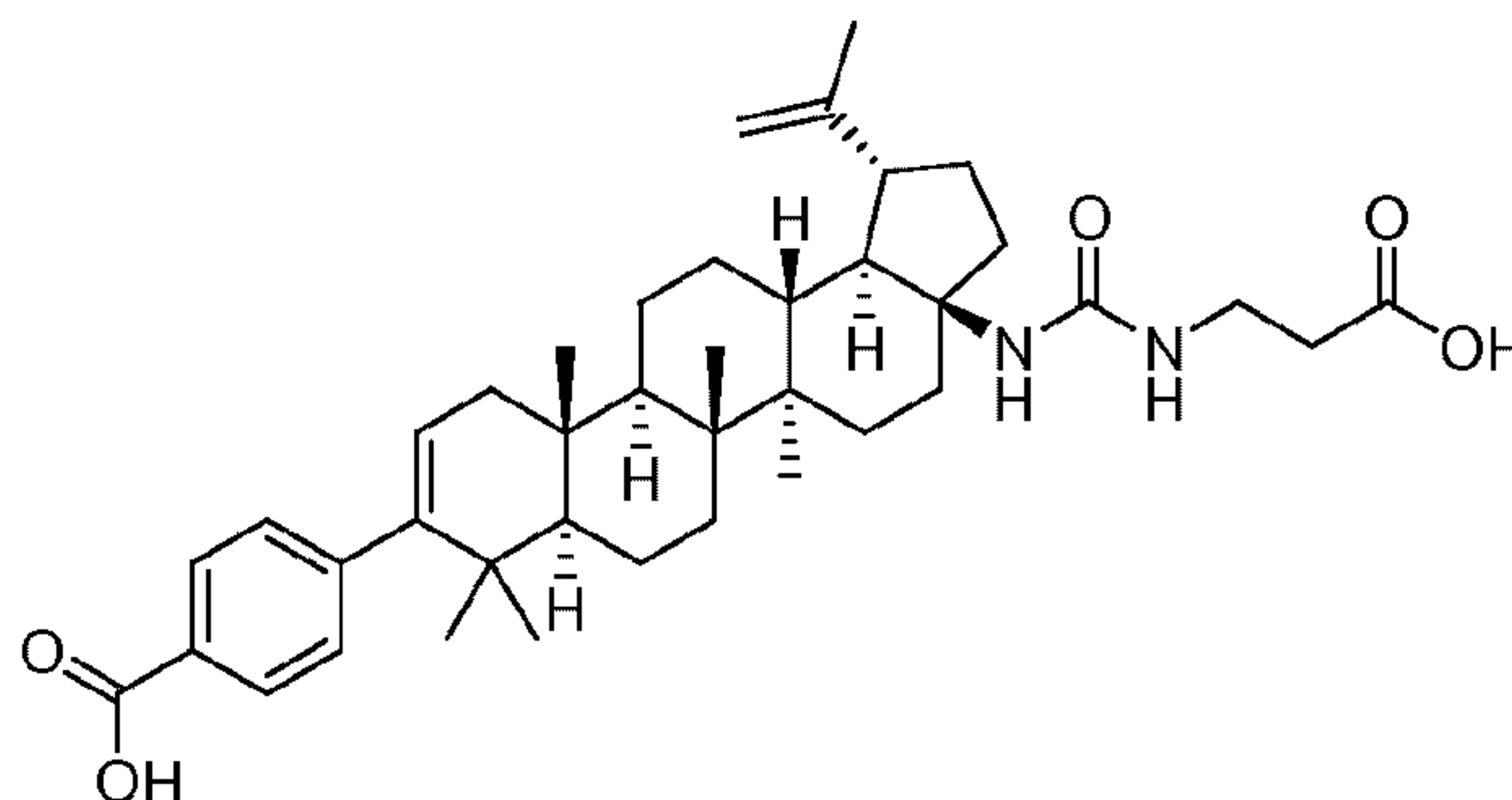
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-dimethylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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).

## Example 33

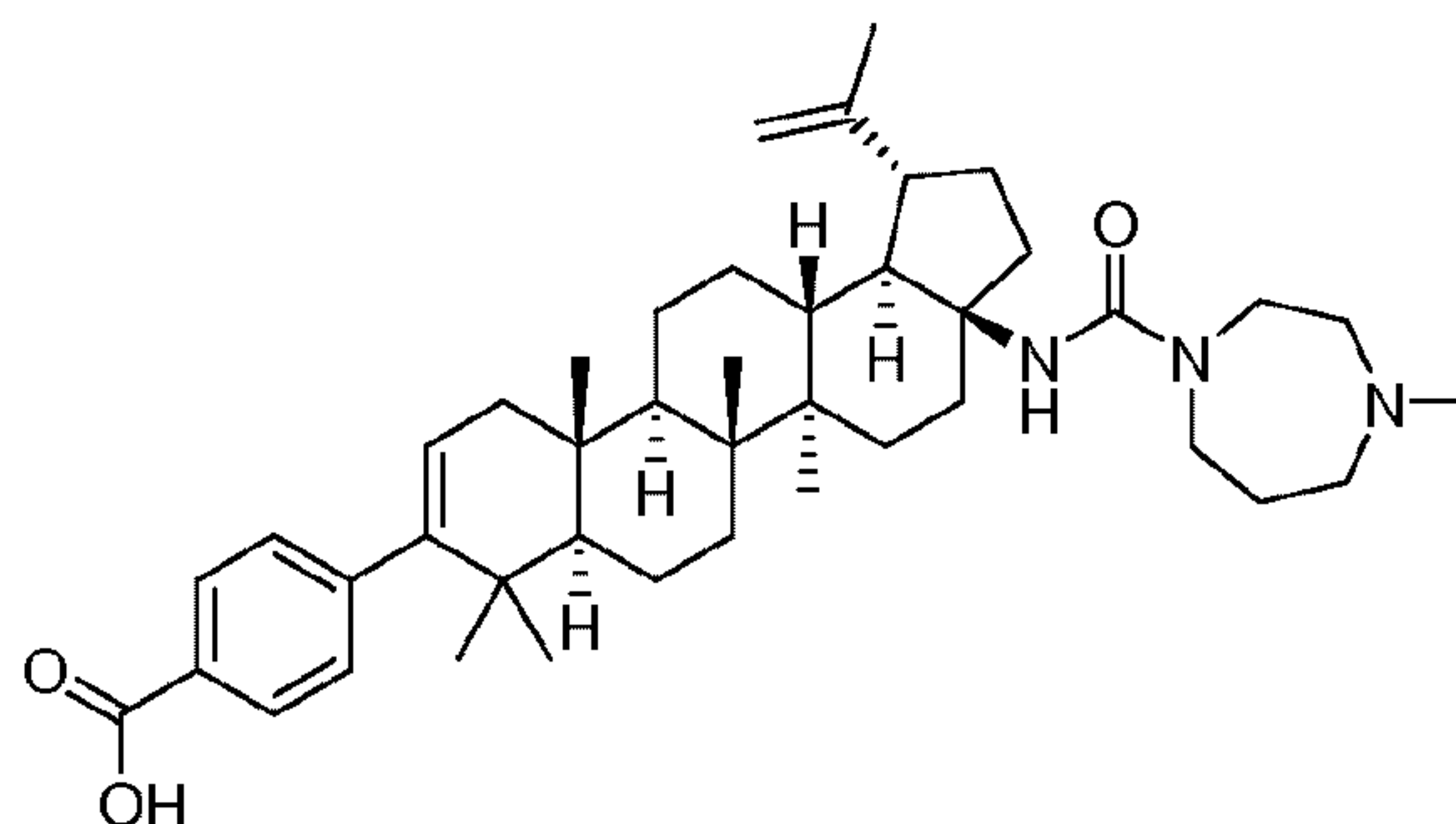
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-  
 carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

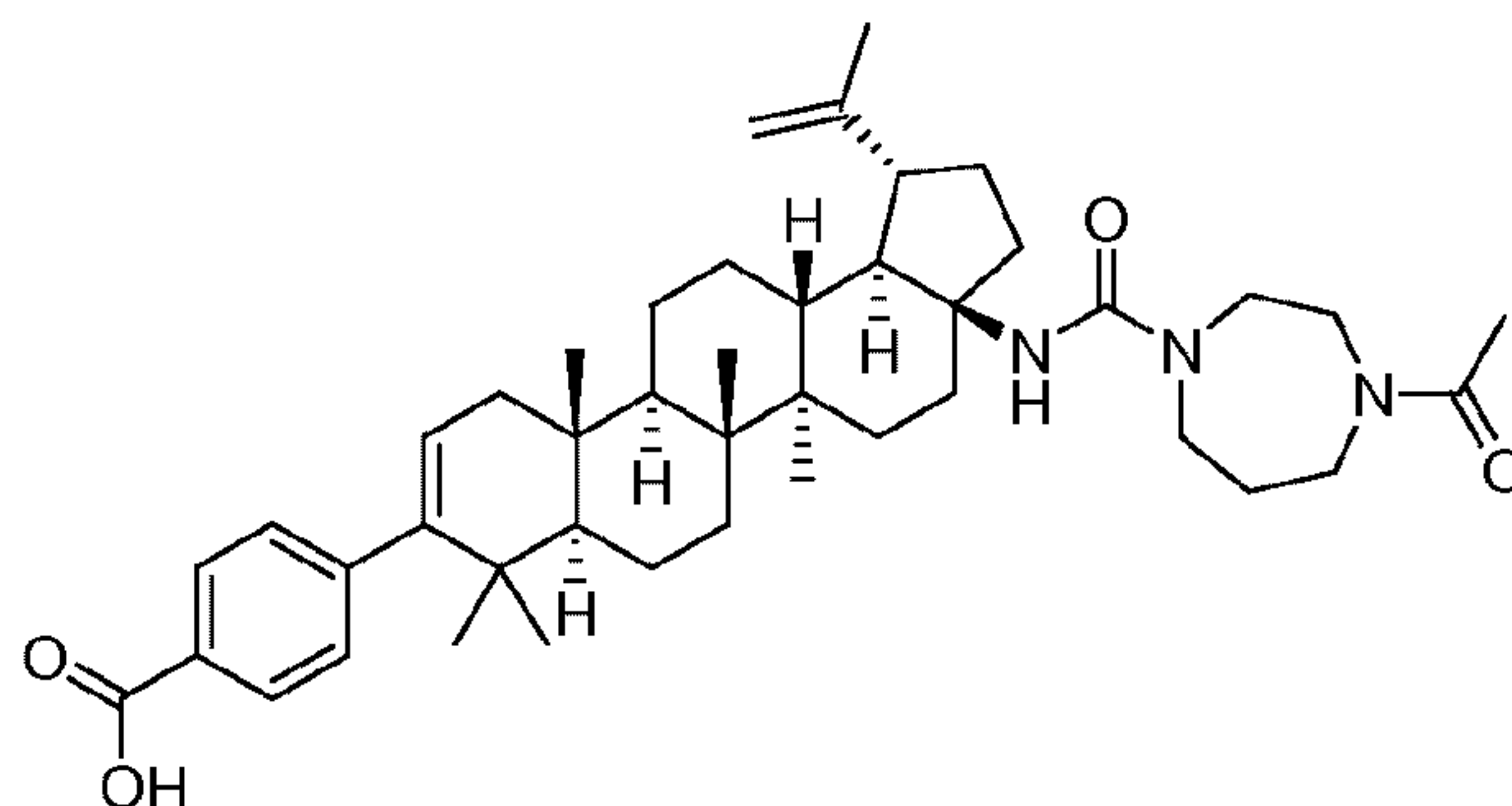
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-methyl-1,4-diazepane-1-carboxamido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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,  
 15 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  ppm 0.94 (s, 6 H), 1.00 (s, 3 H), 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

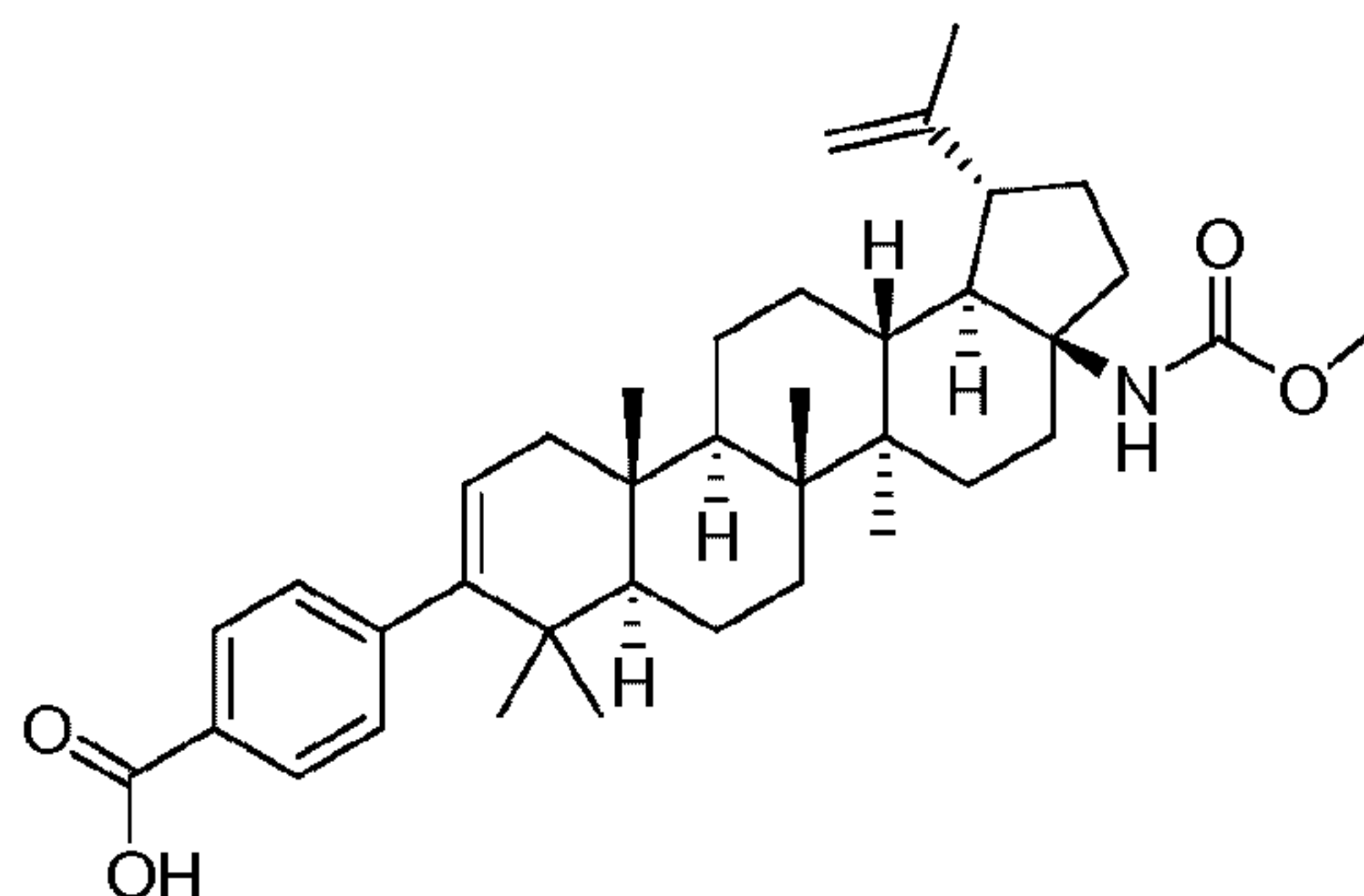
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetyl-1,4-diazepane-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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  
 15 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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  
 20 H), 7.92 (d,  $J=8.24$  Hz, 2 H).

## Example 36

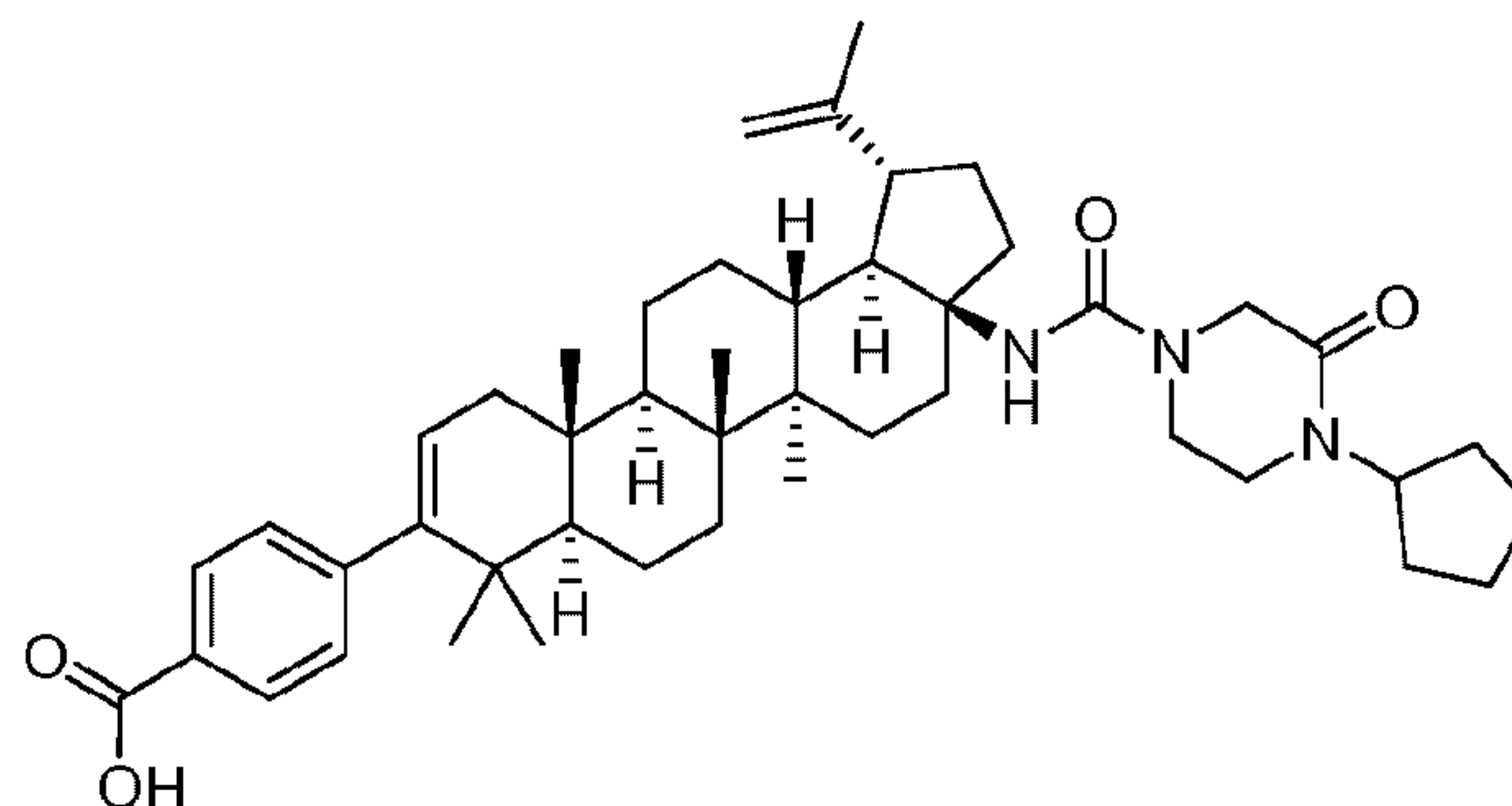
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(methoxycarbonylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was formed as a byproduct during the 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  
 15 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)  $\delta$  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  
 20 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

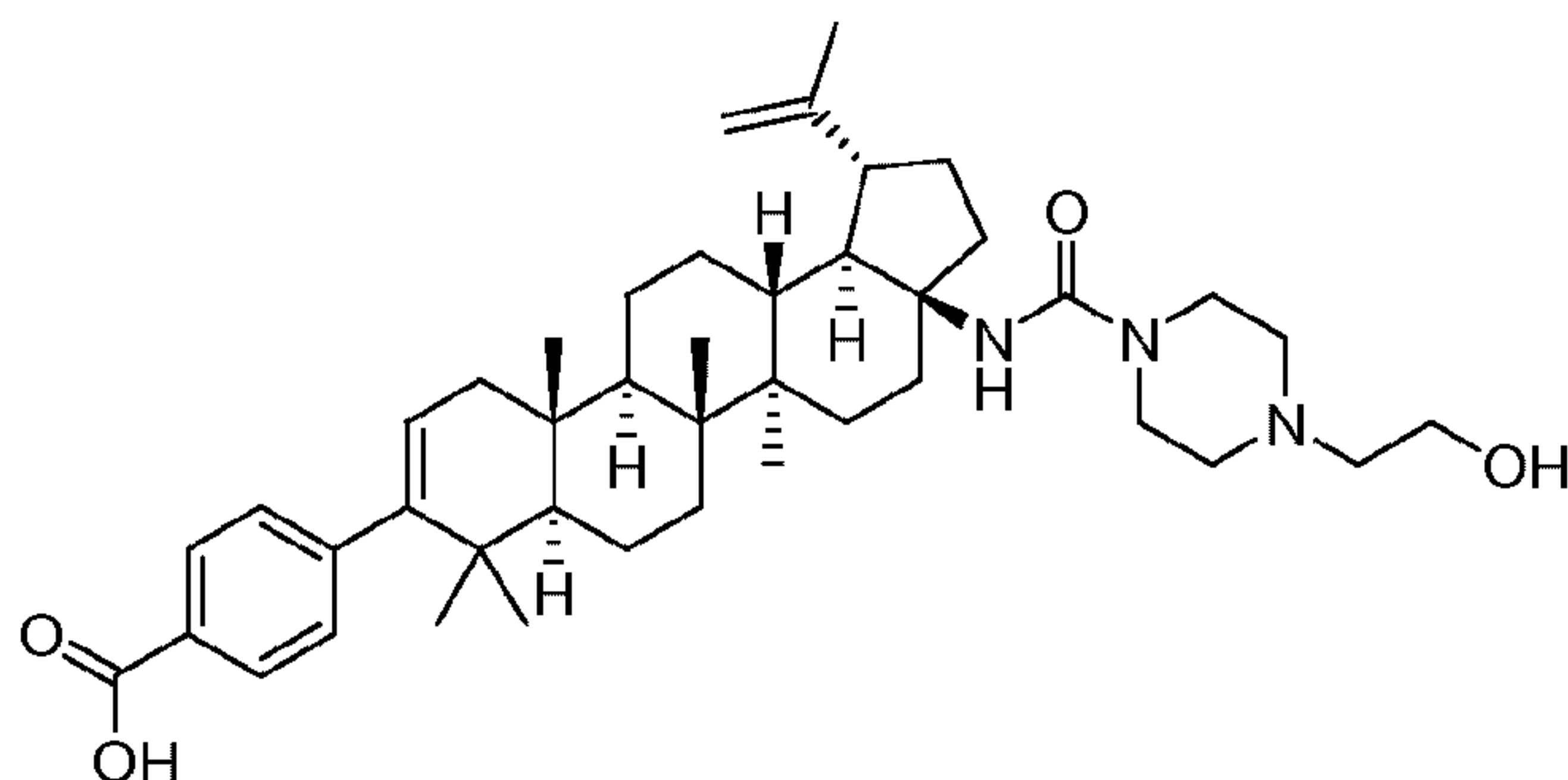
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-cyclopentyl-3-oxopiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



10 The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-cyclopentylpiperazin-2-one, HCl, 0.5 H<sub>2</sub>O 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<sup>+</sup>), retention time 2.97 min (method 11). <sup>1</sup>H NMR  
 15 (500 MHz, 1:1 mixture of *CDCl*<sub>3</sub> 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 -  
 20 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

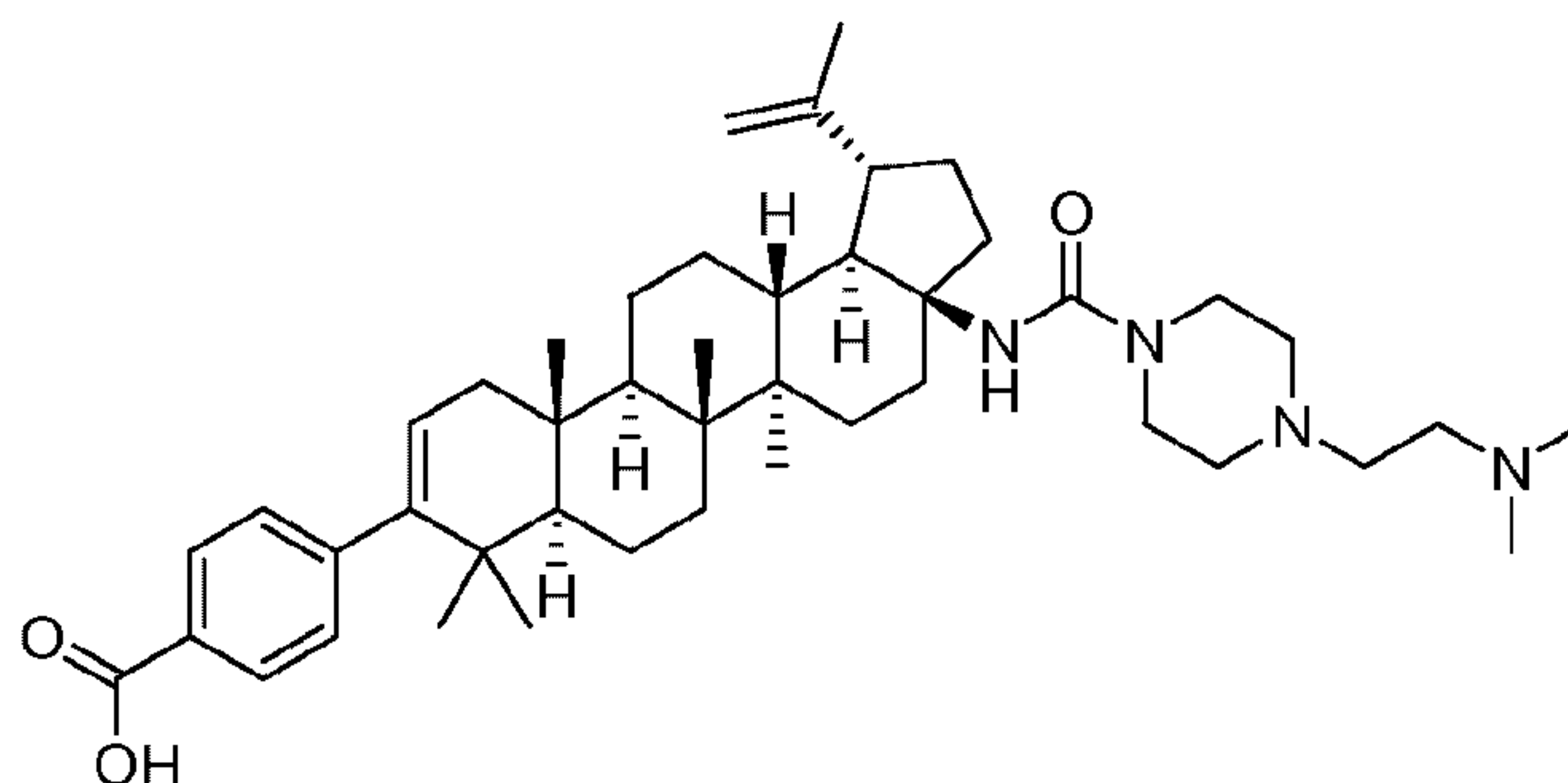
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hydroxyethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

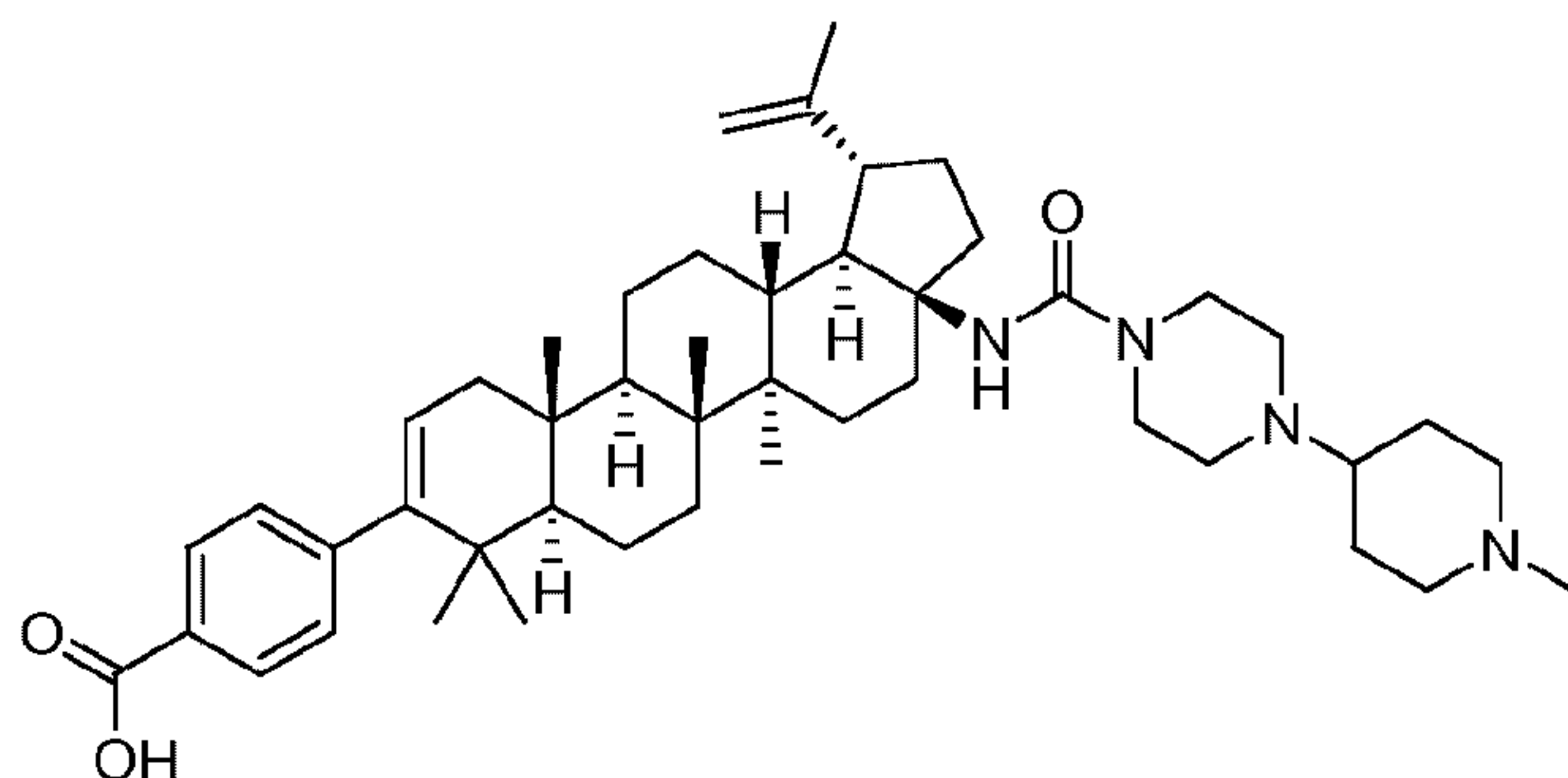
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-(  
 (dimethylamino)ethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-  
 5 1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 cyclopenta[a]chrysen-9-yl)benzoic acid.



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*-  
 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  
 15 11).  $^1H$  NMR (500 MHz, 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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  
 20 - 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

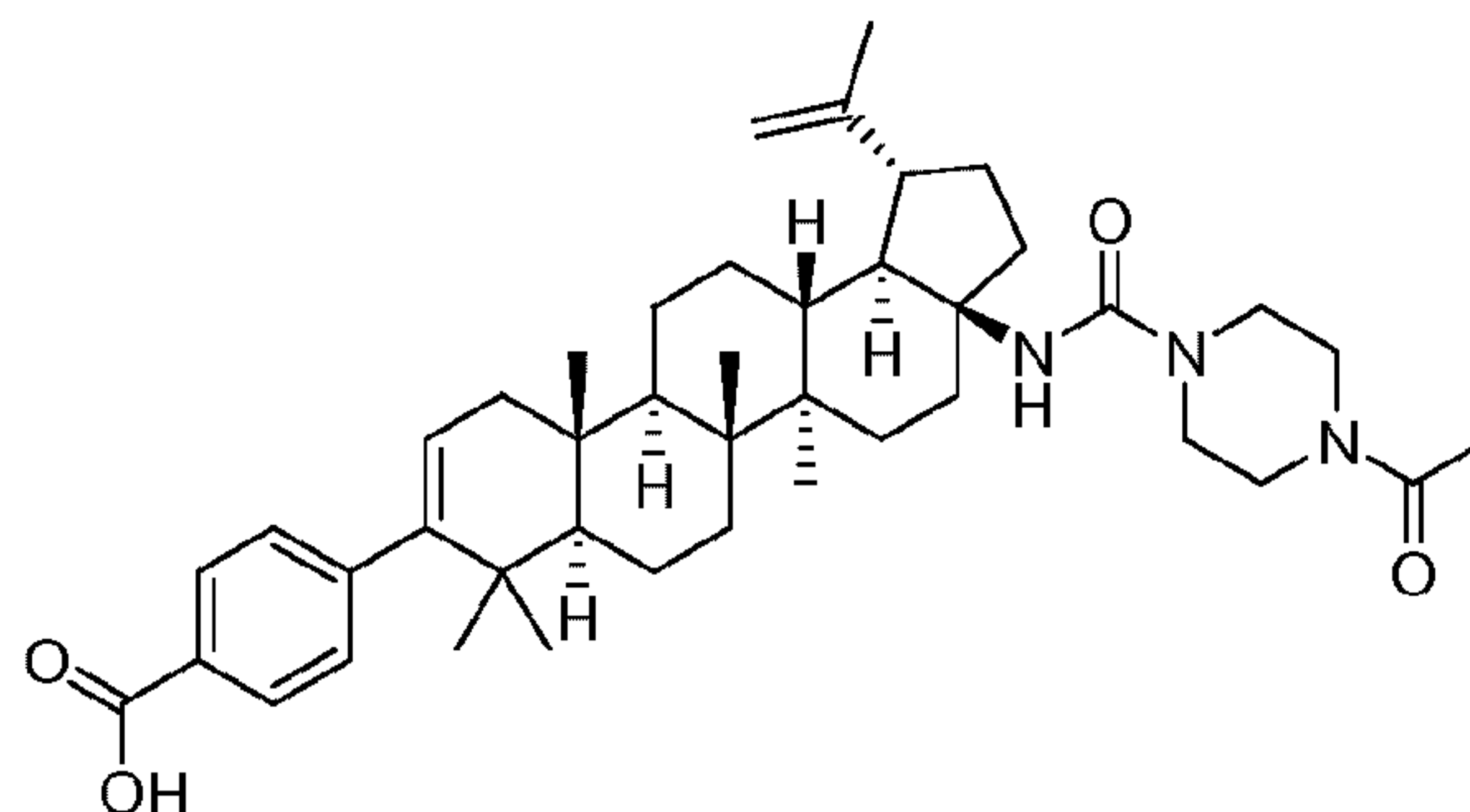
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-(1-methylpiperidin-4-yl)piperazine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

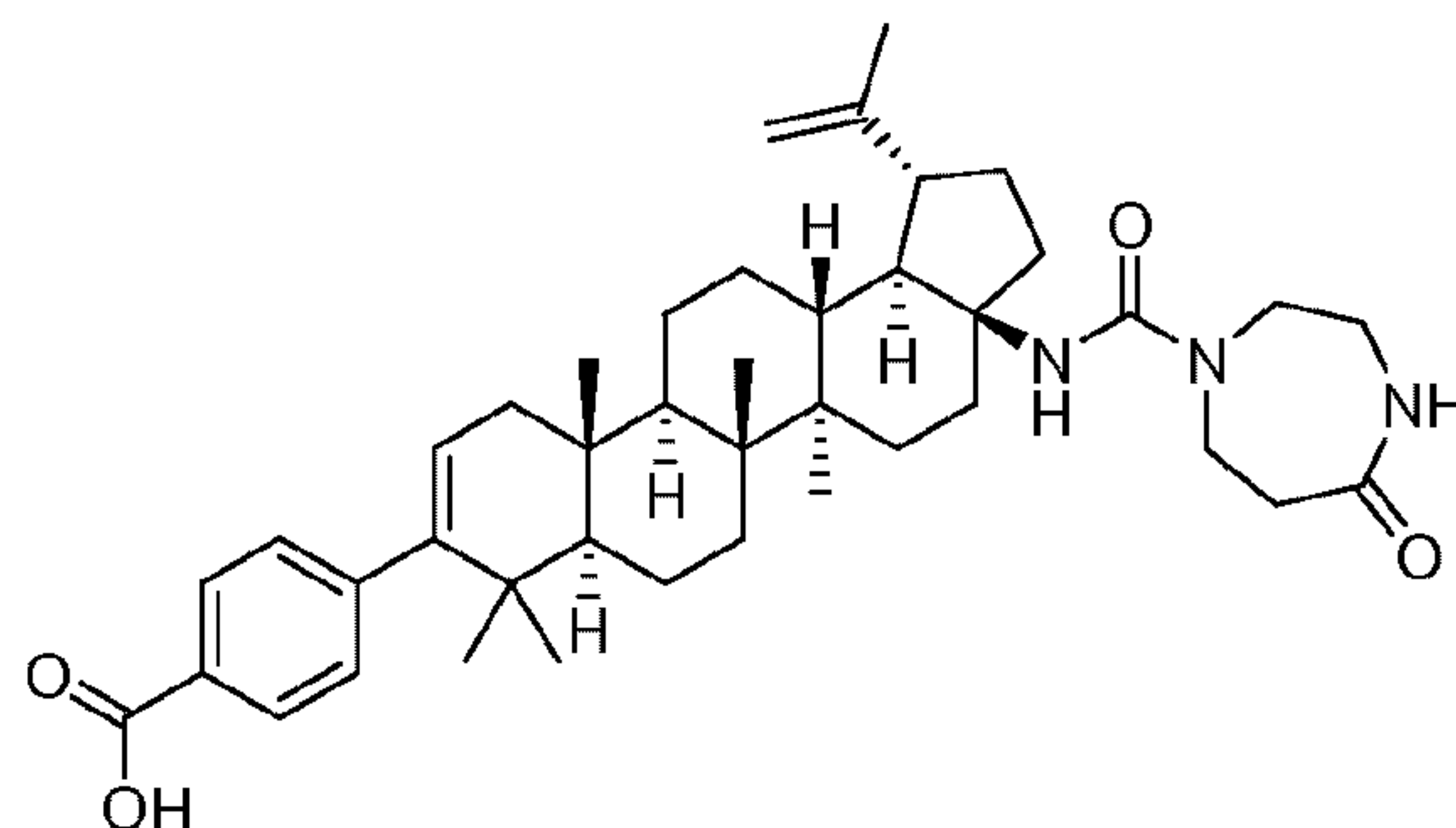
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-  
acetylpiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

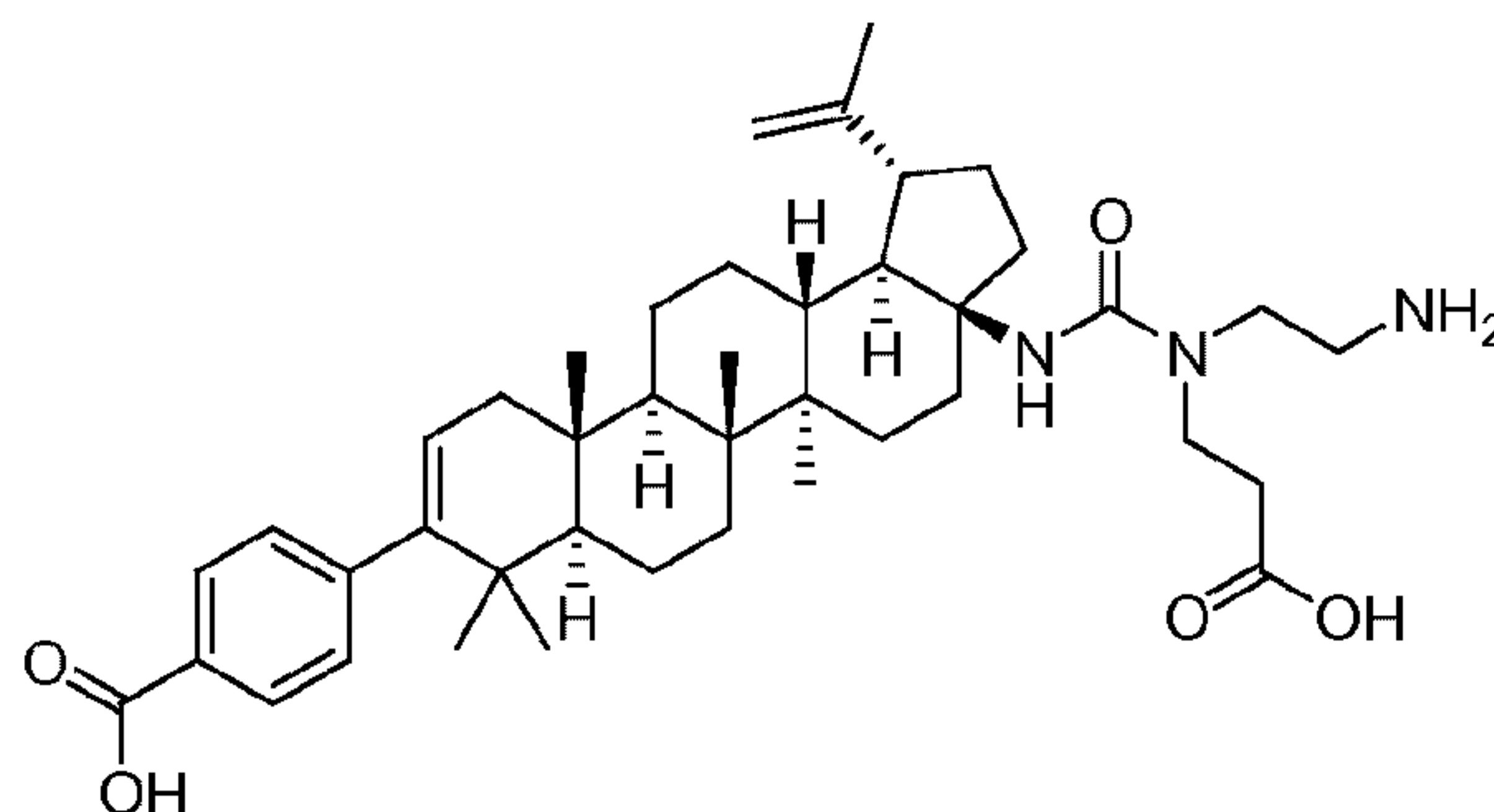
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(5-oxo-1,4-diazepane-1-carboxamido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

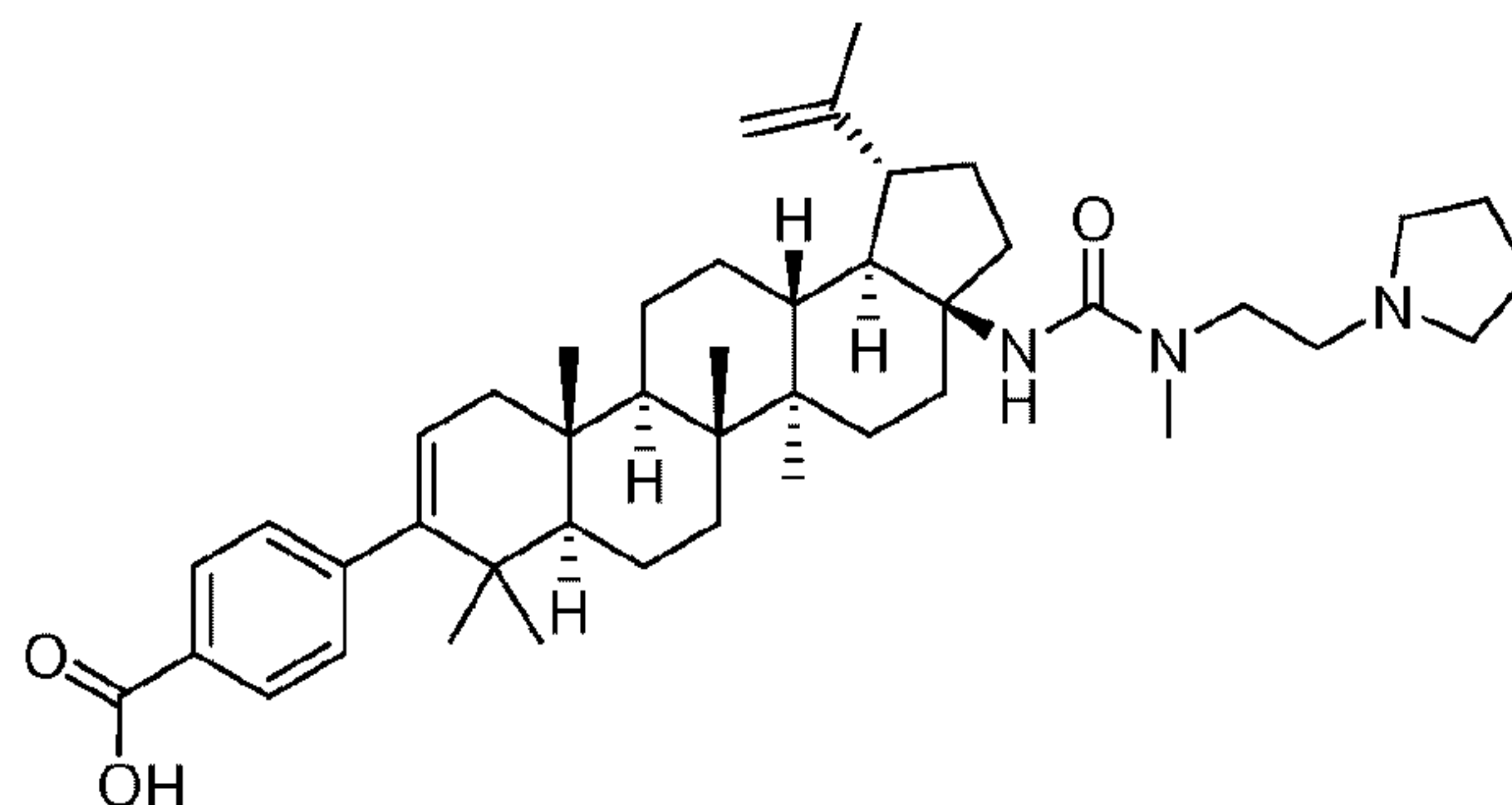
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoethyl)-3-(2-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 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)  $\delta$  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

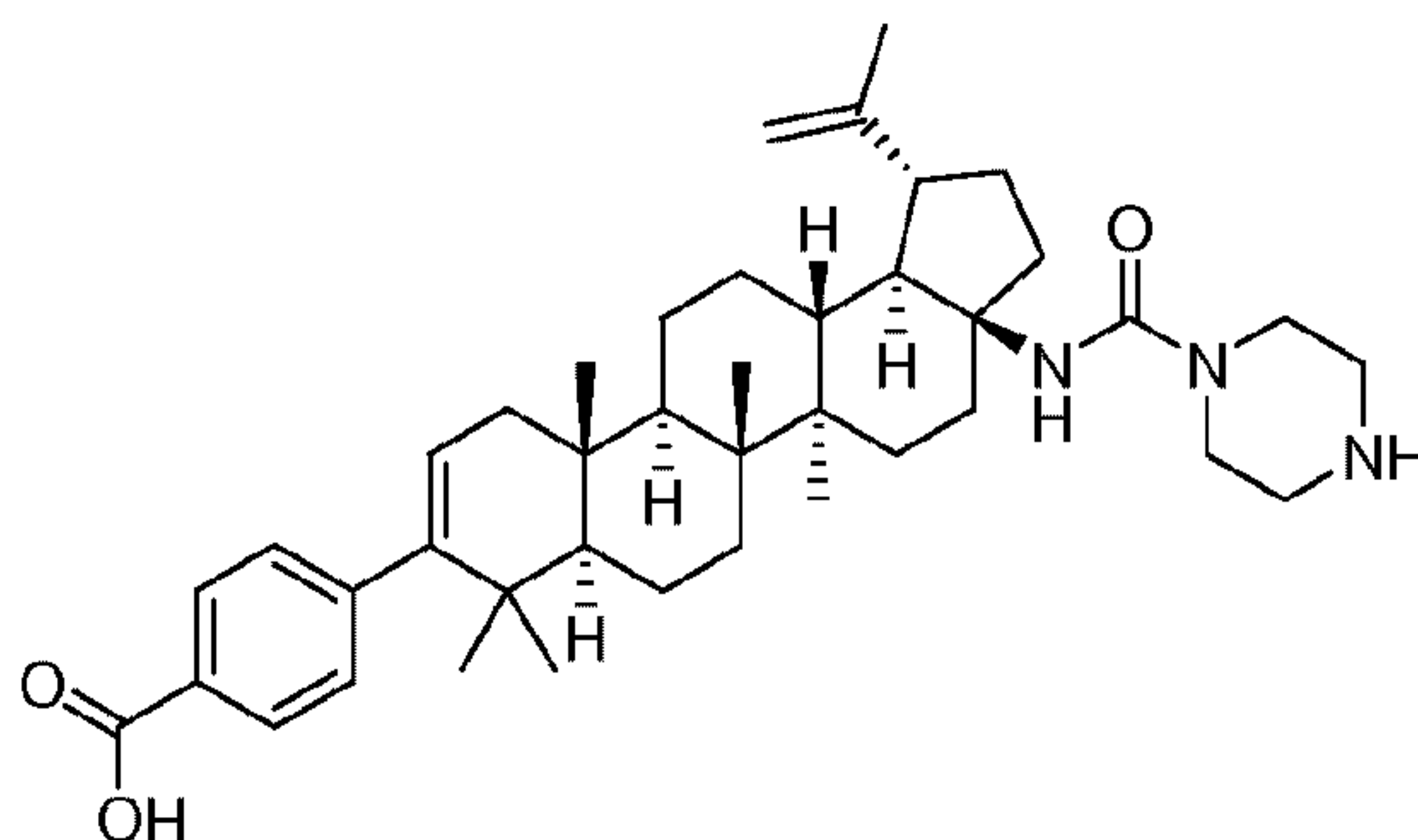
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-methyl-3-(2-(pyrrolidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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*<sub>3</sub> and *MeOD*, *MeOD* lock)  $\delta$  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

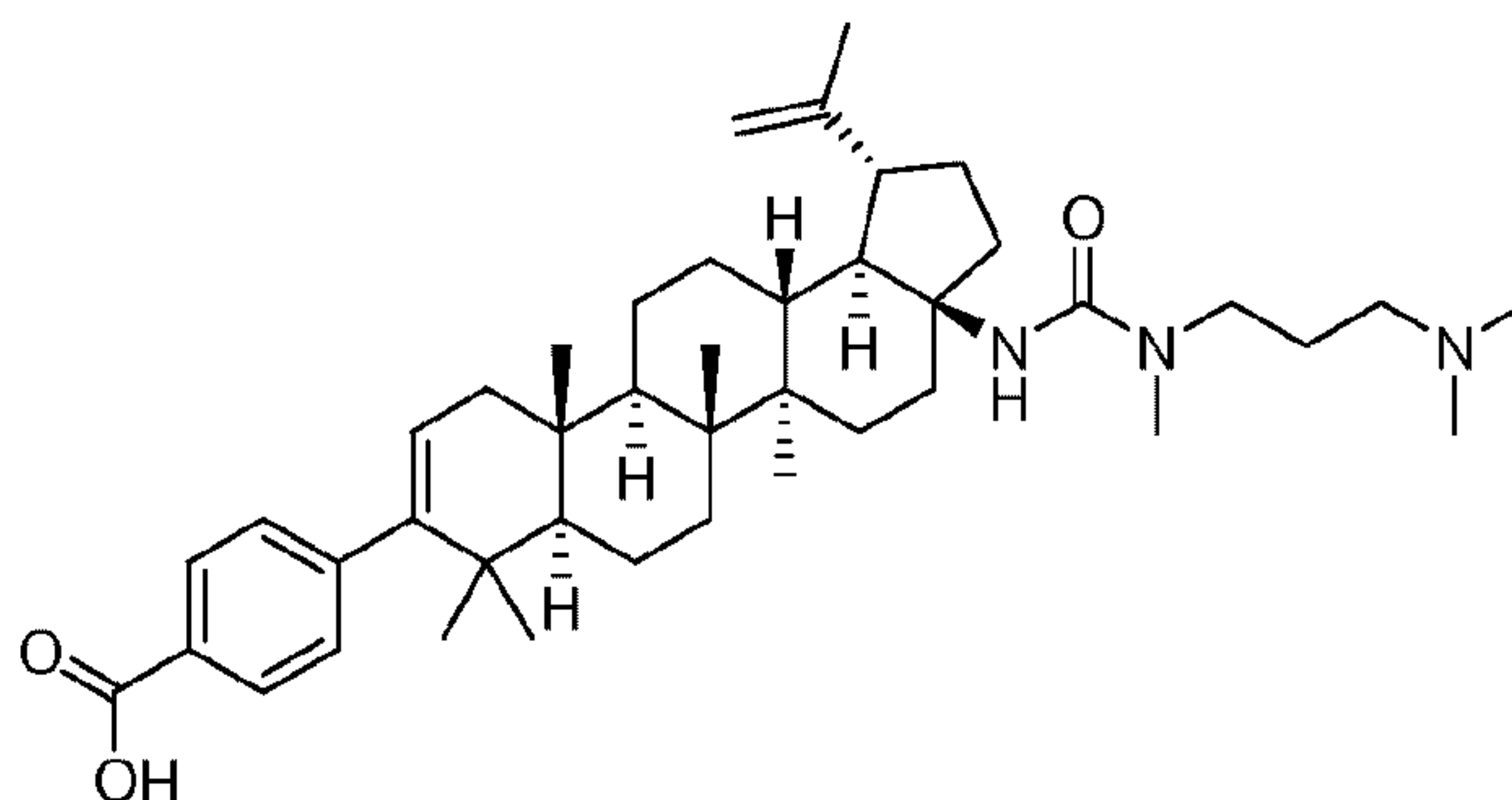
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperazine-1-carboxamido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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

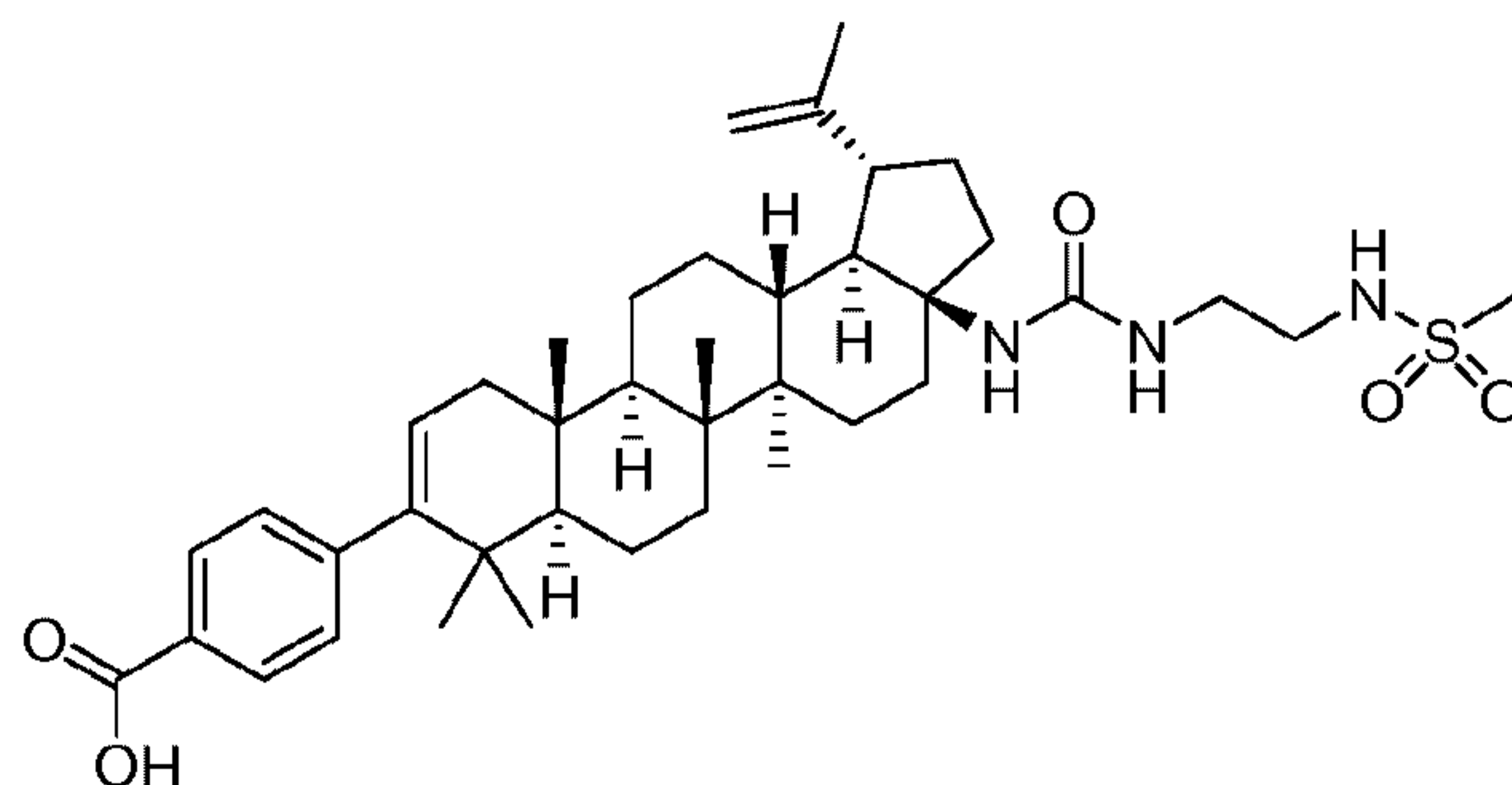


The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1,N3*-  
 trimethylpropane-1,3-diamine as the reactant amine. The product was isolated after  
 reverse phase preparative HPLC purification as 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 *CDCl3* and *MeOD*, *MeOD* lock)  $\delta$  ppm 0.94 (s, 3 H)  
 15 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

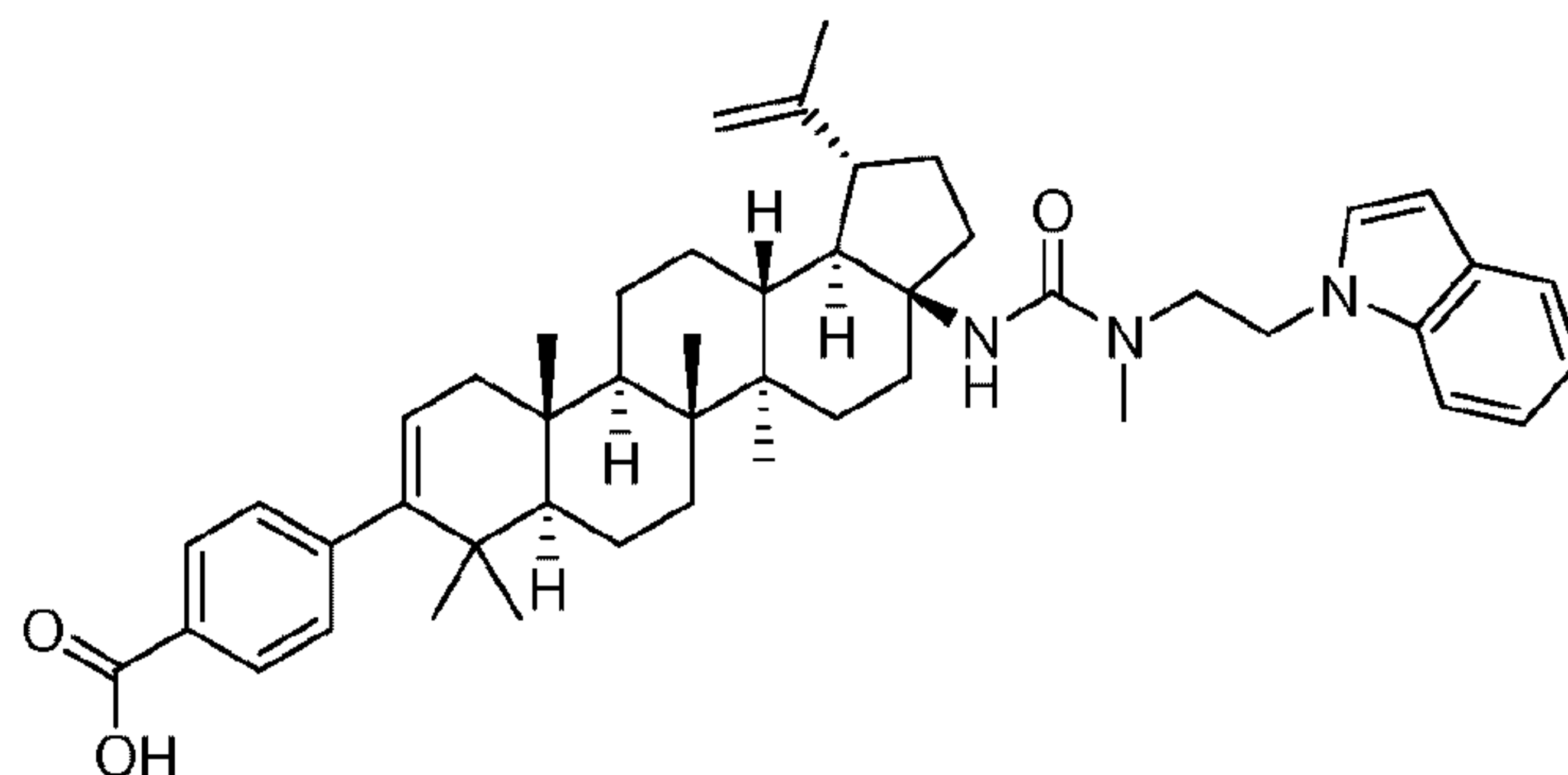
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(methylsulfonamido)ethyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

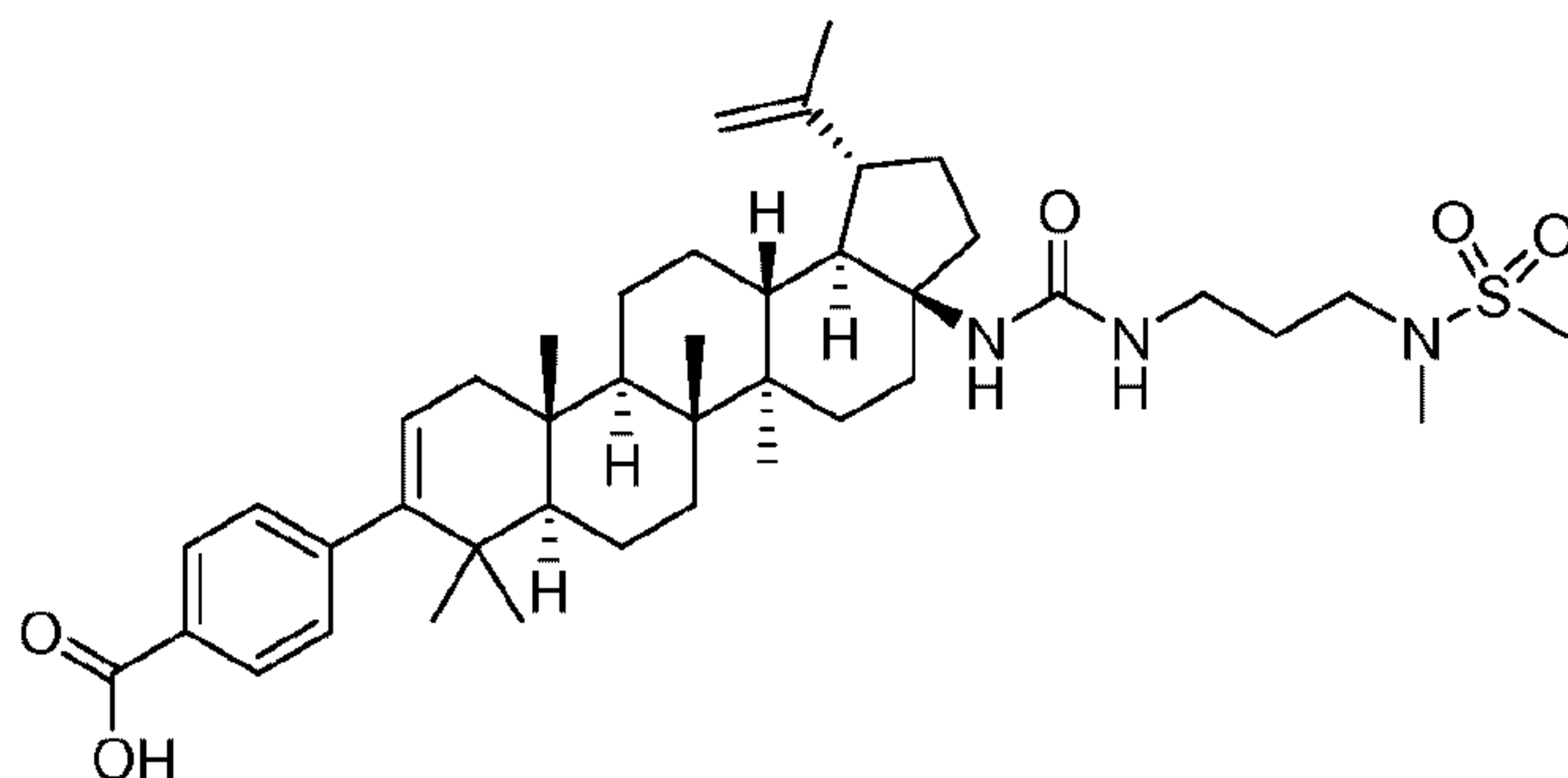
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-indol-1-yl)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using 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)  $\delta$  ppm 0.94 (br. s., 3  
 15 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  
 20 (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

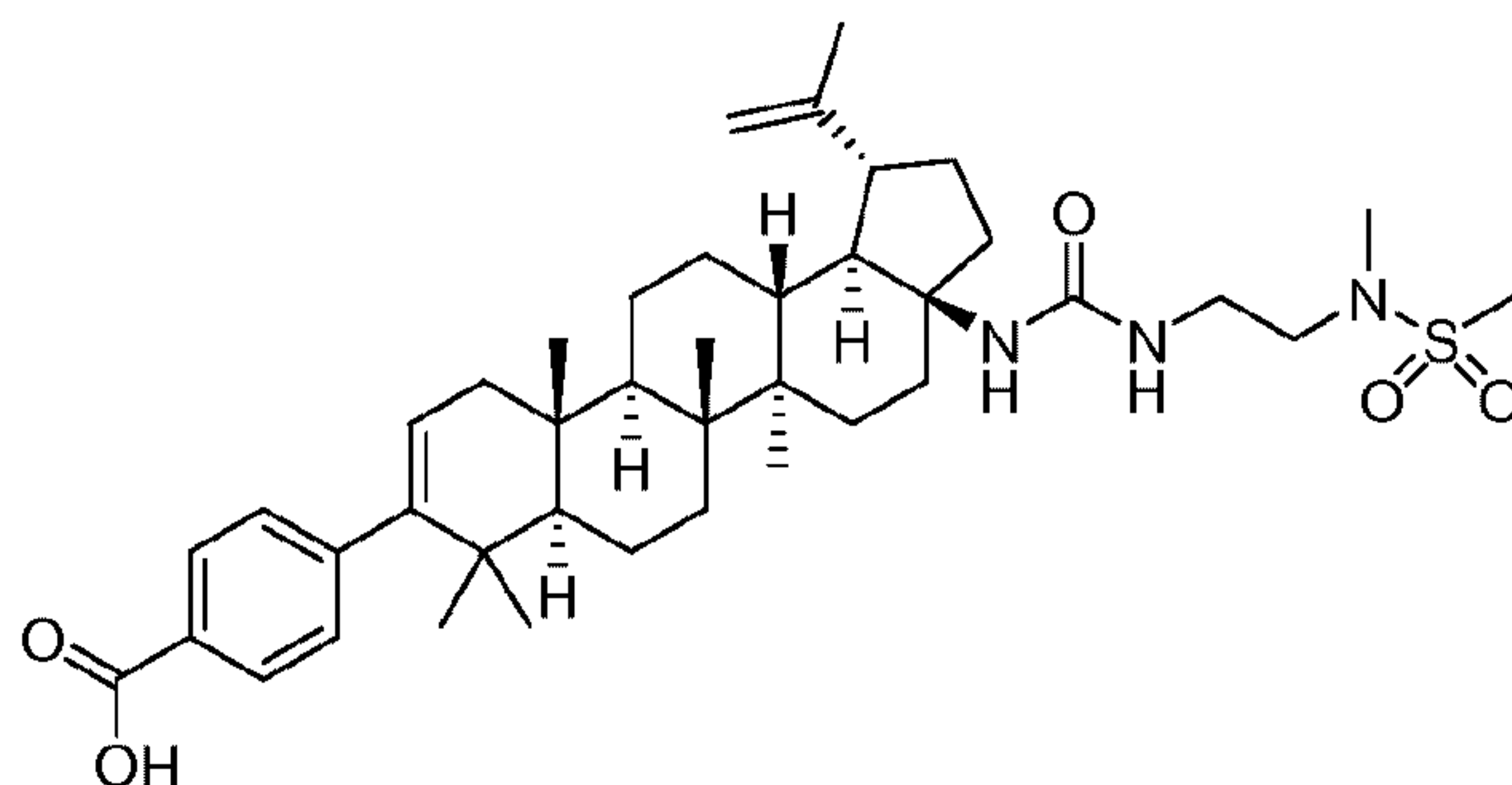
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(*N*-methylmethanesulfonamido)propyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[*a*]chrysen-9-yl)benzoic acid.



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)  $\delta$  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).

## Example 50

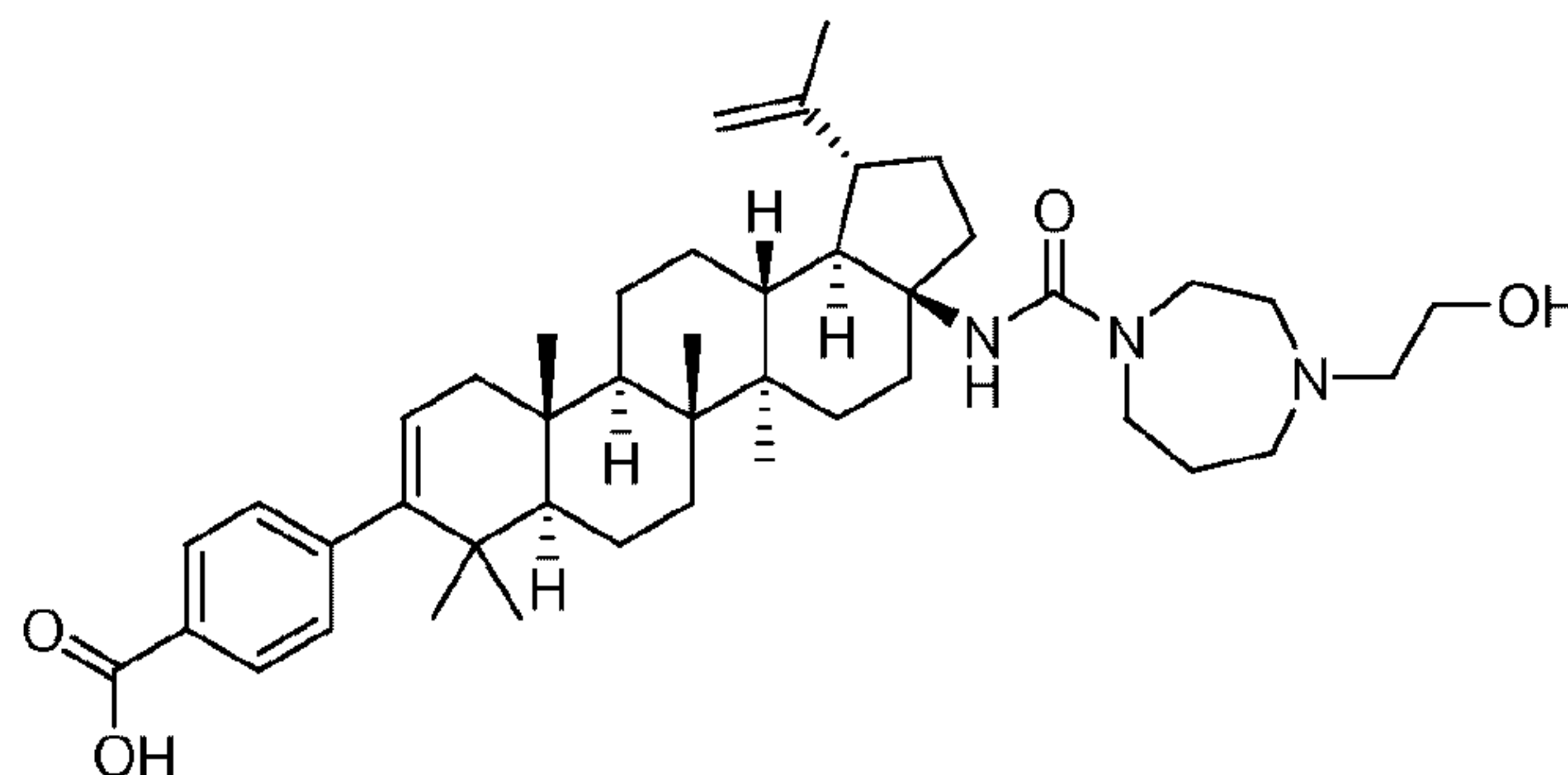
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(N-methylmethanesulfonamido)ethyl)ureido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

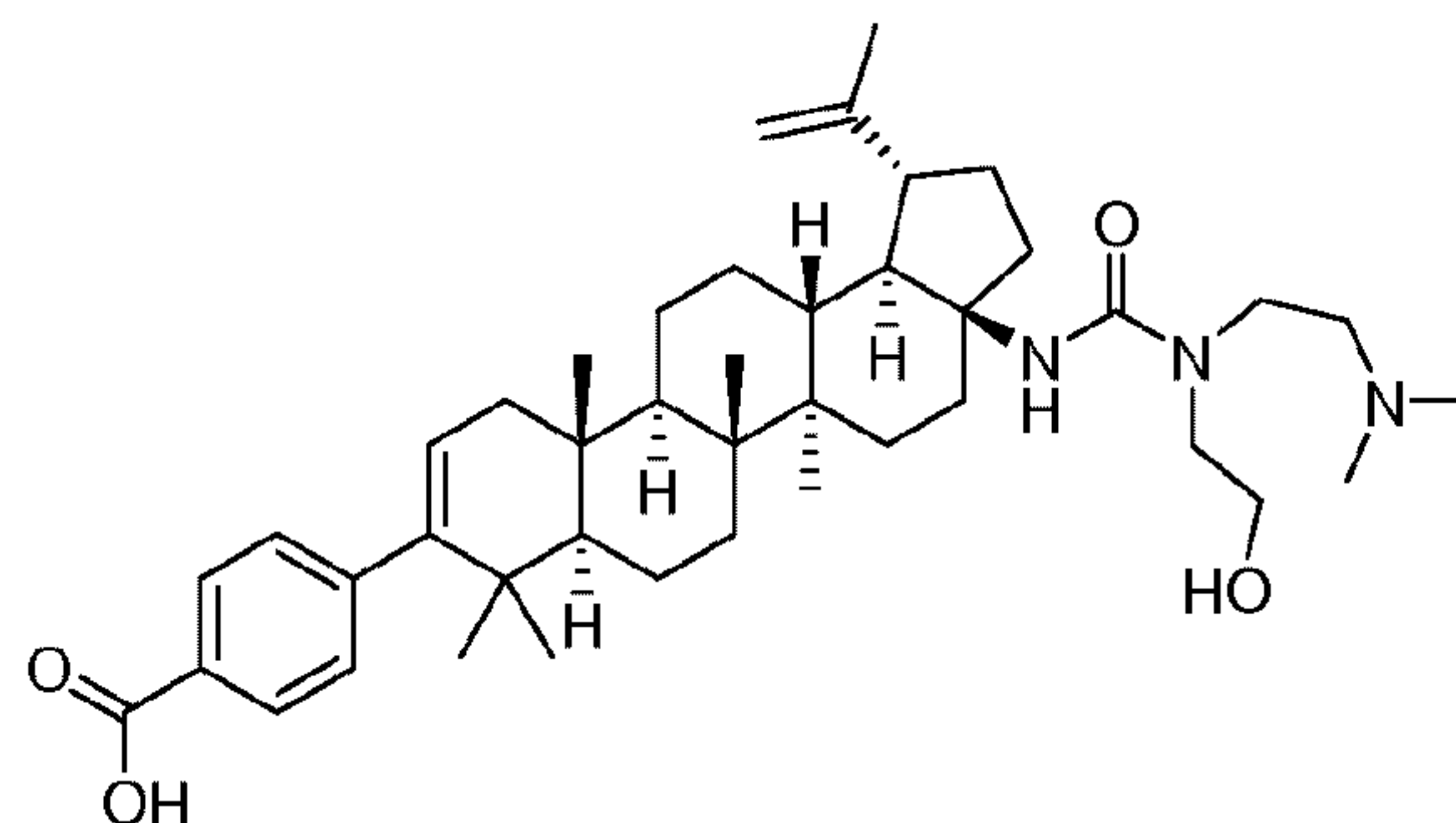
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hydroxyethyl)-1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

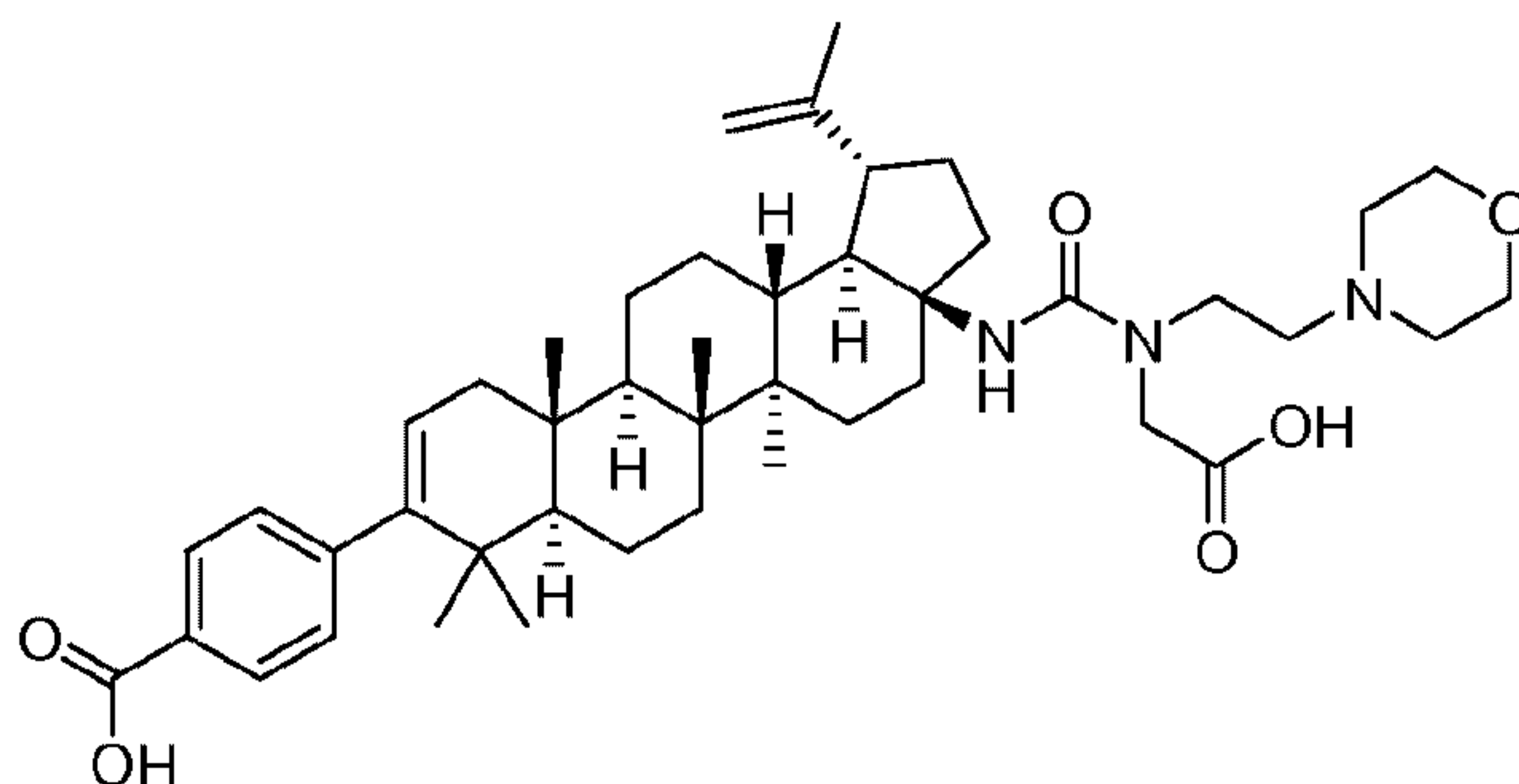
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-  
 (dimethylamino)ethyl)-3-(2-hydroxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-  
 5 1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using 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)  $\delta$  ppm 0.93 (br. s., 3  
 15 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).

## Example 53

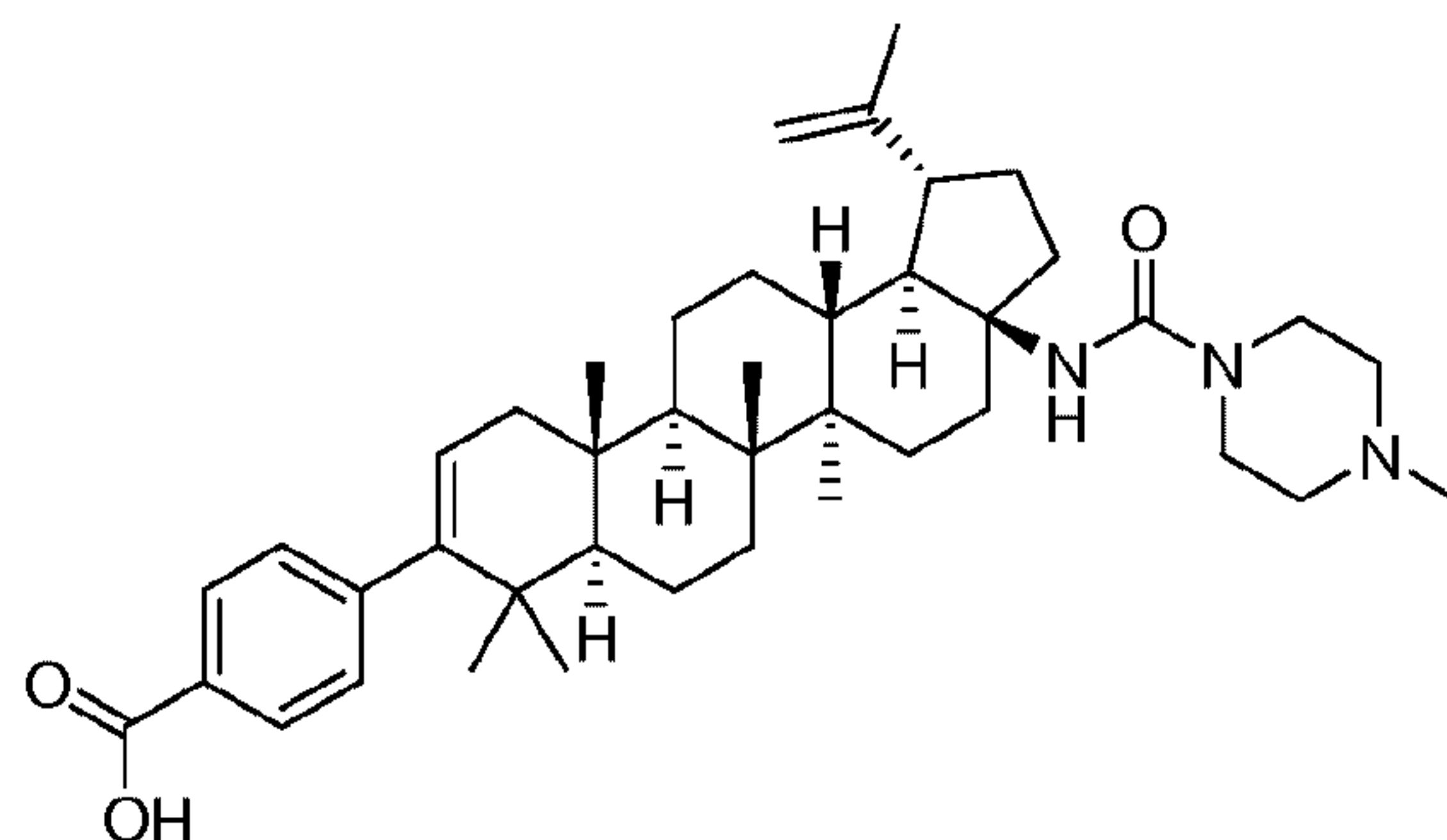
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-  
 (carboxymethyl)-3-(2-morpholinoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-  
 5 en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 cyclopenta[a]chrysen-9-yl)benzoic acid.



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-(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)  $\delta$  ppm 0.94 (br. s., 3 H)  
 15 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,  
 20  $J=8.24$  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.

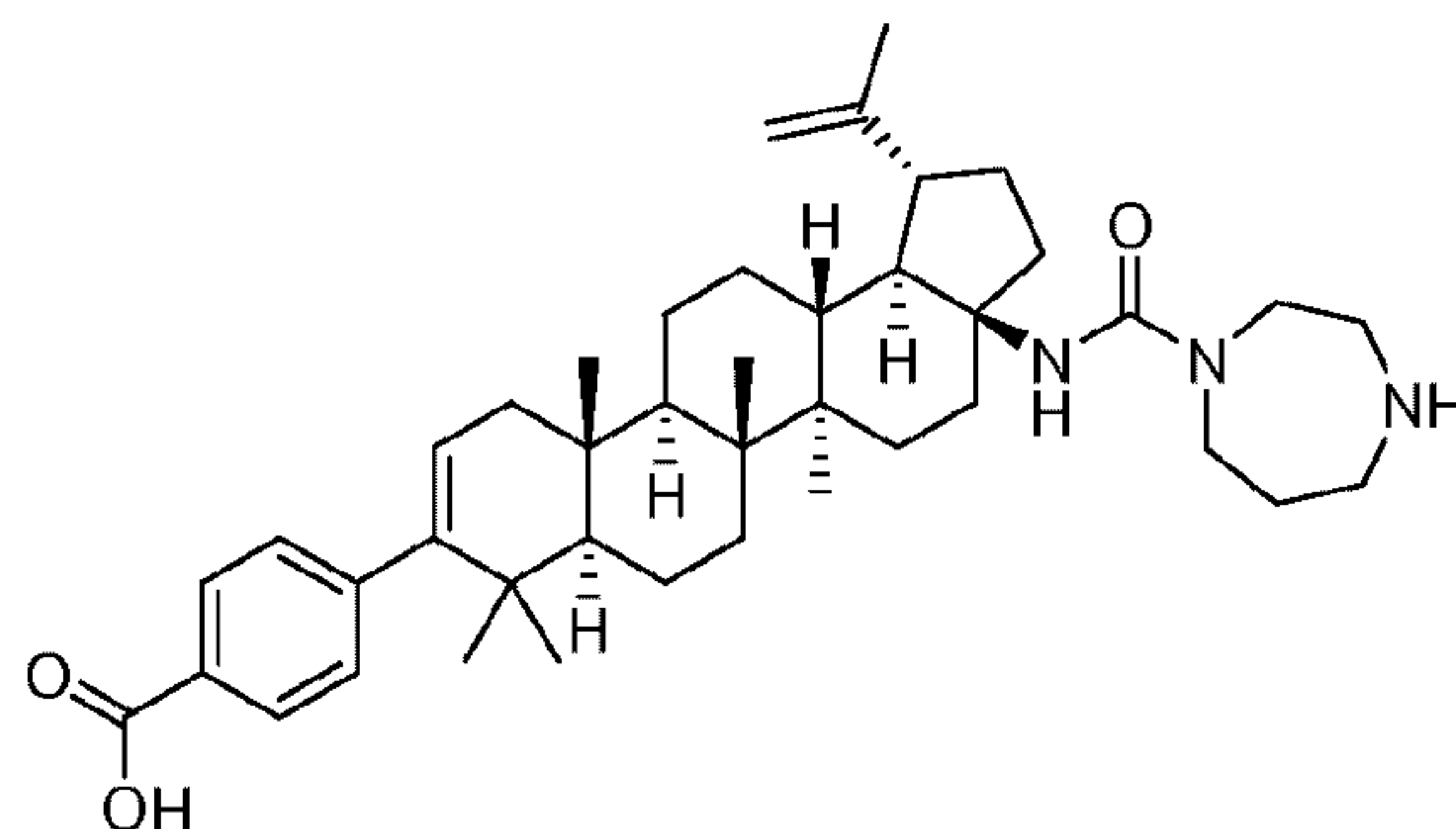


The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using 1-methylpiperazine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (49 mg, 75% yield) 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)  $\delta$  ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 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.

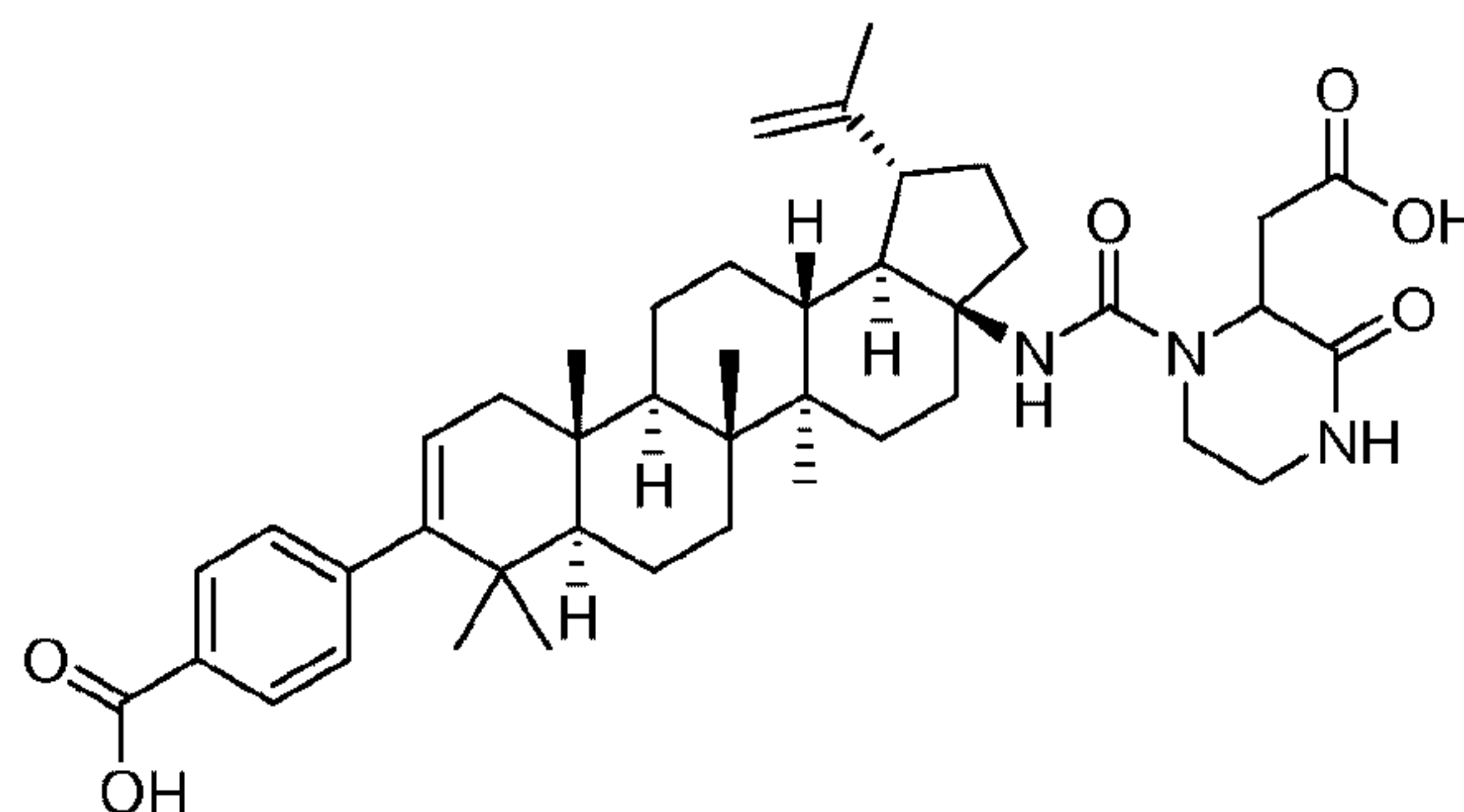


The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using  
 homopiperazine as the reactant amine. The product was isolated after reverse phase  
 preparative HPLC purification as a white solid (33 mg, 53% 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)  $\delta$  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

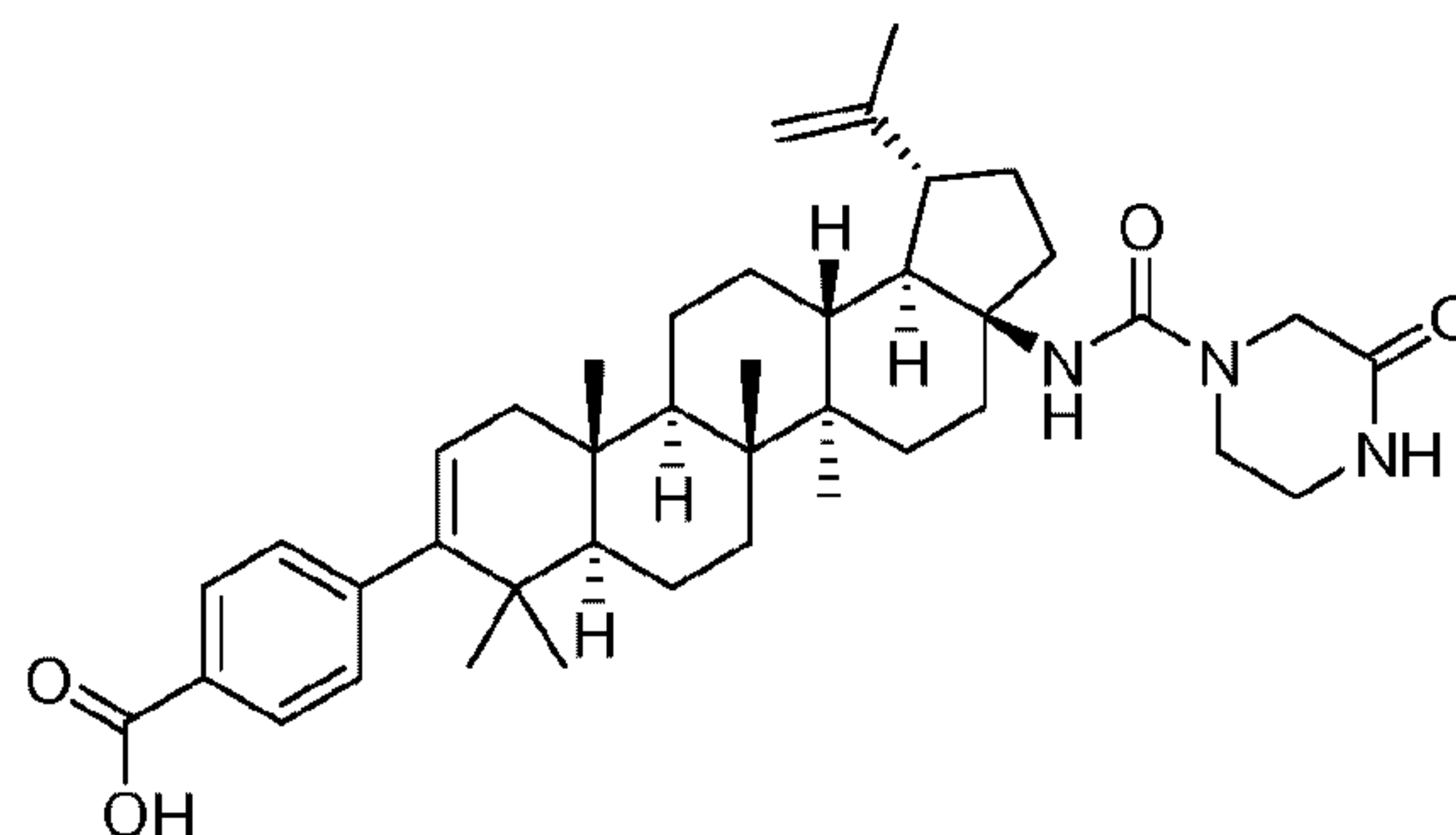
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-  
 (carboxymethyl)-3-oxopiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-  
 5 (prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-  
 1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

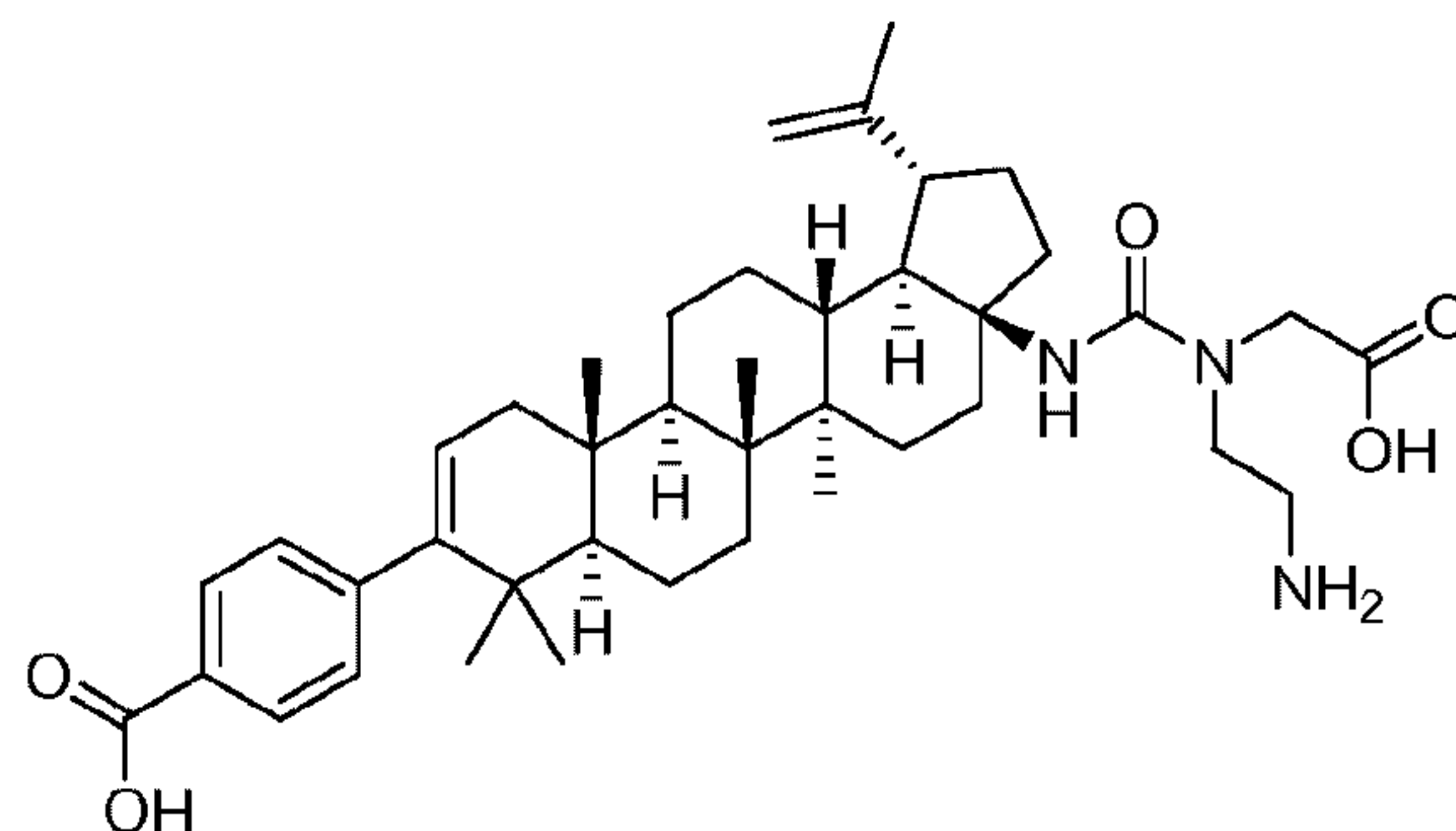
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-oxopiperazine-1-carboxamido)-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  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

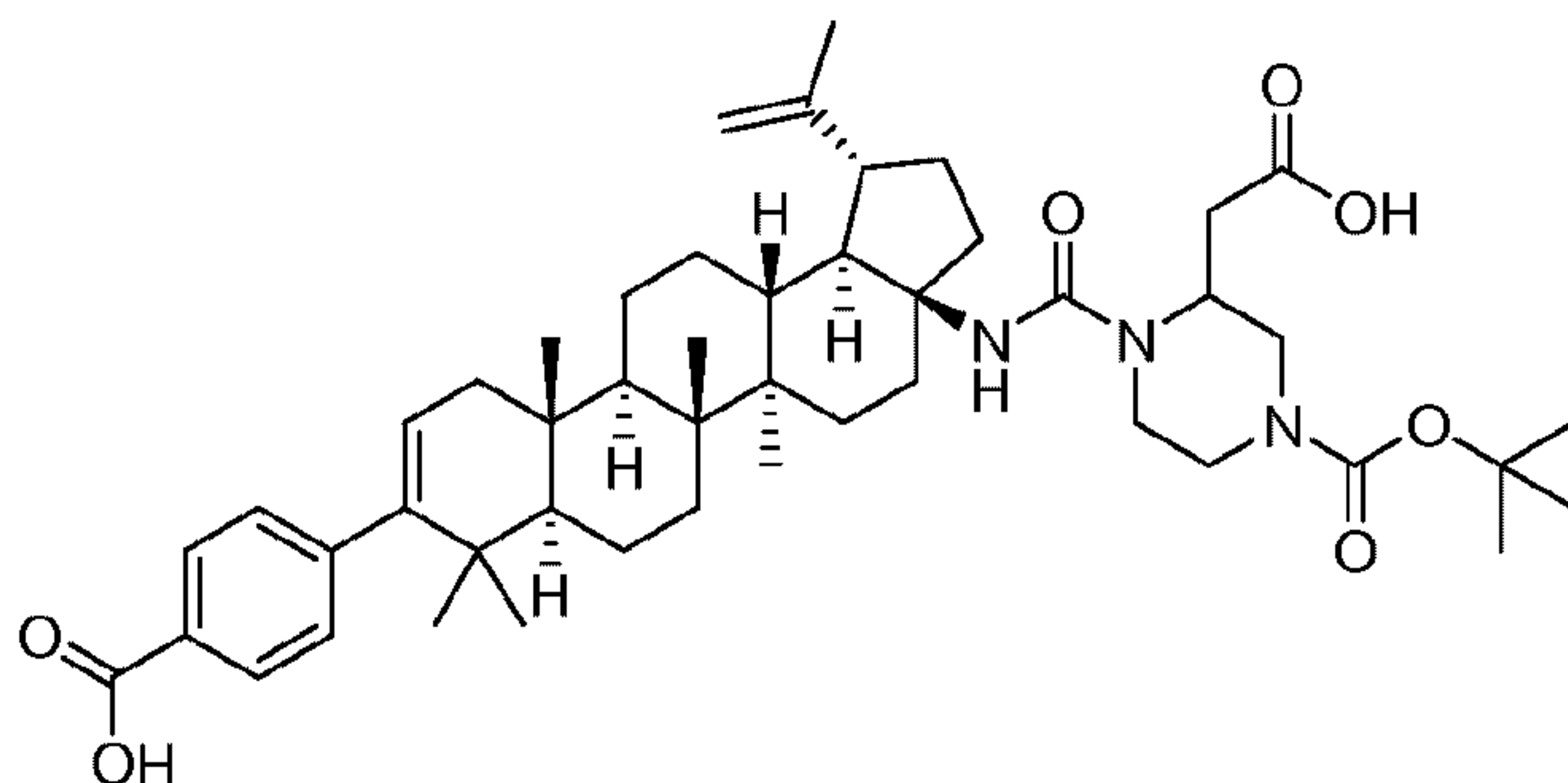
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoethyl)-3-(carboxymethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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<sup>+</sup>), retention time 2.41 min (method 11). <sup>1</sup>H NMR (400 MHz, 1:1 mixture of CDCl<sub>3</sub> 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

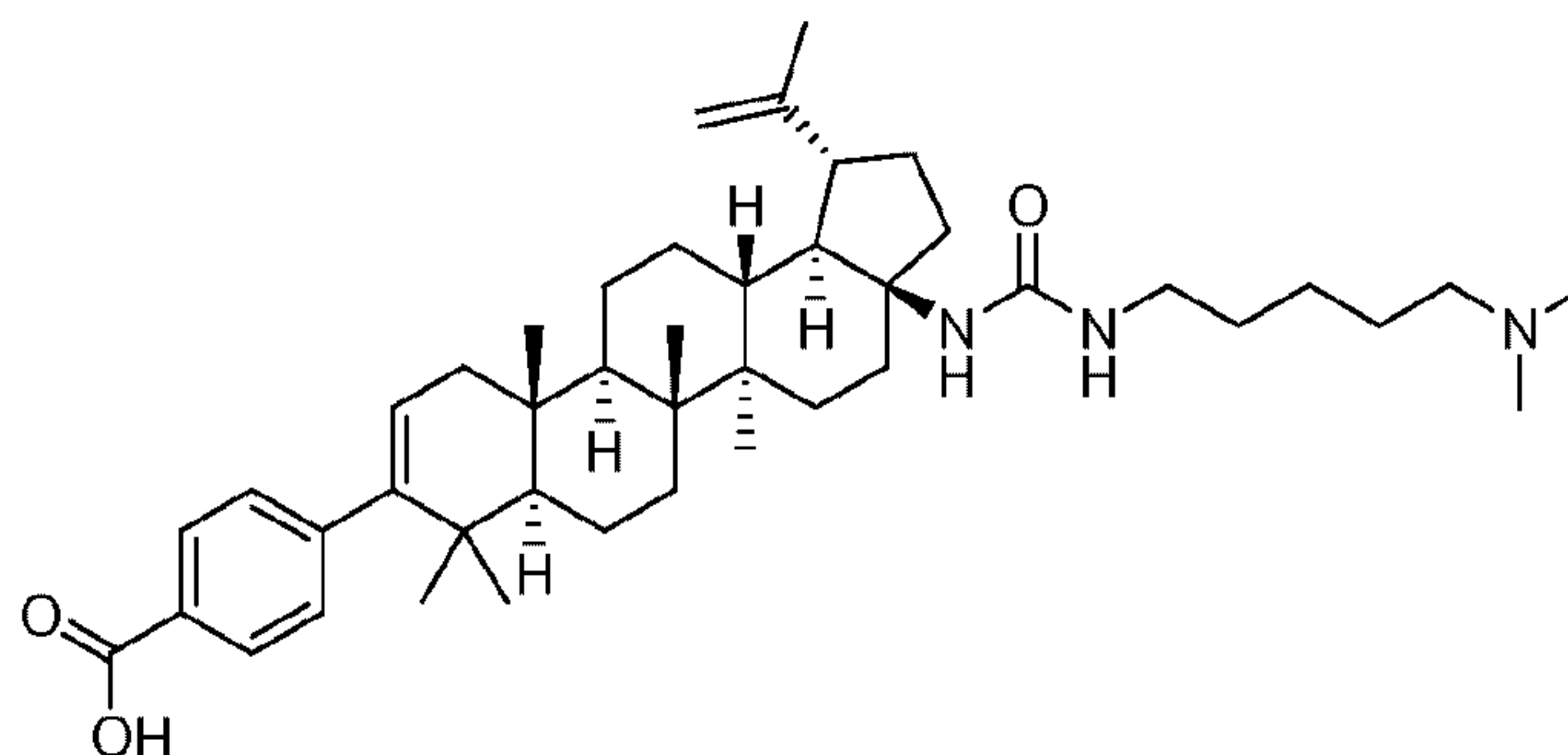
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(*tert*-  
butoxycarbonyl)-2-(carboxymethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-  
5 pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)  $\delta$  ppm 1H NMR (500 MHz,  $MeOD$ )  $\delta$  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).

## 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)-  
 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.

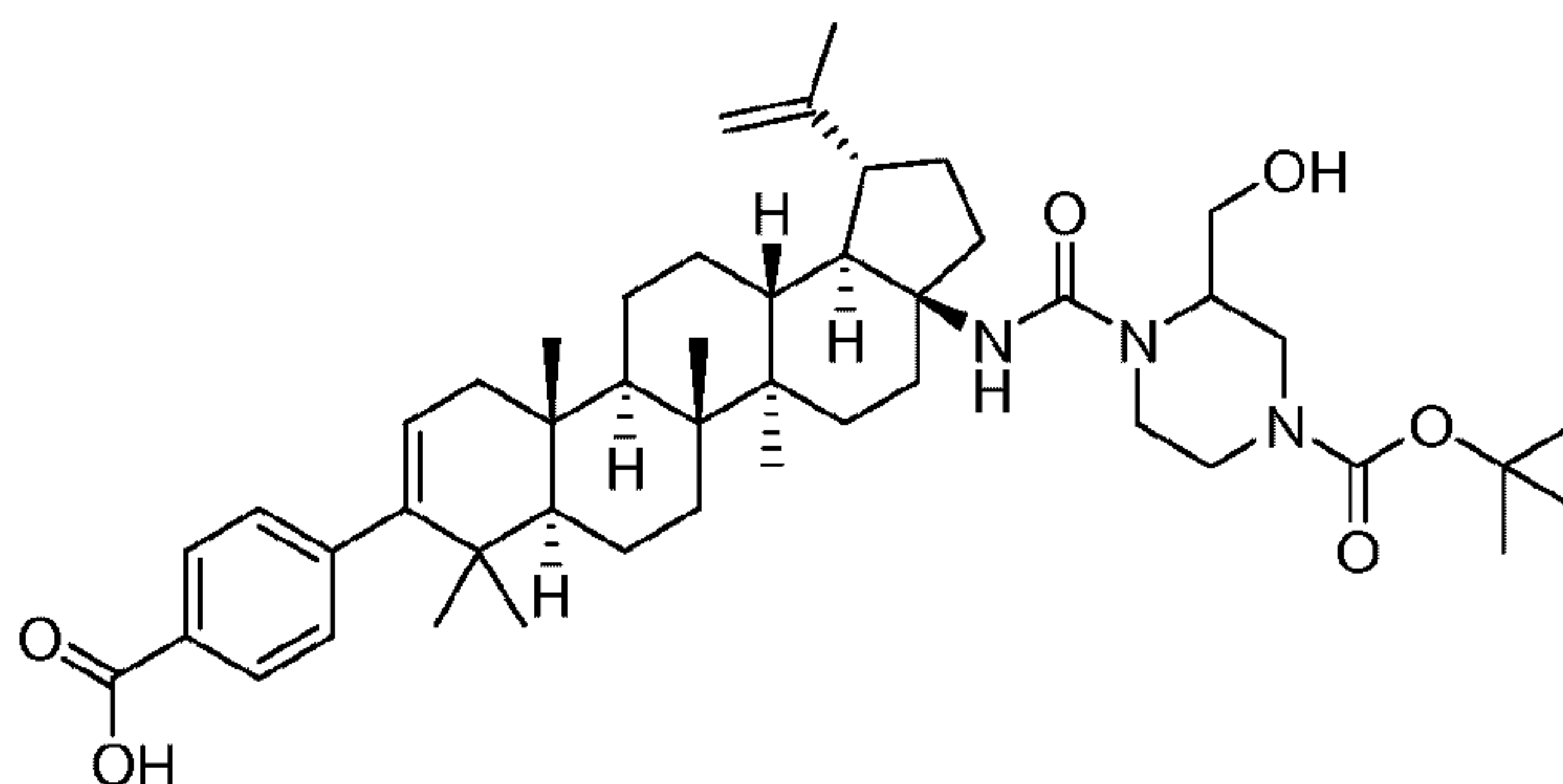


The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using *N*1,*N*1-  
 dimethylpentane-1,5-diamine as the reactant amine. The mono-TFA salt product was  
 isolated after reverse phase preparative HPLC purification 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)  $\delta$  ppm 0.93 (br. s., 3 H)  
 15 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).

20

## 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.

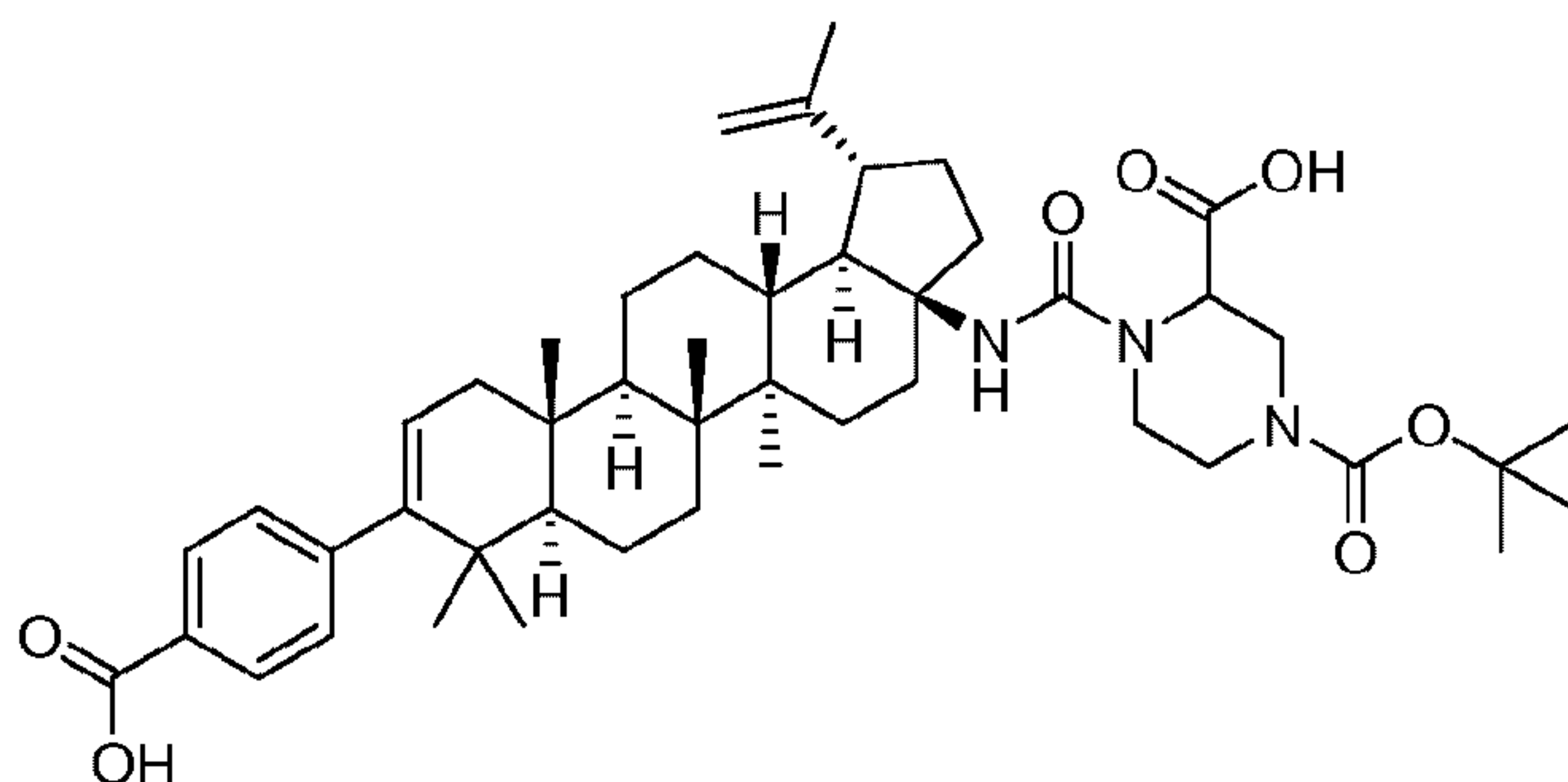


The title compound was prepared following the general procedures described  
10 above for the C-17 urea formation and subsequent ester hydrolysis using *tert*-butyl 3-(hydroxymethyl)piperazine-1-carboxylate as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse 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)  $\delta$  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,  $J=18.63, 13.87, 4.64$  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-

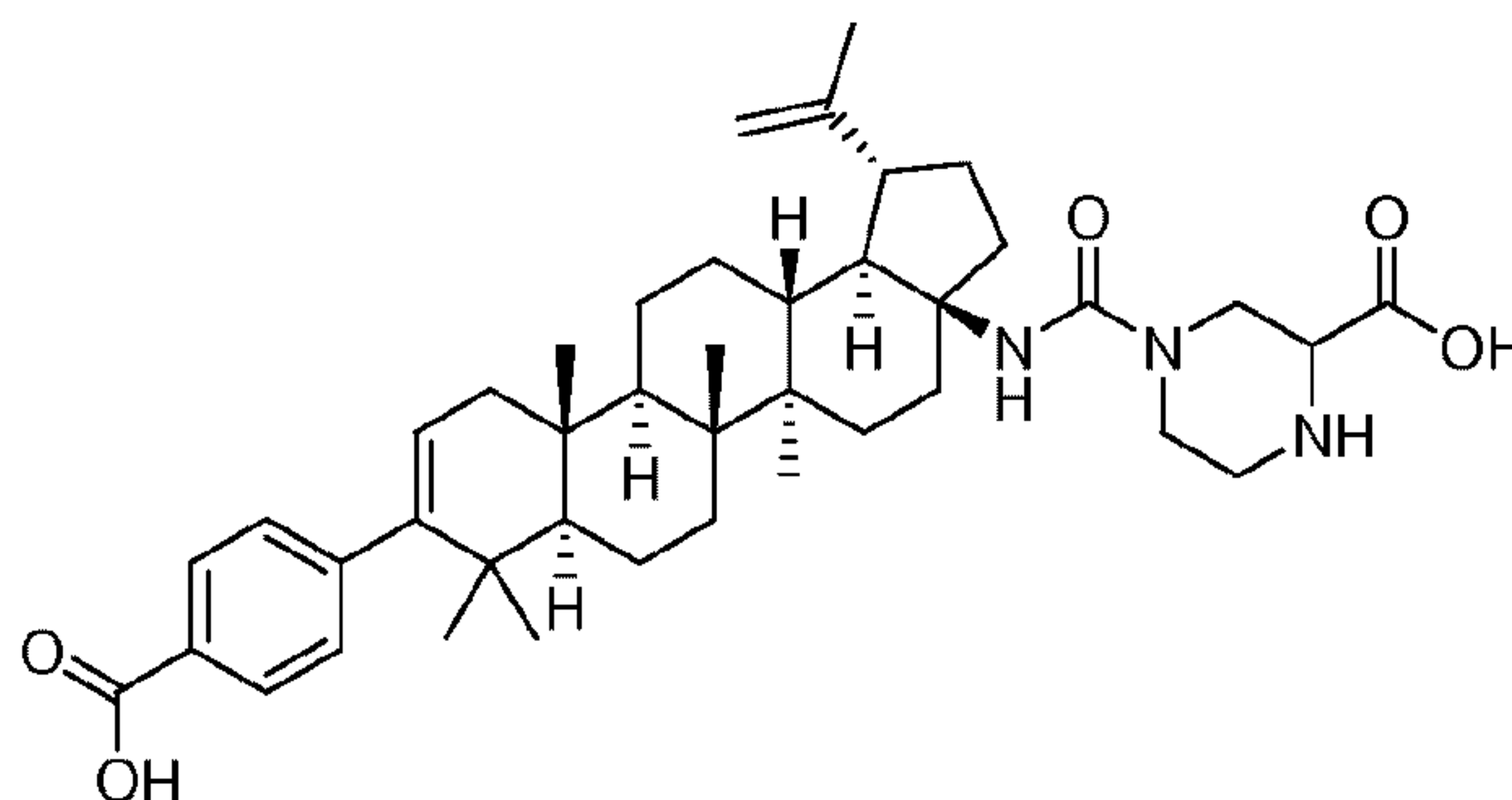
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-  
 5 pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-3a-ylcarbamoyl)piperazine-2-carboxylic  
 acid.



- 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  
 15 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)  $\delta$  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,  $J=12.21, 8.24$   
 20 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).

## 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.

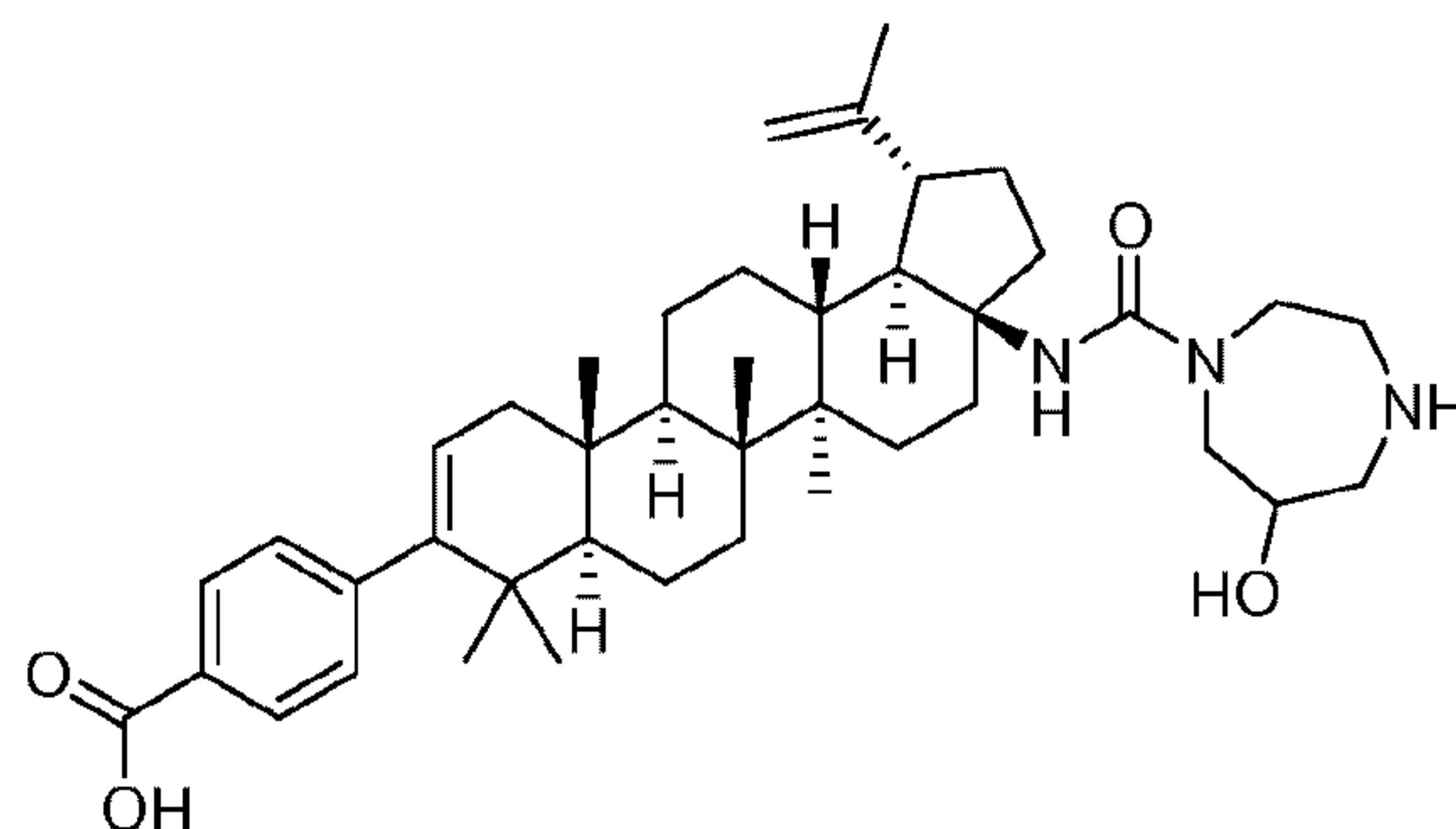


The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using methyl piperazine-2-carboxylate as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC 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)  $\delta$  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

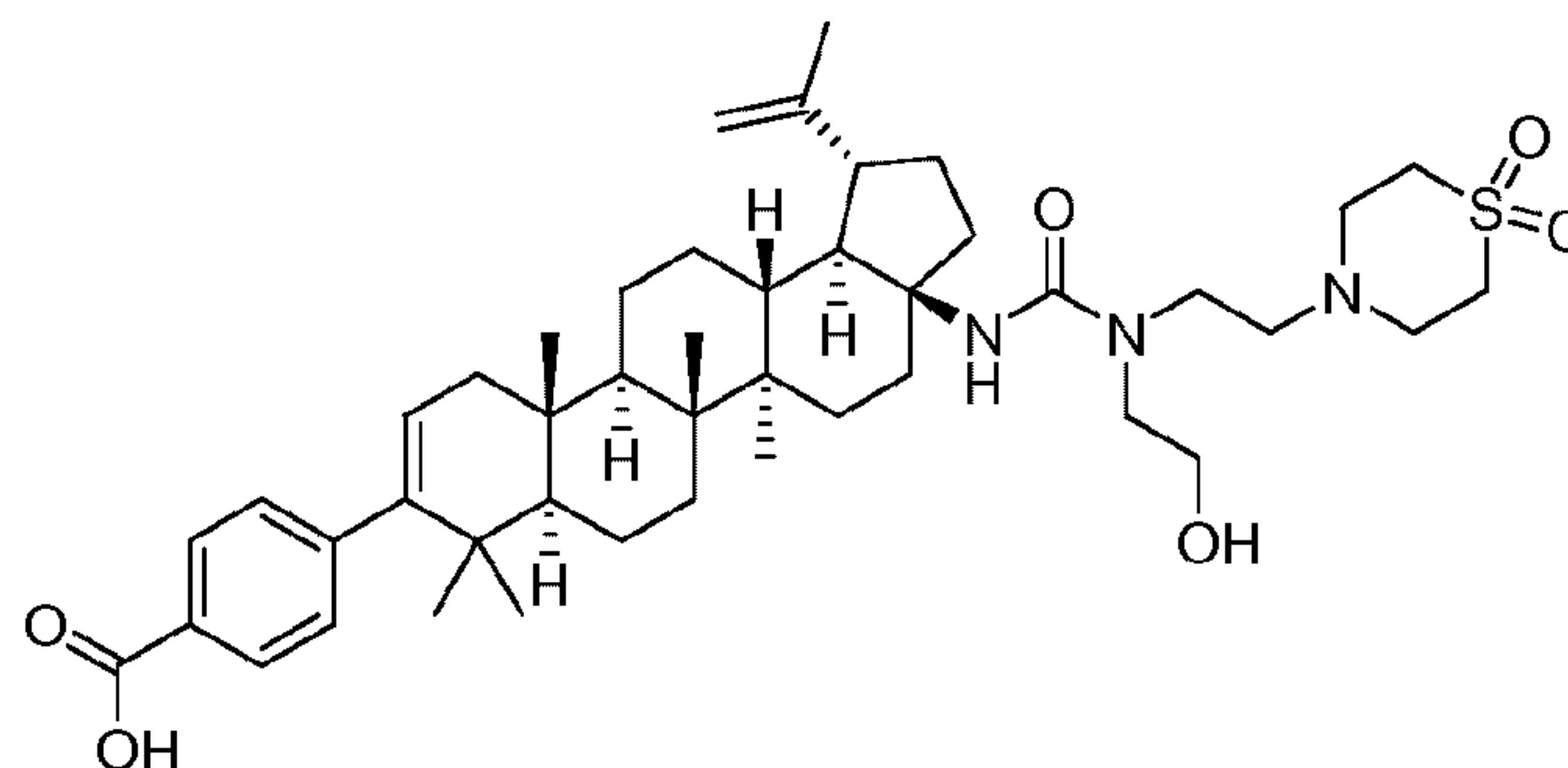
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(6-hydroxy-1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described  
 10 above for the C-17 urea formation and subsequent ester hydrolysis using 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)  $\delta$  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).

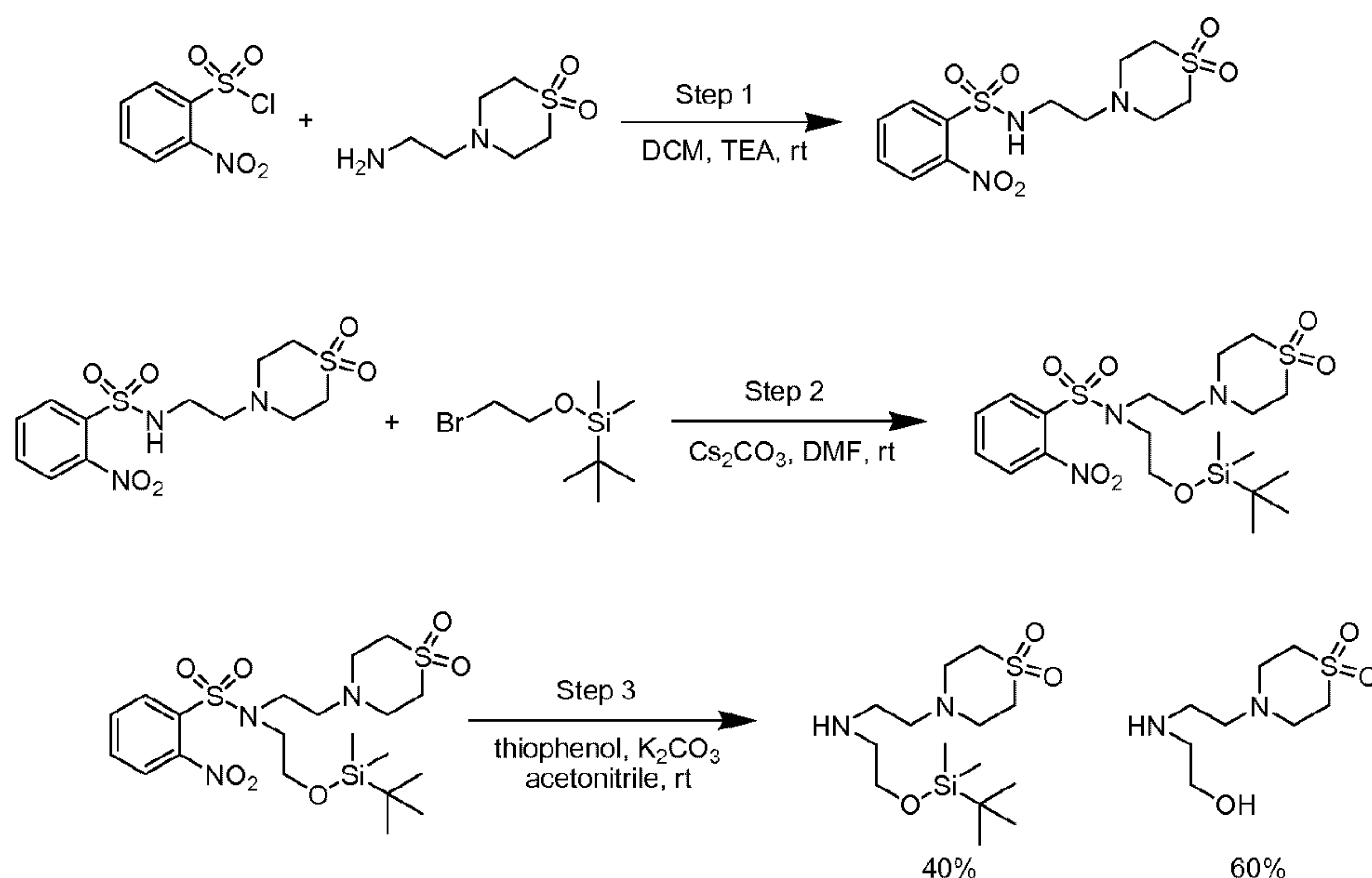
## Example 65

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-  
 5 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.



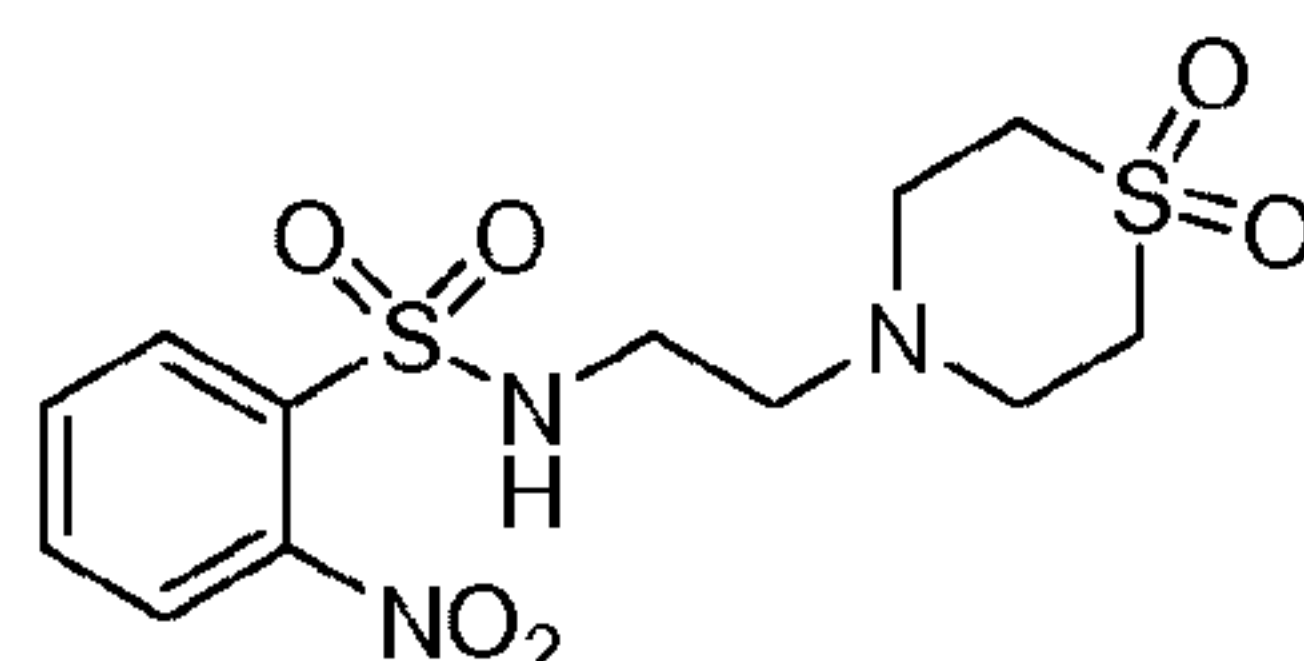
- 10 The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using the mixture of 2-(((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine and 2-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)ethanol 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)  $\delta$
- 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,  $J=4.77$  Hz, 1 H) 7.20 (m,  $J=8.28$  Hz, 2 H) 7.92 (m,  $J=8.28$  Hz, 2 H).
- 25

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.



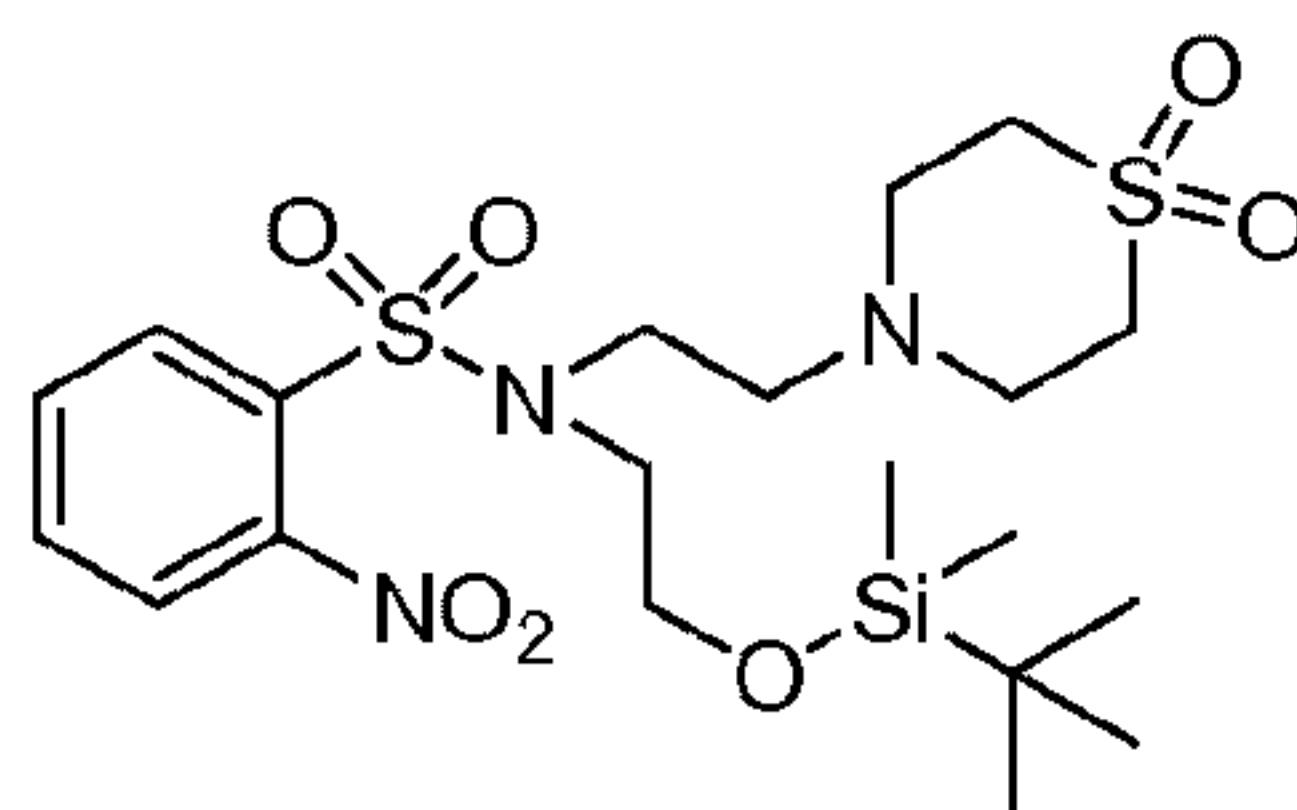
15

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).

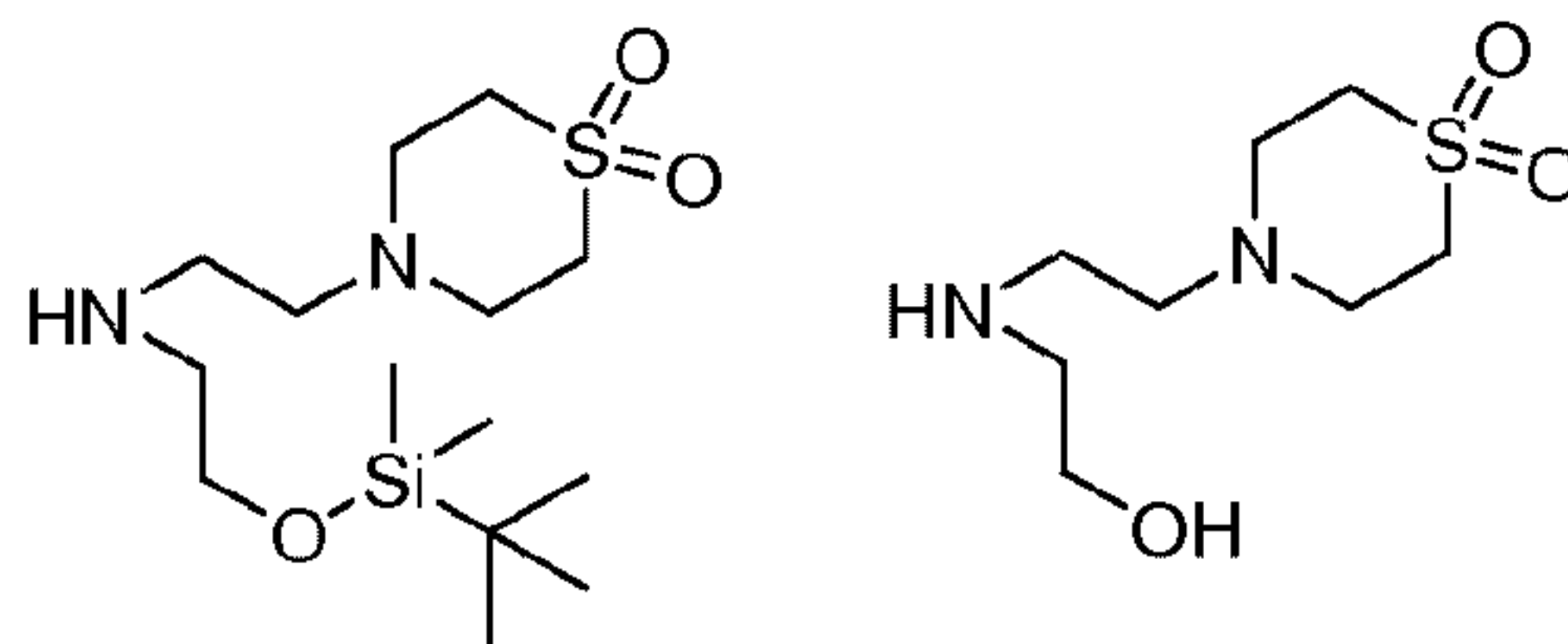
- 5 LCMS:  $m/z$  364 ( $M+H^+$ ), retention time 0.98 min (method 11).  $^1H$  NMR (500 MHz, CHLOROFORM- $d$ )  $\delta$  ppm 2.71 (t,  $J=5.49$  Hz, 2 H) 2.96 (br. s., 4 H) 3.05 (br. s., 4 H) 3.20 (q,  $J=5.49$  Hz, 2 H) 5.93 (br. s., 1 H) 7.73 - 7.84 (m, 2 H) 7.84 - 7.93 (m, 1 H) 8.11 - 8.23 (m, 1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

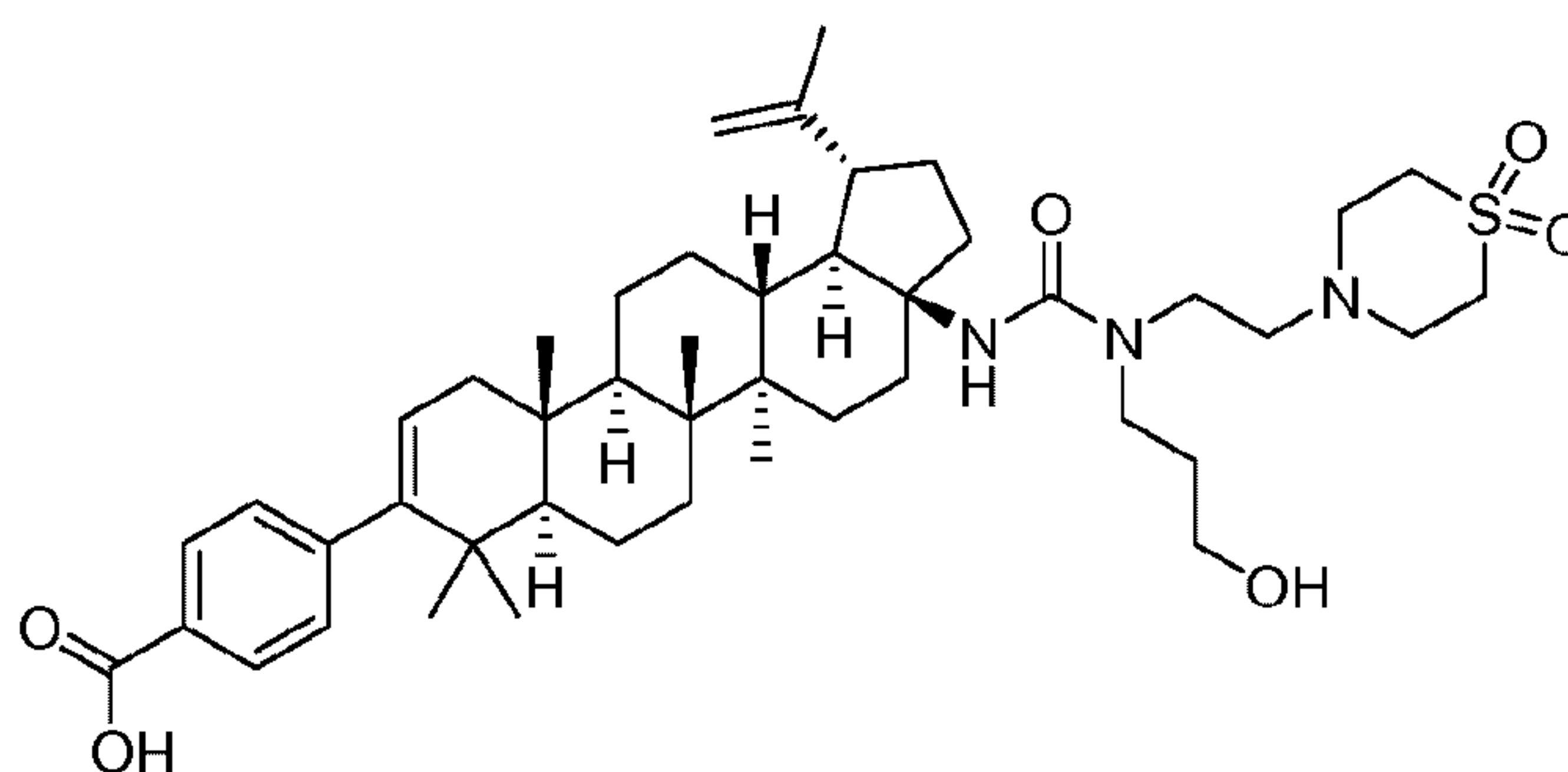
- Step 3. Preparation of a mixture of 2-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine and 2-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)ethanol



- N*-(2-((*tert*-butyl(dimethyl)silyl)oxy)ethyl)-*N*-(2-(1,1-dioxido-4-
- 5 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
- 10 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). <sup>1</sup>H NMR revealed that the material collected was a roughly 2:3 mixture of desired product and
- 15 desilylated desired material. No further purification was performed and the mixture was carried forward to the next step.

### Example 66

- 20 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.

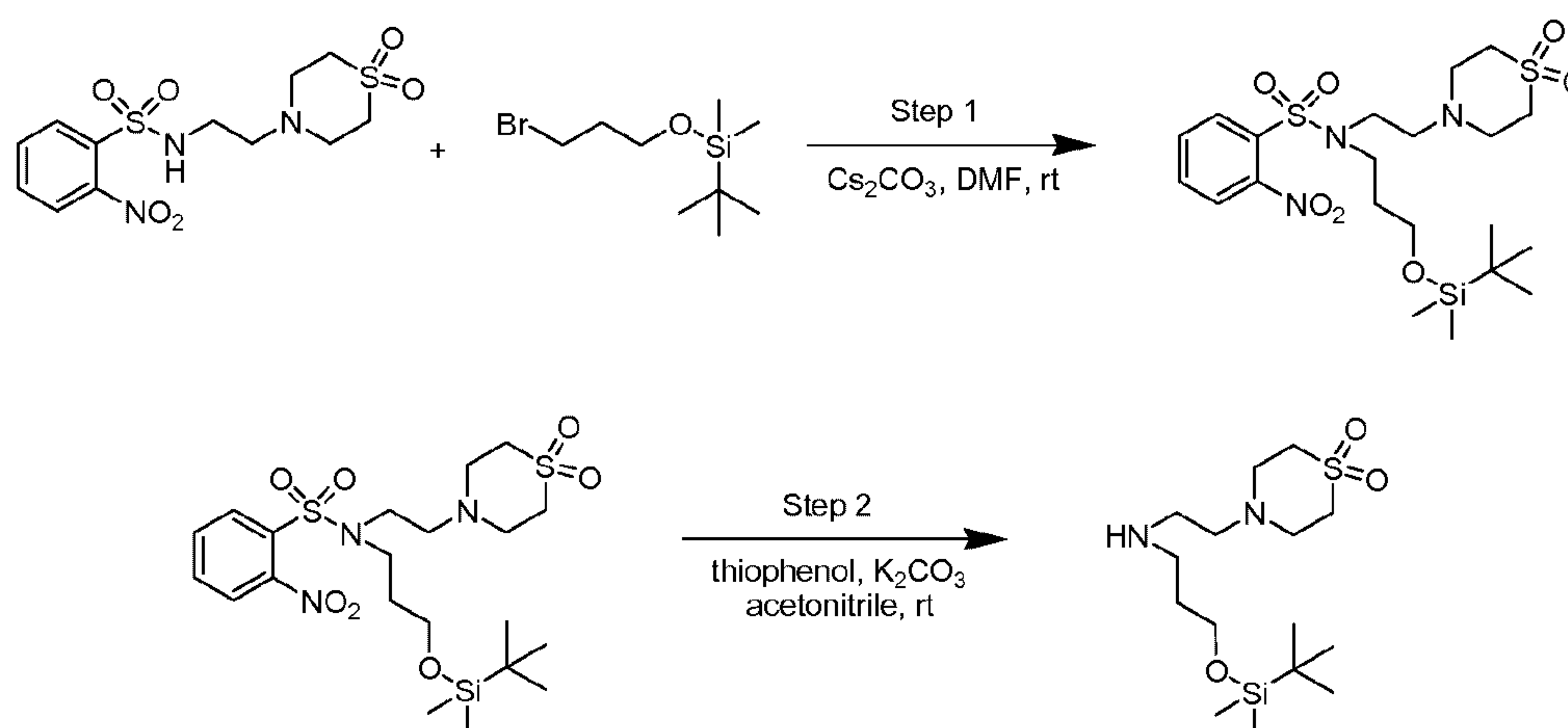


The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using 3-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-1-propanamine  
 5 as the reactant amine (prepared as described below). The urea 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,  
 10 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)  $\delta$  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  
 15 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).

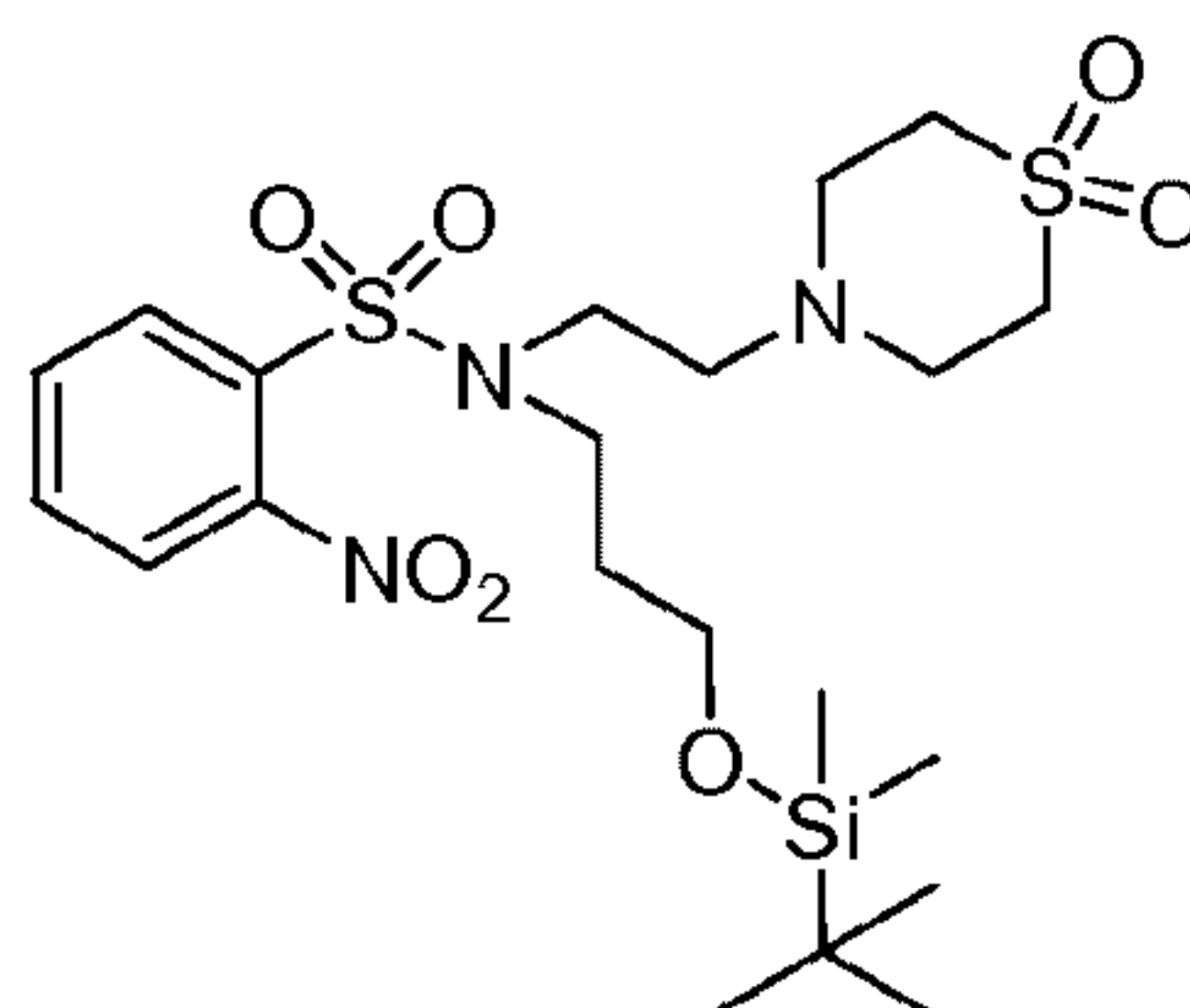
20

Synthesis of amine used in preparation of 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-hydroxypropyl)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-  
 25 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid:



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



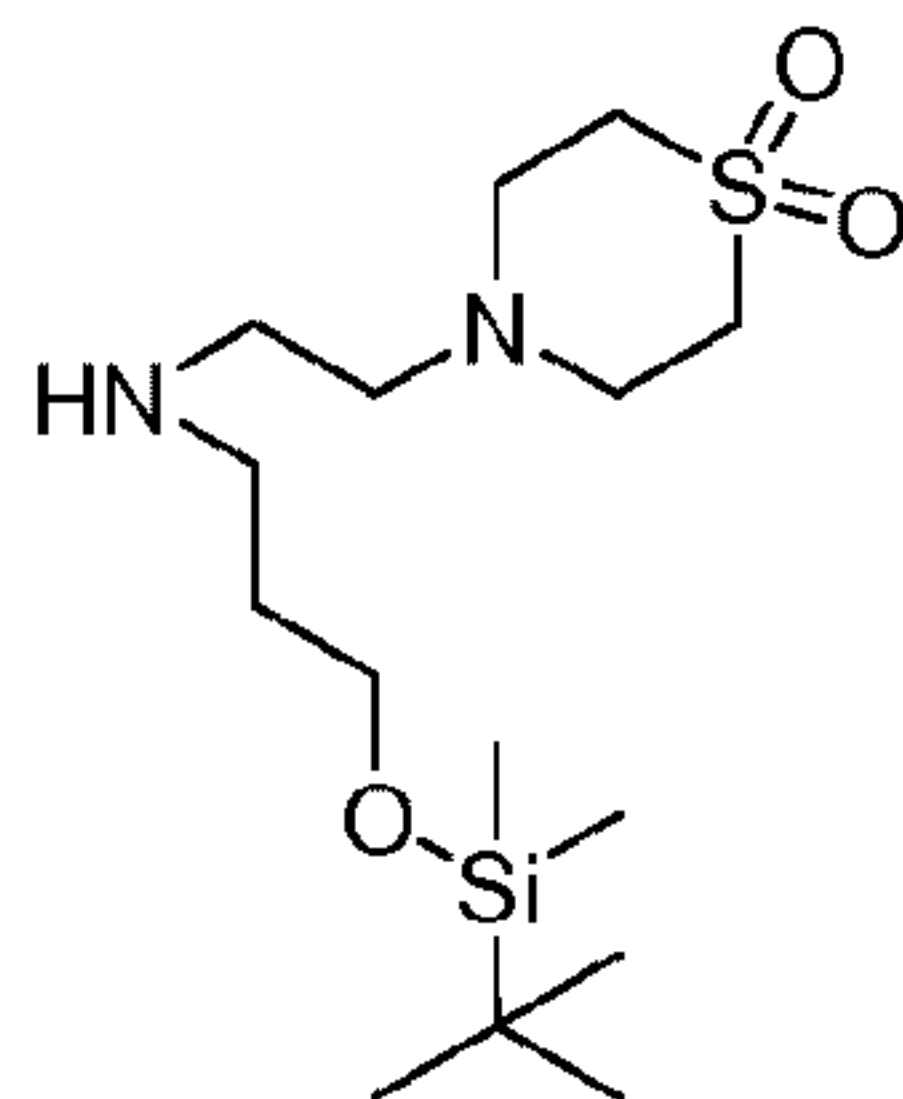
5

*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,

20

CHLOROFORM-*d*)  $\delta$  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).

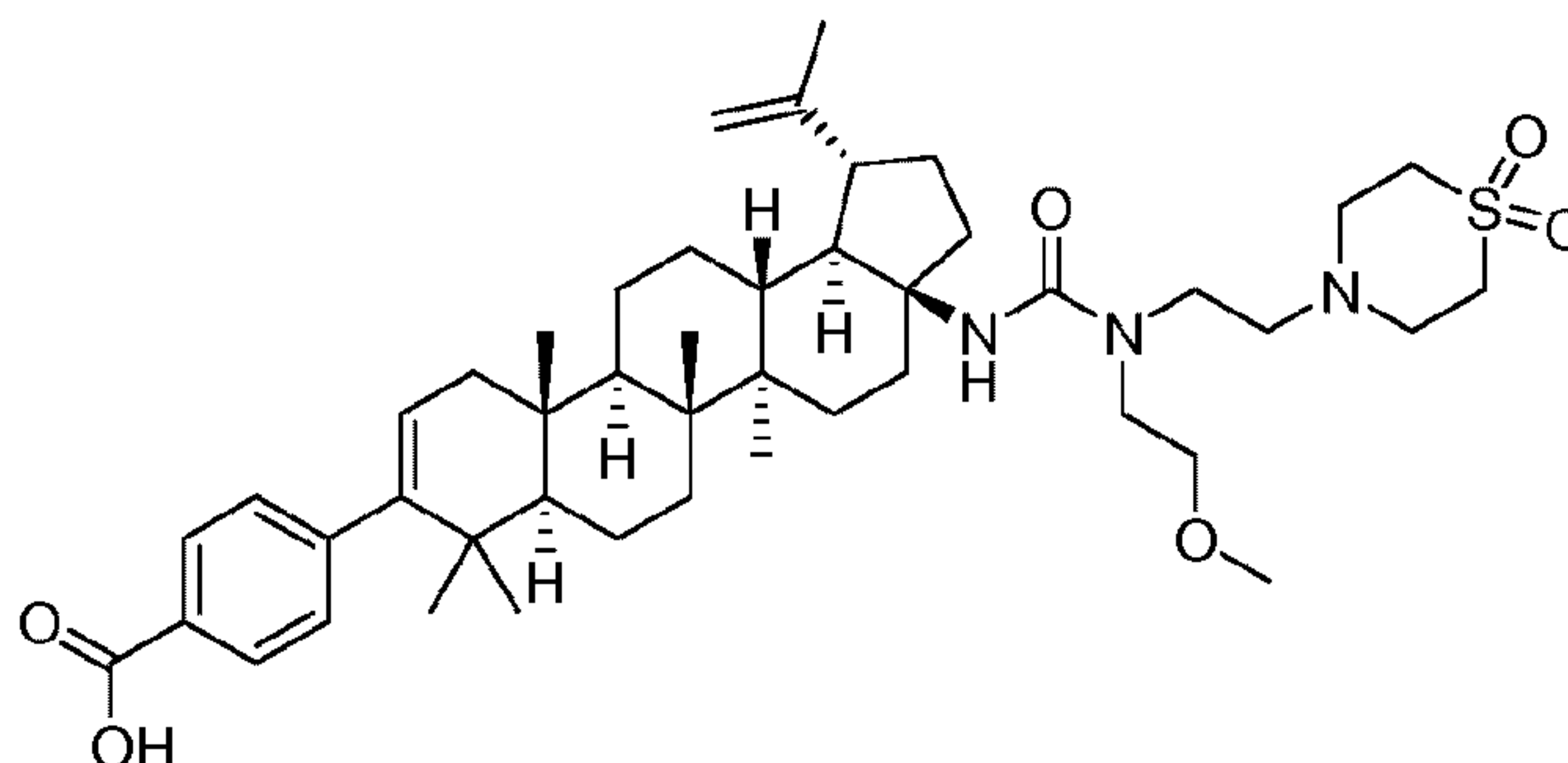
- 5 Step 2. Preparation of 3-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-1-propanamine.



- 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*)  $\delta$  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).

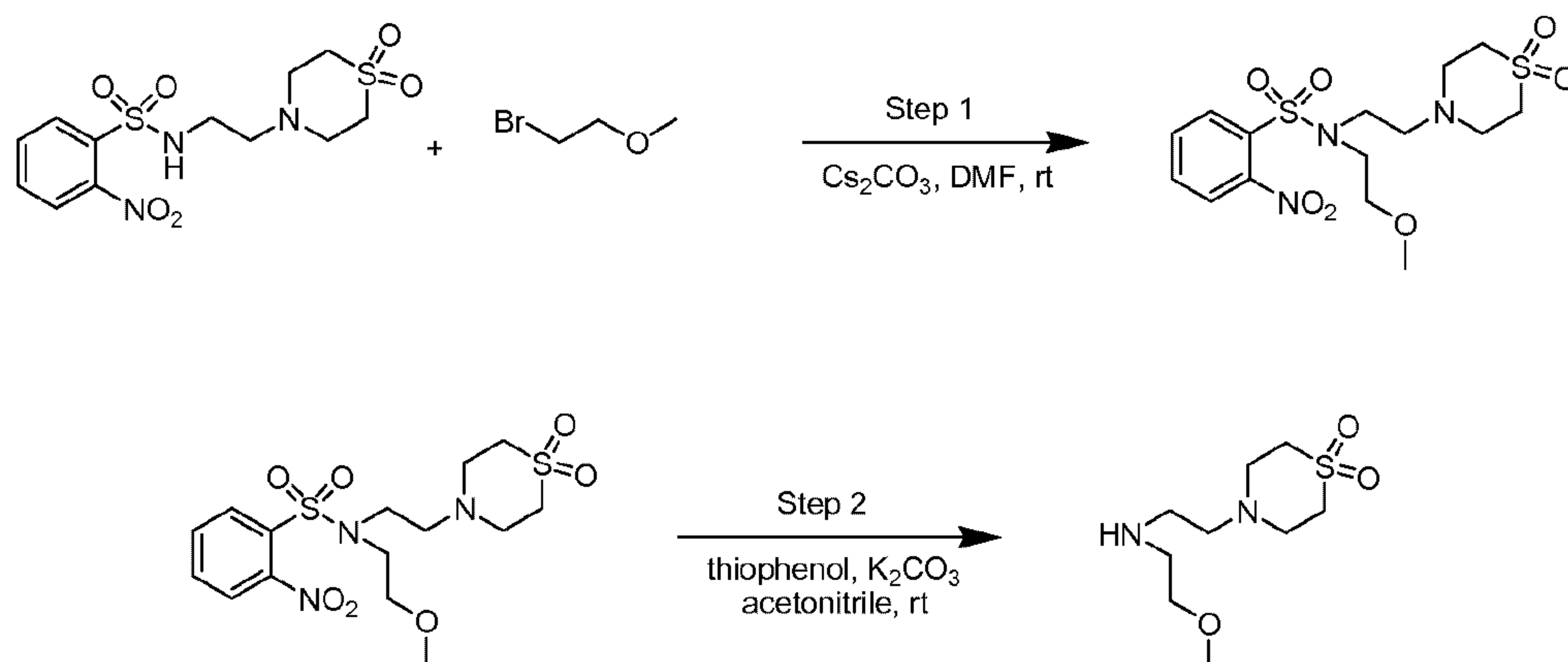
## Example 67

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-  
 5 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.

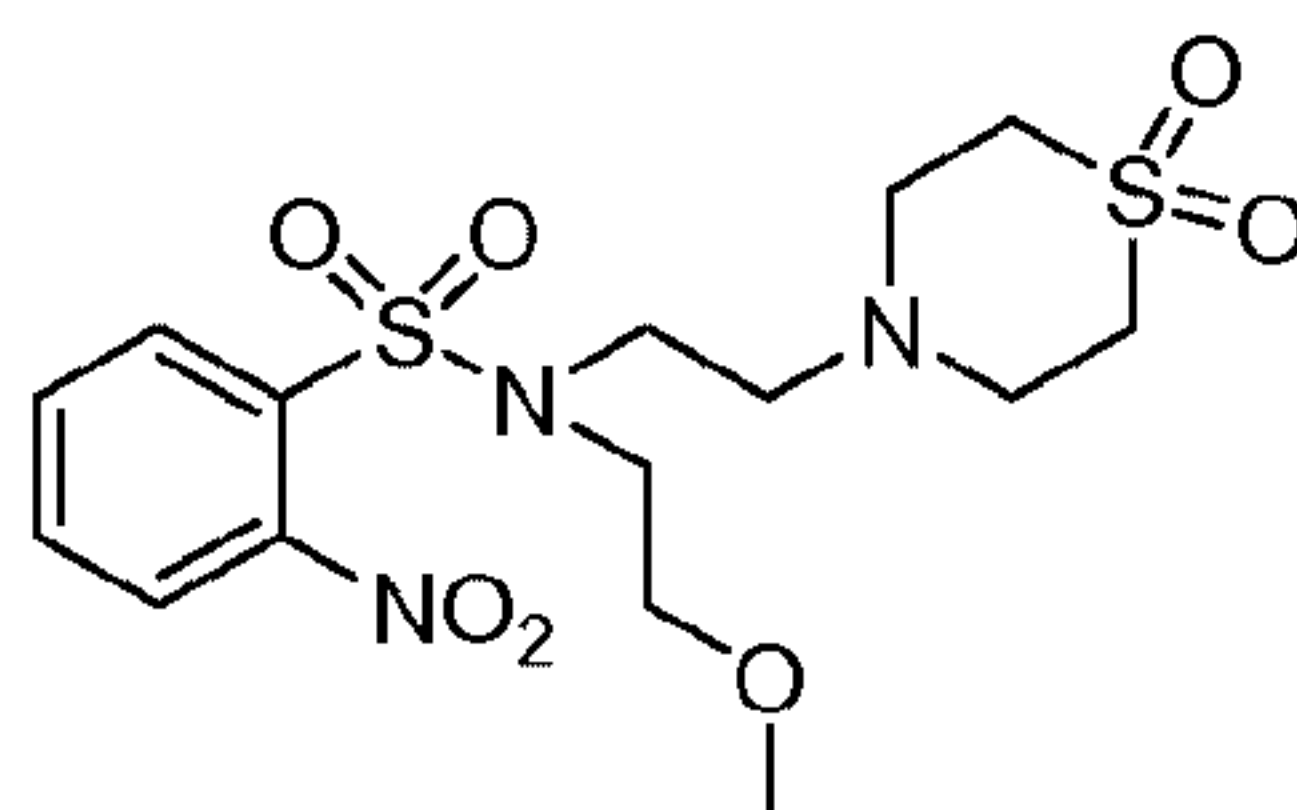


10 The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,1-dioxido-4-thiomorpholinyl)-N-(2-methoxyethyl)ethanamine (prepared as described below) as the reactant amine. After ester hydrolysis, the mono-TFA salt 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)  $\delta$  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-  
 25 ((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:



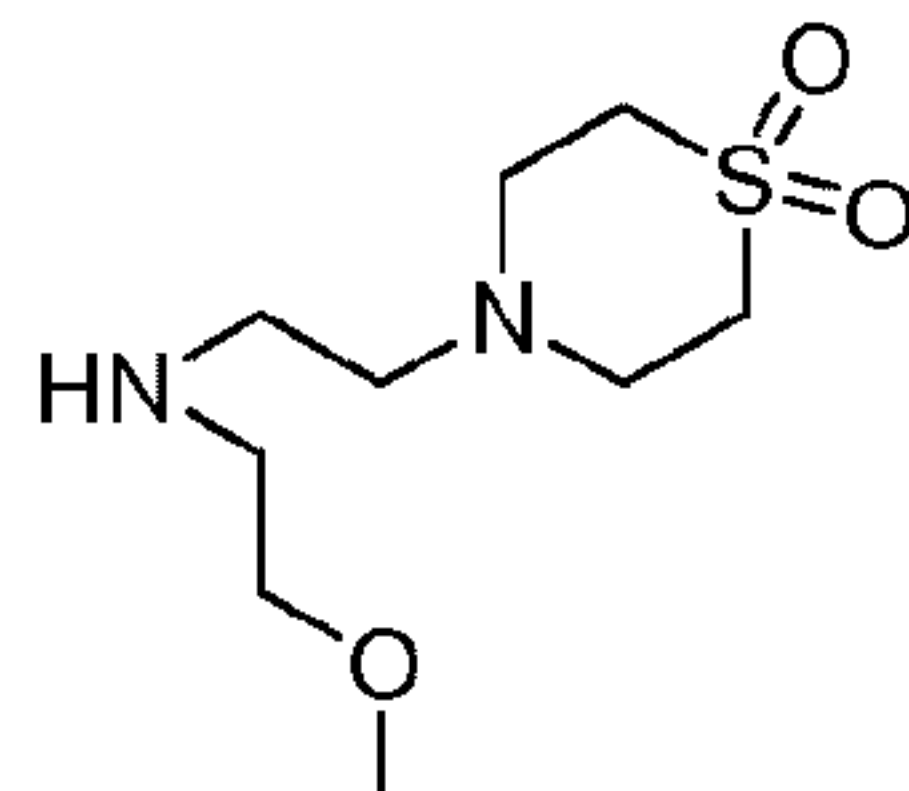
Step 1. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(2-methoxyethyl)-2-nitrobenzenesulfonamide.



*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*)  $\delta$  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).

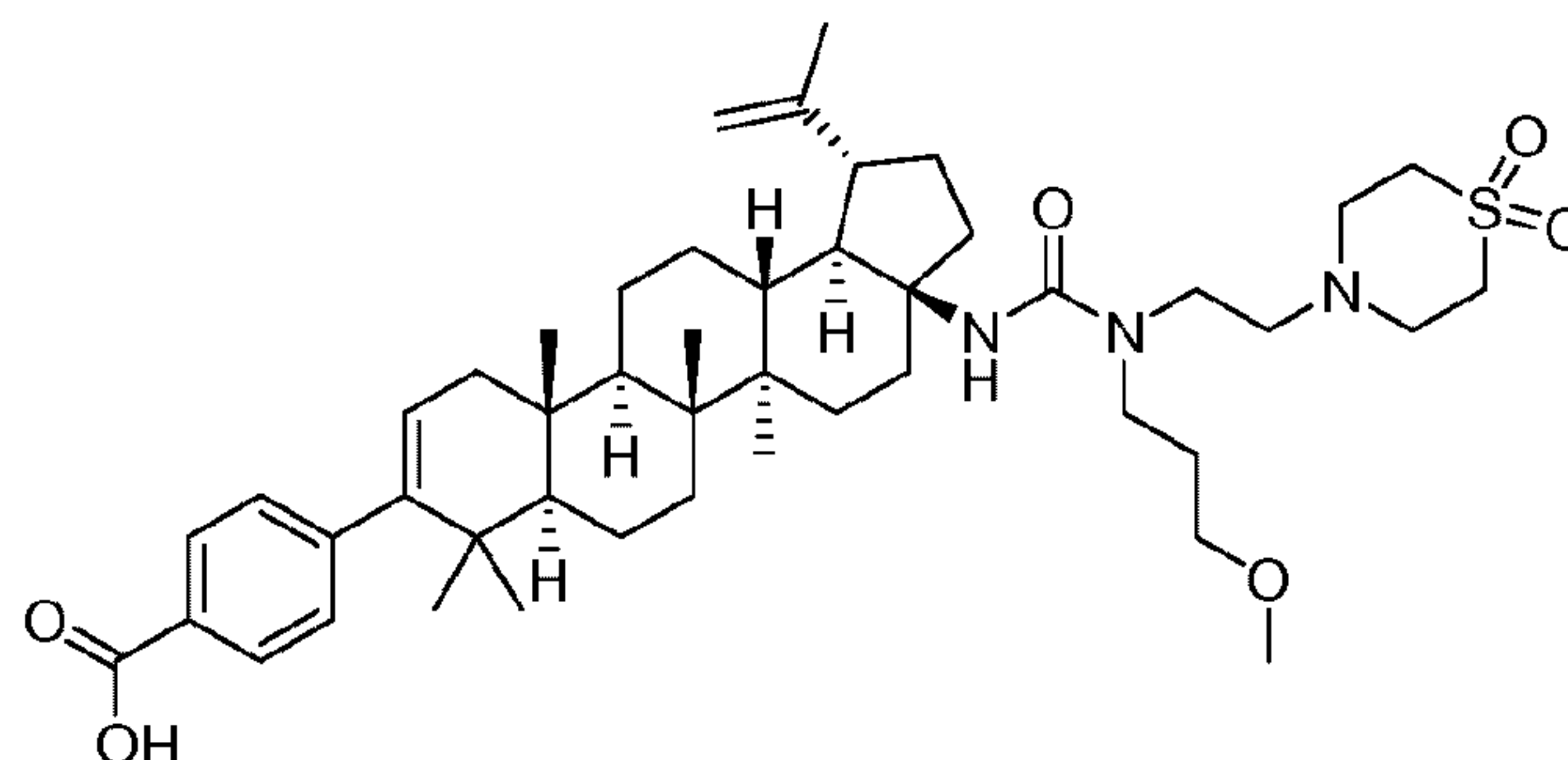
Step 2. Preparation of 2-(1,1-dioxido-4-thiomorpholinyl)-*N*-(2-methoxyethyl)ethanamine.



*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*)  $\delta$  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

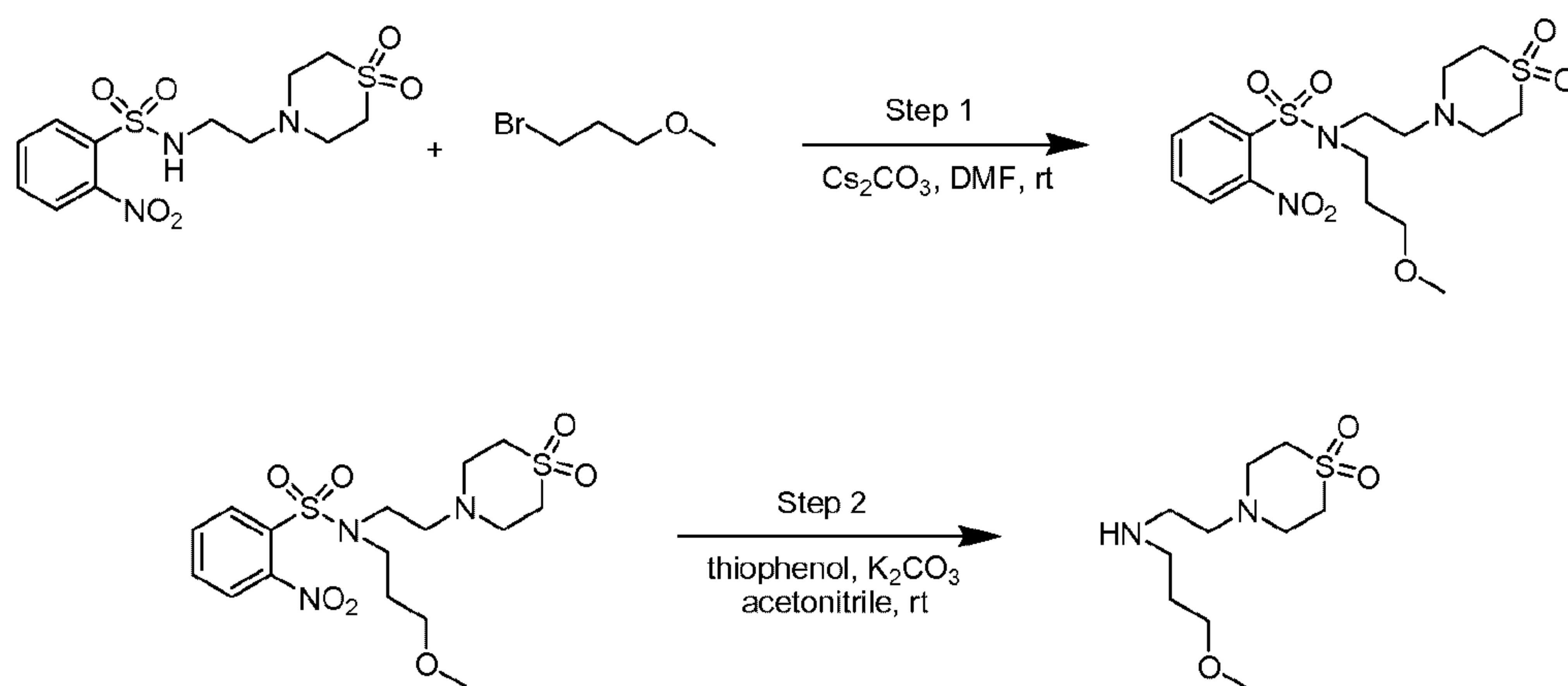
Preparation of 4-((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,11*aS*,11*bR*,13*aR*,13*bR*)-3*a*-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-methoxypropyl)carbamoyl)amino)-1-isopropenyl-5*a*,5*b*,8,8,11*a*-pentamethyl-2,3,3*a*,4,5,5*a*,5*b*,6,7,7*a*,8,11,11*a*,11*b*,12,13,13*a*,13*b*-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl)benzoic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



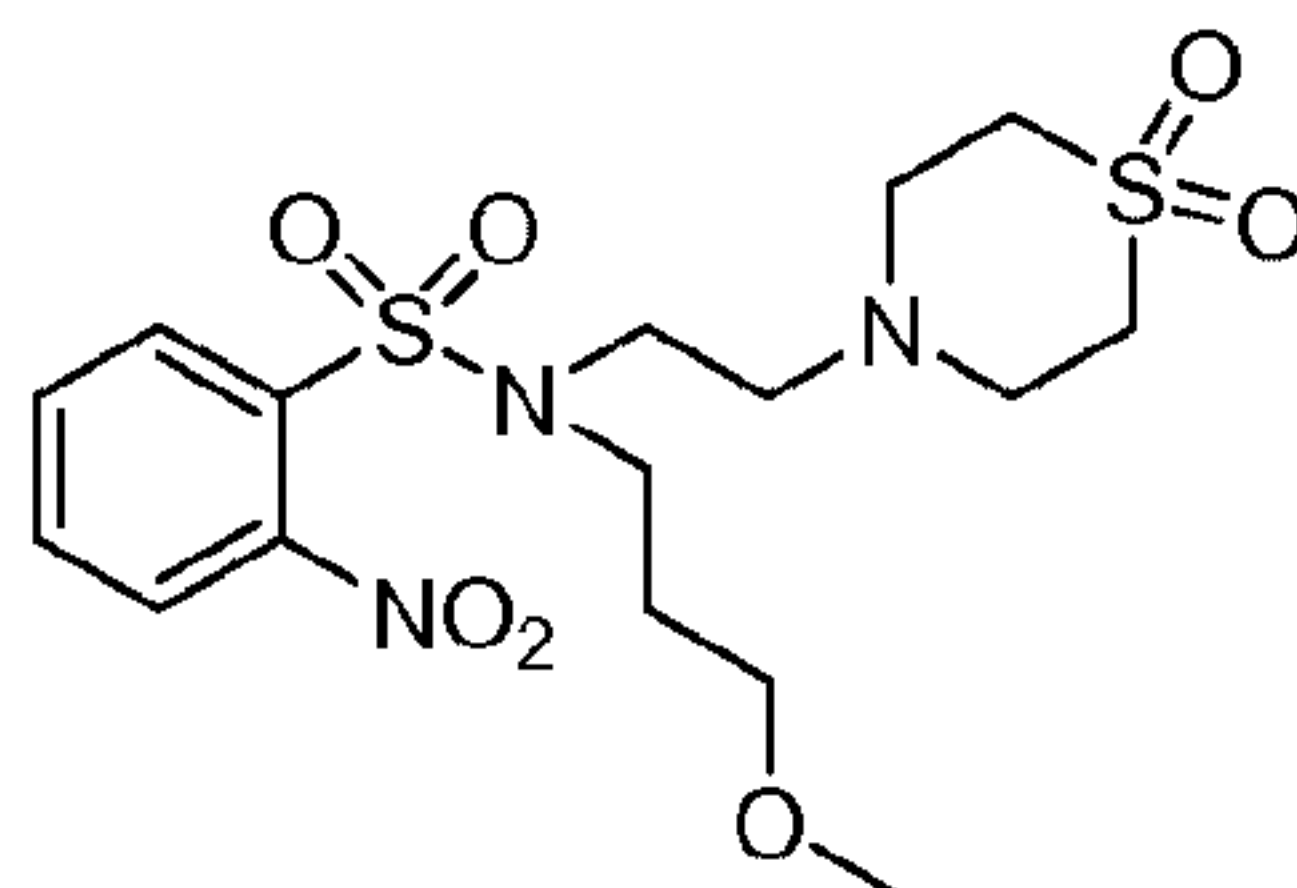
The title compound was prepared following the general procedures described  
 5 for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-3-methoxy-1-propanamine (prepared as described below) as the reactant amine. After ester hydrolysis, the mono-TFA 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,  
 10 1:1 mixture of  $CDCl_3$  and  $MeOD$ ,  $MeOD$  lock)  $\delta$  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  
 15 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-

20 ((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.

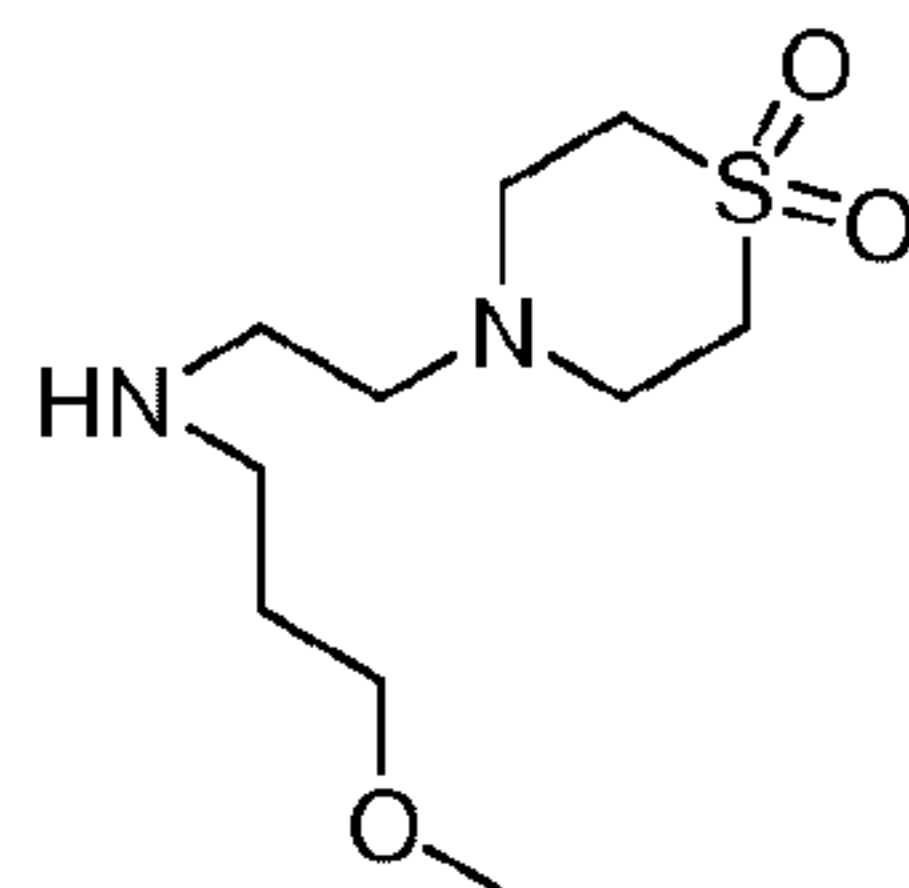


5

*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*)  $\delta$  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

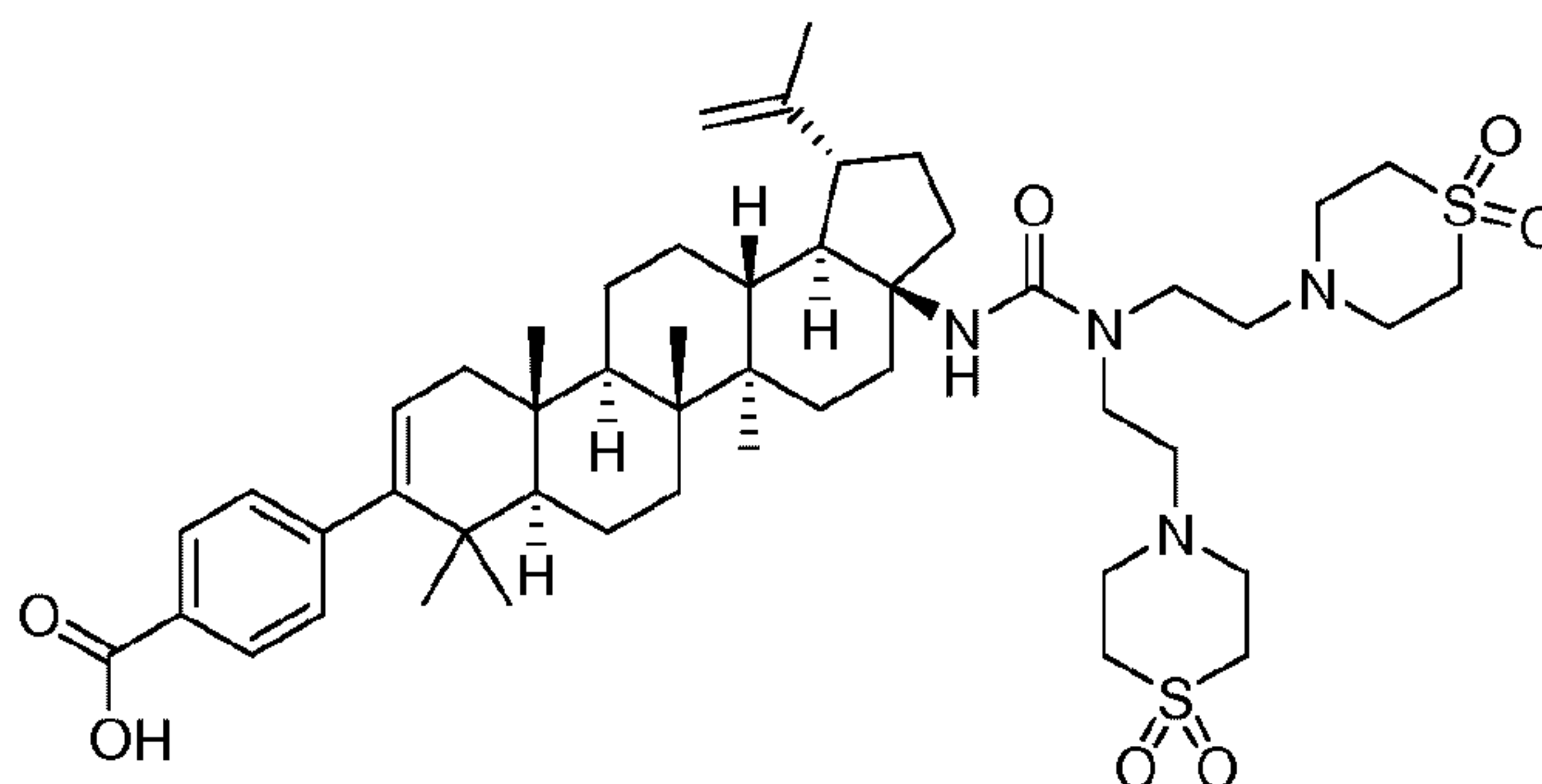
*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(3-methoxypropyl)-2-nitrobenzenesulfonamide (0.510 g, 1.17 mmol) and thiophenol (0.387 g, 3.51 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.647 g, 4.68 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was 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*)  $\delta$  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.

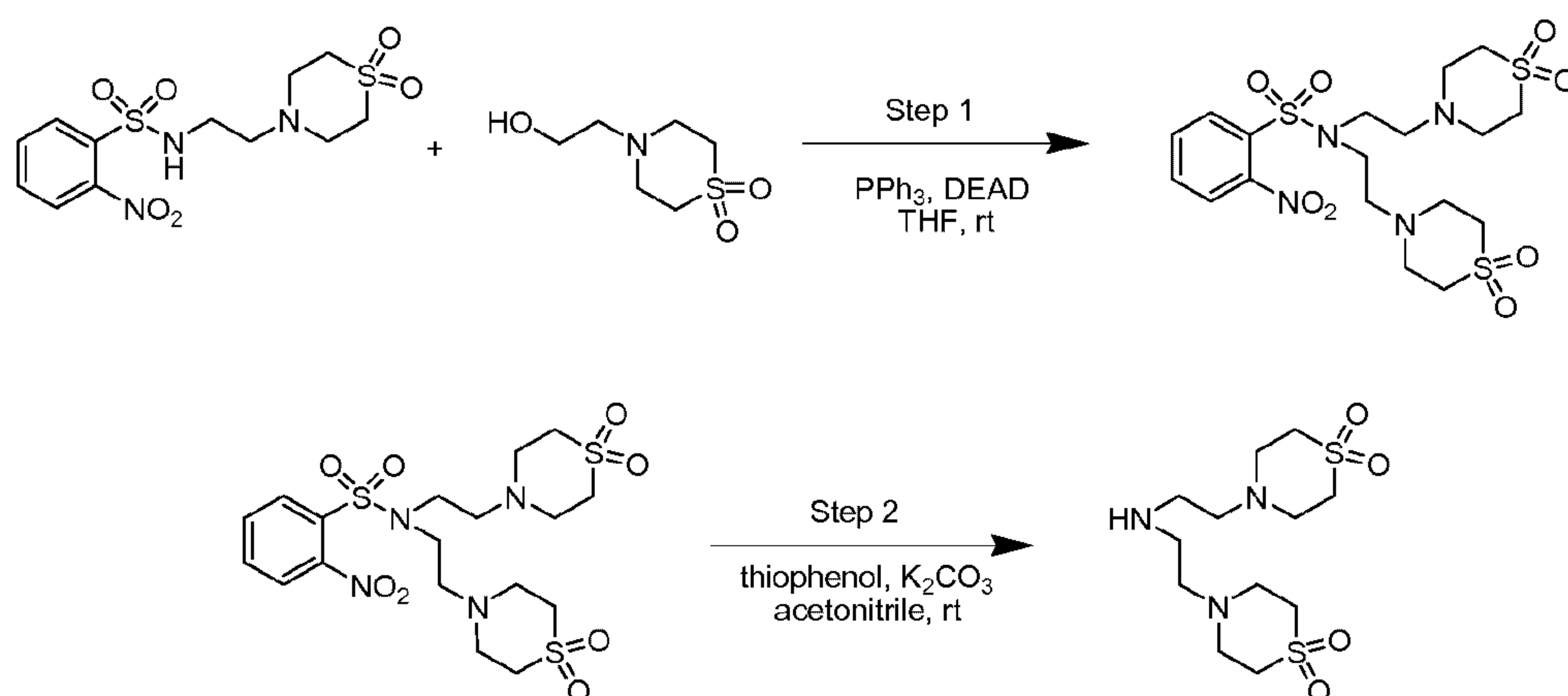
25



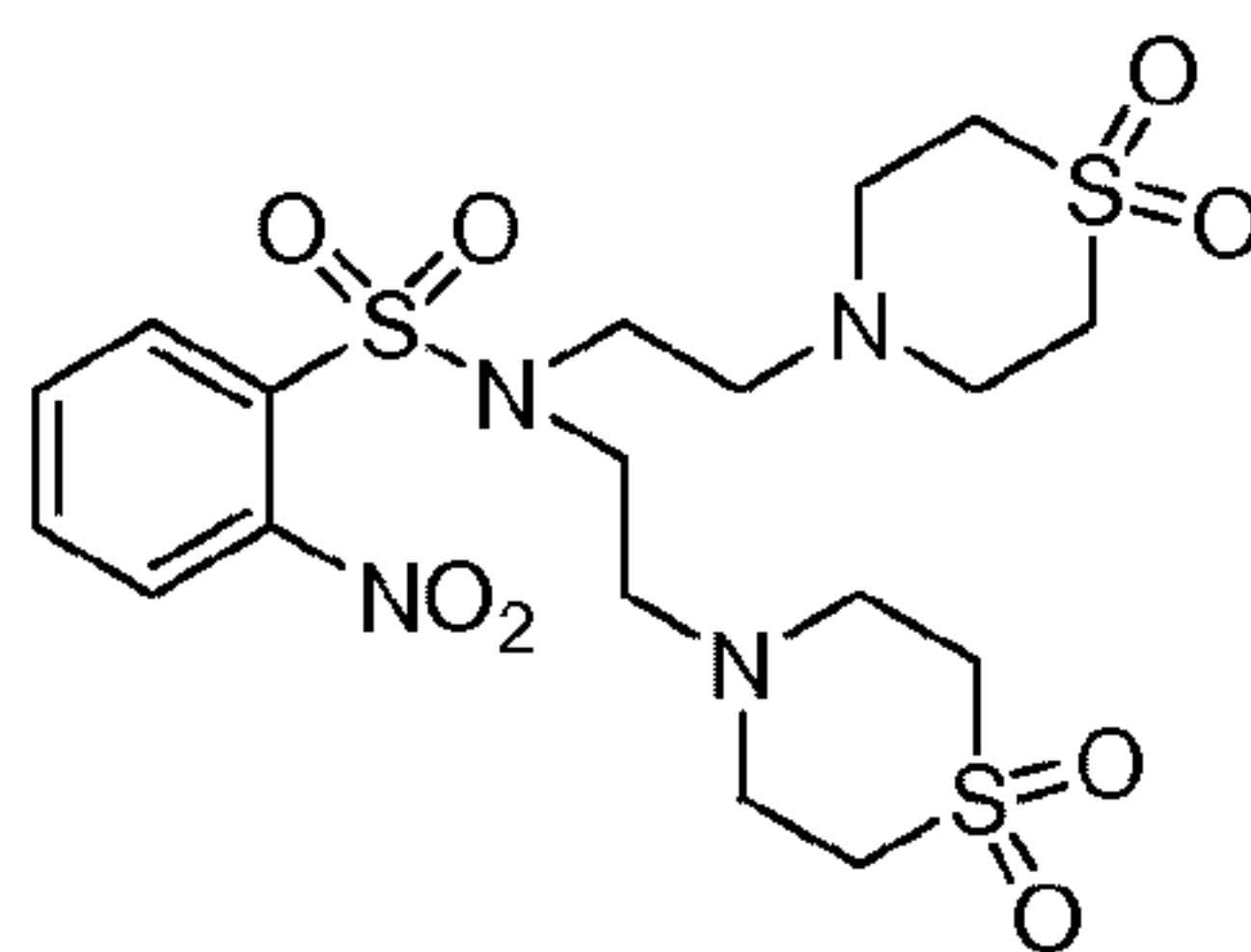
The title compound was prepared following the general procedures described  
 5 for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,1-dioxido-4-  
 thiomorpholinyl)-N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine (prepared as  
 described below) as the reactant amine. After ester 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)  $\delta$   
 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-

20 ((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:



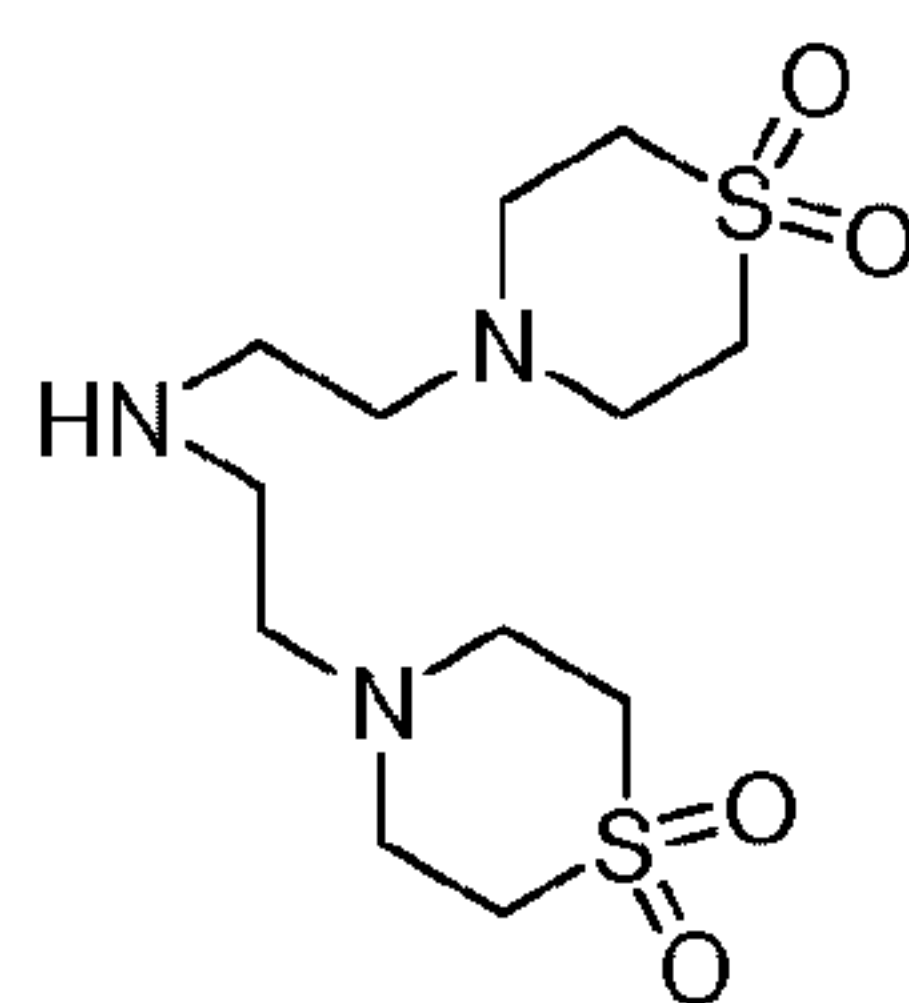
Step 1. Preparation of *N,N*-bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.



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 ( $\text{M}+\text{H}^+$ ), retention time 1.25 min (method 11).  $^1\text{H}$  NMR (500 MHz, MeOD)  $\delta$  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).

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

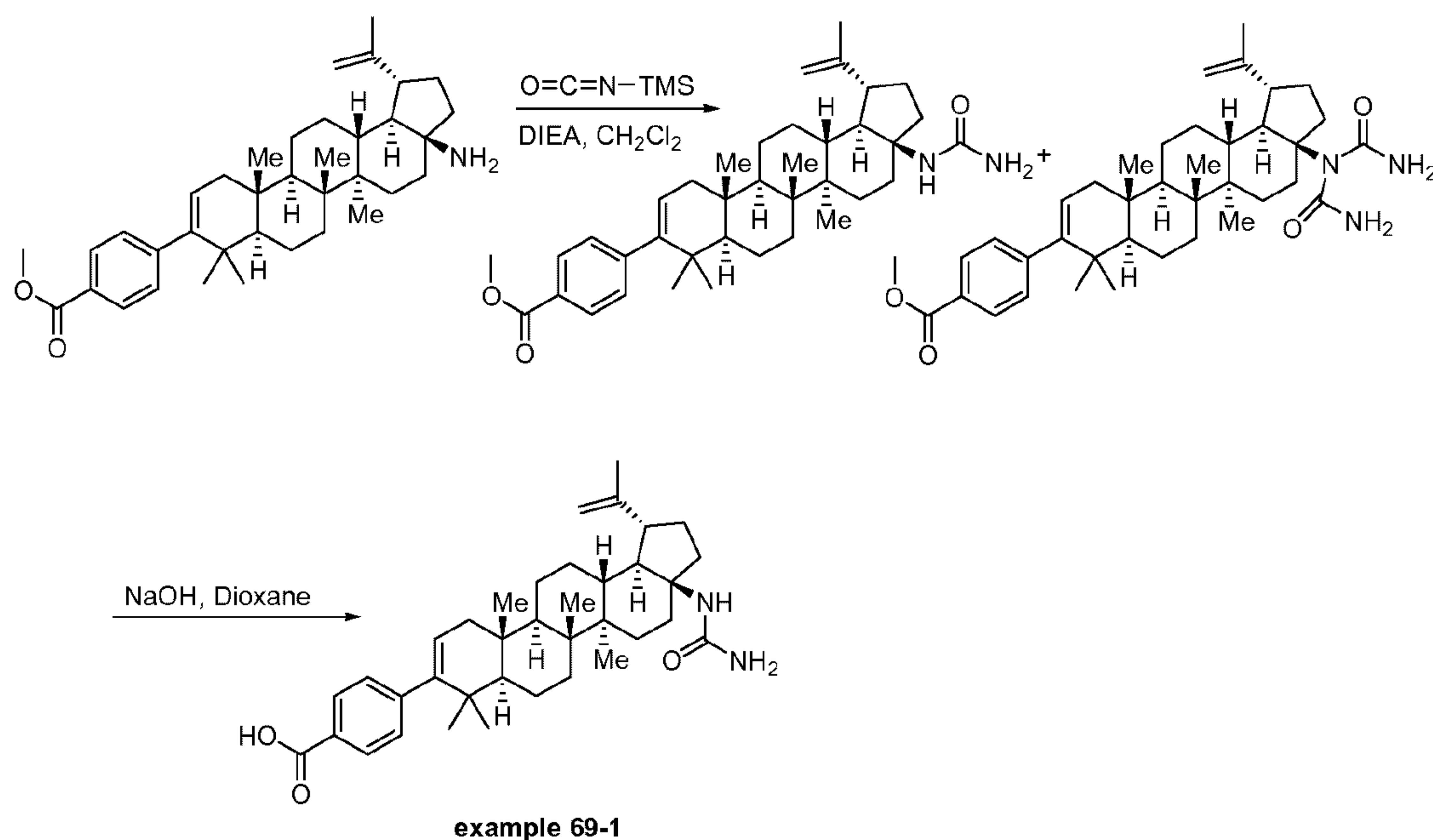


5 *N,N*-bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide  
 (0.85 g, 1.13 mmol) and thiophenol (0.373 g, 3.39 mmol) were combined in dry  
 acetonitrile (10 mL). Potassium carbonate (0.936 g, 6.78 mmol) was added and the  
 mixture was stirred at rt for 18h. The mixture was diluted 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-urcido-2,3,3a,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)<sup>+</sup>, 2.67 min (method 13). <sup>1</sup>H NMR (400MHz, METHANOL-d<sub>4</sub>) δ 7.94 (d, J=8.5 Hz, 2H), 7.24 (d, J=8.5

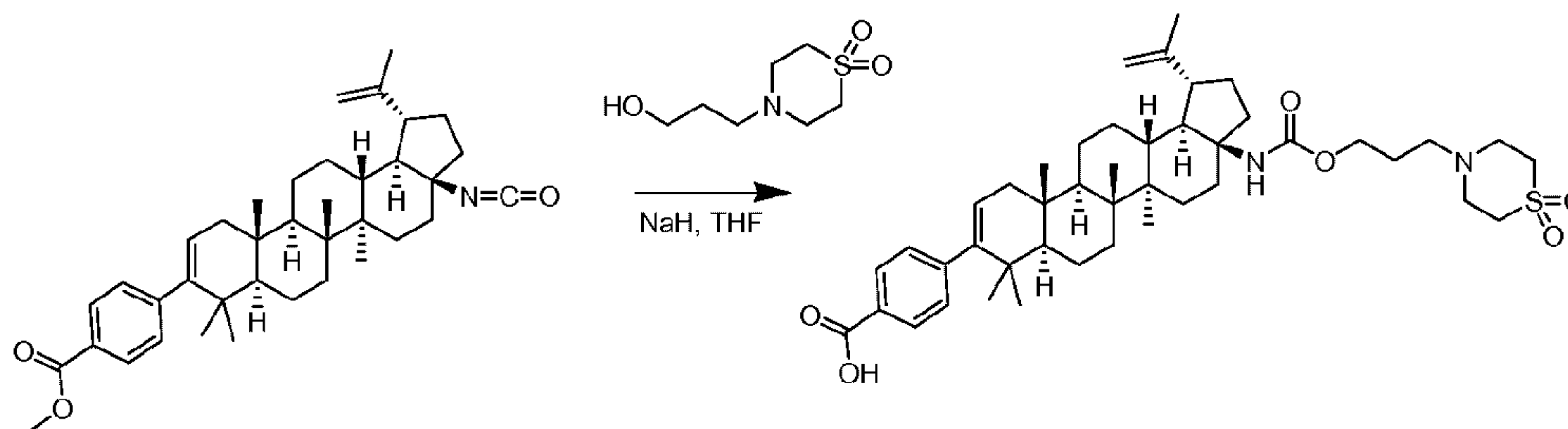
Hz, 2H), 5.32 (dd,  $J=6.1, 1.6$  Hz, 1H), 4.78 (d,  $J=1.8$  Hz, 1H), 4.67 - 4.63 (m, 1H),  
 2.69 - 2.59 (m, 2H), 2.40 (dd,  $J=12.2, 8.2$  Hz, 1H), 2.17 (dd,  $J=17.2, 6.4$  Hz, 1H),  
 2.04 - 1.84 (m, 2H), 1.74 (s, 3H), 1.82 - 1.67 (m, 3H), 1.63 - 1.48 (m, 6H), 1.46 - 1.26  
 (m, 6H), 1.16 (s, 3H), 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  $\text{MgSO}_4$ , filtered and  
 concentrated to give a white foam product. The crude material was dissolved in 2

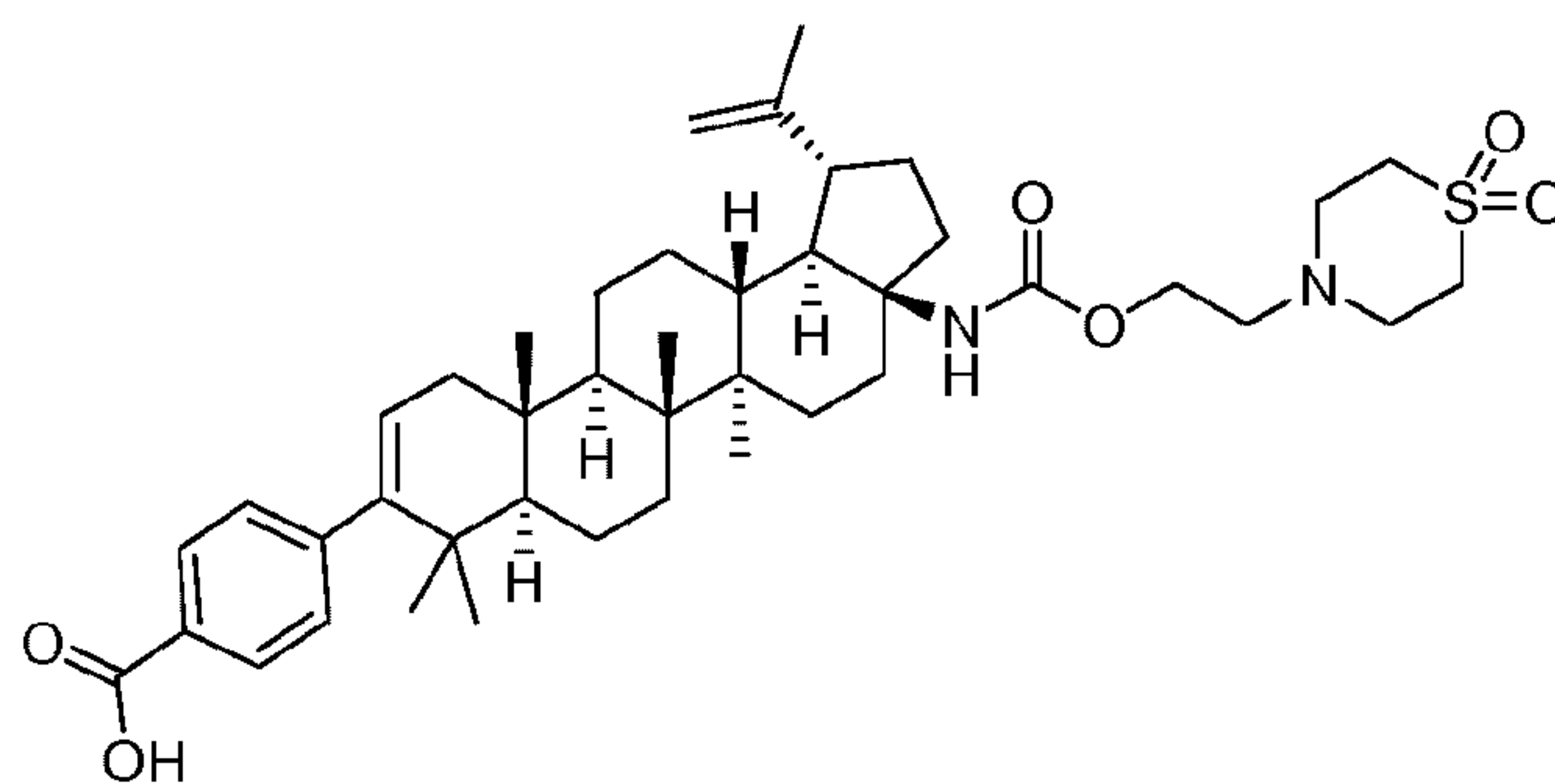
mL THF, filtered and purified by reverse phase preparative HPLC using HPLC method 1 to give the mono-TFA salt of the title compound (123.1 mg, 0.143 mmol, 40.6% yield) as white solid. LCMS:  $m/e$  749.5 ( $M+H$ )<sup>+</sup>, 2.10 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 MeOD:CDCl<sub>3</sub>)  $\delta$  = 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). <sup>13</sup>C NMR (1:1 MeOD:CDCl<sub>3</sub>)  $\delta$  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-

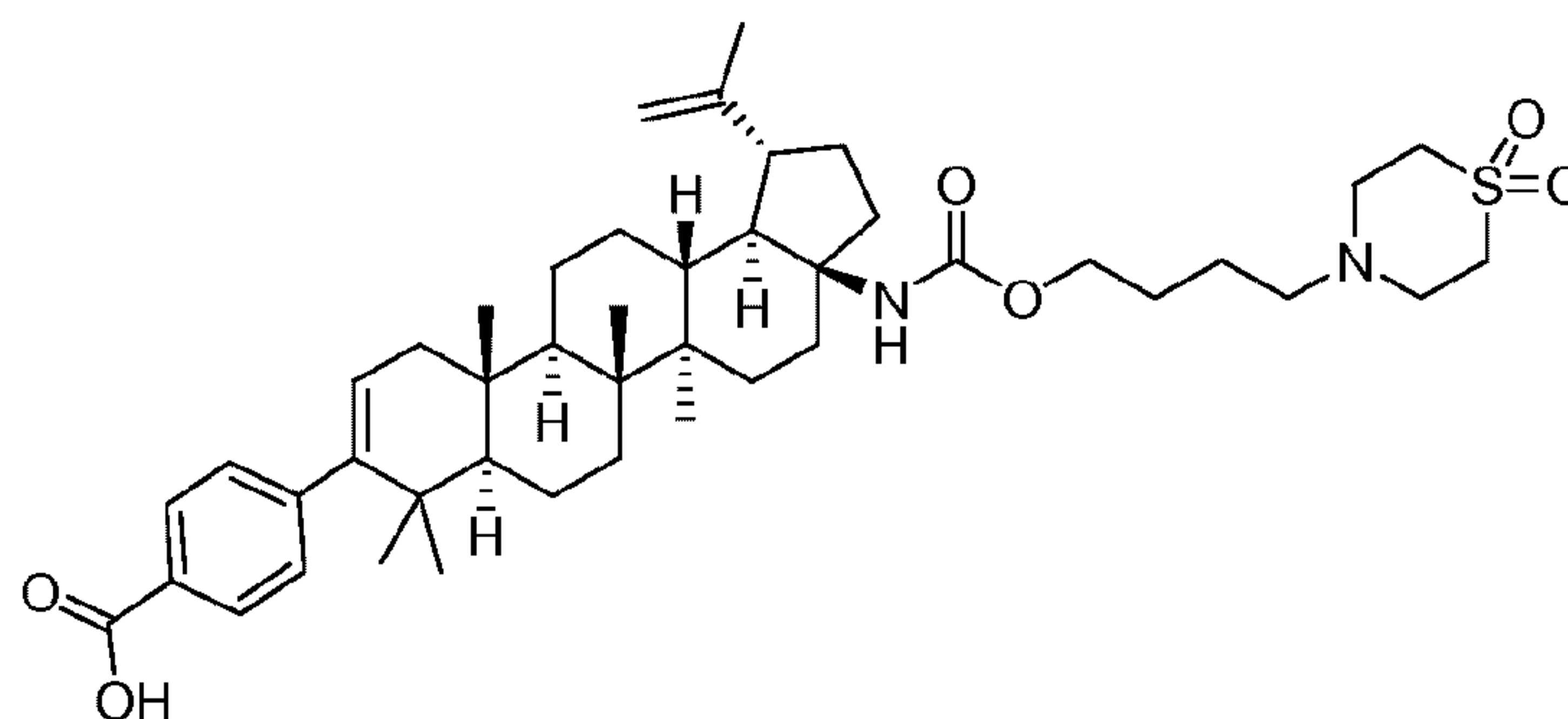
- 5 hydroxypropyl)thiomorpholine 1,1-dioxide. LCMS:  $m/e$  735.3 (M+H)<sup>+</sup>, 2.63 min (method 6). <sup>1</sup>H NMR (500MHz, *METHANOL-d<sub>4</sub>*)  $\delta$  = 7.95 (d,  $J$  = 8.5 Hz, 2 H), 7.25 (d,  $J$  = 8.5 Hz, 2 H), 5.33 (dd,  $J$  = 1.7, 6.3 Hz, 1 H), 4.79 (d,  $J$  = 1.8 Hz, 1 H), 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  
10 (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]-

- 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 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-
- 25

thiomorpholinyl)propoxy]carbonyl]amino]-

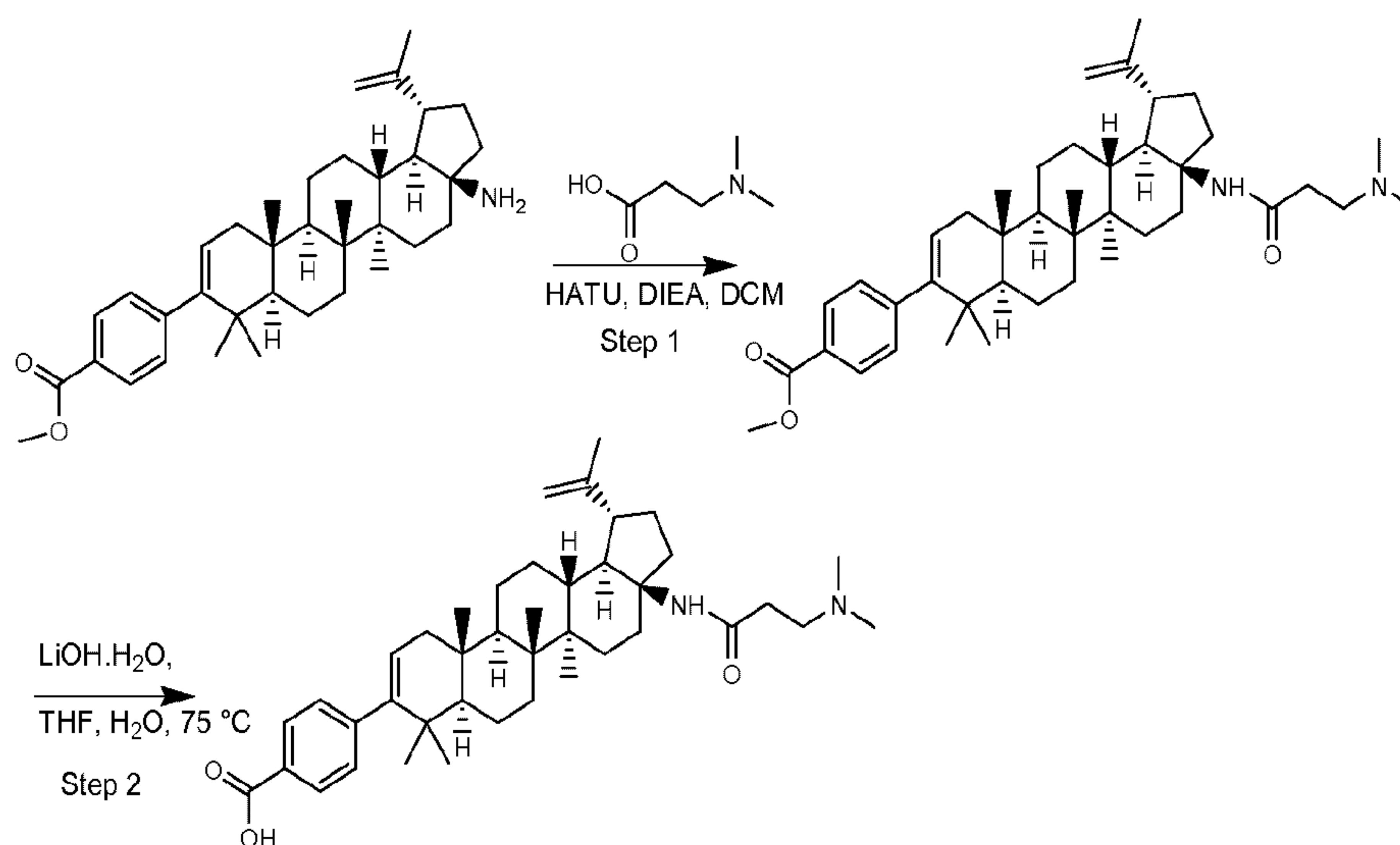
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl], except 4-(4-hydroxybutyl)thiomorpholine 1,1-dioxide was used instead of 4-(3-

- 5 hydroxypropyl)thiomorpholine 1,1-dioxide. LCMS:  $m/e$  763.5 ( $M+H$ )<sup>+</sup>, 2.14 min (method 6). <sup>1</sup>H NMR (500MHz, *METHANOL-d*<sub>4</sub>)  $\delta$  = 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

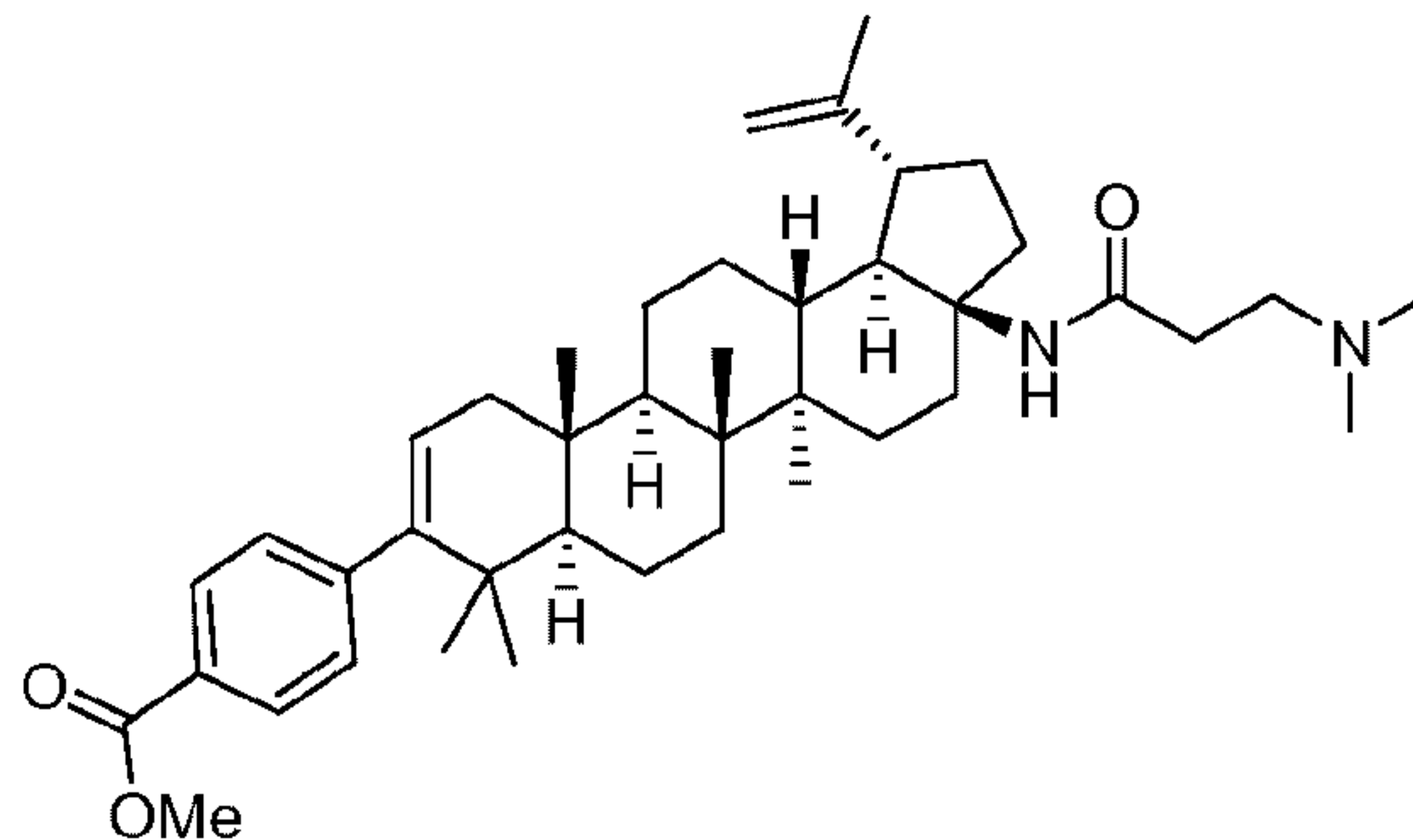
### 15 Section 3. Amides

#### Example 73

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



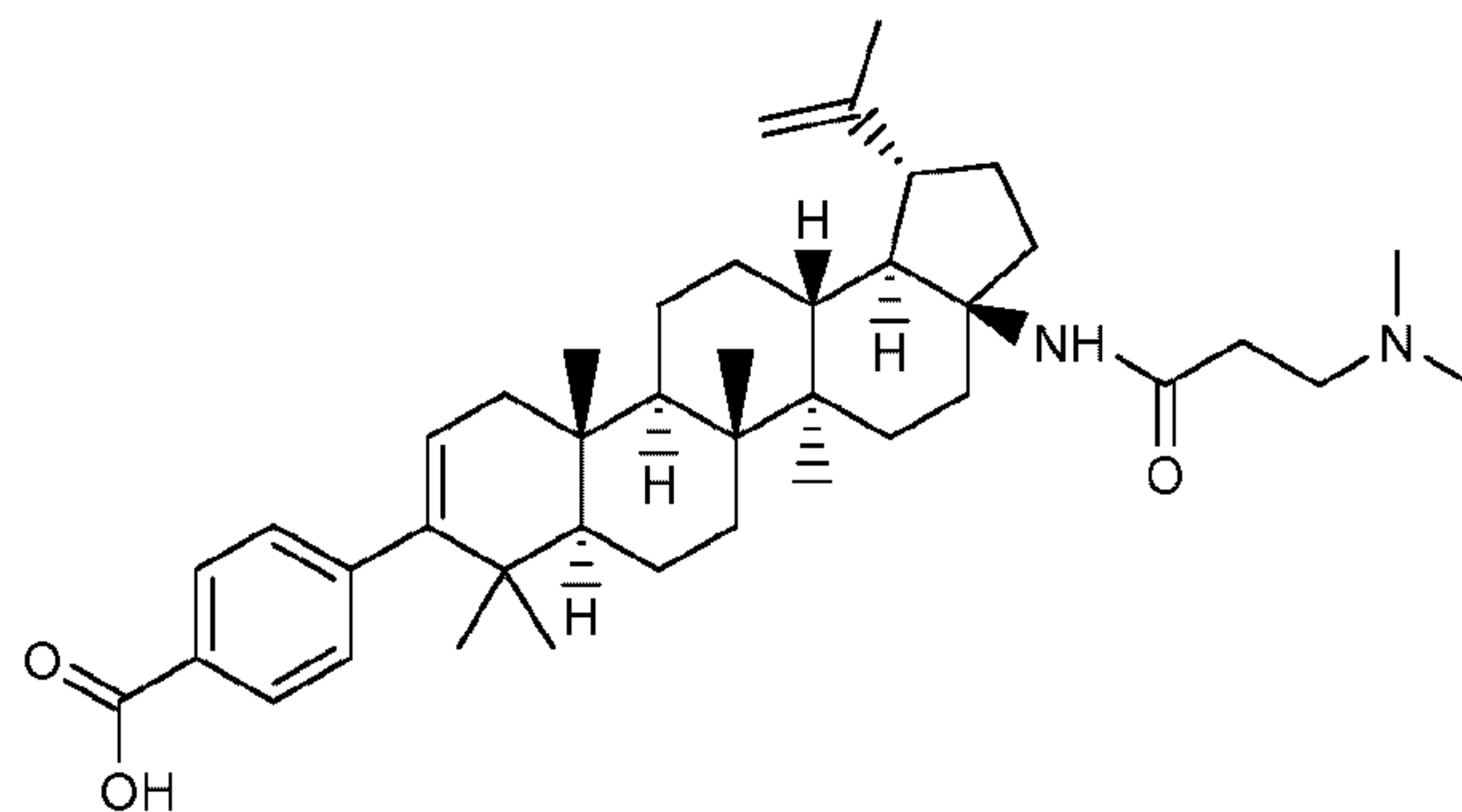
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-  
 (3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 5 cyclopenta[a]chrysen-9-yl)benzoate.



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% NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, 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)<sup>+</sup>, 4.17 min (method 8). <sup>1</sup>H NMR (500MHz ,  
 25 1:1 *MeOD:CDCl*<sub>3</sub>)  $\delta$  = 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).  $^{13}\text{C}$  NMR (1:1 *MeOD:CDCl*<sub>3</sub>)  $\delta$  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.



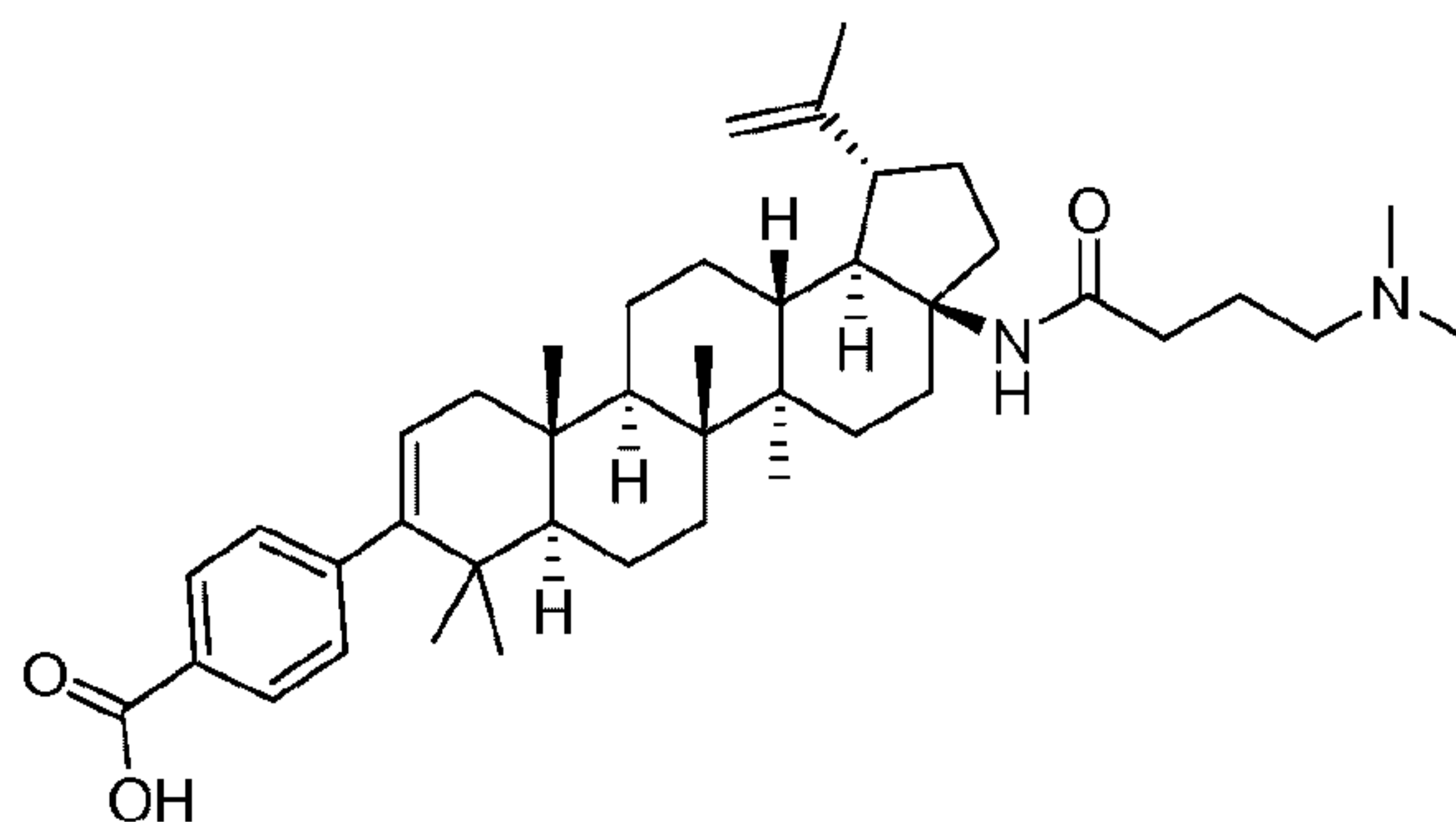
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, TFA (87.9 mg, 0.116 mmol) in THF (5 mL) was added 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 ( $\text{M}+\text{H}$ )<sup>+</sup>, 4.17 min (method 8).  $^1\text{H}$  NMR (500MHz, *METHANOL-d*<sub>4</sub>)  $\delta$  = 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).  $^{13}\text{C}$  NMR (*MeOD*)  $\delta$  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)-  
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 26% 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-(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).  $^1\text{H}$  NMR (500MHz, *METHANOL-d*<sub>4</sub>)  $\delta$  = 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),

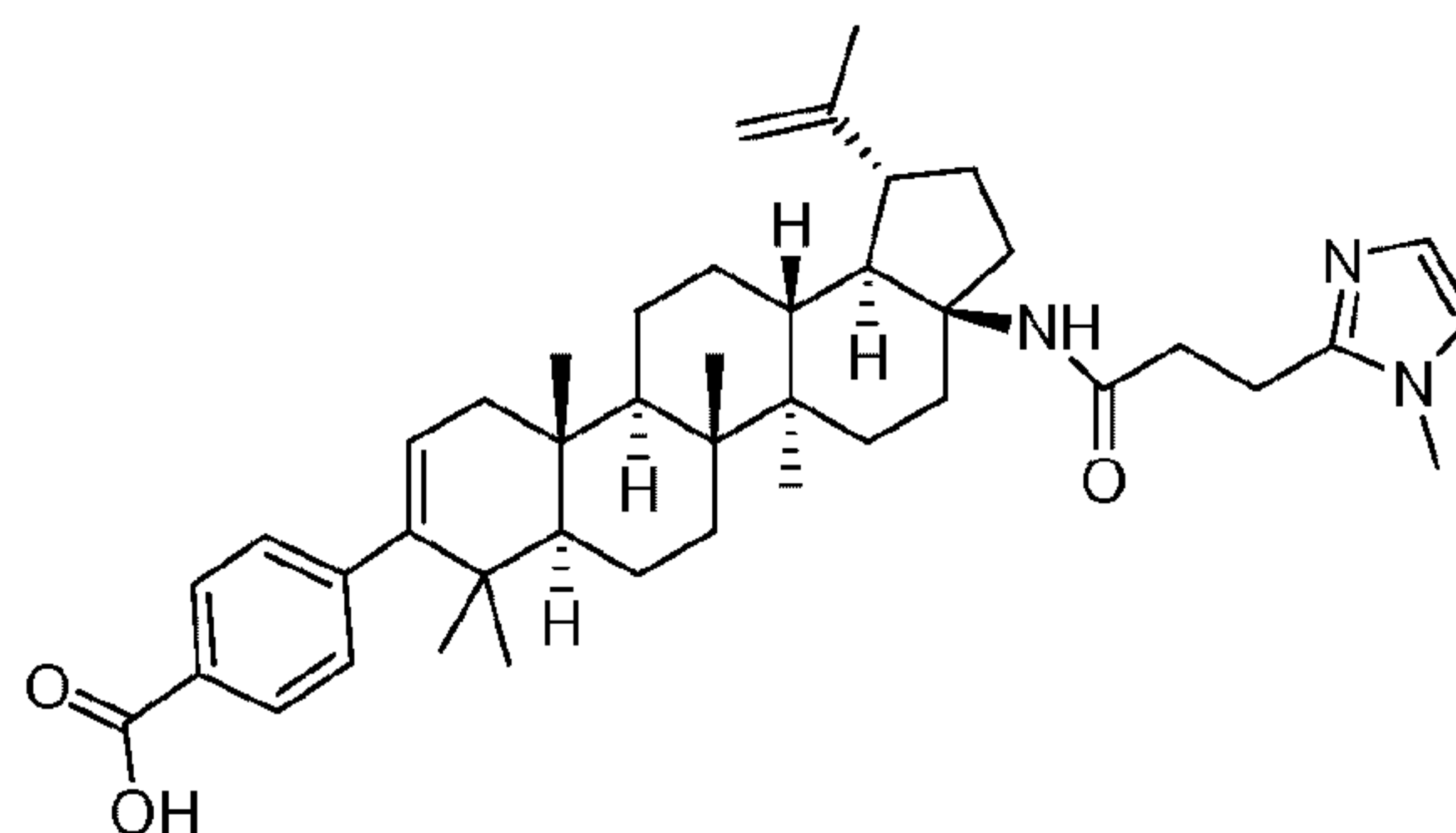
1.55 - 1.48 (m, 4 H), 1.47 - 1.38 (m, 3 H), 1.35 (d,  $J = 12.2$  Hz, 1 H), 1.33 - 1.27 (m, 1 H), 1.21 - 1.17 (m, 1 H), 1.15 (s, 3 H), 1.12 (d,  $J = 3.4$  Hz, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

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.

10



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 ( $M+H$ )<sup>+</sup>, 4.15 min (method 8). <sup>1</sup>H NMR (500MHz, *METHANOL-d<sub>4</sub>*)  $\delta$  = 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),

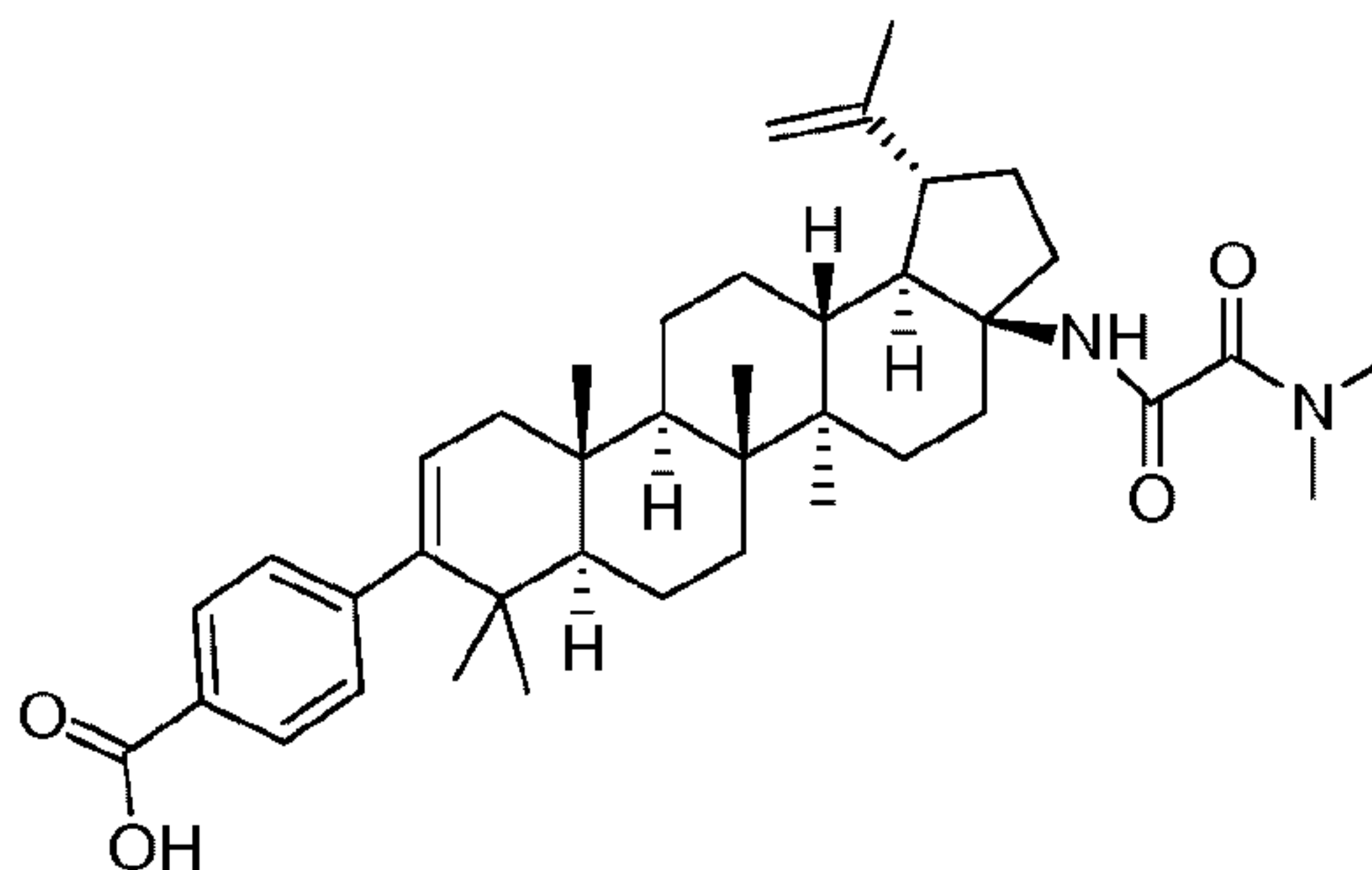
25

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

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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)<sup>-</sup>, 1.91 min (method 5). <sup>1</sup>H NMR (500MHz, 2:1 *MeOD:CDCl*<sub>3</sub>) 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

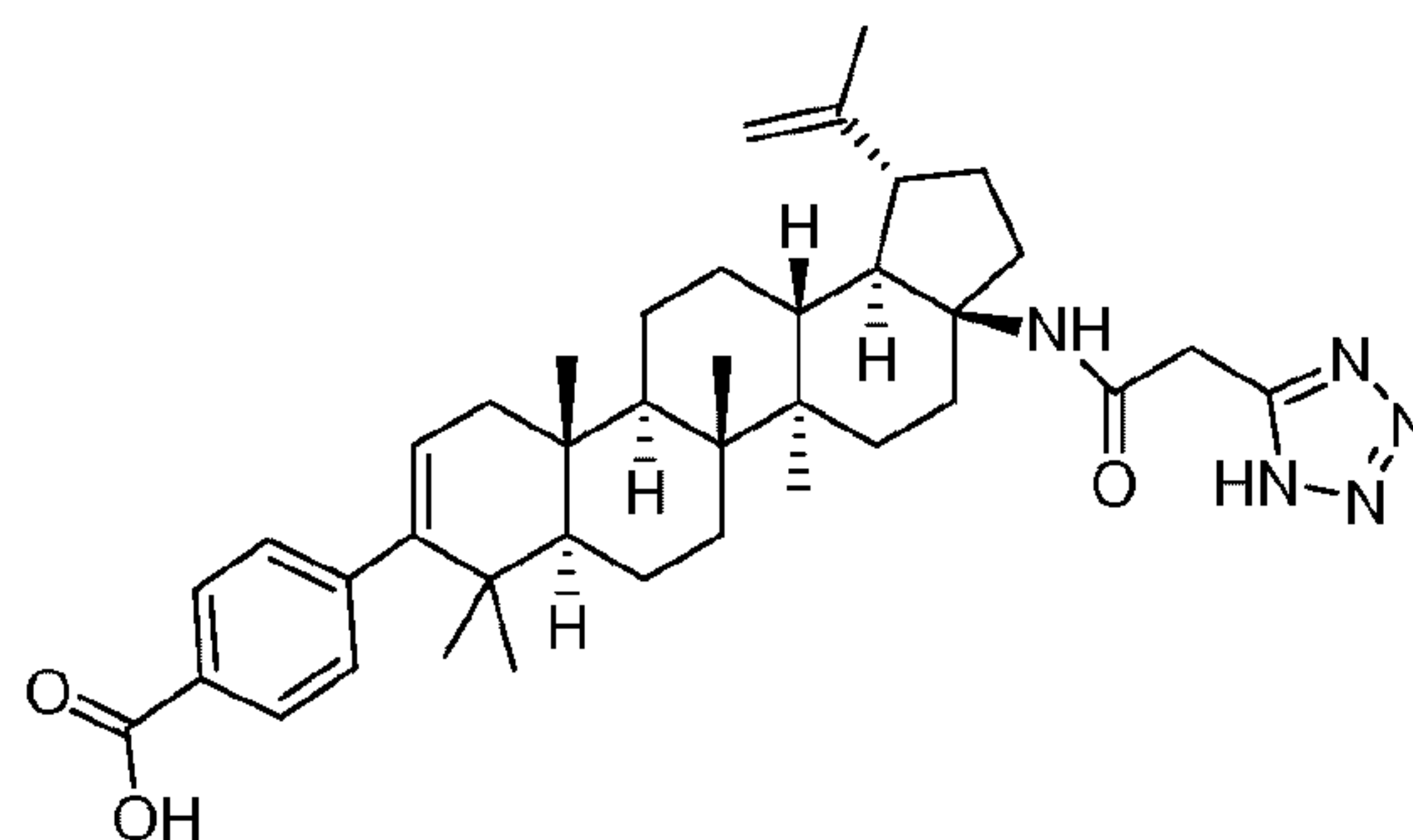
25

(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

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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.



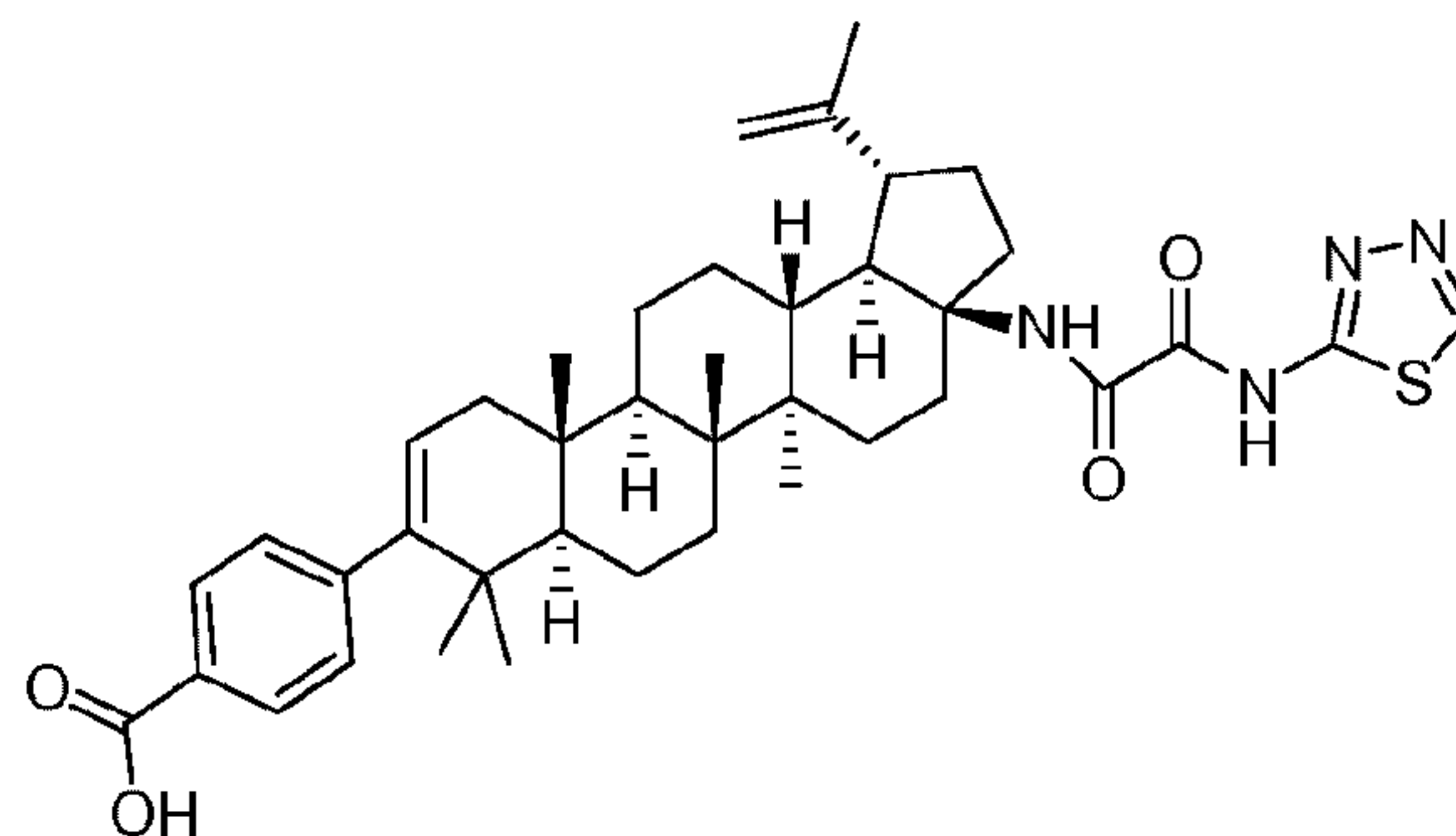
10

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)<sup>+</sup>, 1.58 min (method 6). <sup>1</sup>H NMR (500MHz, *METHANOL-d*<sub>4</sub>) 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

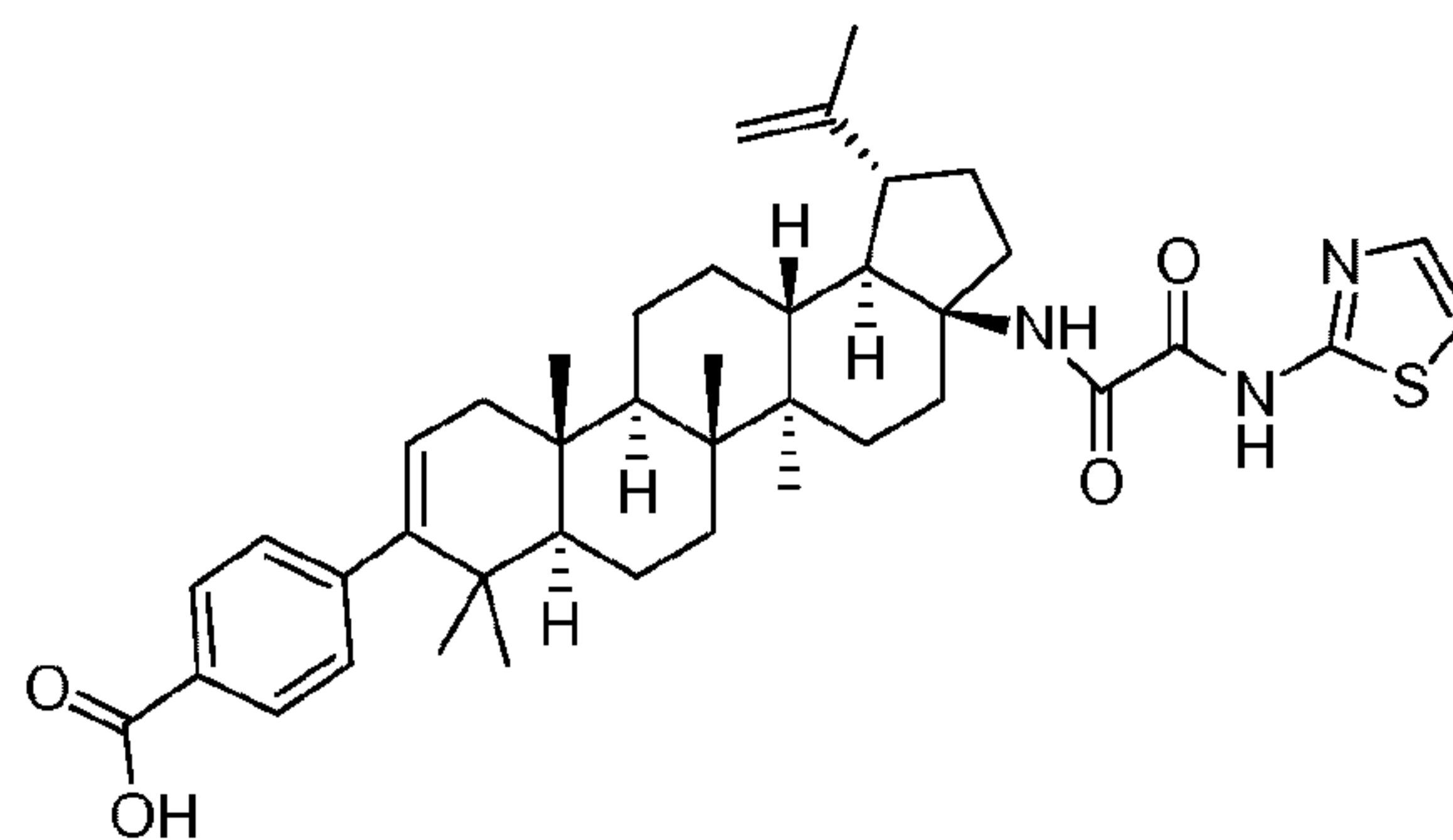
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,3,4-  
 5 thiadiazol-2-ylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)<sup>-</sup>, 1.77 min (method 9). <sup>1</sup>H NMR (500MHz, 2:1  
 20 MeOD:CDCl<sub>3</sub>)  $\delta$  = 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 ( $M+H$ )<sup>+</sup>, 2.04 min (method 9). <sup>1</sup>H NMR (500MHz, 1:1 *MeOD:CDCl*<sub>3</sub>)  $\delta$  = 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).

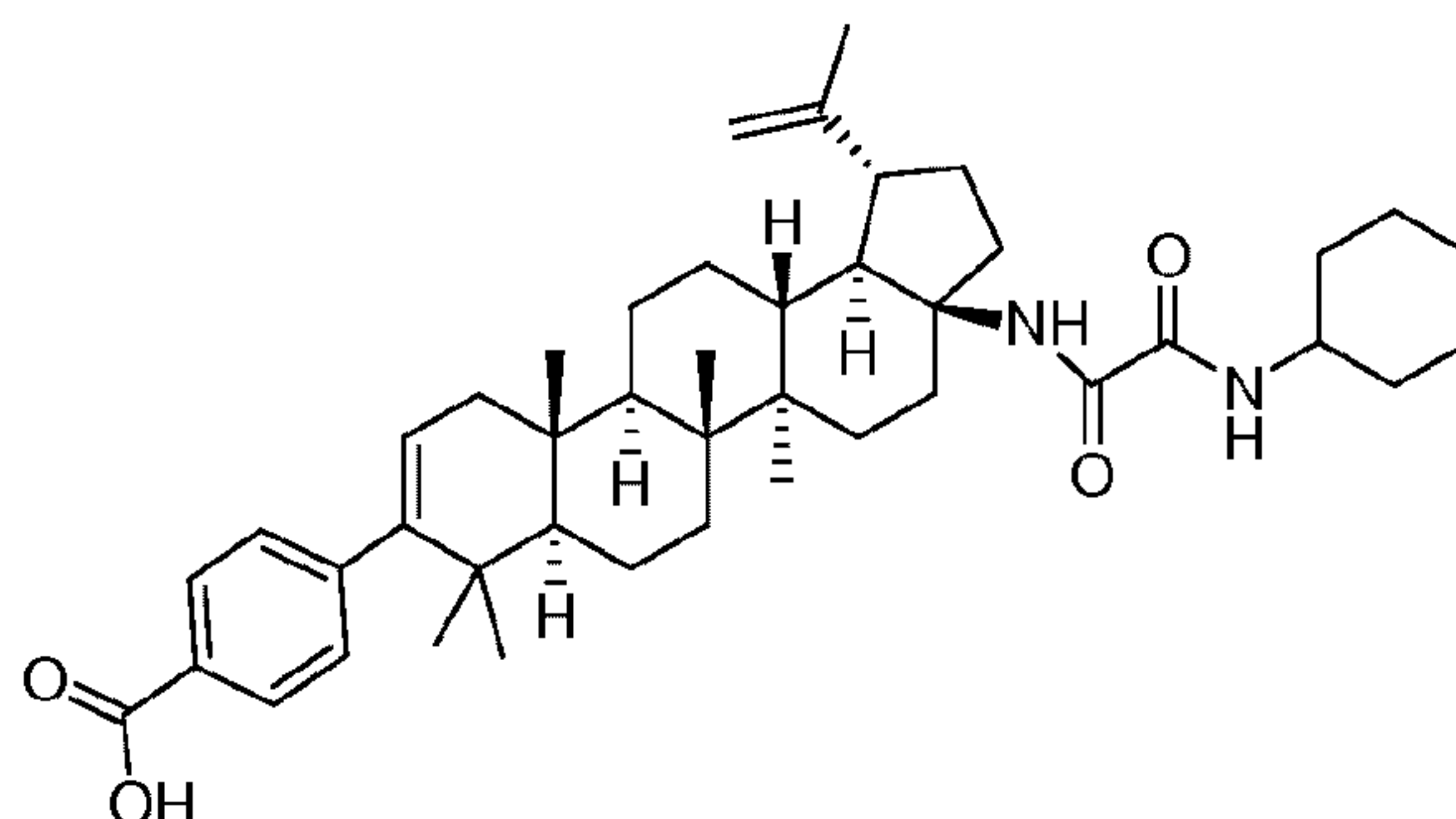
20

### Example 80

25

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)-

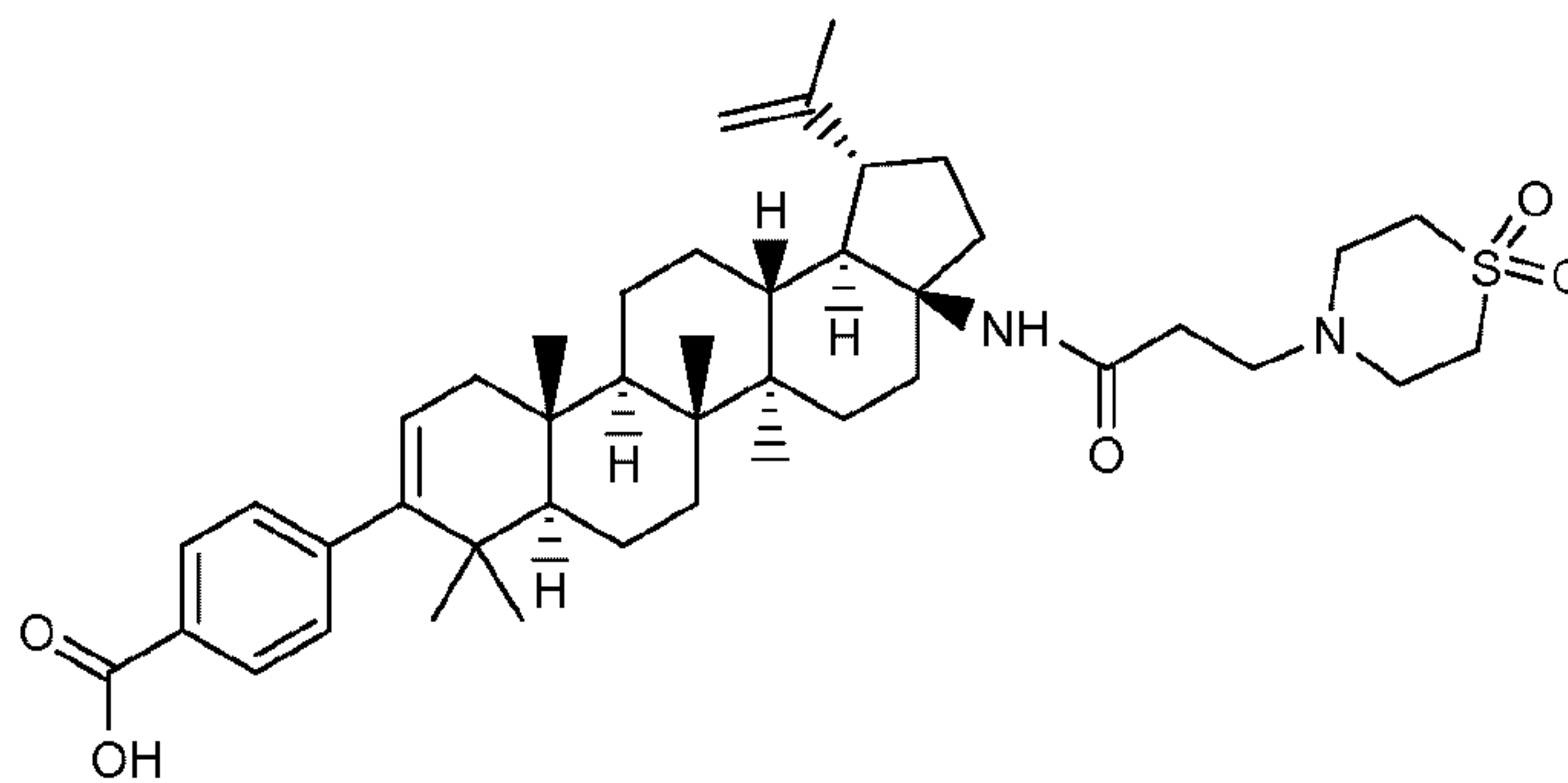
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



- 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)<sup>+</sup>, 2.42 min (method 9). <sup>1</sup>H NMR (500MHz, *CHLOROFORM-d*)  $\delta$  = 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].

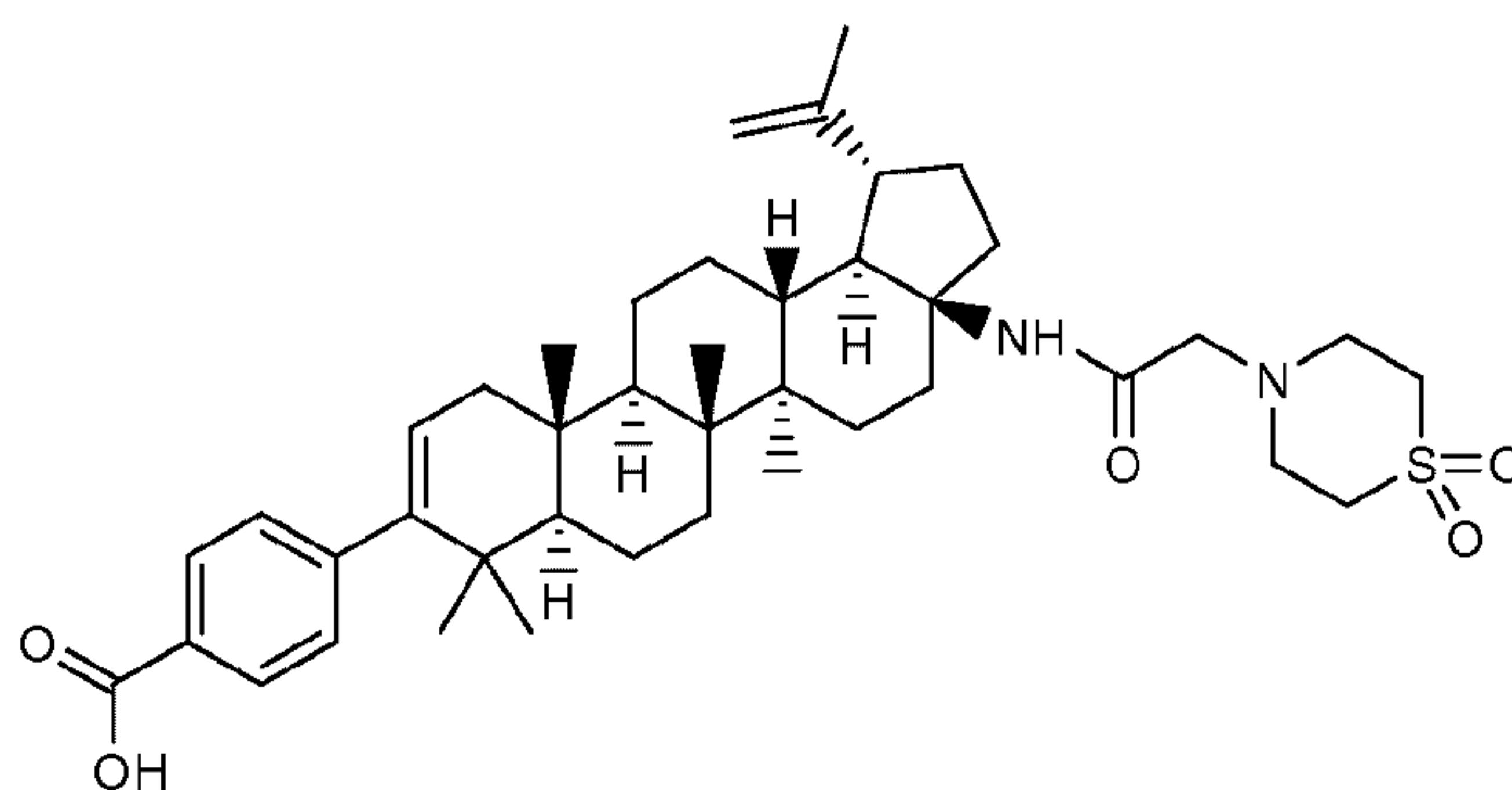


The title compound was prepared in 70% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 3-(1,1-dioxo-1 $\lambda$ 6,4-thiazinan-4-  
 yl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride  
 in Step 1. LCMS:  $m/e$  719.5 ( $M+H$ )<sup>+</sup>, 1.88 min (method 6). <sup>1</sup>H NMR (500MHz, 2:1  
*MeOD:CDCl*<sub>3</sub>)  $\delta$  = 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.,  
 15 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).

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**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-  
 25 pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



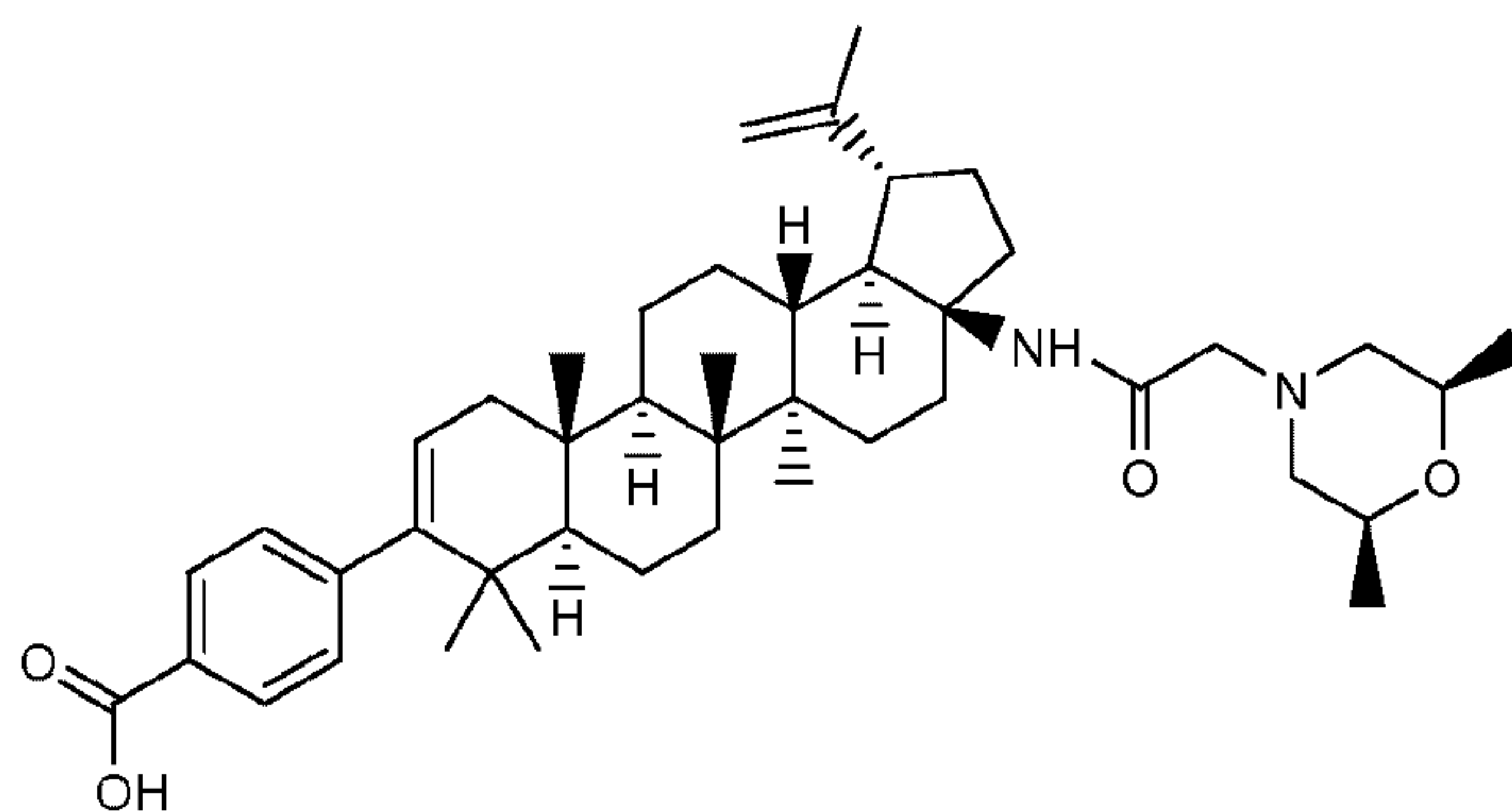
The title compound was prepared in 61% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 ( $M+H$ )<sup>+</sup>, 1.90 min (method 6). <sup>1</sup>H NMR (500MHz, 2:1  
*MeOD:CDCl<sub>3</sub>*)  $\delta$  = 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).

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### 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.

25

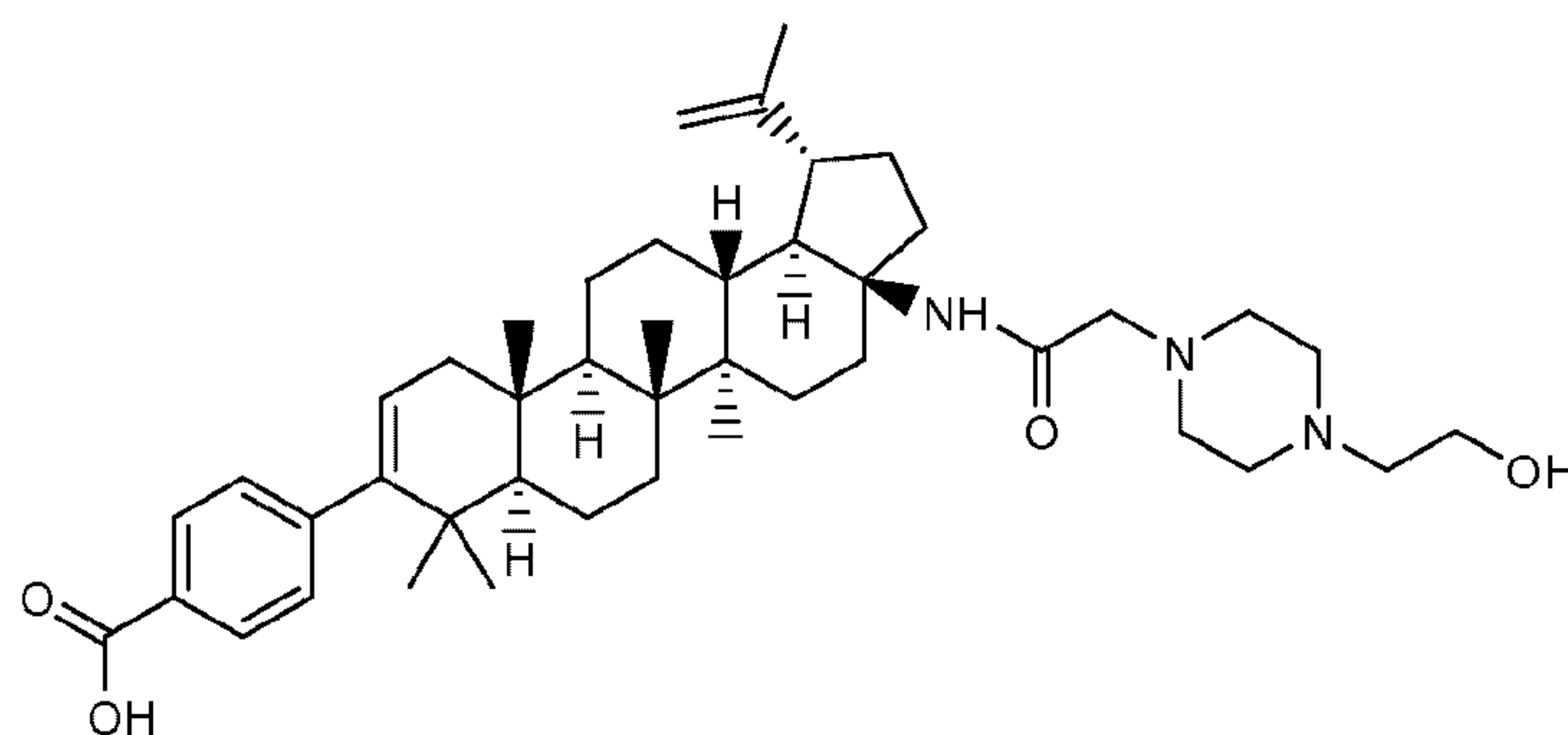


The title compound was prepared in 43% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 [(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 ( $M+H$ )<sup>+</sup>, 2.48 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
*CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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.  
 15 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).

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### 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-  
 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.

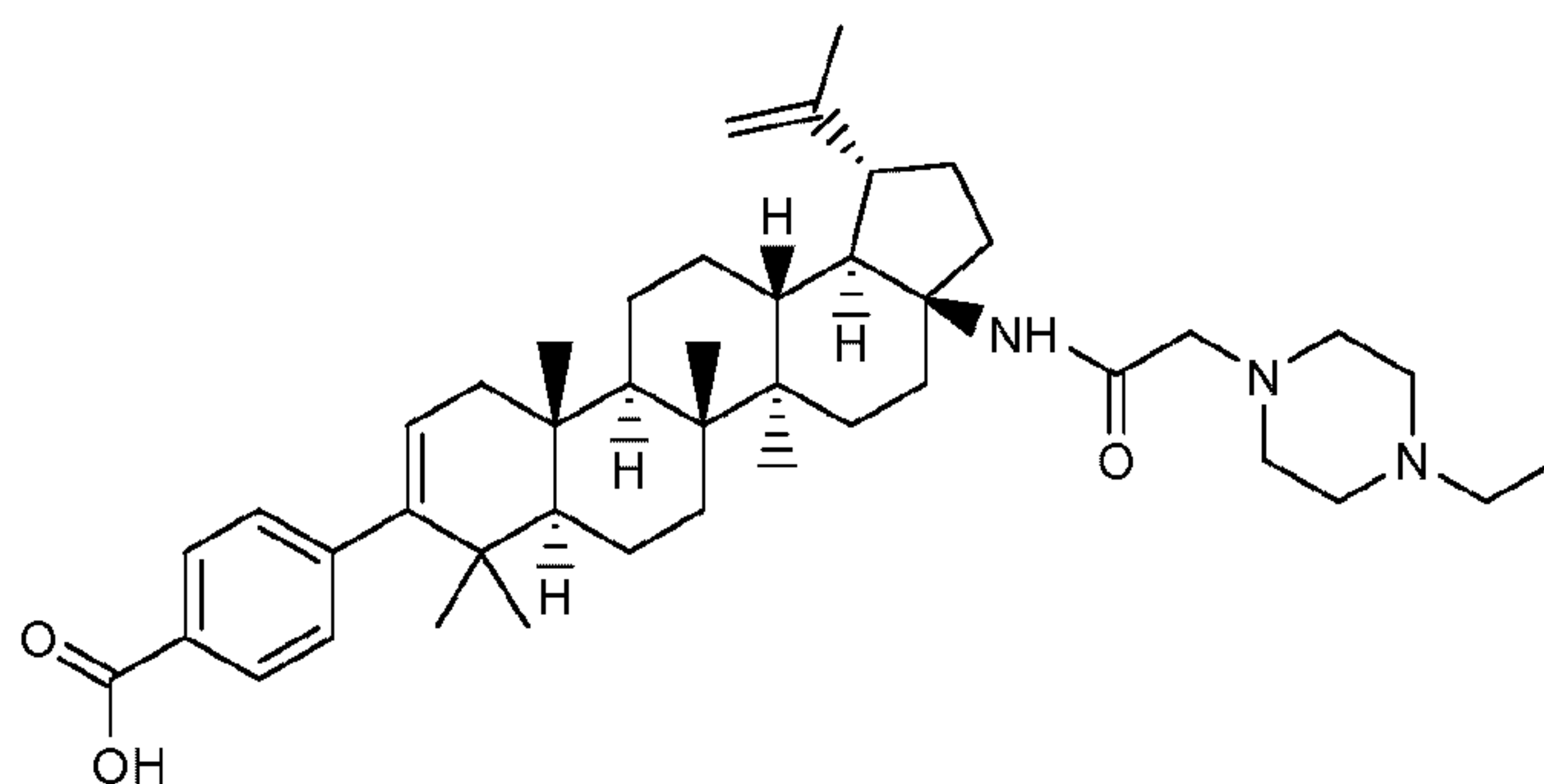


The title compound was prepared in 23% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 [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 ( $M+H$ )<sup>+</sup>, 2.03 min (method 6). <sup>1</sup>H NMR  
 (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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  
 15 (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).

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### 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)-  
 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.

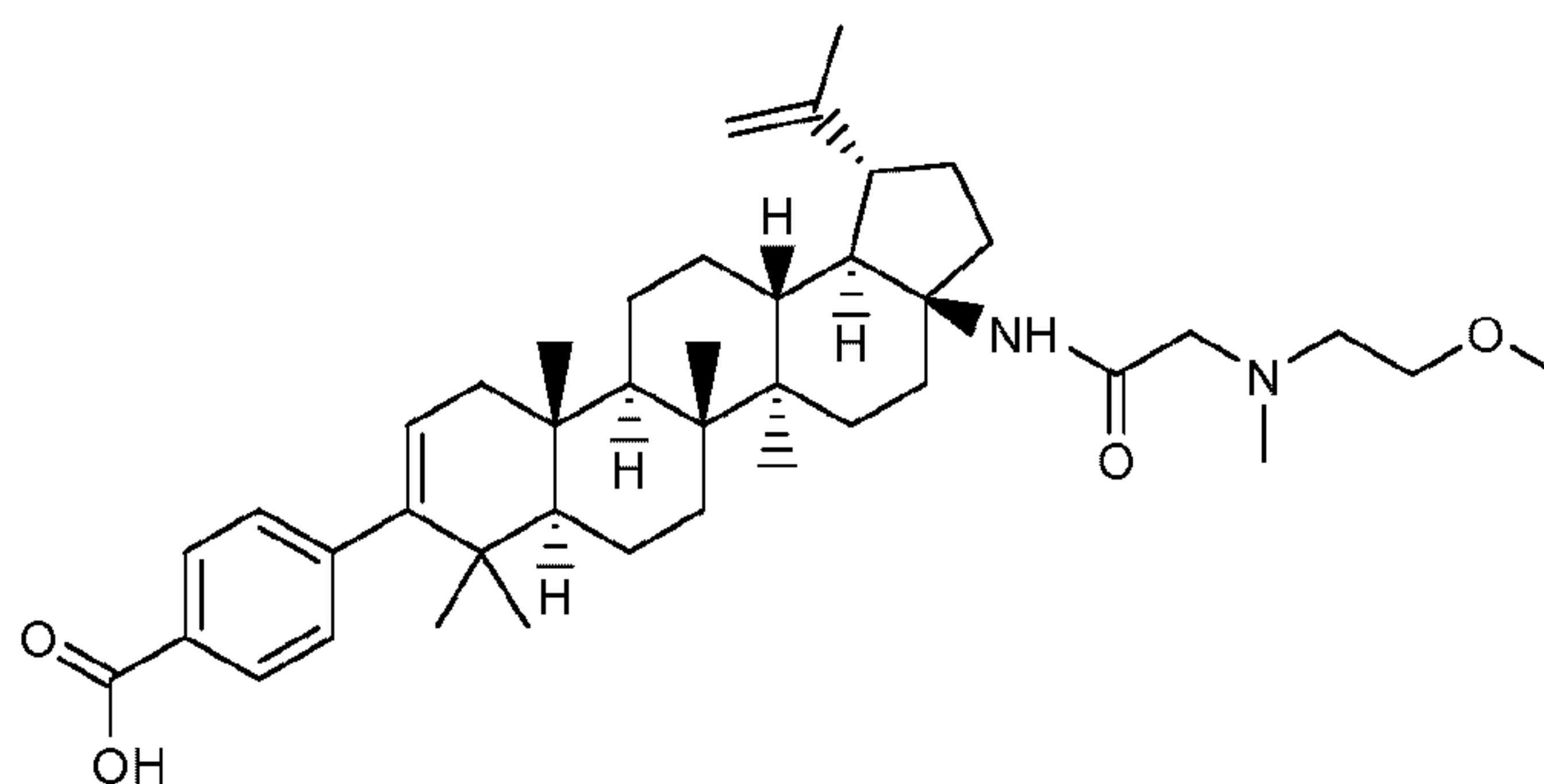


The title compound was prepared in 34% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 ( $M+H$ )<sup>+</sup>, 2.35 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
*CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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).

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**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.



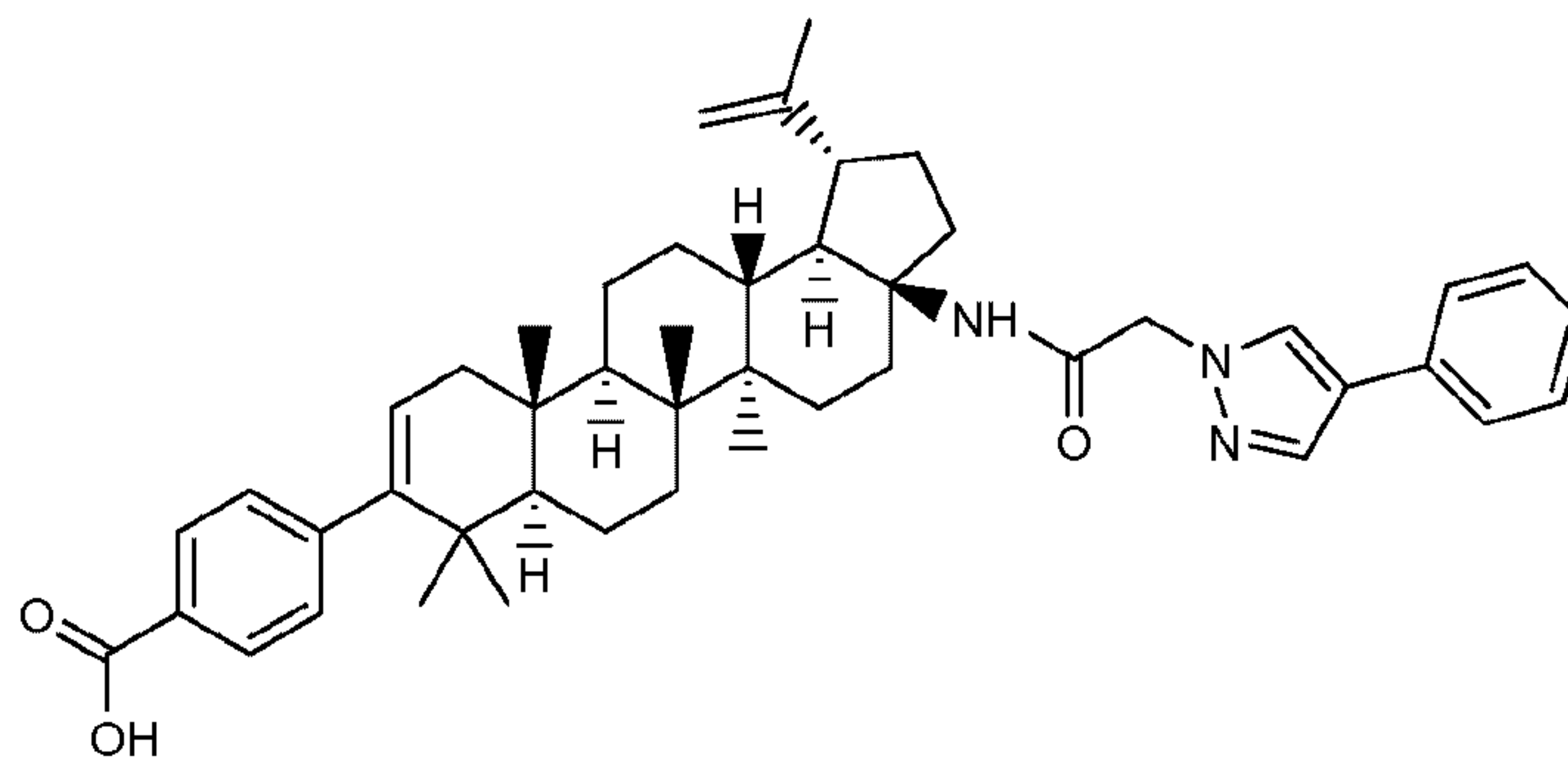
The title compound was prepared in 38% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 ( $M+H$ )<sup>+</sup>, 2.41 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
*CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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).

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### 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.

25

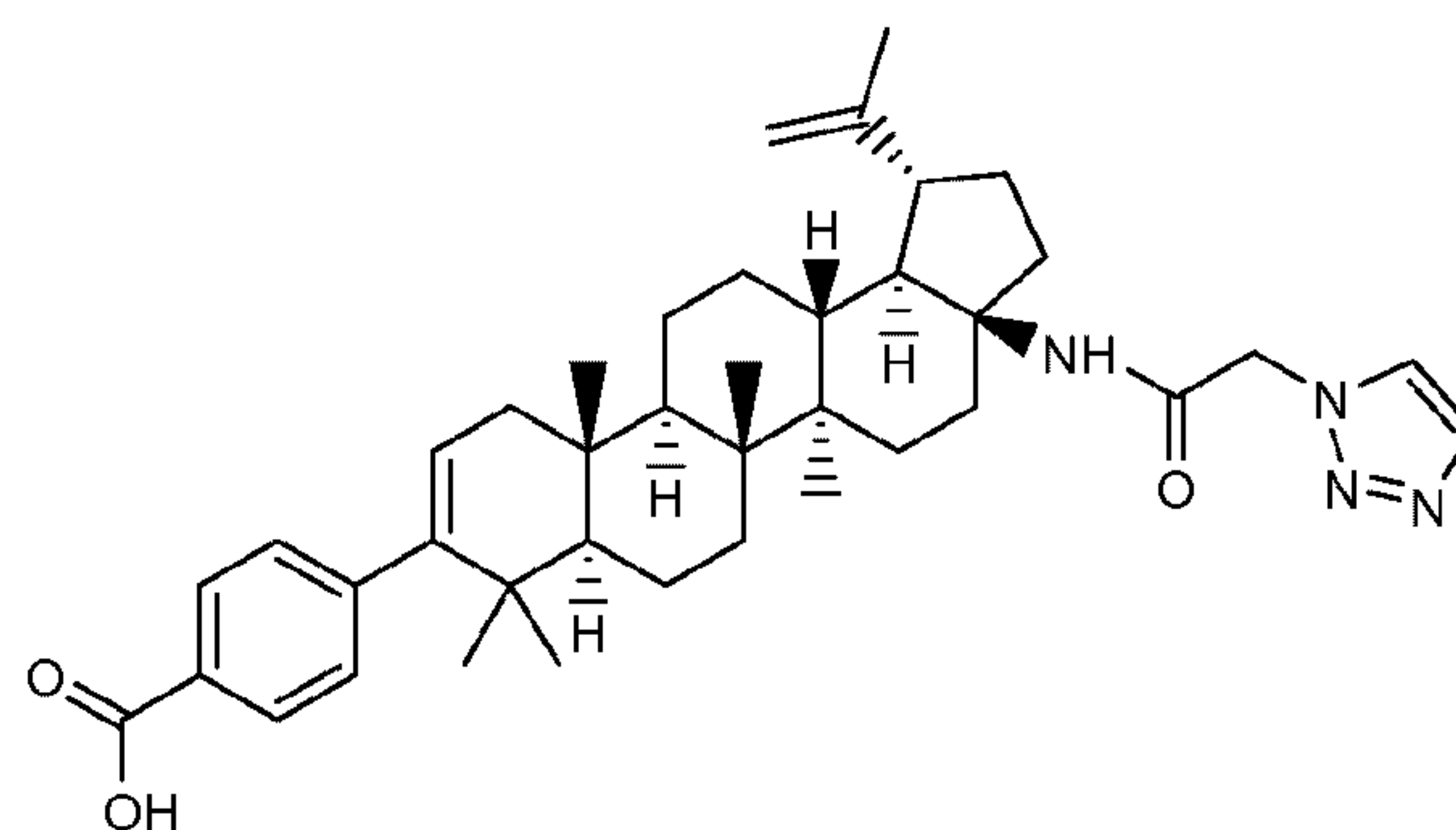


The title compound was prepared in 22% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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-(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 ( $M+H$ )<sup>+</sup>, 2.59 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
*CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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  
 15 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)-  
 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.

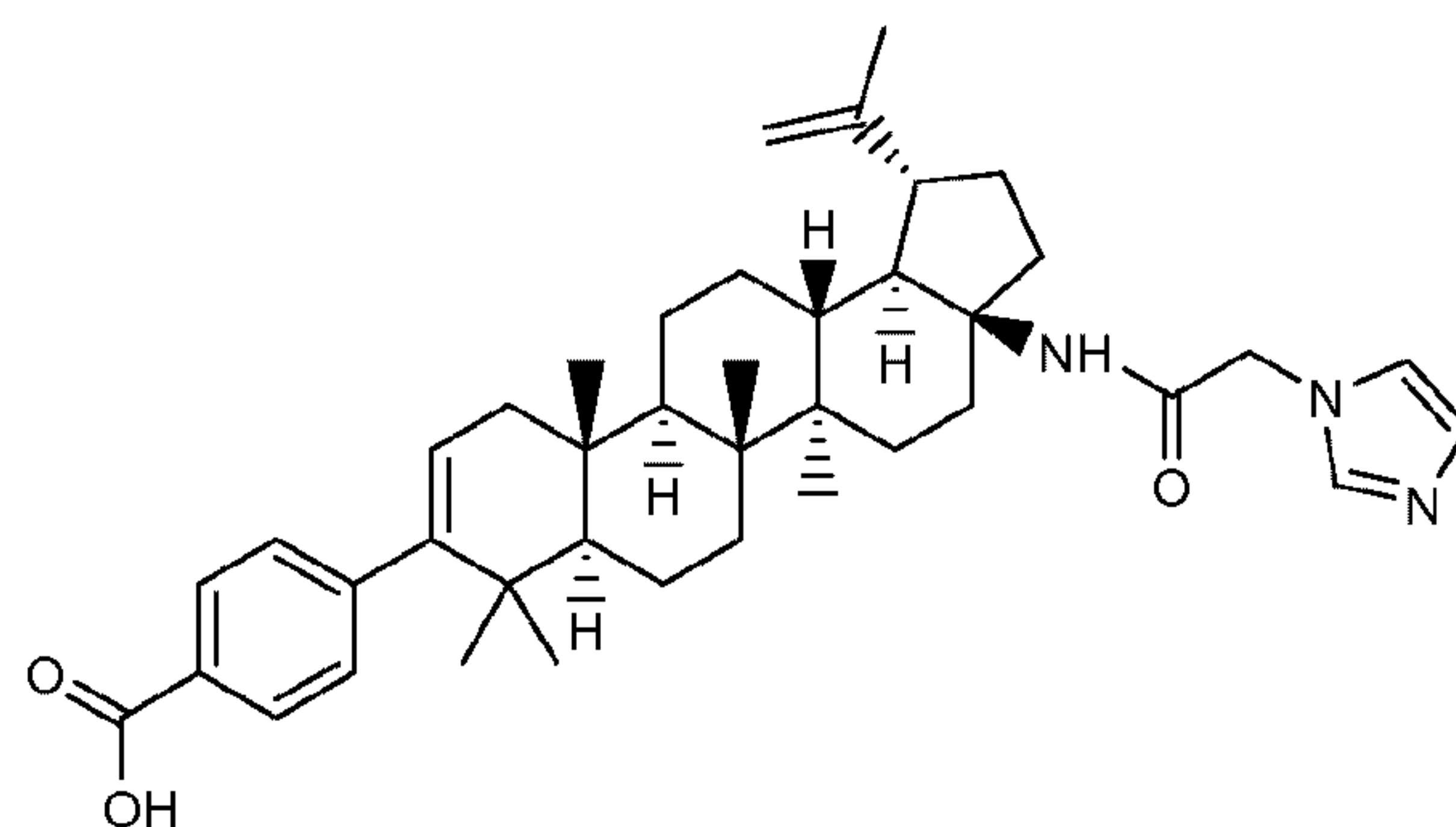


The title compound was prepared in 36% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 5 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 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 ( $M+H$ )<sup>+</sup>, 2.04 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
*CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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  
 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).

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### 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)-  
 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.

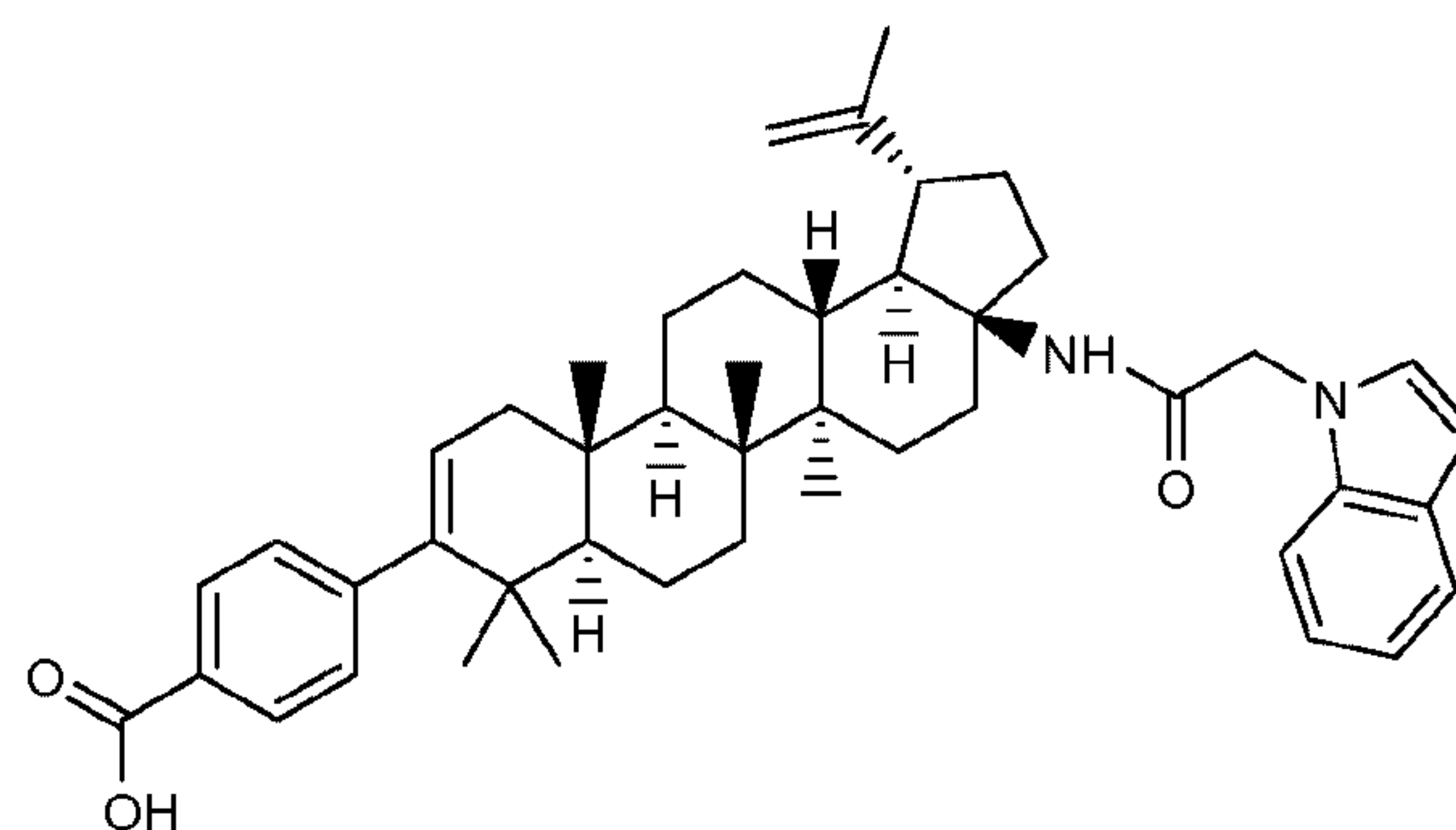


The title compound was prepared in 60% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 5 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 imidazol-1-ylacetic acid was used  
 instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS:  $m/e$   
 638.5 ( $M+H$ )<sup>+</sup>, 2.05 min (method 6). <sup>1</sup>H NMR (400MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  =  
 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,  $J$   
 15 = 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)-  
 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.

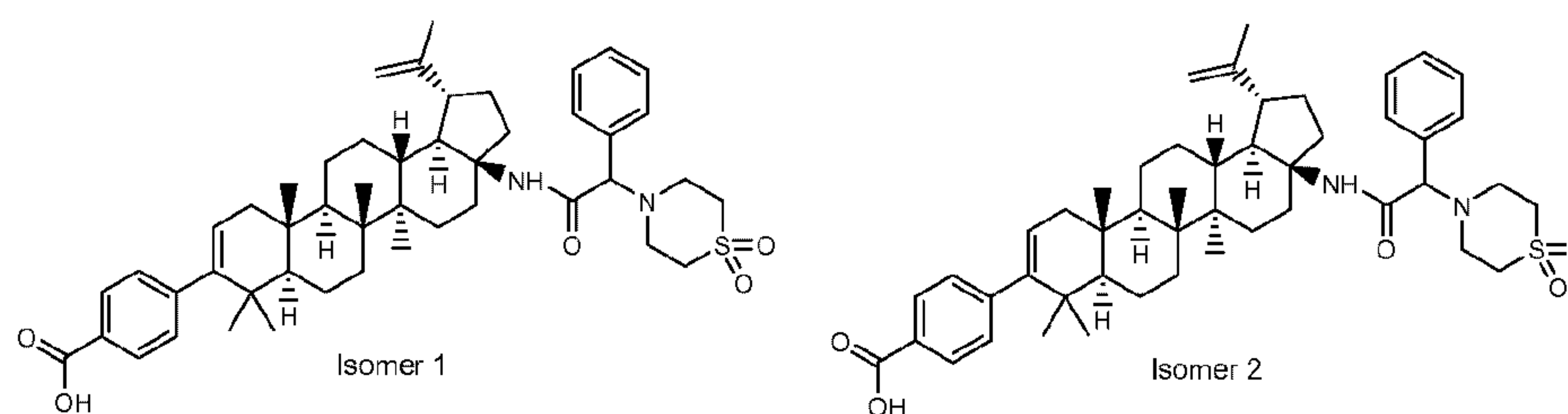


The title compound was prepared in 31% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 5 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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-(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)<sup>+</sup>, 2.60 min (method 6). <sup>1</sup>H NMR (400MHz, 1:1 CDCl<sub>3</sub>: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  
 15 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).

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### 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]-  
 25 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.

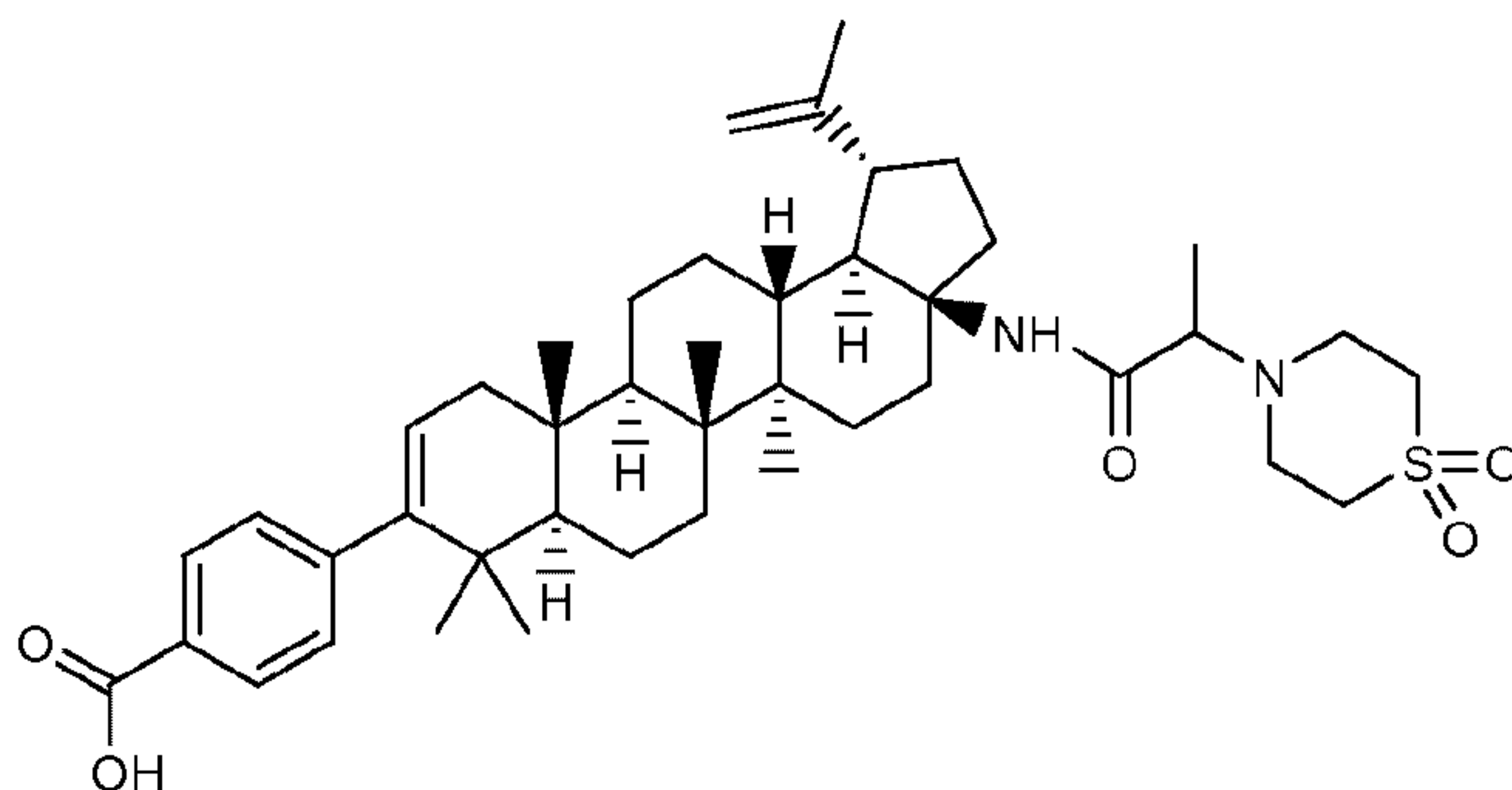
Isomer 1: LCMS:  $m/e$  781.6 ( $M+H$ )<sup>+</sup>, 2.21 min (method 6). <sup>1</sup>H NMR (400MHz, 1:1  $CDCl_3:MeOD$ )  $\delta$  = 7.92 (d,  $J$  = 8.5 Hz, 2 H), 7.49 - 7.44 (m, 2 H), 7.43 - 7.36 (m, 3 H), 7.20 (d,  $J$  = 8.3 Hz, 2 H), 6.62 (s, 1 H), 5.29 (dd,  $J$  = 1.6, 6.1 Hz, 1 H), 4.76 (d,  $J$  = 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 ( $M+H$ )<sup>+</sup>, 2.22 min (method 6). <sup>1</sup>H NMR (400MHz, 1:1  $CDCl_3:MeOD$ )  $\delta$  = 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-(1,1-dioxido-4-thiomorpholinyl)-1-oxopropyl]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].



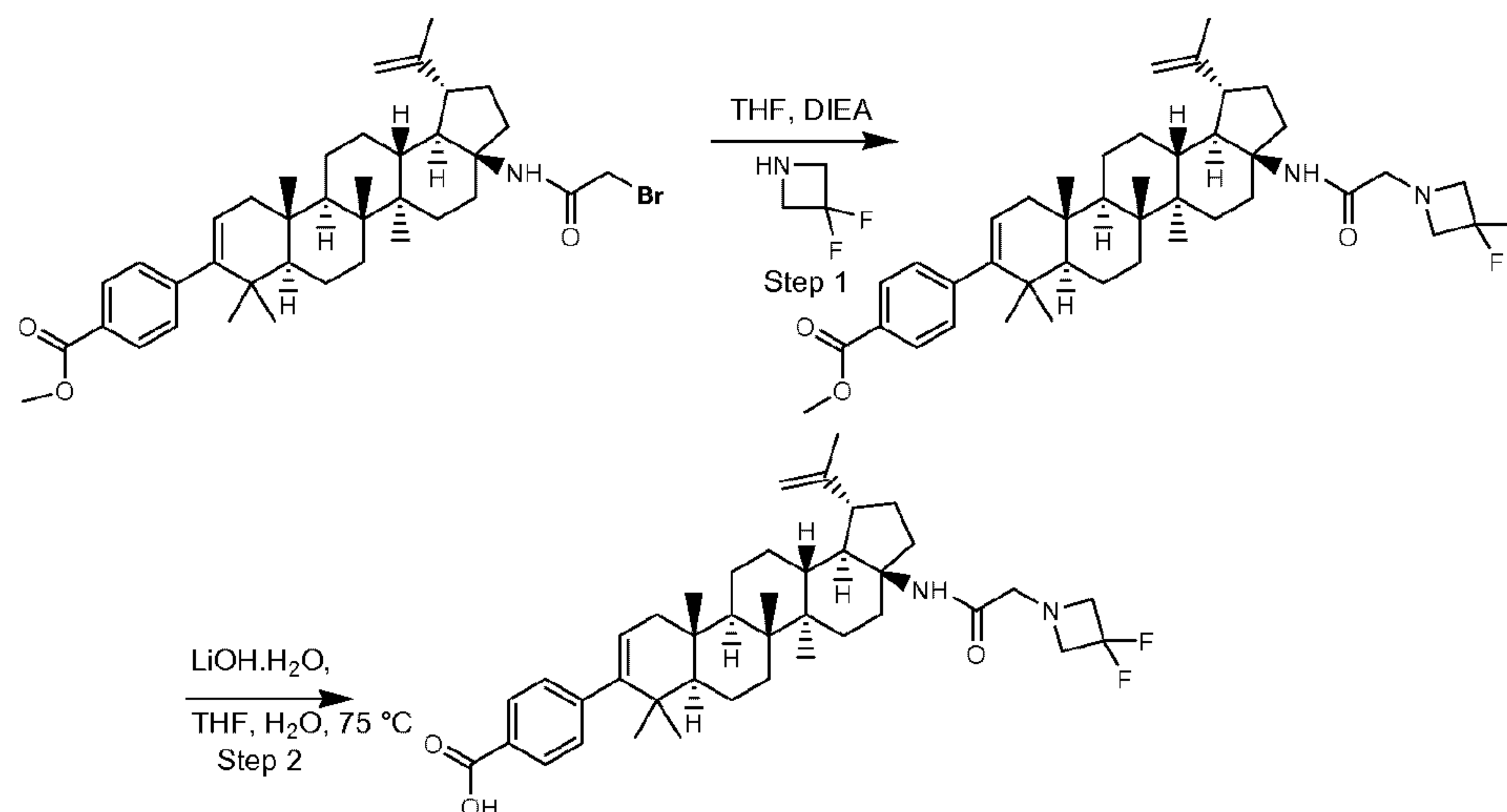
The title compound was prepared in 44% yield from methyl 4-  
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 ( $M+H$ )<sup>+</sup>, 2.03 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
*CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 7.92 (d,  $J$  = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.20 (d,  $J$  = 7.9 Hz, 2 H),  
 20 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).

25

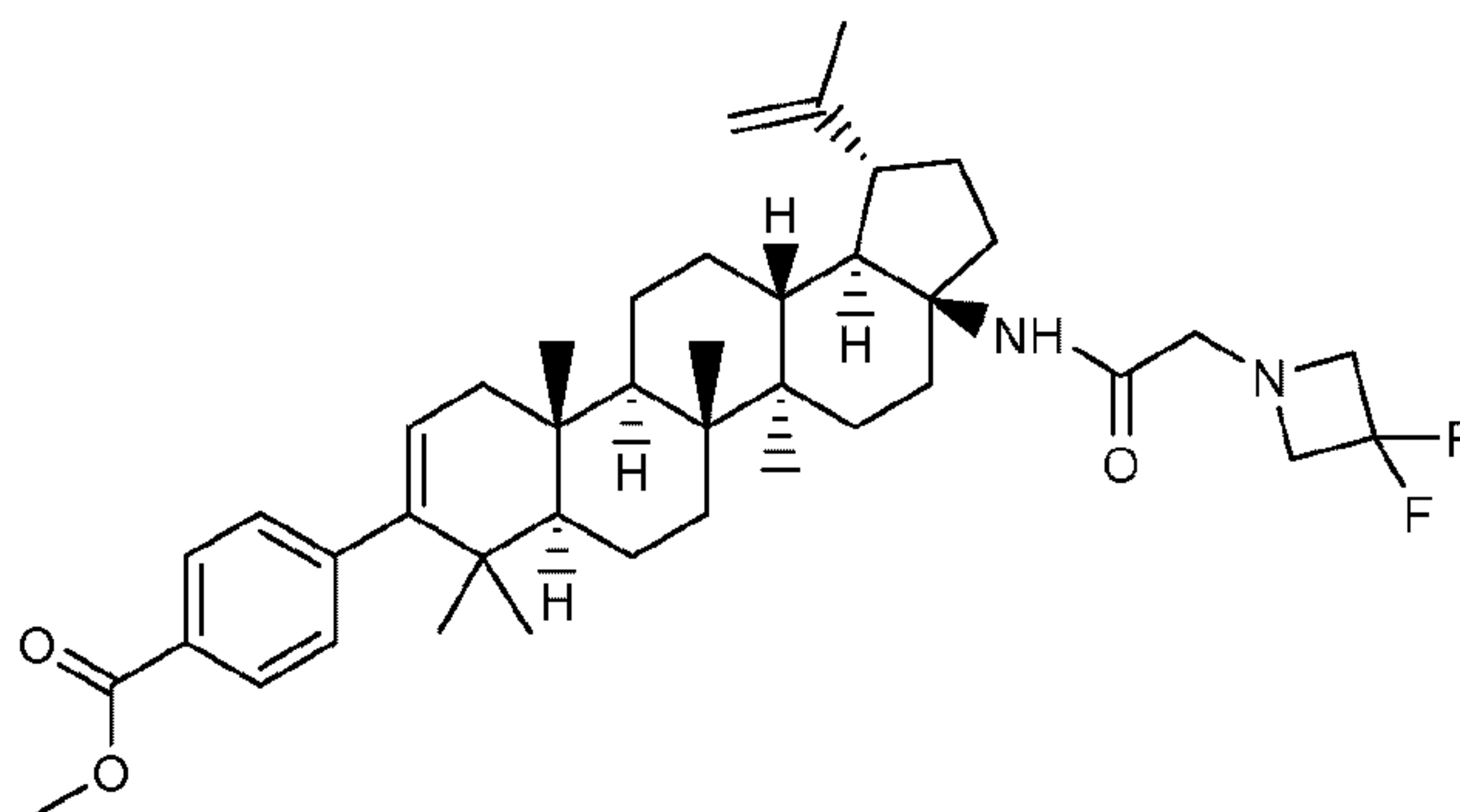
### Example 94

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.

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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.

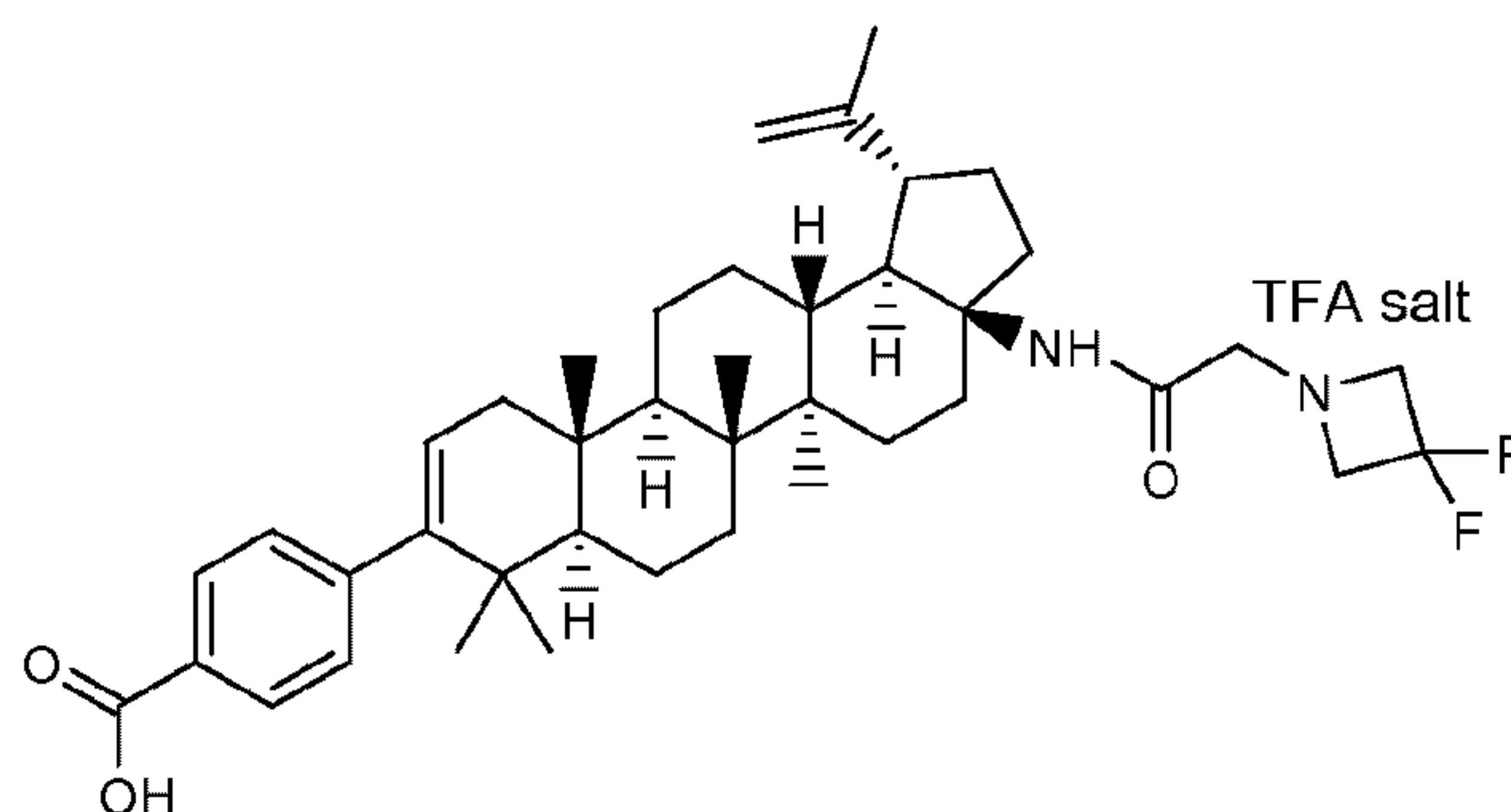


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (129 mg, 0.194 mmol) in THF (3 mL) was added *N,N*-diisopropylethylamine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

(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)<sup>+</sup>, 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

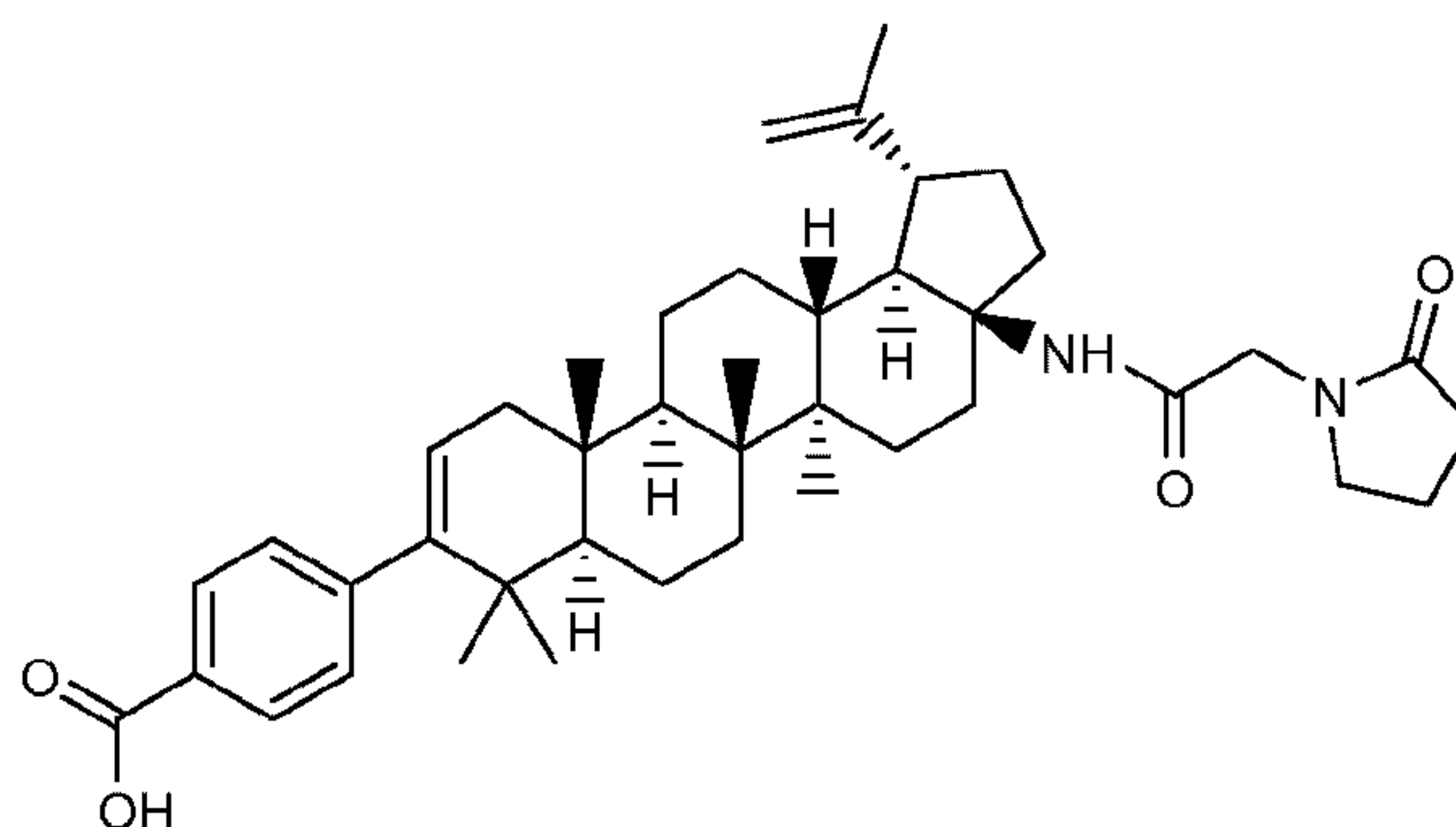
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (28.8 mg, 0.043 mmol) in THF (Volume: 3 mL) was added a 0.753 molar solution of Li . H O . H<sub>2</sub>O (0.340 mL, 0.170 mmol) in H<sub>2</sub>O. 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)<sup>+</sup>, 2.22 min (method 2). <sup>1</sup>H NMR

(500MHz, 1:1  $CDCl_3$ :*METHANOL- $d_4$* )  $\delta$  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.

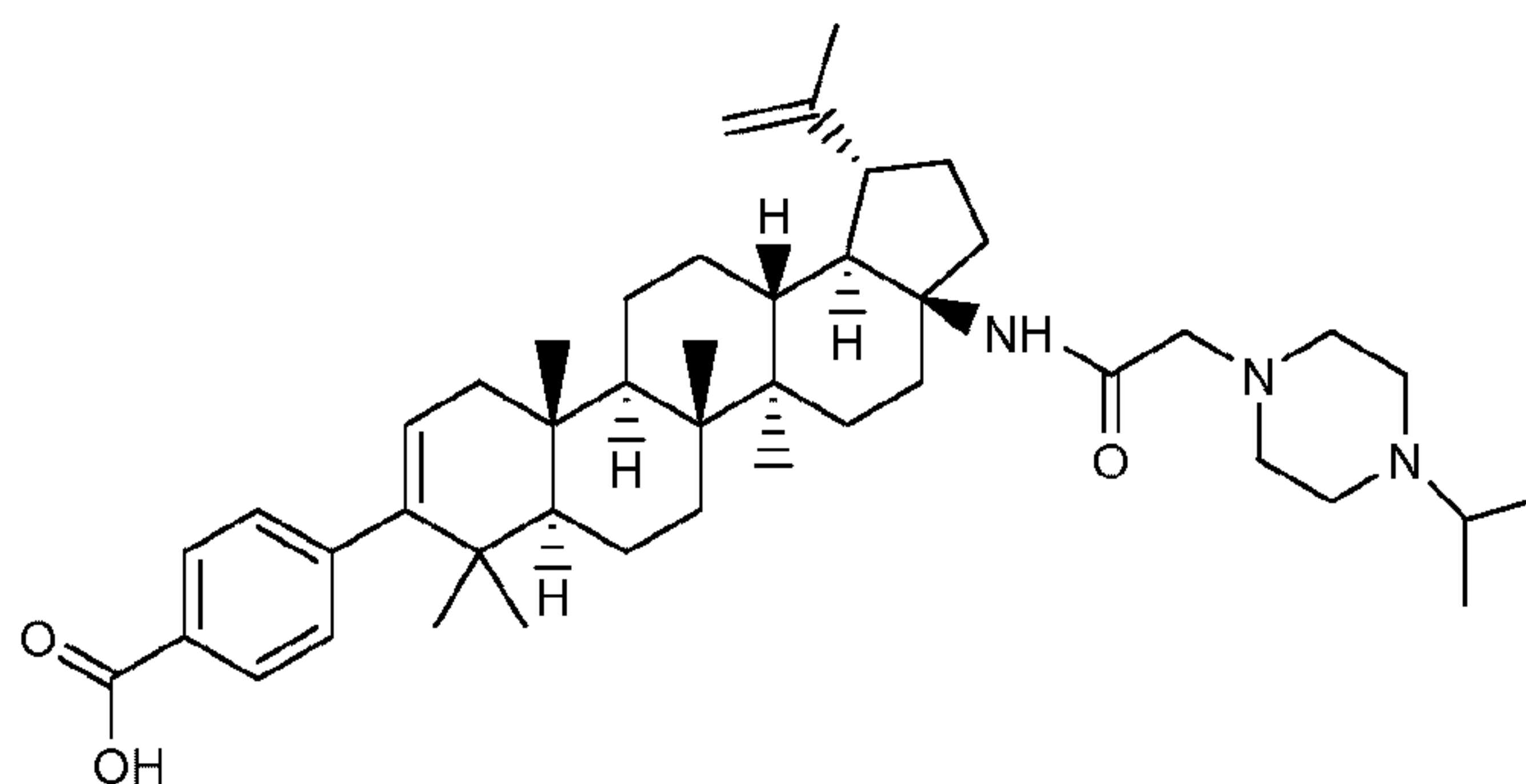
25 LCMS:  $m/e$  655.5 ( $M+H$ )<sup>+</sup>, 1.99 min (method 6).  $^1H$  NMR (500MHz, 1:1  $CDCl_3$ :*MeOD*)  $\delta$  = 7.92 (d,  $J = 7.9$  Hz, 2 H), 7.20 (d,  $J = 7.9$  Hz, 2 H), 6.77 (s, 1 H), 5.29 (d,  $J = 4.7$  Hz, 1 H), 4.75 (d,  $J = 1.3$  Hz, 1 H), 4.63 (s, 1 H), 3.97 - 3.85 (m, 2 H),

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 ( $M+H$ )<sup>+</sup>, 2.64 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  $CDCl_3:MeOD$ )  $\delta$  = 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,

25

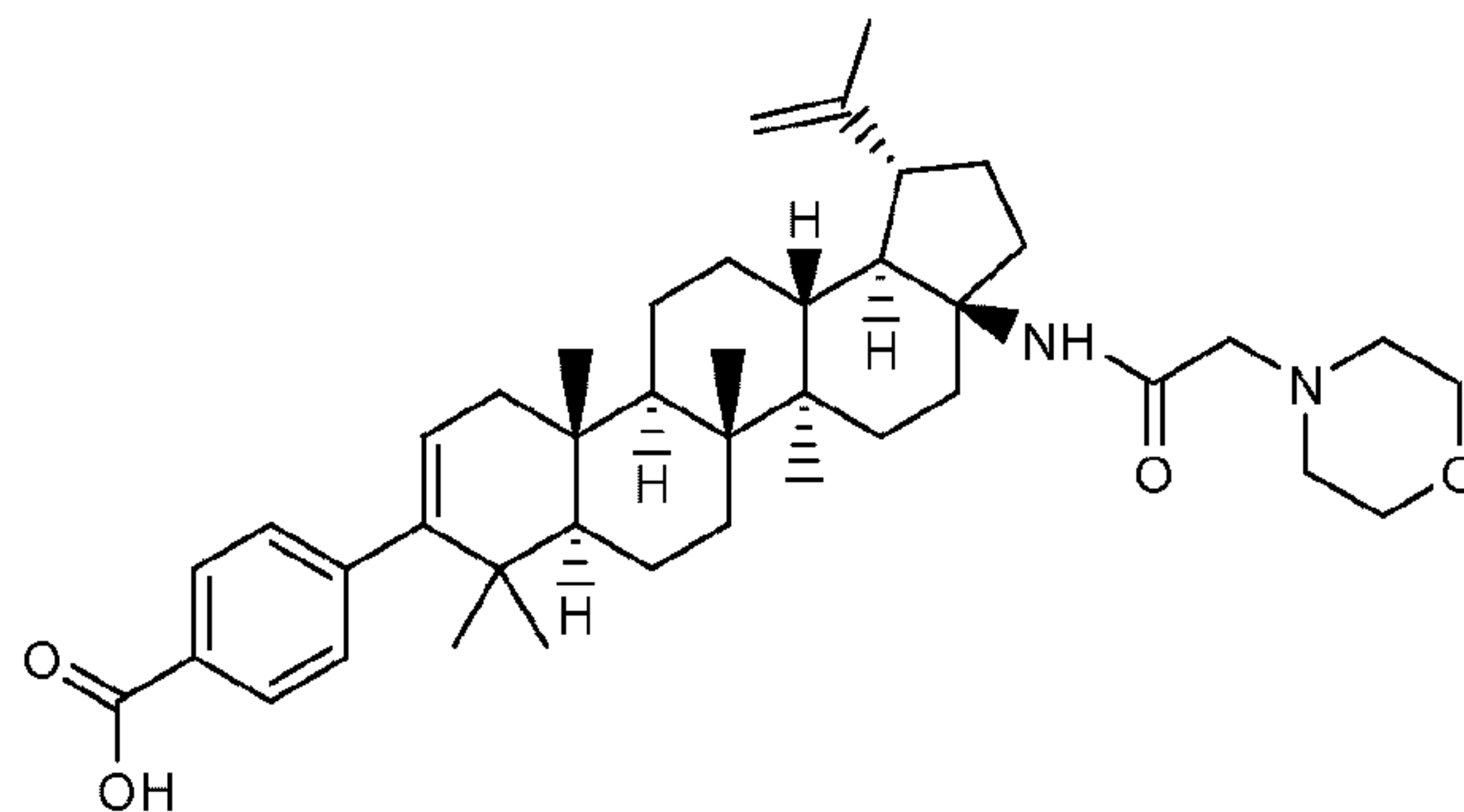
2 H), 1.79 (d,  $J = 12.5$  Hz, 1 H), 1.76 - 1.65 (m, 5 H), 1.59 - 1.40 (m, 14 H), 1.35 (t,  $J = 7.2$  Hz, 4 H), 1.29 - 1.21 (m, 1 H), 1.15 (d,  $J = 6.1$  Hz, 1 H), 1.10 (br. s., 3 H), 1.02 (s, 3 H), 1.01 (br. s., 2 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

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**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 ( $M+H$ )<sup>+</sup>, 2.20 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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

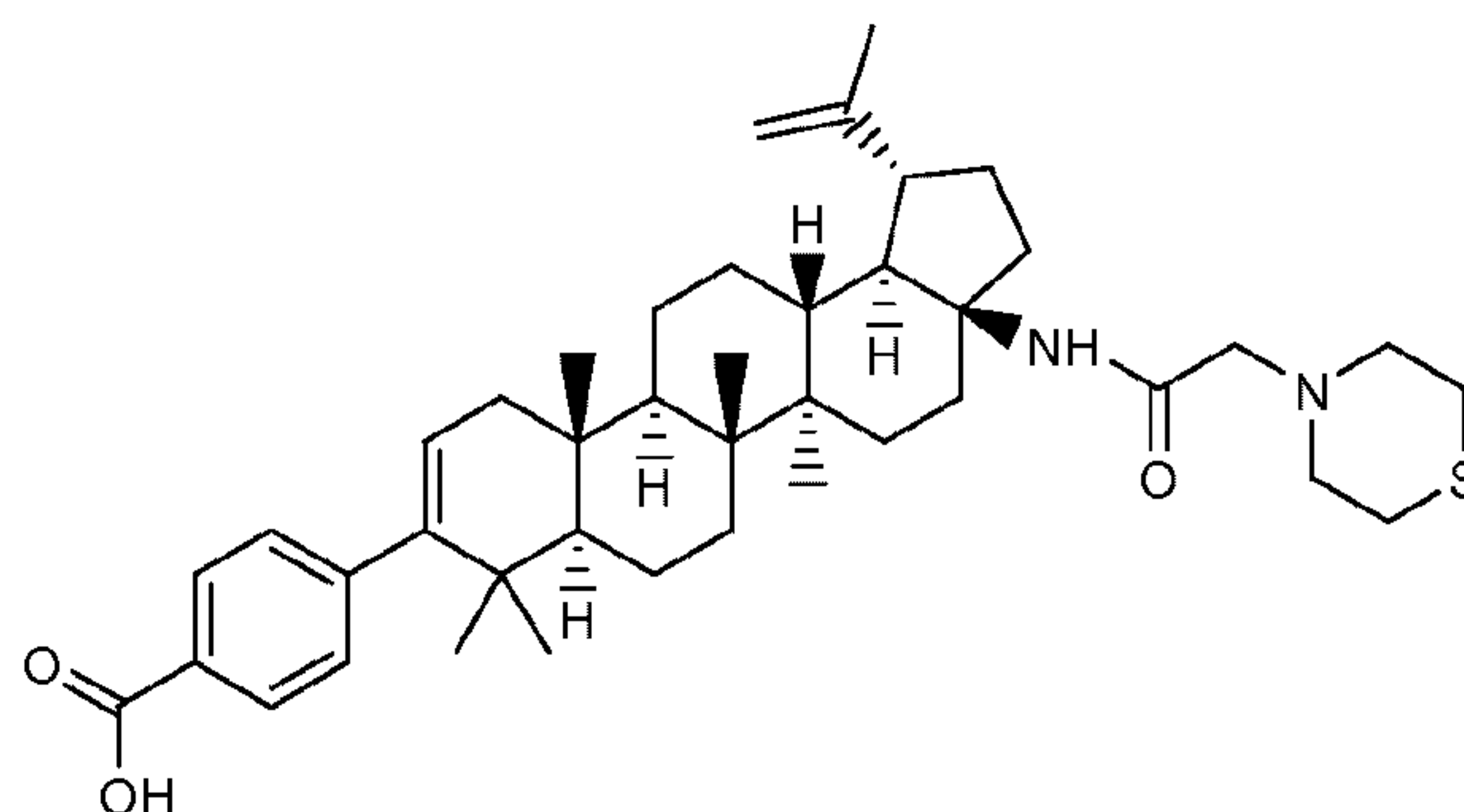
25

(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

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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-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.



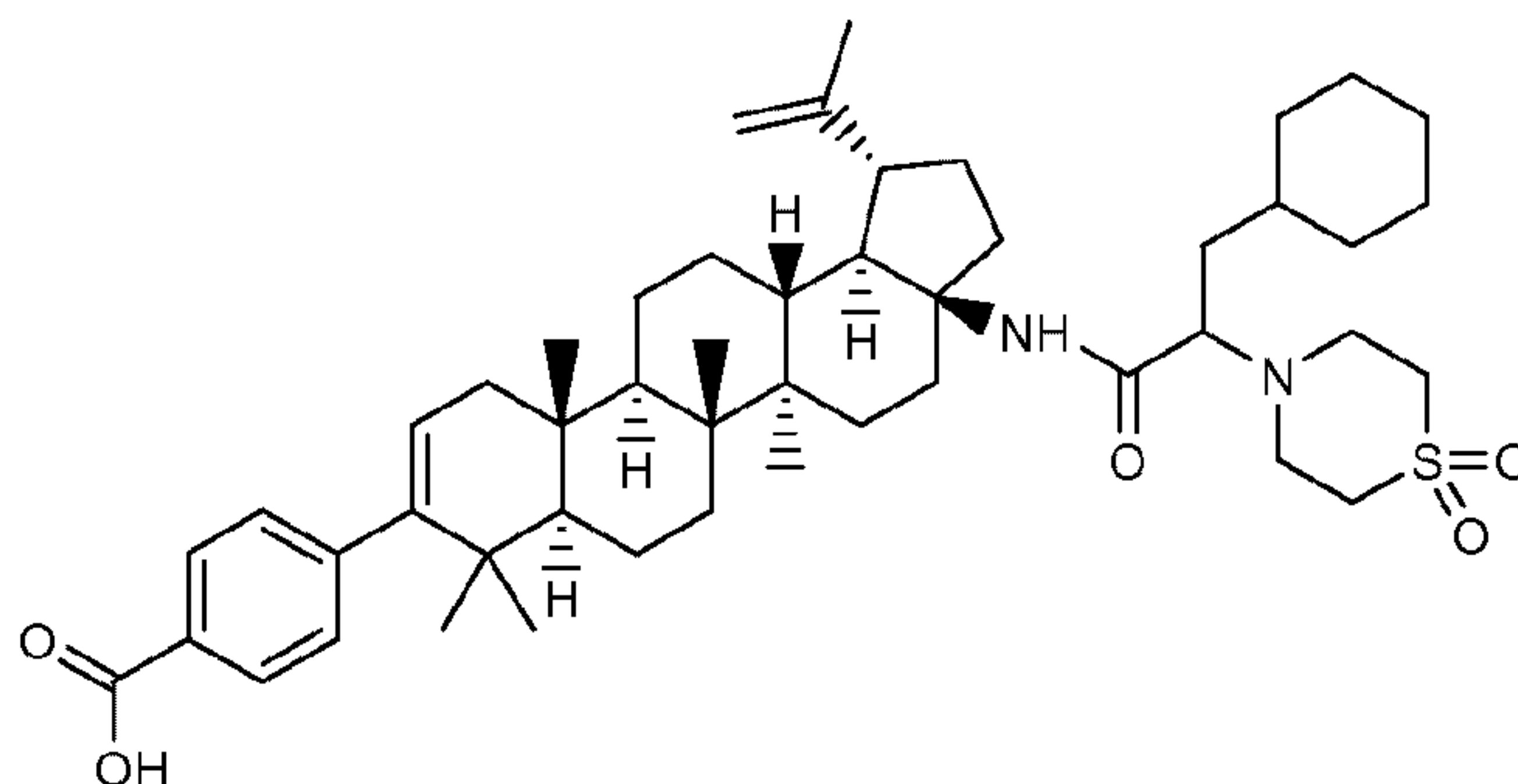
10

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)<sup>-</sup>, 2.37 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 CDCl<sub>3</sub>: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

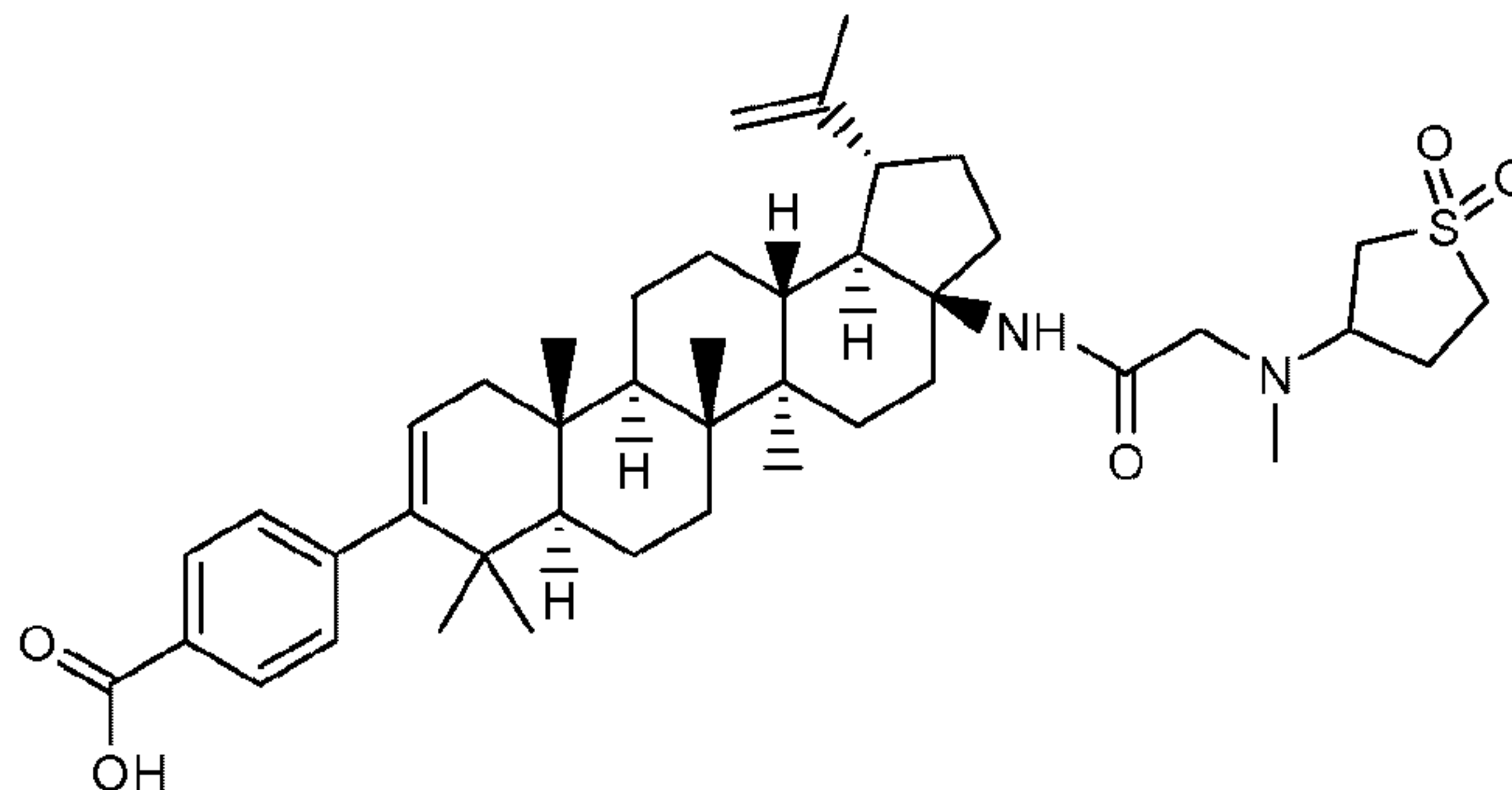
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-  
 5 cyclohexyl-2-(1,1-dioxido-4-thiomorpholinyl)-1-oxopropyl]amino]-  
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-  
 pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



10 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)-  
 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 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 ( $M+H$ )<sup>+</sup>,  
 20 2.43 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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 -  
 25 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

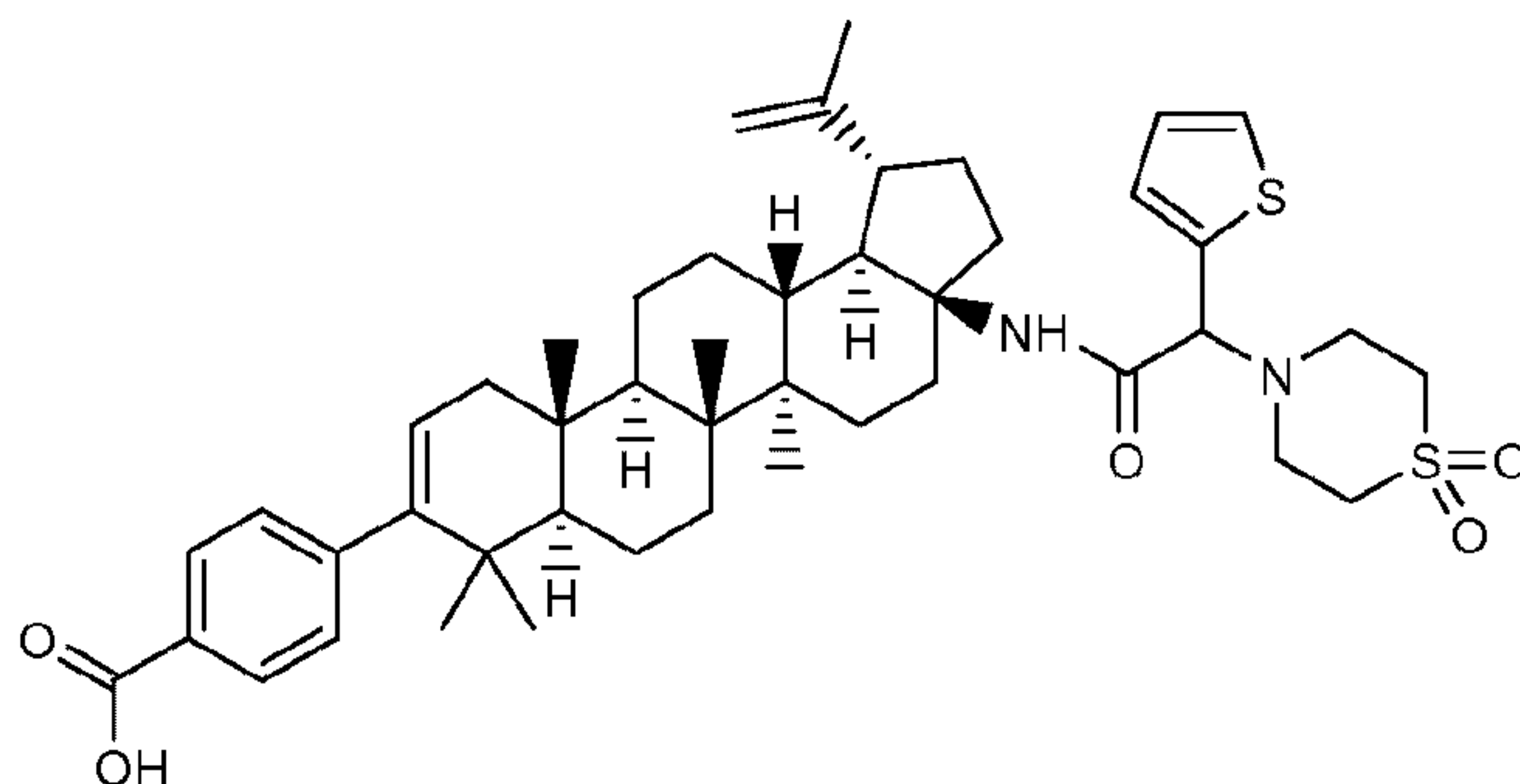
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-  
 pentamethyl-1-(1-methylethenyl)-3a-[[[methyl(tetrahydro-1,1-dioxido-3-  
 thienyl)amino]acetyl]amino]-1H-cyclopenta[a]chrysen-9-yl].



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 ( $M+H$ )<sup>+</sup>, 2.00 min (method 6). <sup>1</sup>H NMR (500MHz,  
 20  $CDCl_3:MeOD$ )  $\delta$  = 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

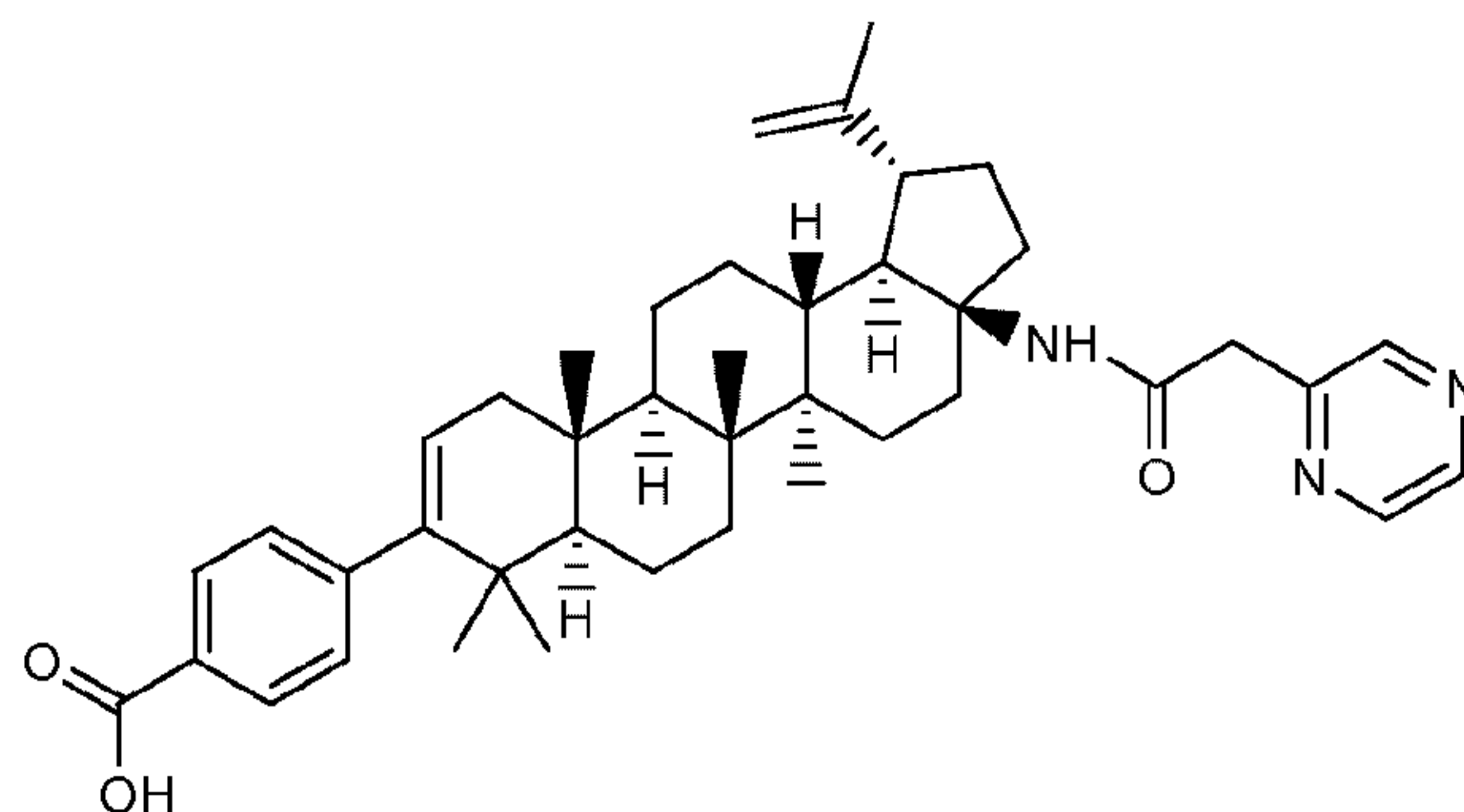
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)-1-oxo-3-(2-thienyl)propyl]amino]-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl.



The title compound was prepared in 39% 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 3-(1,1-dioxo-1λ<sup>6</sup>,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)<sup>+</sup>, 2.16 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 CDCl<sub>3</sub>: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.,  
 20 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.

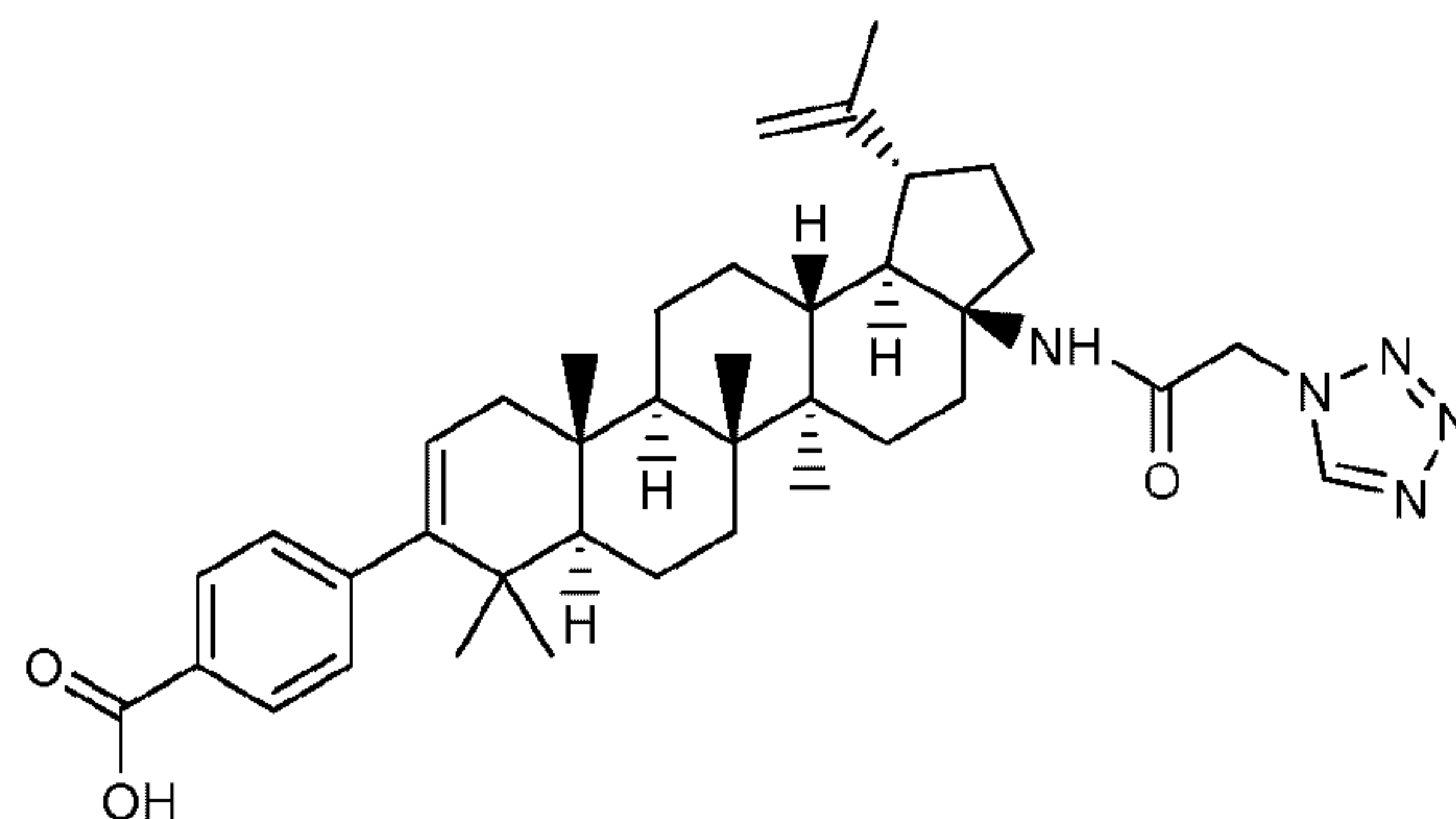


The title compound was prepared in 14% yield from methyl 4-  
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described 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 ( $M+H$ )<sup>+</sup>, 2.12 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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,  $J$  = 1.7, 6.0 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)-

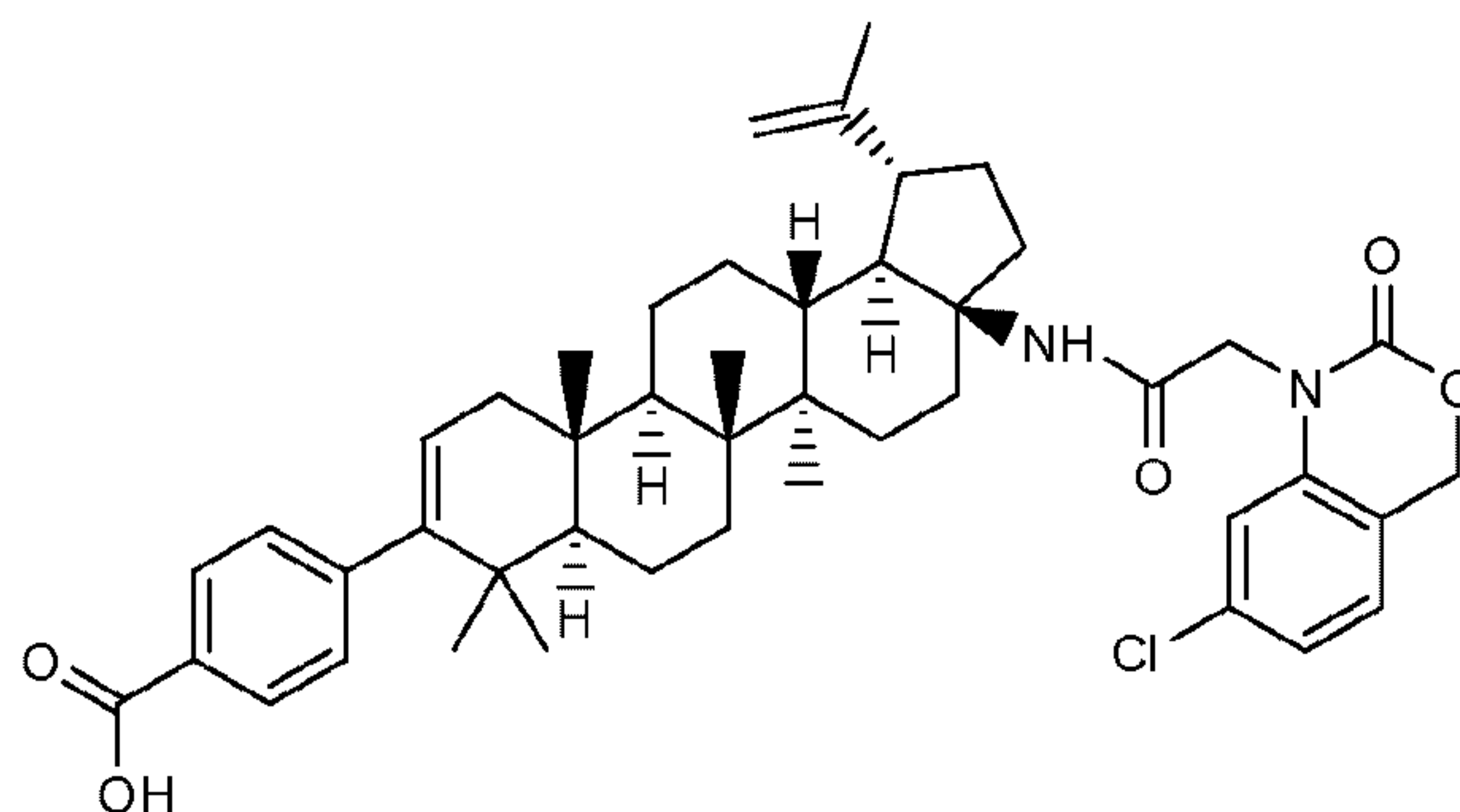
5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)<sup>-</sup>, 1.98 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 CDCl<sub>3</sub>:MeOD)  $\delta$  = 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

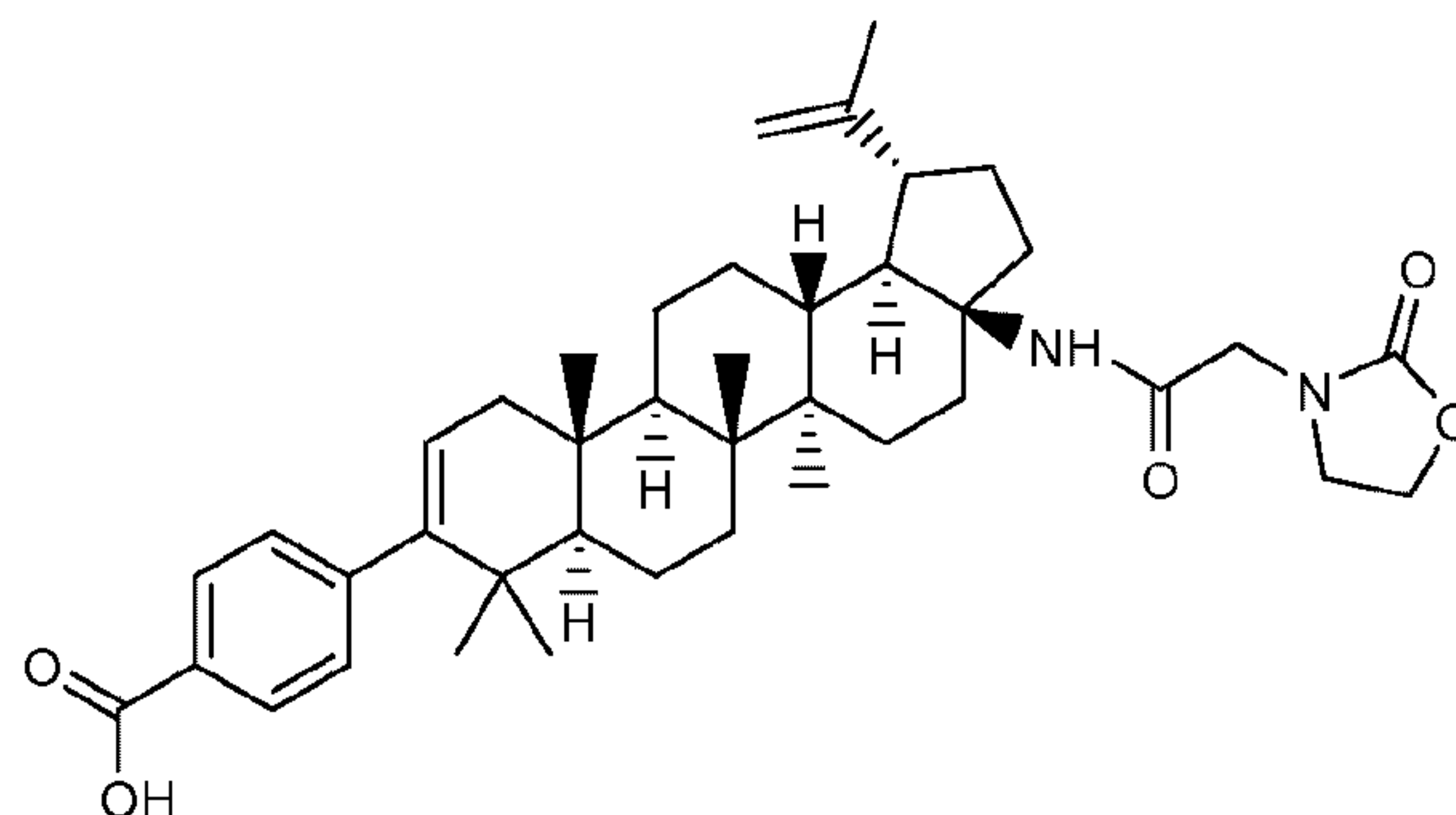
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(7-chloro-2-oxo-2,4-dihydro-1H-benzo[d][1,3]oxazin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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 ( $M+H$ )<sup>+</sup>, 2.29 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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.

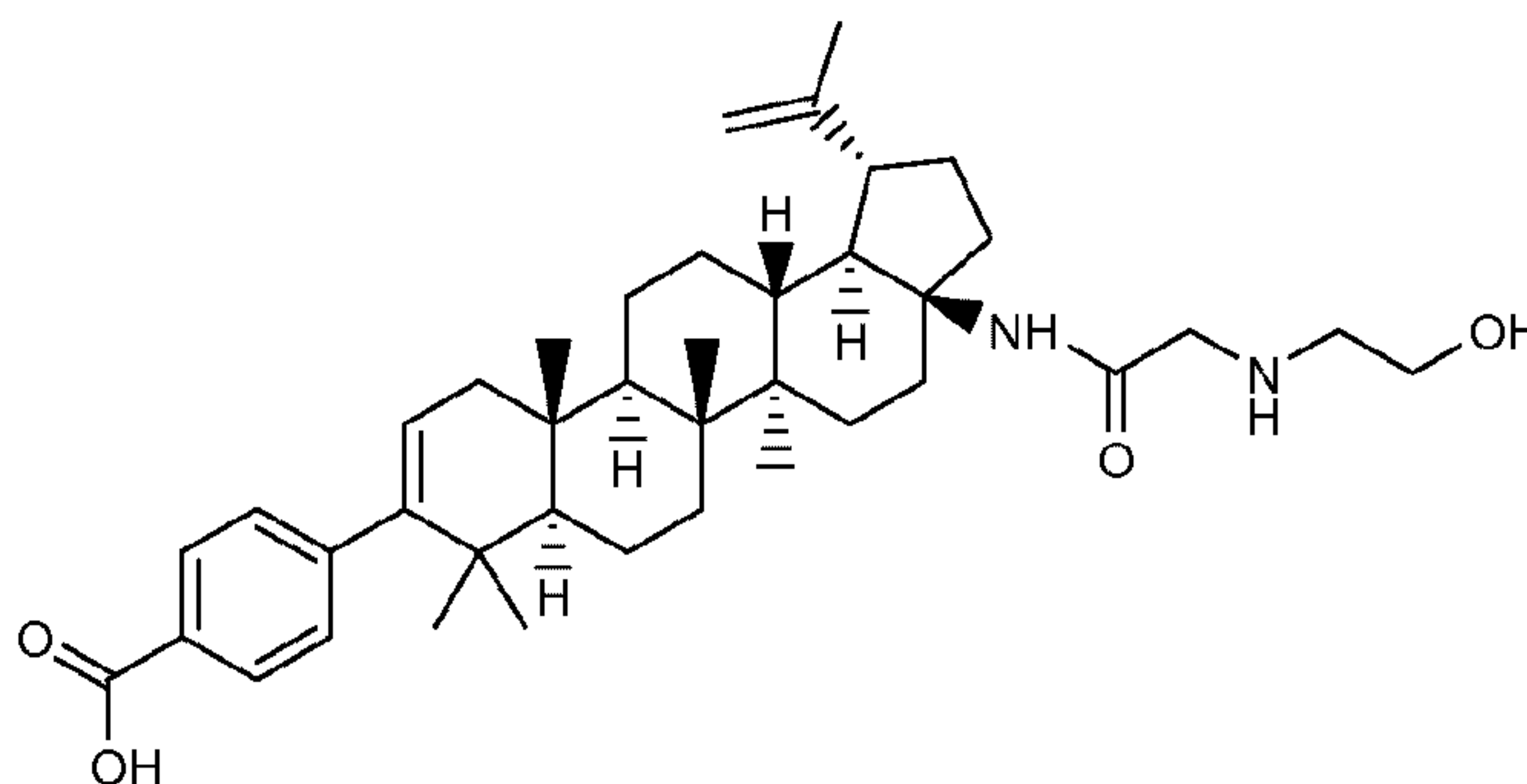


The title compound was prepared in 29% yield from methyl 4-  
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described 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 ( $M+H$ )<sup>+</sup>, 1.97 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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**

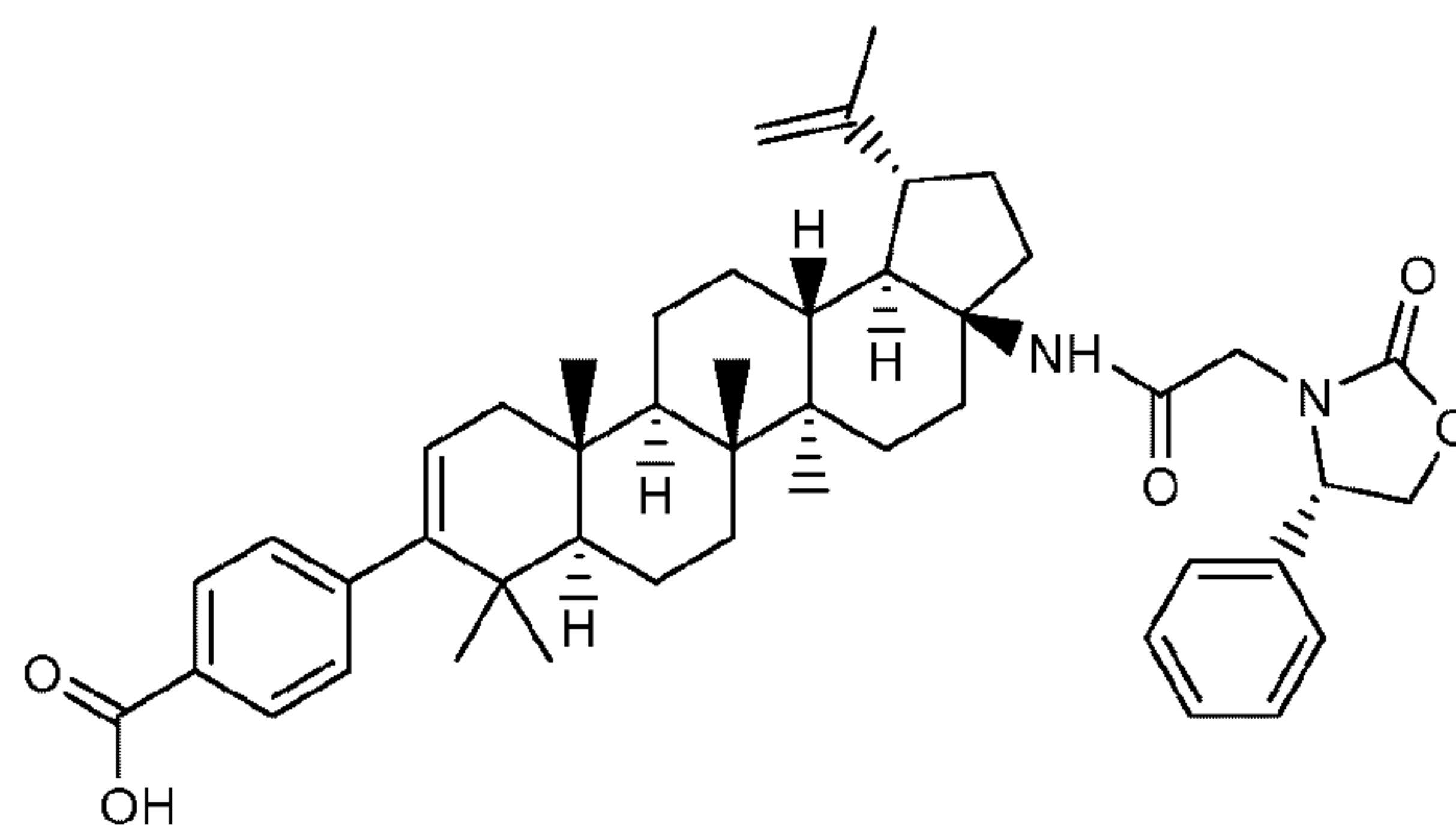
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylamino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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 ( $M+H$ )<sup>+</sup>, 1.94 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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.

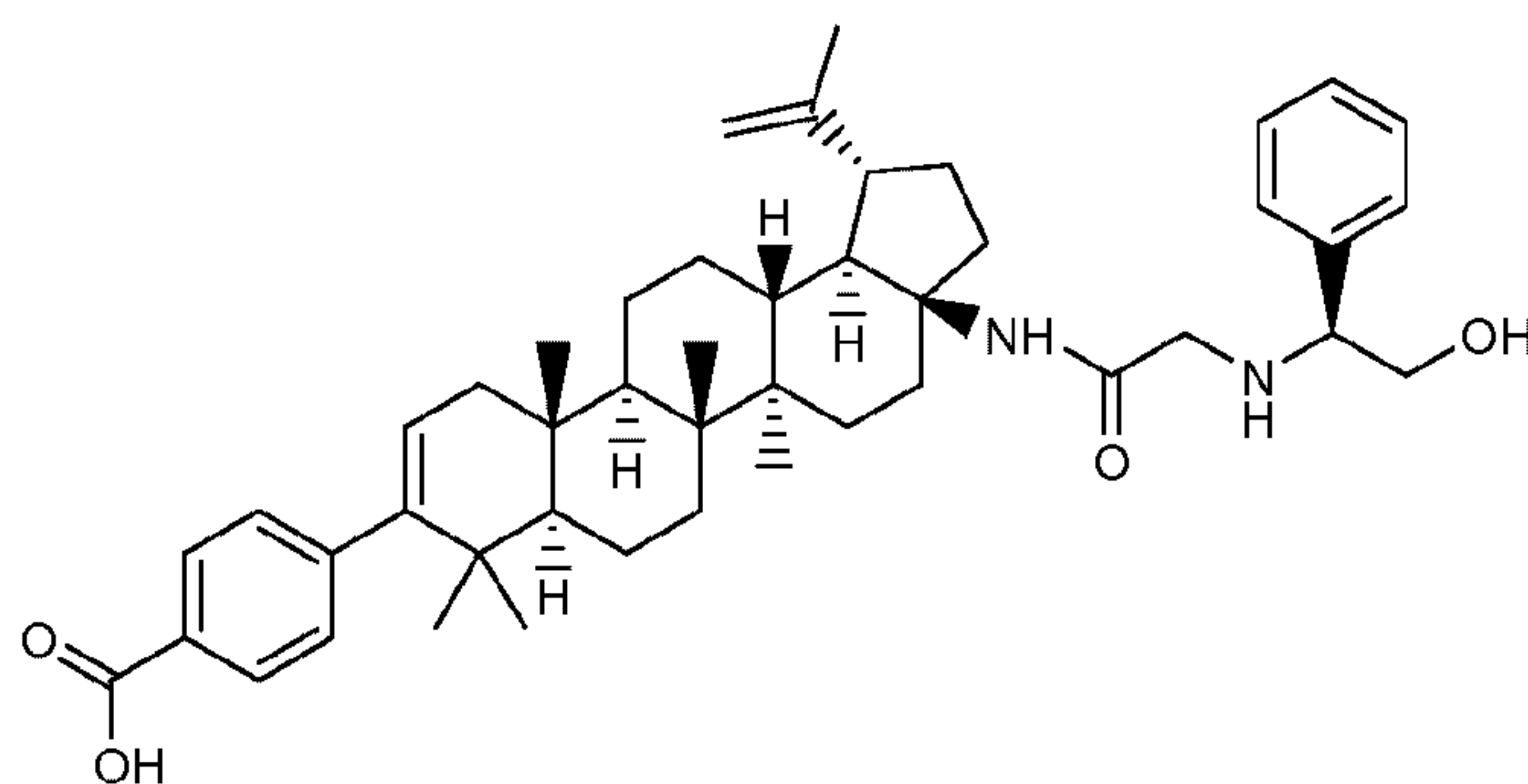


The title compound was prepared in 30% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 5 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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-  
 cyclopenta[a]chrysen-9-yl)benzoic acid, except (S)-(+)-2-oxo-4-phenyl-3-  
 10 oxazolidineacetic acid was used instead of 3-(dimethylamino)propionic acid  
 hydrochloride in Step 1. LCMS:  $m/e$  733.5 ( $M+H$ )<sup>+</sup>, 2.25 min (method 6). <sup>1</sup>H NMR  
 (400MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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 -  
 15 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).

20

### 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-  
 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.



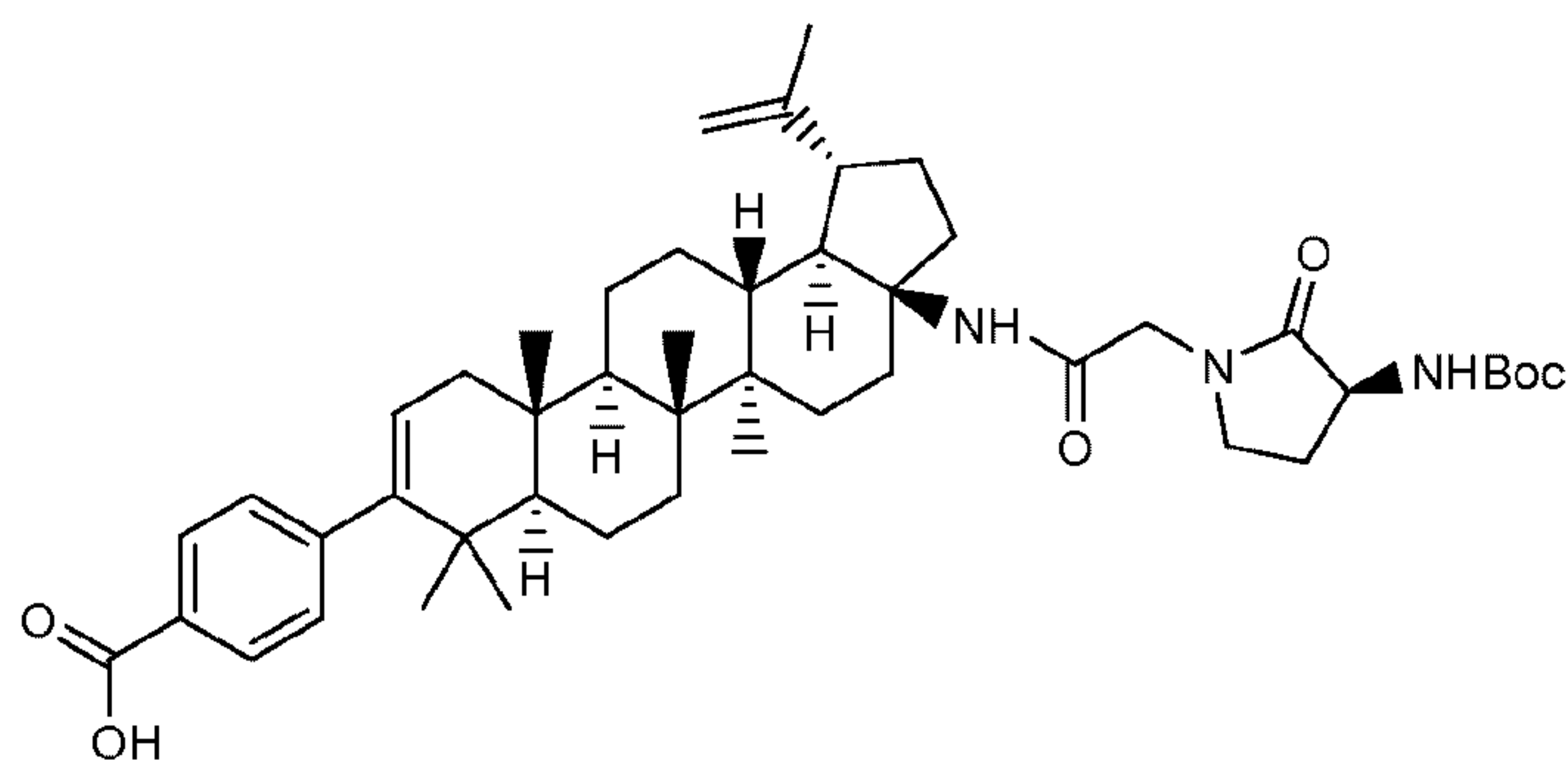
The title compound was prepared in 8% yield as a by-product during the above described preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-((S)-2-oxo-4-phenyloxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. LCMS:  $m/e$  707.5 ( $M+H$ )<sup>+</sup>, 2.18 min (method 6). <sup>1</sup>H NMR (400MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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

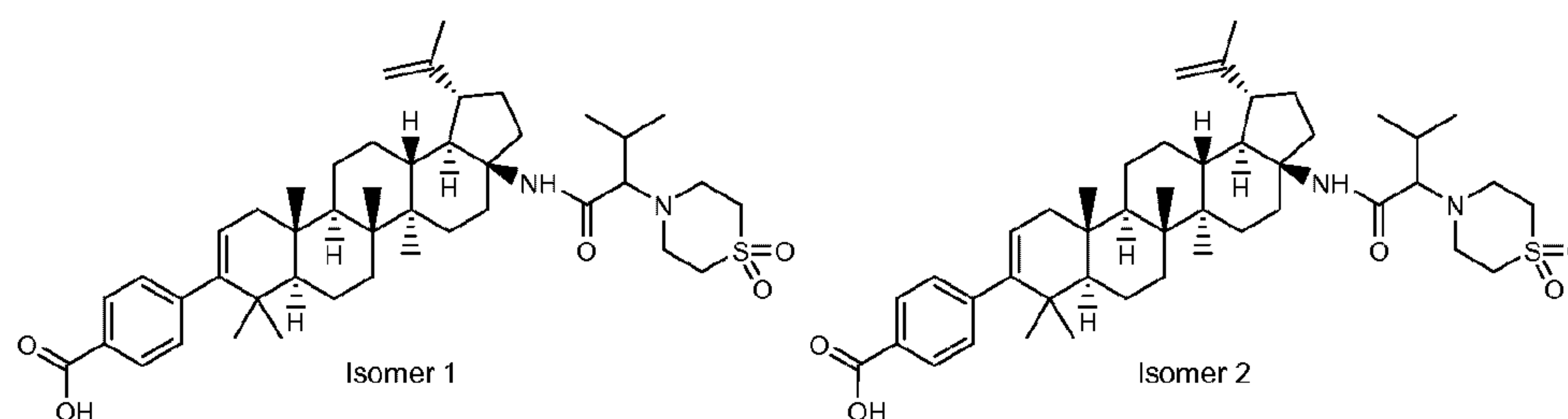


The title compound was prepared in 34% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 5 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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 (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 ( $M+H$ )<sup>+</sup>, 2.07 min (method 6). <sup>1</sup>H NMR  
 (400MHz, 1:1  $CDCl_3$ : $MeOD$ )  $\delta$  = 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 -  
 15 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]-  
 25 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 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.

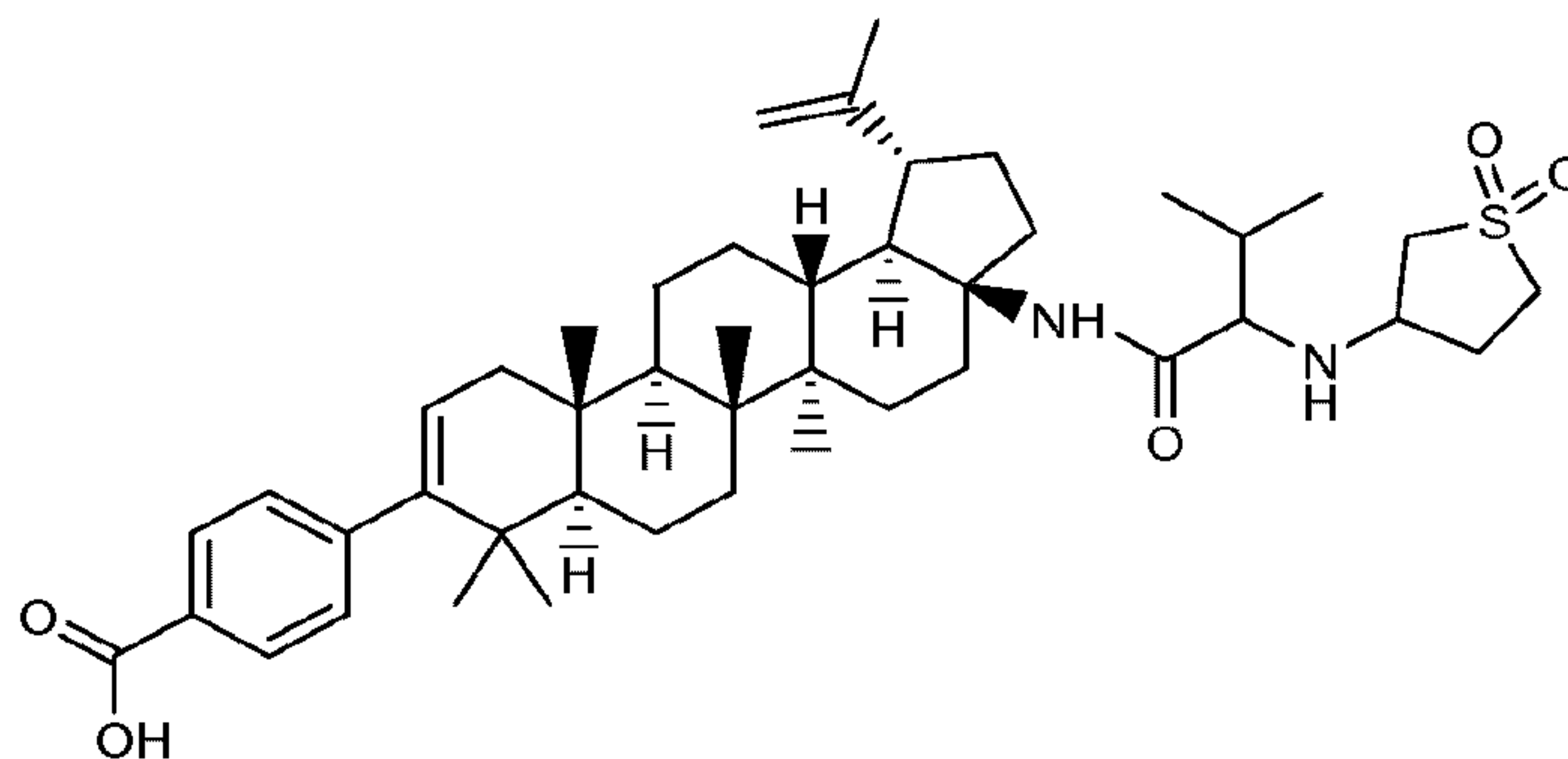
Isomer 1: LCMS:  $m/e$  747.5 ( $M+H$ )<sup>+</sup>, 2.23 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
 CDCl<sub>3</sub>:MeOD)  $\delta$  = 7.92 (d,  $J$  = 8.2 Hz, 2 H), 7.20 (d,  $J$  = 8.5 Hz, 2 H), 6.42 (s, 1 H),  
 5.29 (dd,  $J$  = 1.5, 6.1 Hz, 1 H), 4.75 (d,  $J$  = 1.5 Hz, 1 H), 4.64 (br. 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 ( $M+H$ )<sup>+</sup>, 2.29 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1  
 CDCl<sub>3</sub>:MeOD)  $\delta$  = 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

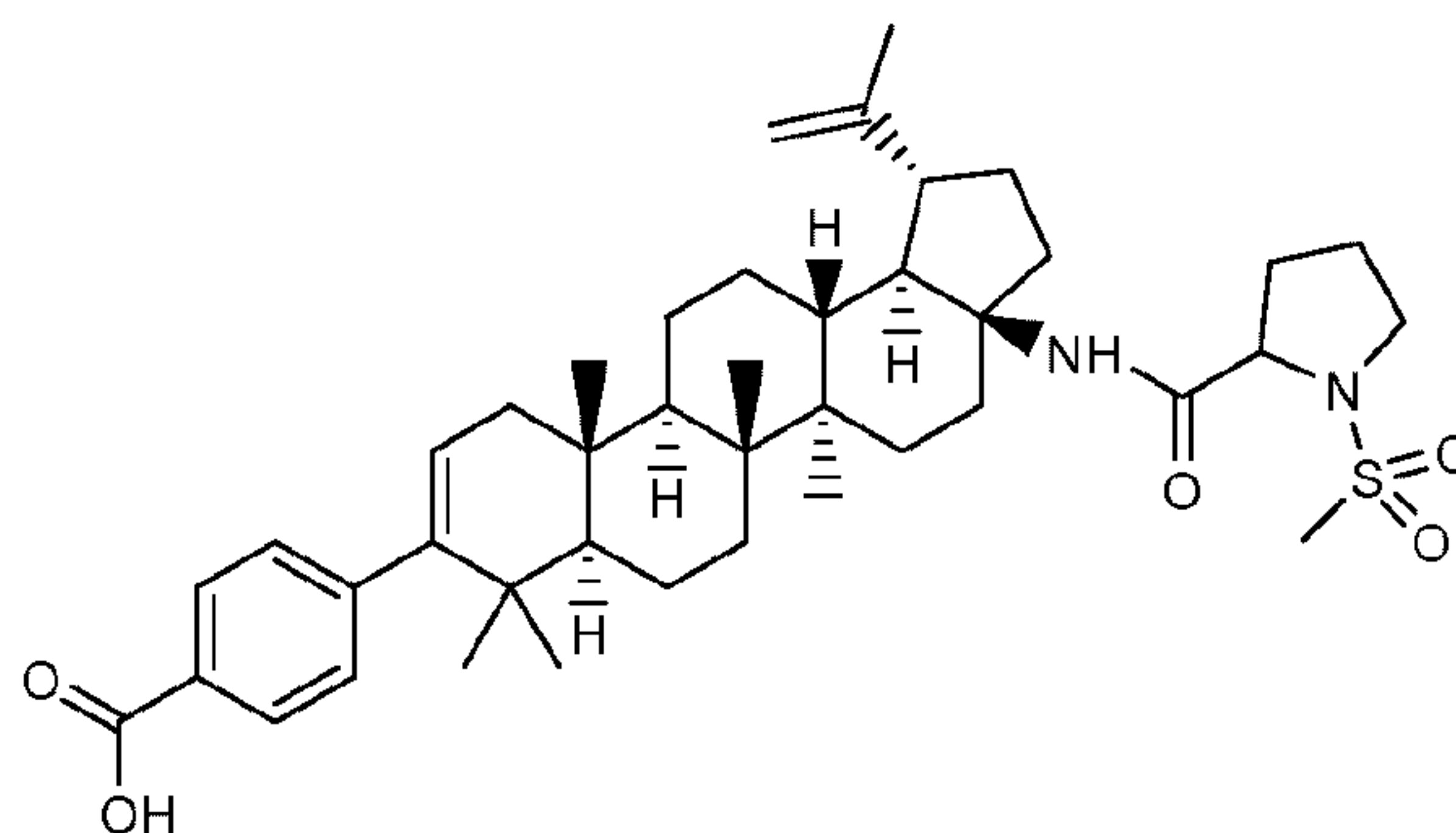
The title compound was prepared in 30% yield from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure  
 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-1λ<sup>6</sup>-  
 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 ( $M+H$ )<sup>+</sup>,  
 2.09 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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.



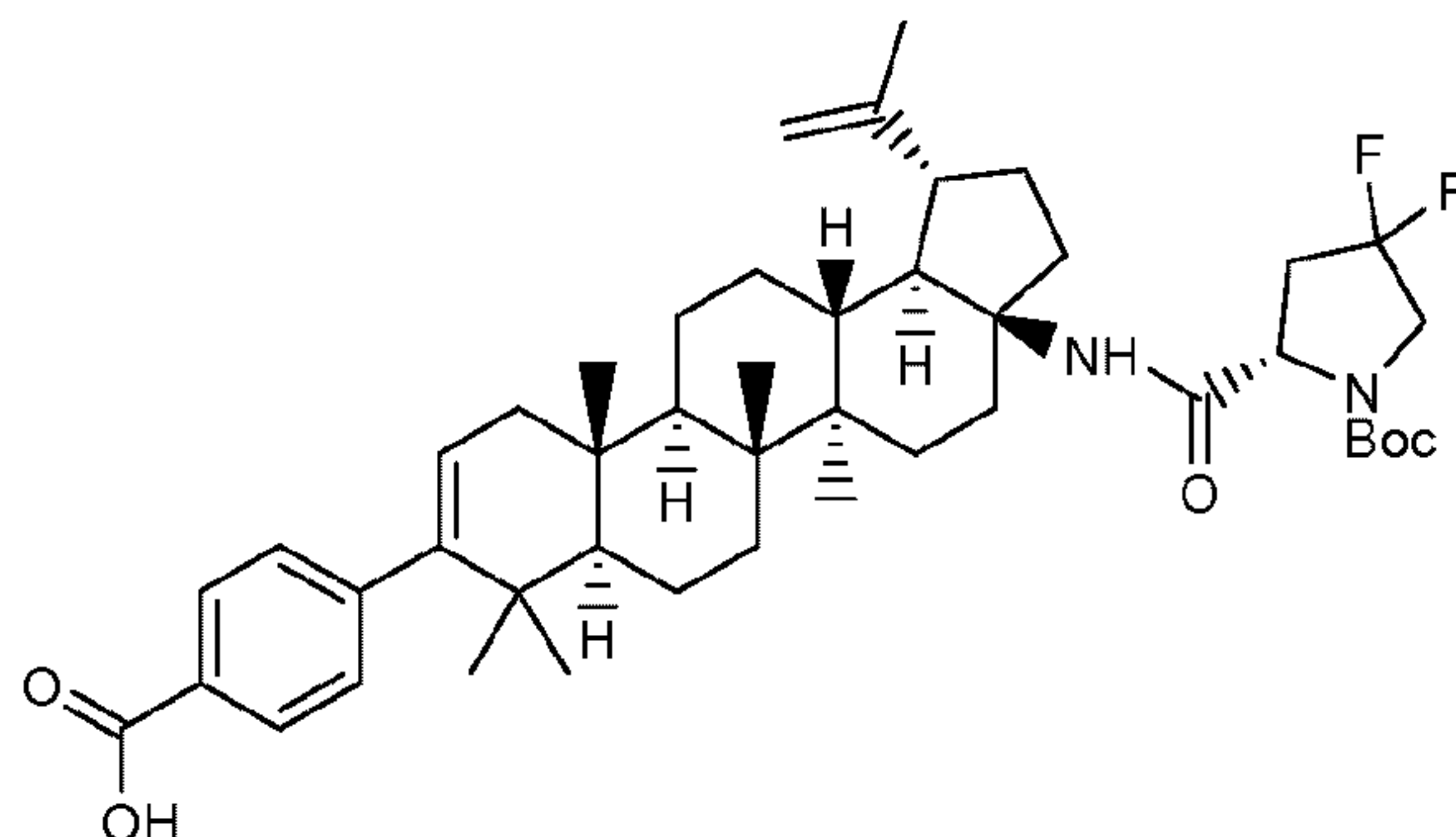
The title compound was prepared in 17% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for 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 ( $M+H$ )<sup>+</sup>, 2.04 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1

$CDCl_3:MeOD$ )  $\delta$  = 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.



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 ( $M+H$ )<sup>+</sup>,

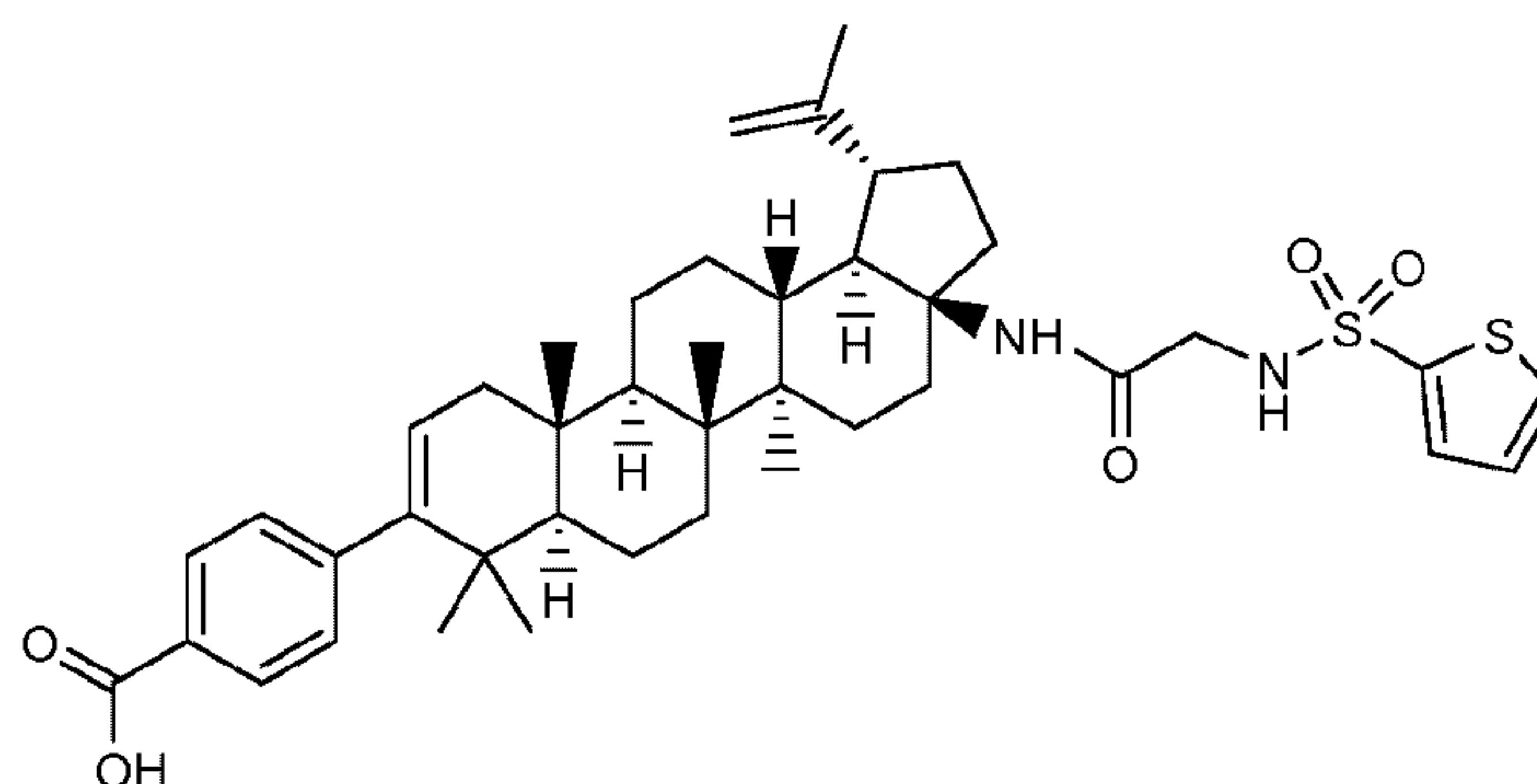
2.55 min (method 6).  $^1\text{H}$  NMR (500MHz, 1:1  $\text{CDCl}_3:\text{MeOD}$ )  $\delta$  = 7.92 (d,  $J$  = 8.5 Hz, 2 H), 7.20 (d,  $J$  = 8.5 Hz, 2 H), 6.46 (br. s., 1 H), 5.29 (dd,  $J$  = 1.7, 6.3 Hz, 1 H), 4.72 (s, 1 H), 4.63 (br. s., 1 H), 4.50 (d,  $J$  = 9.2 Hz, 1 H), 3.84 (br. s., 1 H), 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).

10

**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).  $^1\text{H}$  NMR (500MHz, 1:1

25

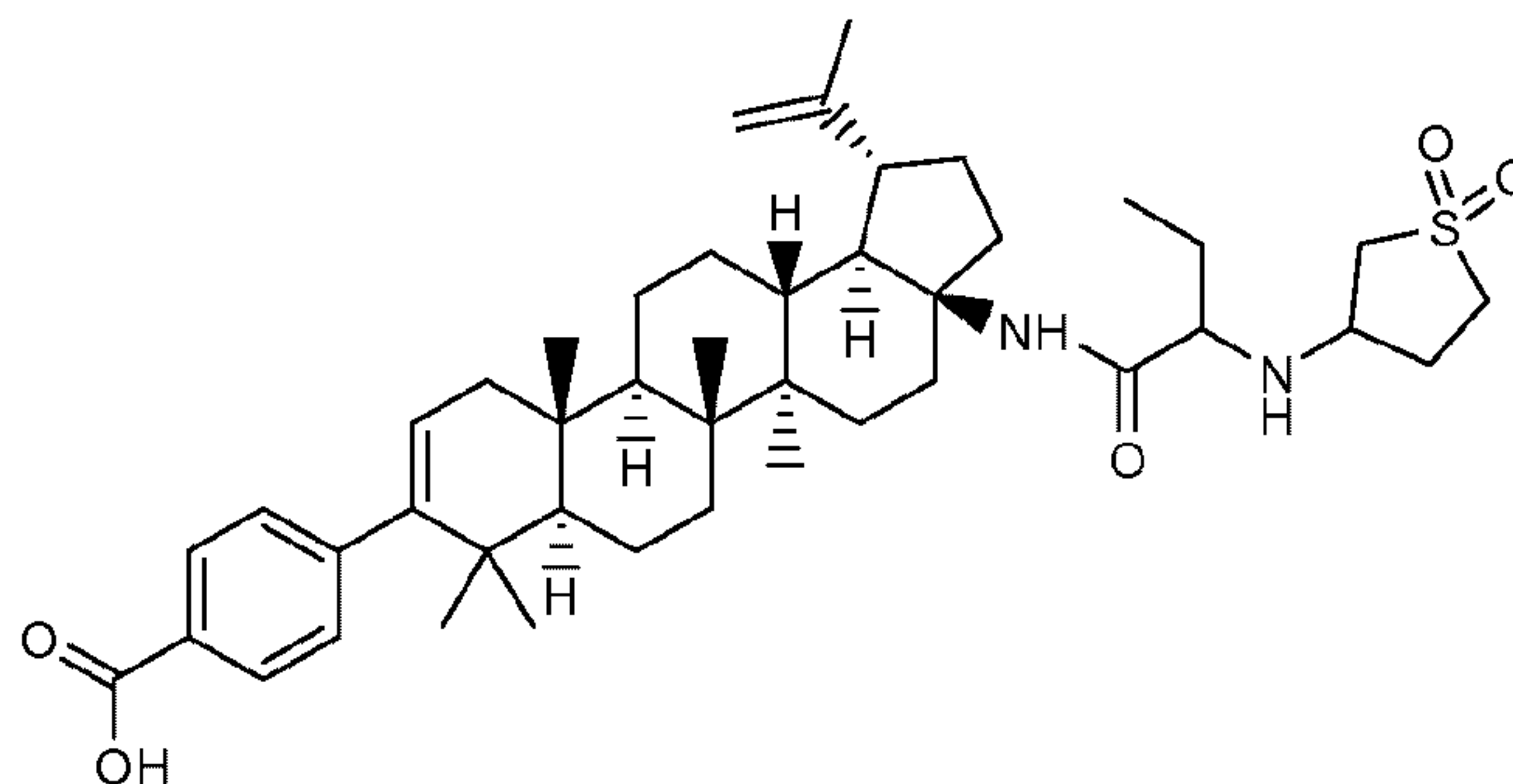
$CDCl_3:MeOD$ )  $\delta$  = 7.92 (d,  $J$  = 8.5 Hz, 2 H), 7.73 (dd,  $J$  = 1.4, 5.0 Hz, 1 H), 7.66 (dd,  $J$  = 1.2, 3.7 Hz, 1 H), 7.20 (d,  $J$  = 8.2 Hz, 2 H), 7.16 (dd,  $J$  = 3.8, 5.0 Hz, 1 H), 6.88 (s, 1 H), 5.32 - 5.26 (m, 1 H), 4.78 (d,  $J$  = 1.5 Hz, 1 H), 3.58 - 3.45 (m, 2 H), 2.63 - 2.57 (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 $\lambda$ 6-thiophene-3-yl-amino)-butyric acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS:  $m/e$  733.6 ( $M+H$ )<sup>+</sup>, 2.00 min (method 6). <sup>1</sup>H

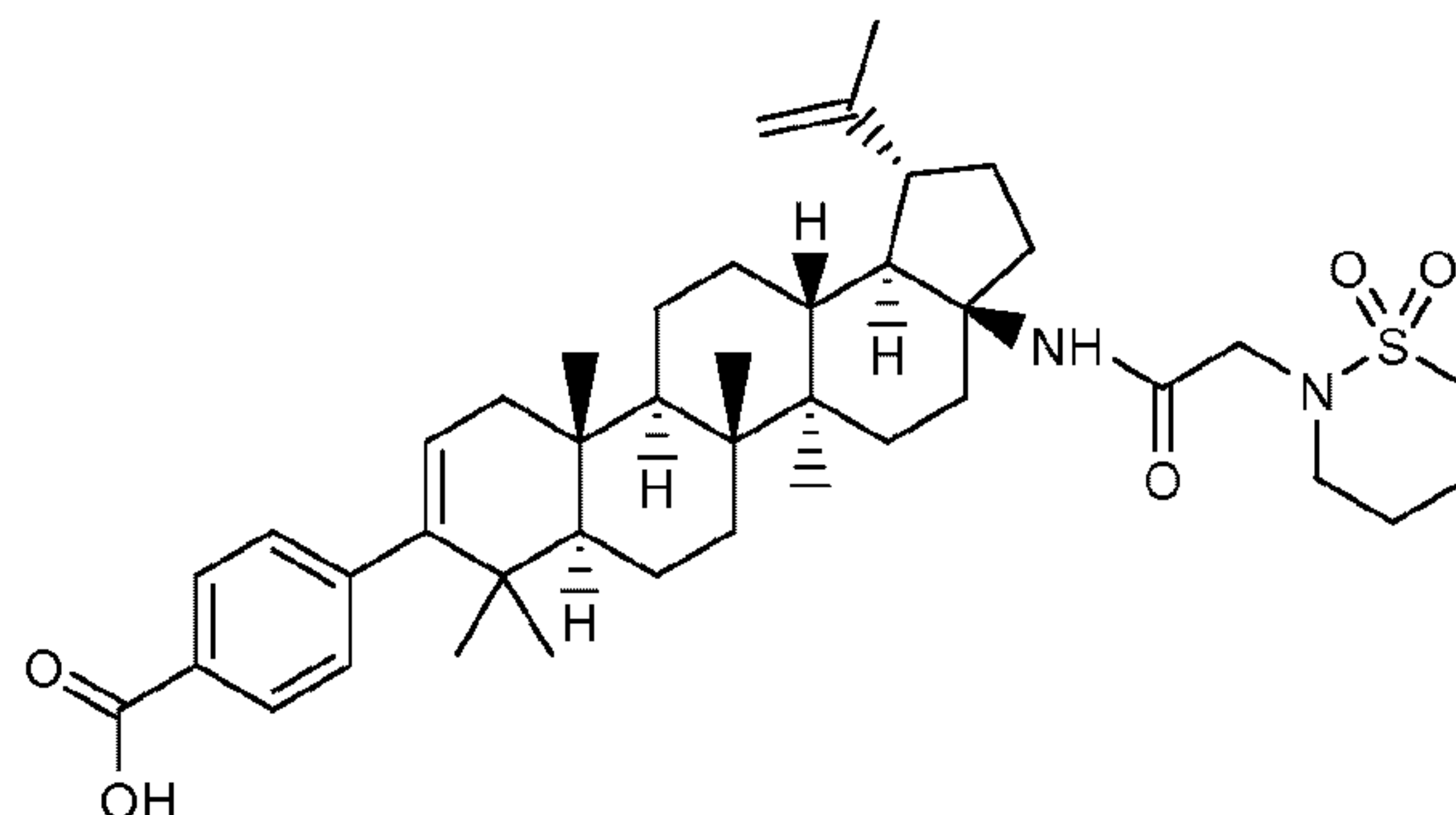
25

NMR (500MHz, 1:1  $CDCl_3$ : $MeOD$ )  $\delta$  = 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),  
 5 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  
 25 Step 1. LCMS:  $m/e$  705.5 ( $M+H$ )<sup>+</sup>, 2.01 min (method 6). <sup>1</sup>H NMR (500MHz,

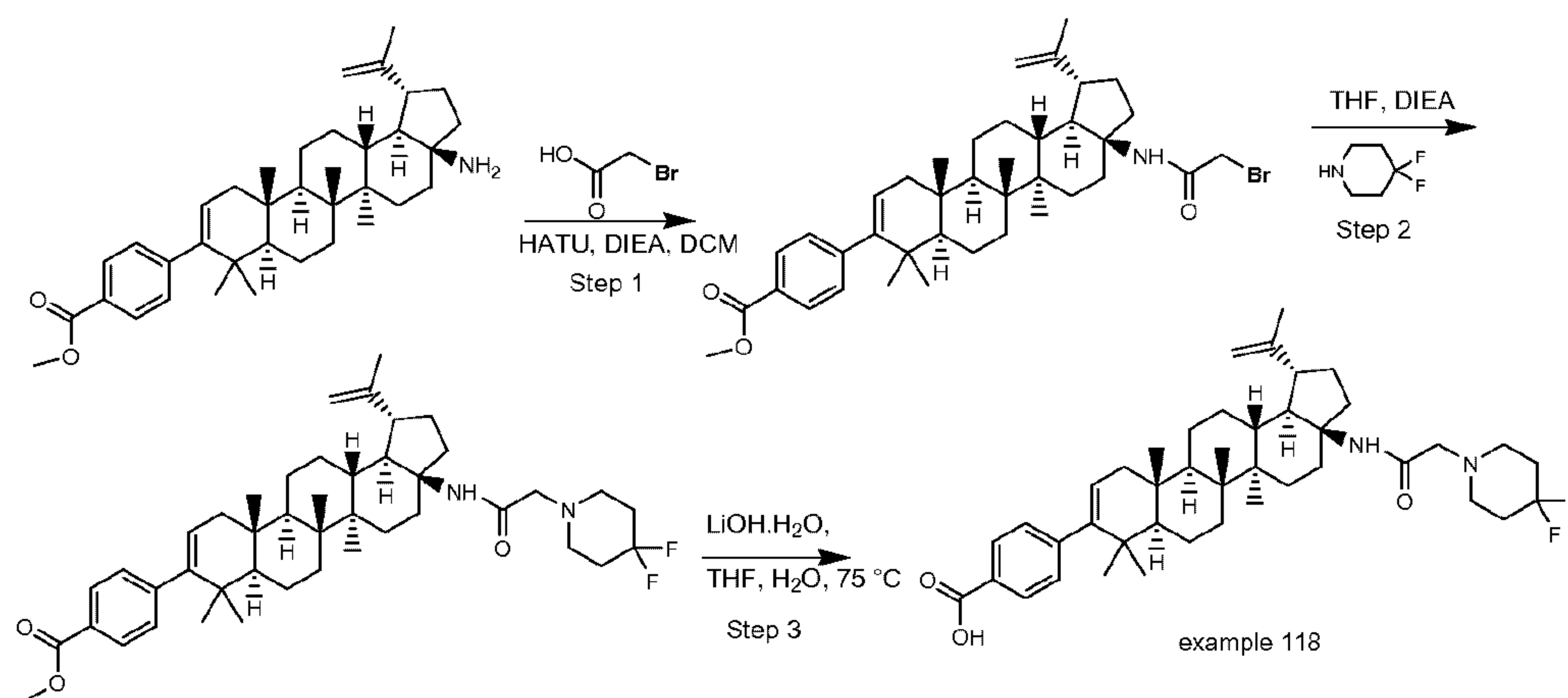
*METHANOL-d<sub>4</sub>*)  $\delta$  = 7.92 (d,  $J$  = 8.5 Hz, 2 H), 7.20 (d,  $J$  = 8.5 Hz, 2 H), 6.83 (s, 1 H), 5.32 - 5.26 (m, 1 H), 4.77 (d,  $J$  = 1.5 Hz, 1 H), 4.64 (s, 1 H), 3.83 - 3.72 (m, 2 H), 3.63 - 3.46 (m, 2 H), 3.37 (s, 2 H), 3.21 - 3.11 (m, 2 H), 2.62 - 2.54 (m, 1 H), 2.53 - 2.50 (m, 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

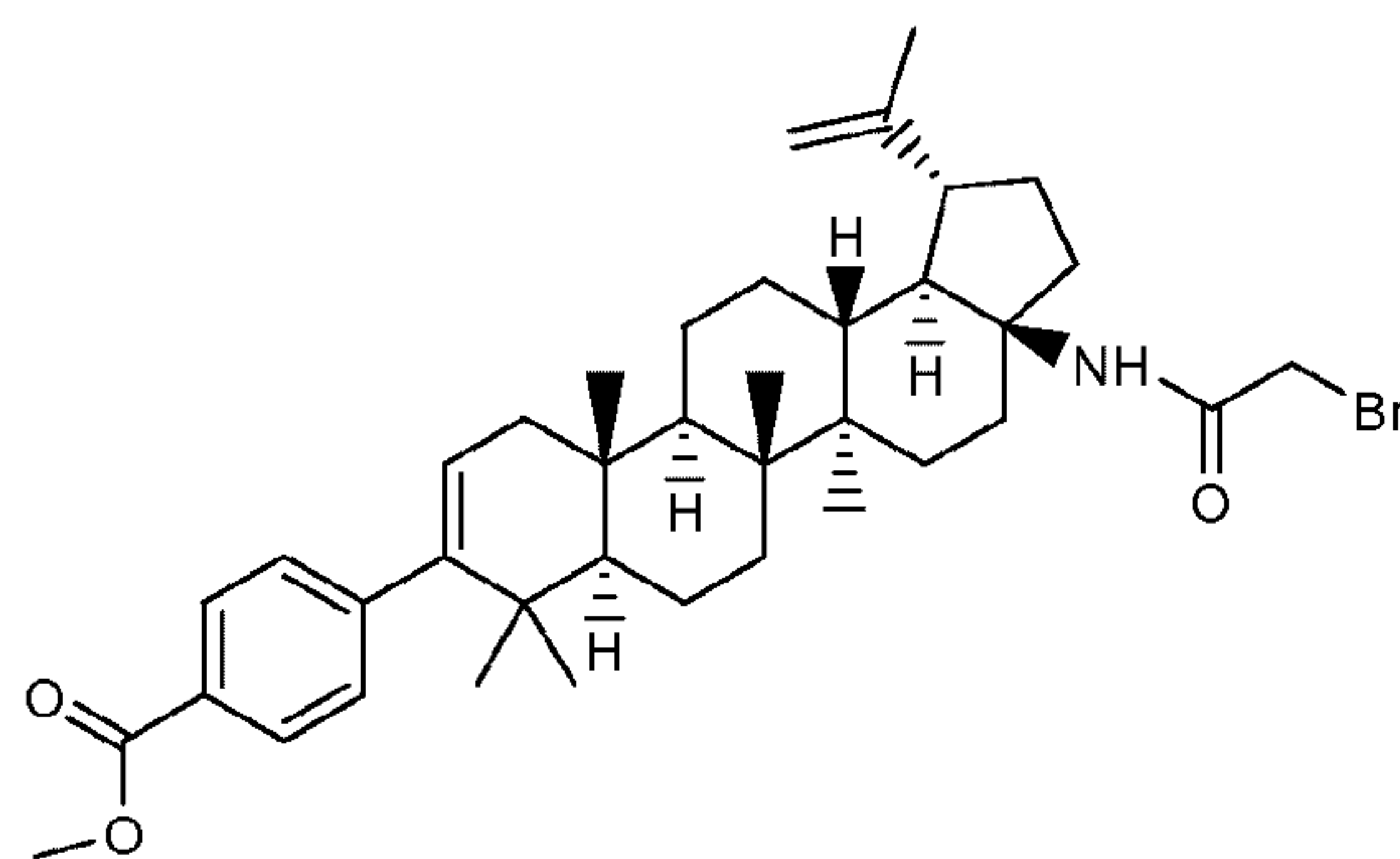
**Example 118**

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.

15

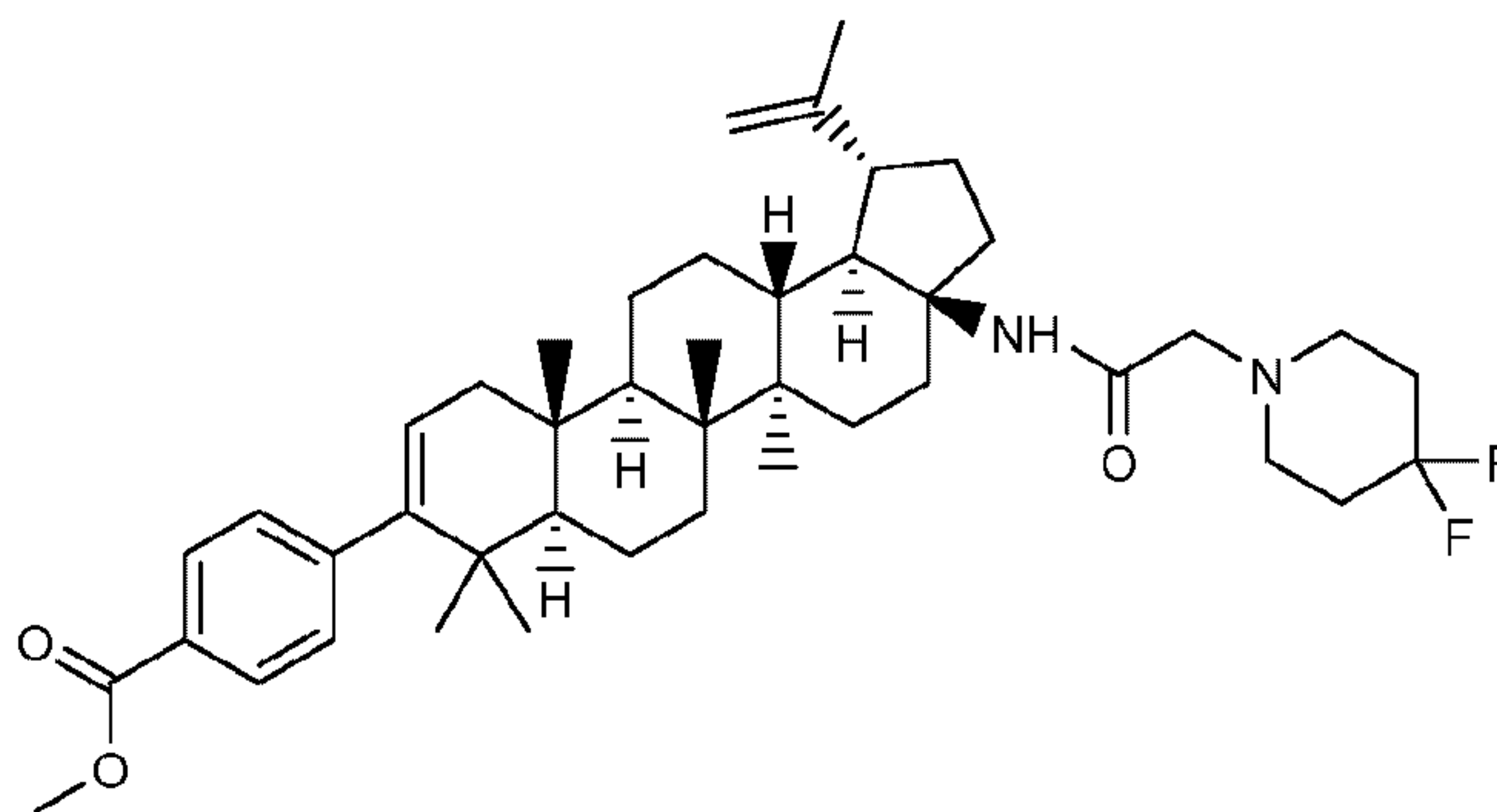


20 Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



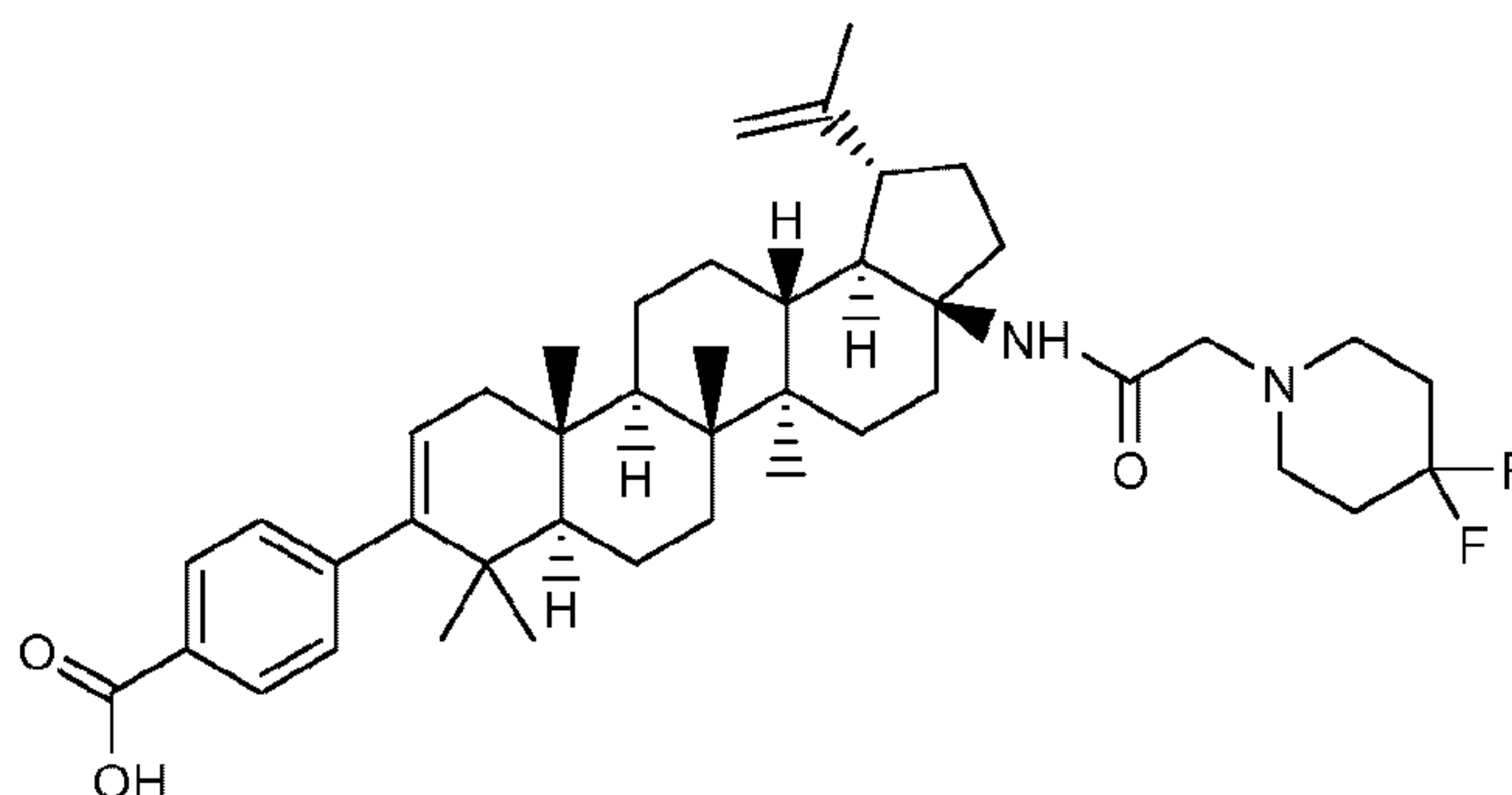
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (403 mg, 0.694 mmol) in DCM (10 mL) was added *N,N*-diisopropylethylamine (0.484 mL, 2.78 mmol), bromoacetic acid (106 mg, 0.764 mmol) and 2-(3H-[1,2,3]triazolo[4,5- $\beta$ ]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)<sup>+</sup>, 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-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-  
 15 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 ( $M+H$ )<sup>+</sup>, 2.95 min (method 6). <sup>1</sup>H NMR (500MHz, *CHLOROFORM-d*)  $\delta$  = 7.94 (d,  $J$  = 8.5 Hz, 2 H), 7.90 - 7.80 (m, 1 H), 7.21 (d,  $J$  =  
 20 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  
 25 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).

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

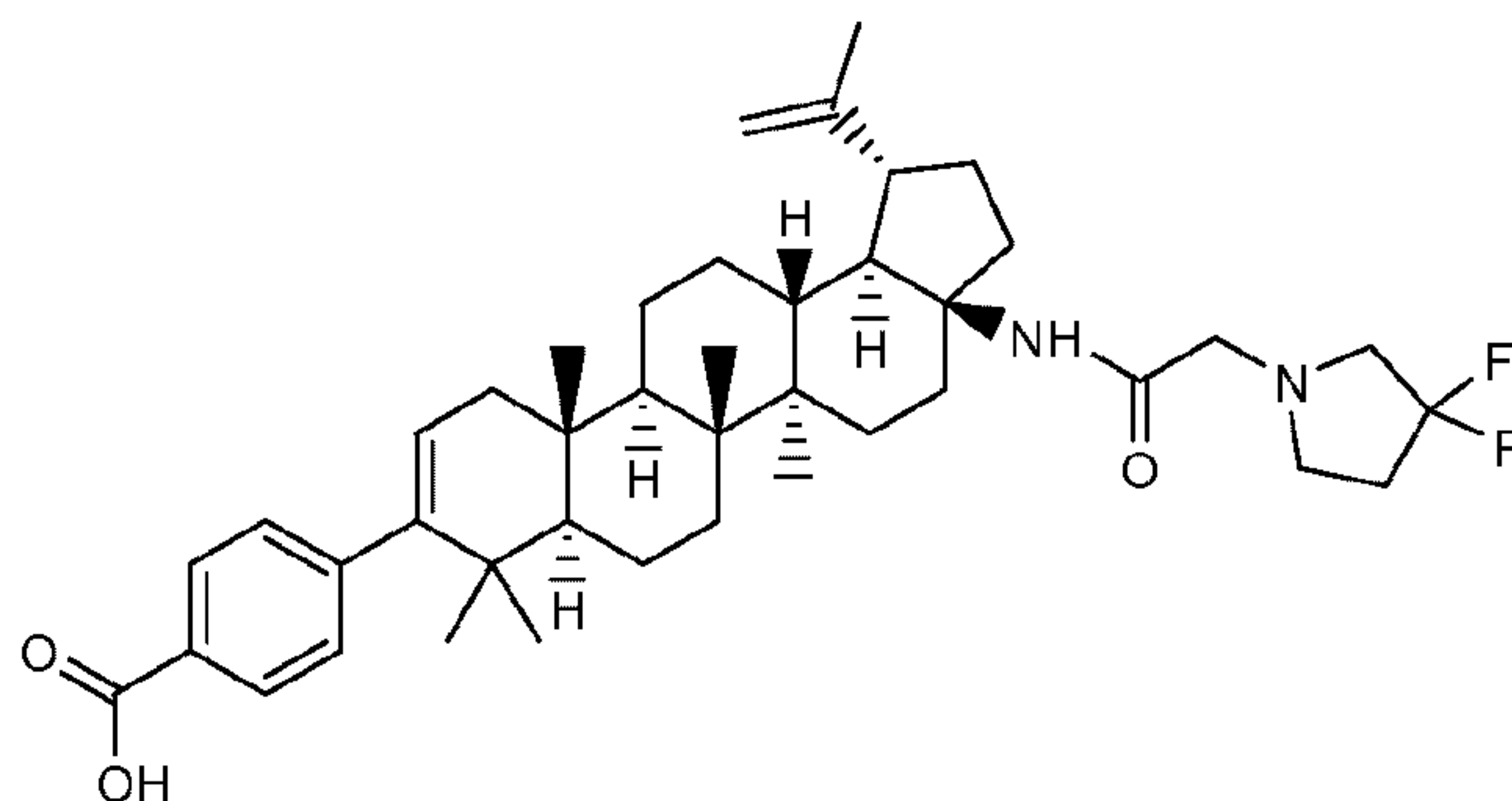
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (13.1 mg, 0.019 mmol) in THF (3 mL) was added a 0.753 molar aqueous solution of LiOH · H<sub>2</sub>O (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)<sup>+</sup>, 2.34 min (method 6). <sup>1</sup>H NMR (500MHz, *METHANOL-d*<sub>4</sub>) 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

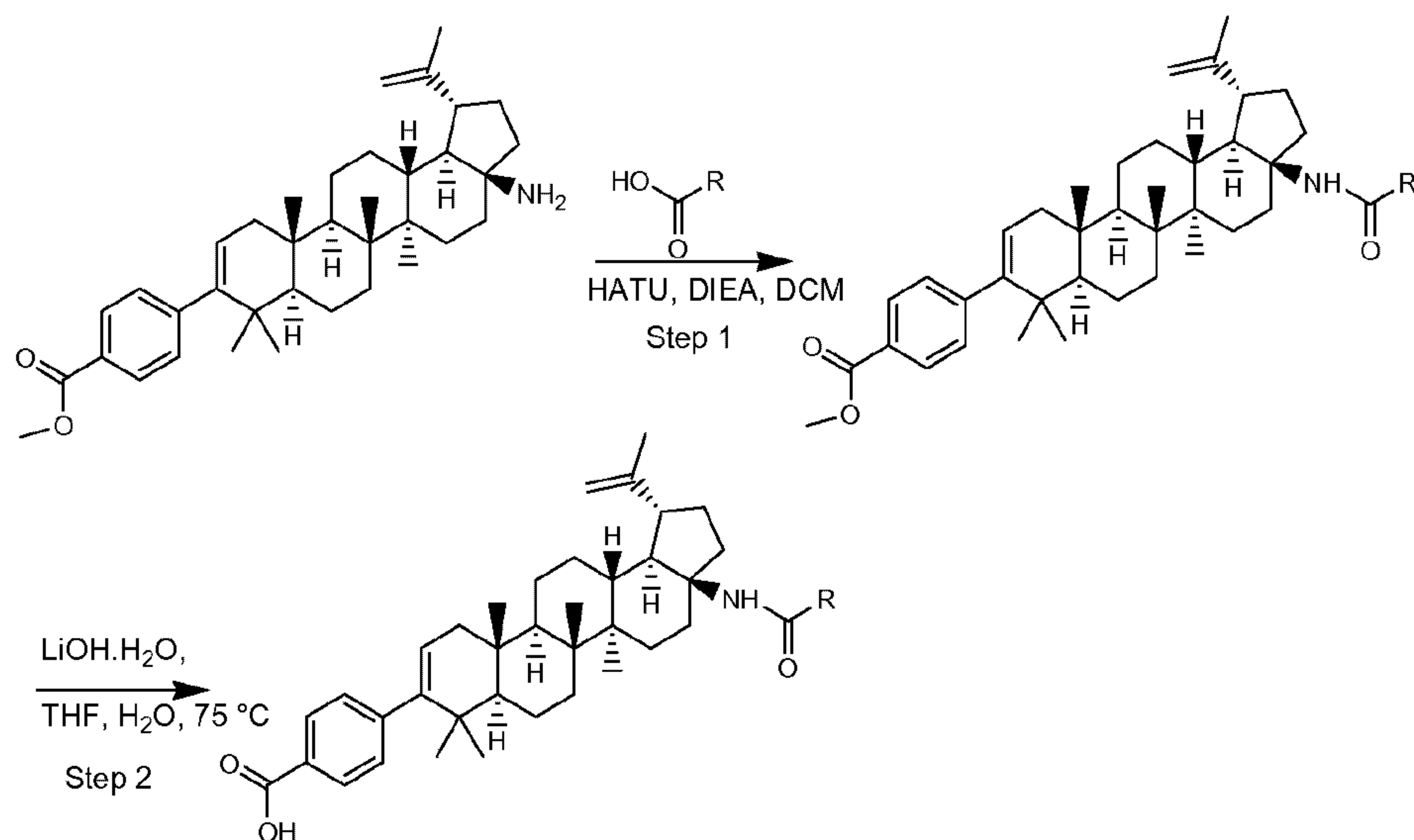
## Example 119

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-en-2-yl)-2,3,3a,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  
 15 was used instead of 4,4-difluoropiperidine, HCl in Step 2. LCMS:  $m/e$  677.5 ( $M+H$ )<sup>+</sup>, 2.26 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeO D*)  $\delta$  = 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), 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  
 20 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

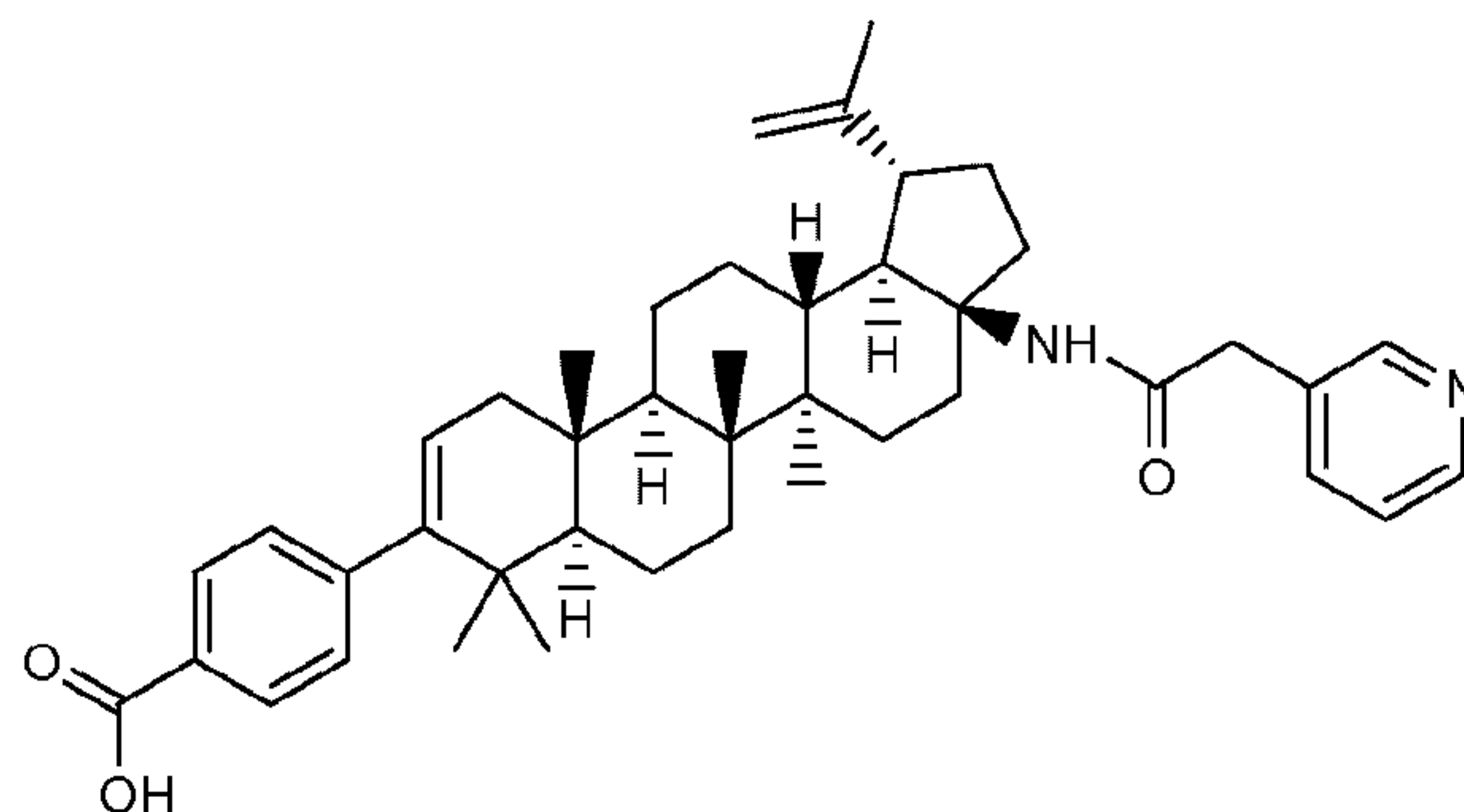
General procedure for parallel synthesis of C-17 amides:



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**

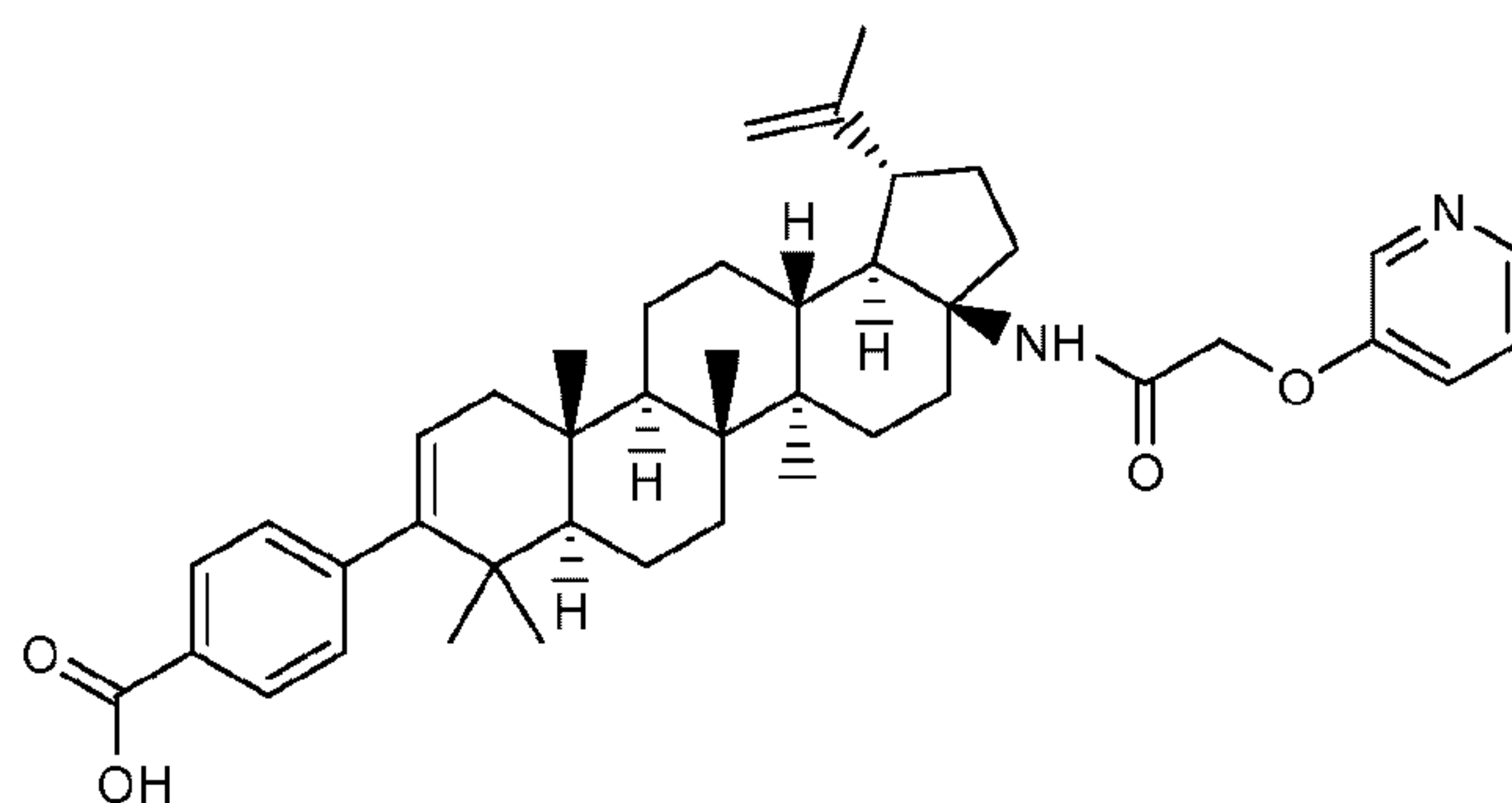
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-  
 pentamethyl-1-(1-methylethenyl)-3a-[(3-pyridinylacetyl)amino]-1H-  
 cyclopenta[a]chrysen-9-yl].



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)<sup>+</sup>, 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.

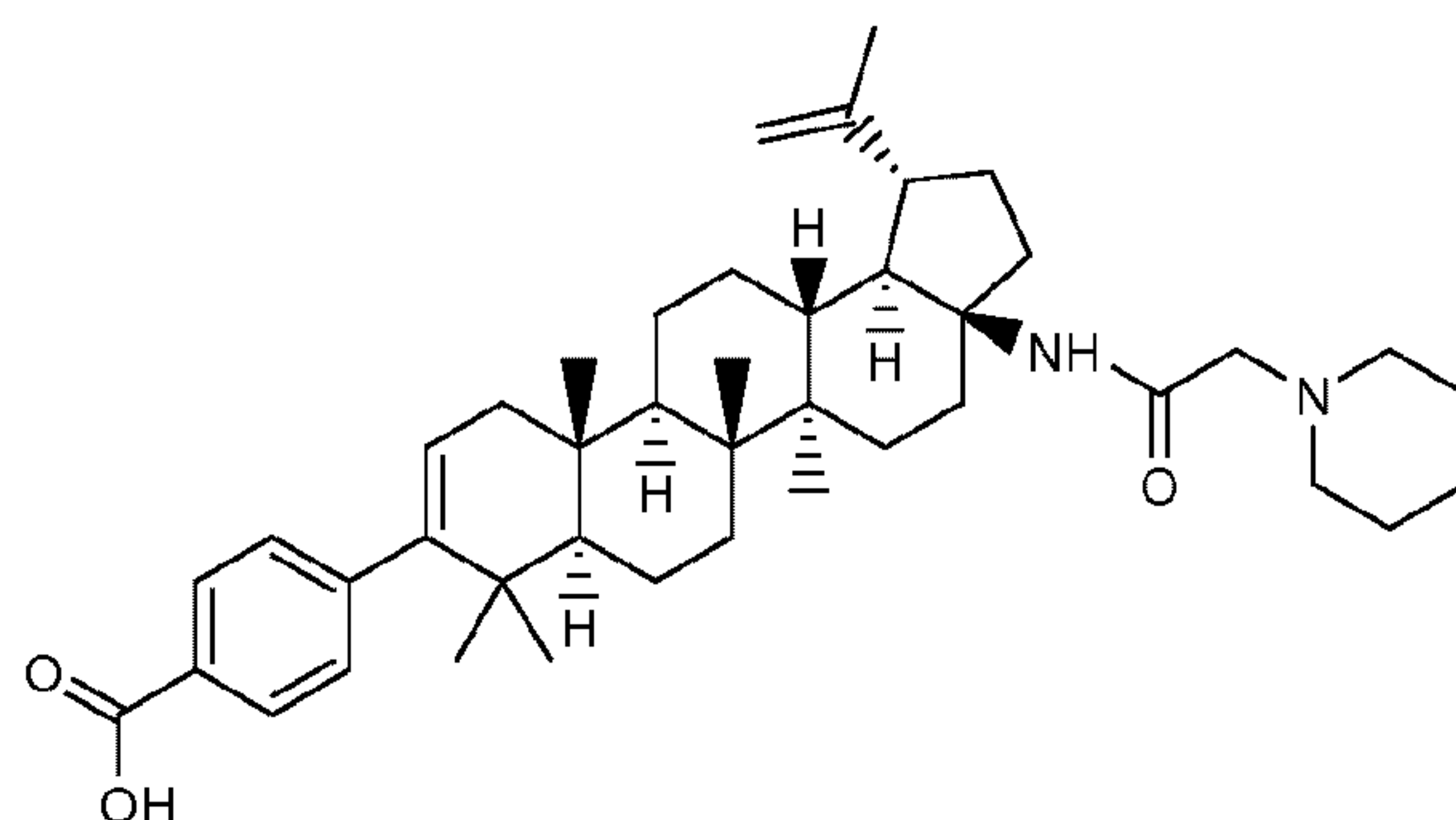


The title compound was prepared from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general  
 procedure described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



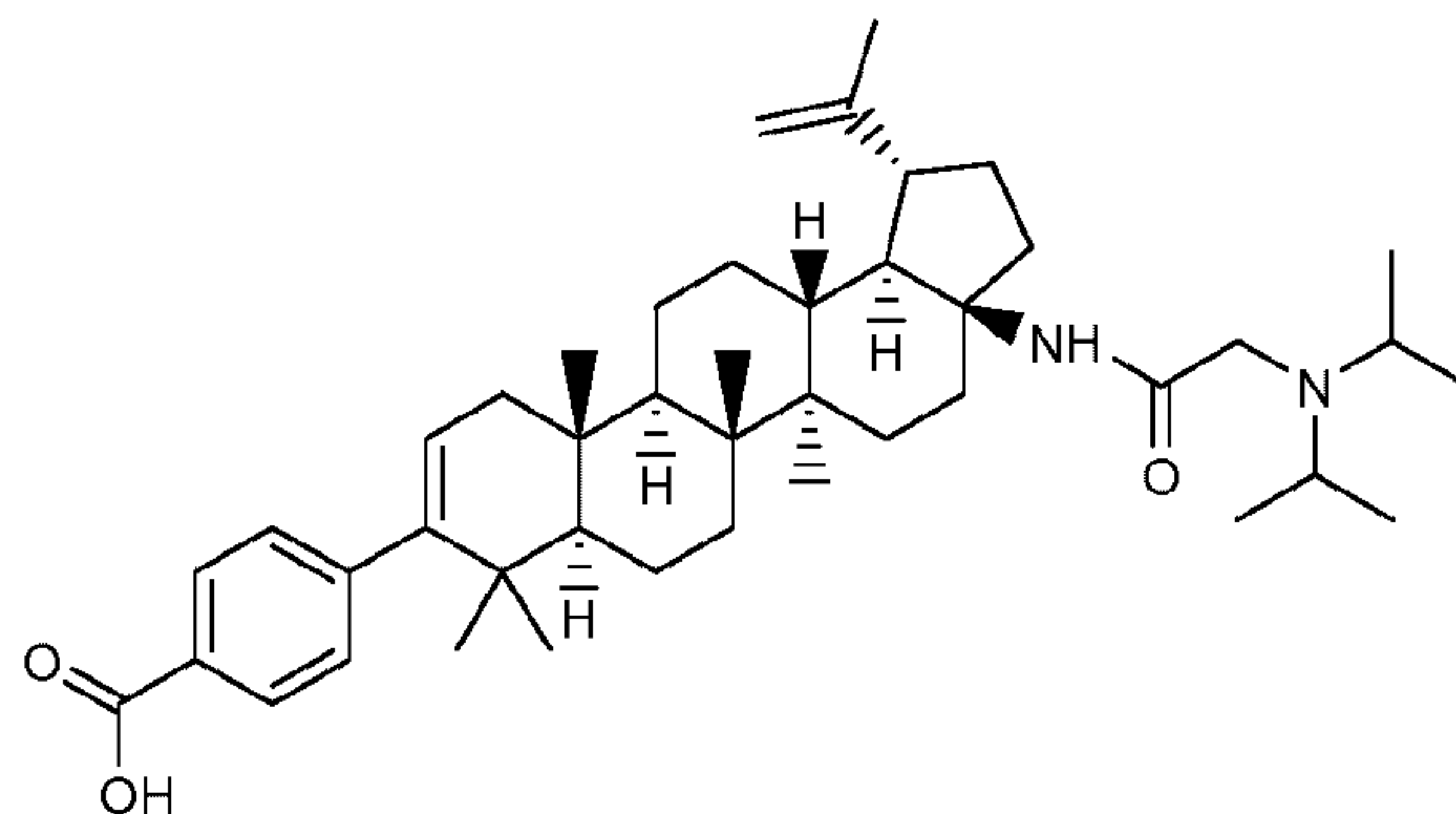
The title compound was prepared from methyl 4-  
 20 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

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)<sup>+</sup>, 4.68 min (method 3).

5

### Example 123

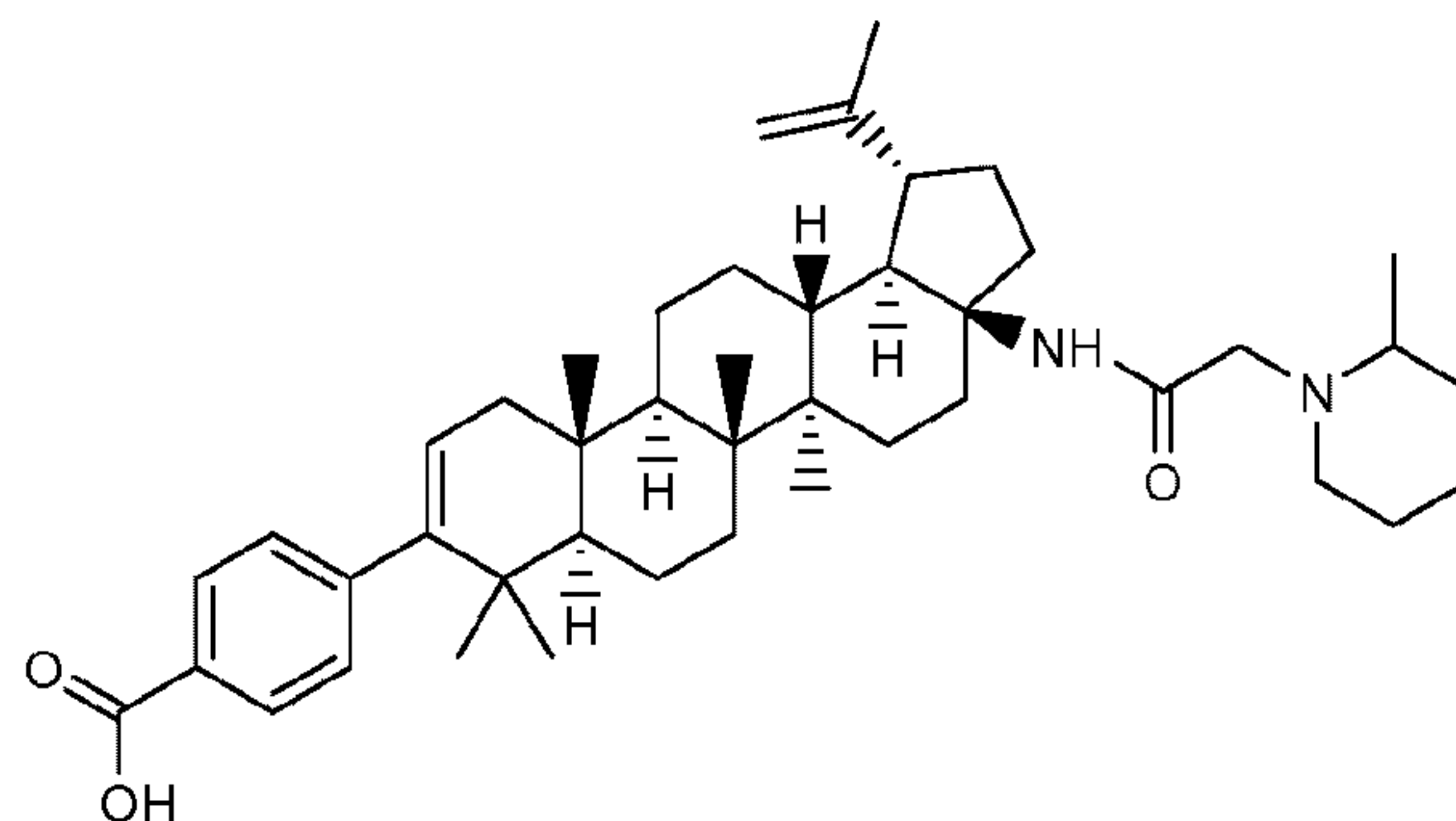
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(diisopropylamino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
10 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared 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 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)<sup>+</sup>, 4.99 min (method 3). <sup>1</sup>H NMR (599MHz, <DMSO-CDCl<sub>3</sub>>)  $\delta$  = 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  
20 (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).

**Example 124**

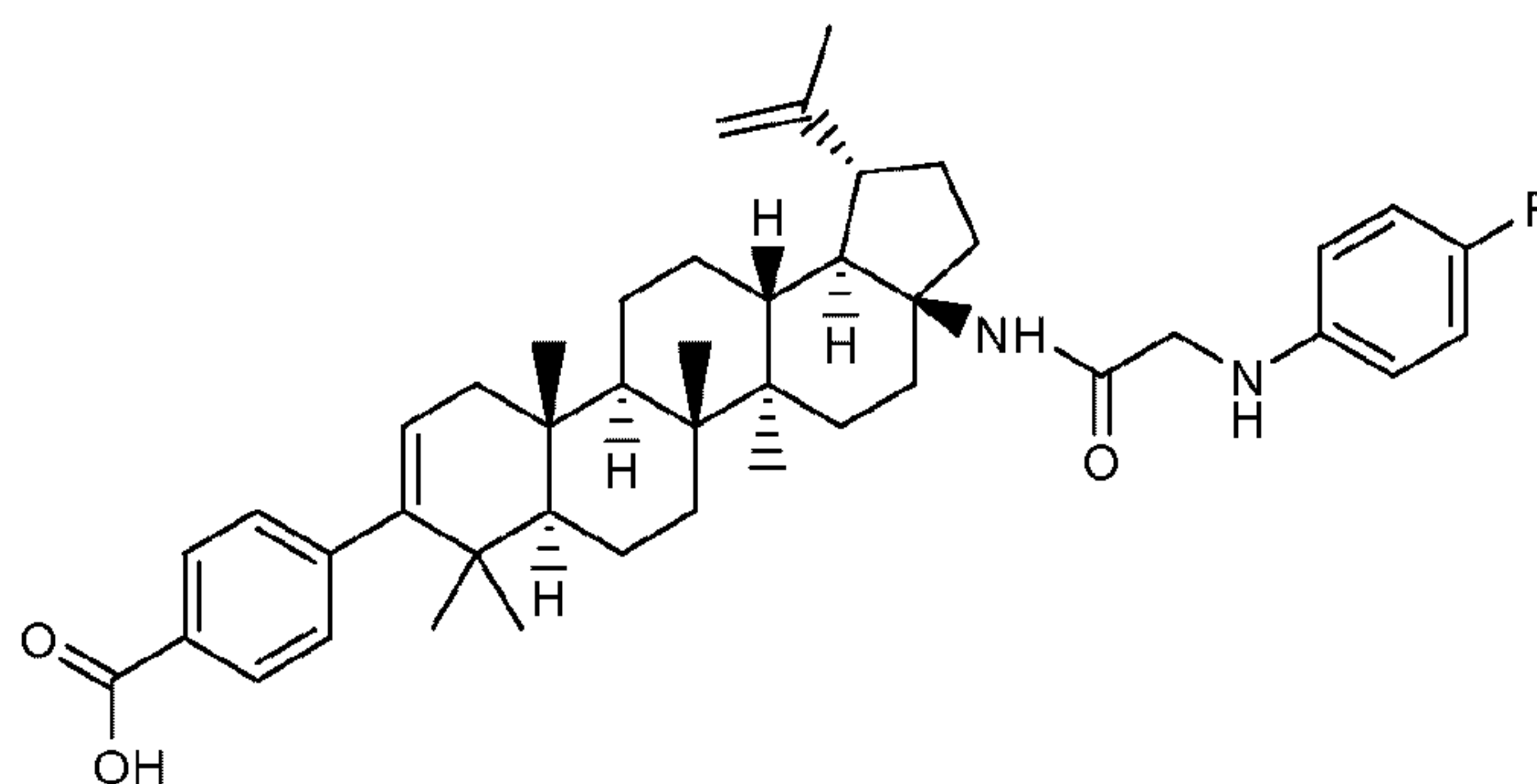
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-  
 5 pentamethyl-3a-(2-(2-methylpiperidin-1-yl)acetamido)-1-(prop-1-en-2-yl)-  
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 cyclopenta[a]chrysen-9-yl)benzoic acid



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 (2-  
 15 methylpiperidin-1-yl)acetic acid as the reacting carboxylic acid. LCMS: m/e 669.7  
 (M+H)<sup>+</sup>, 4.73 min (method 3).

**Example 125**

20 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.

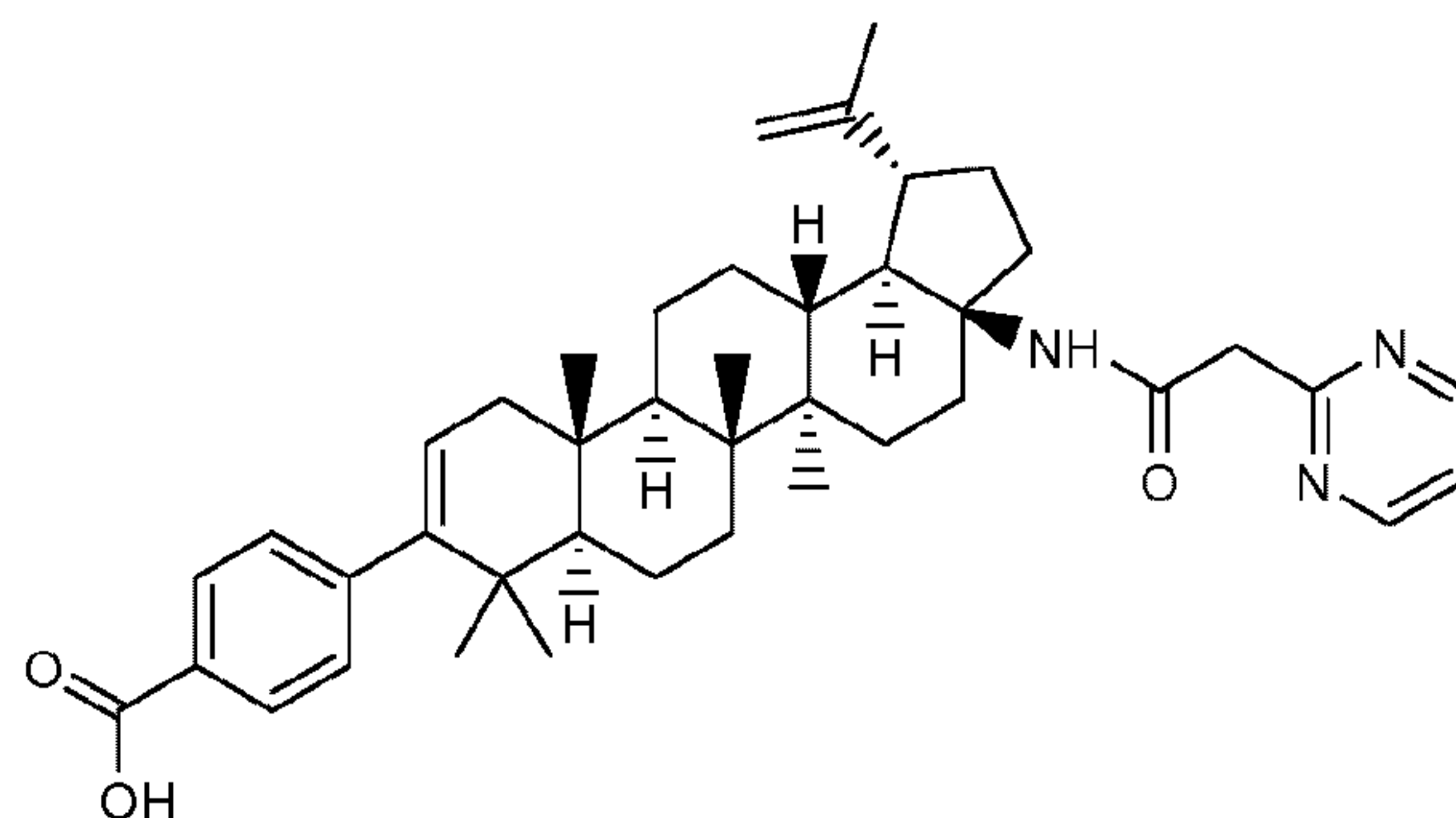


The title compound was prepared from methyl 4-  
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 5 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-  
 octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general  
 procedure described 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)<sup>+</sup>, 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.

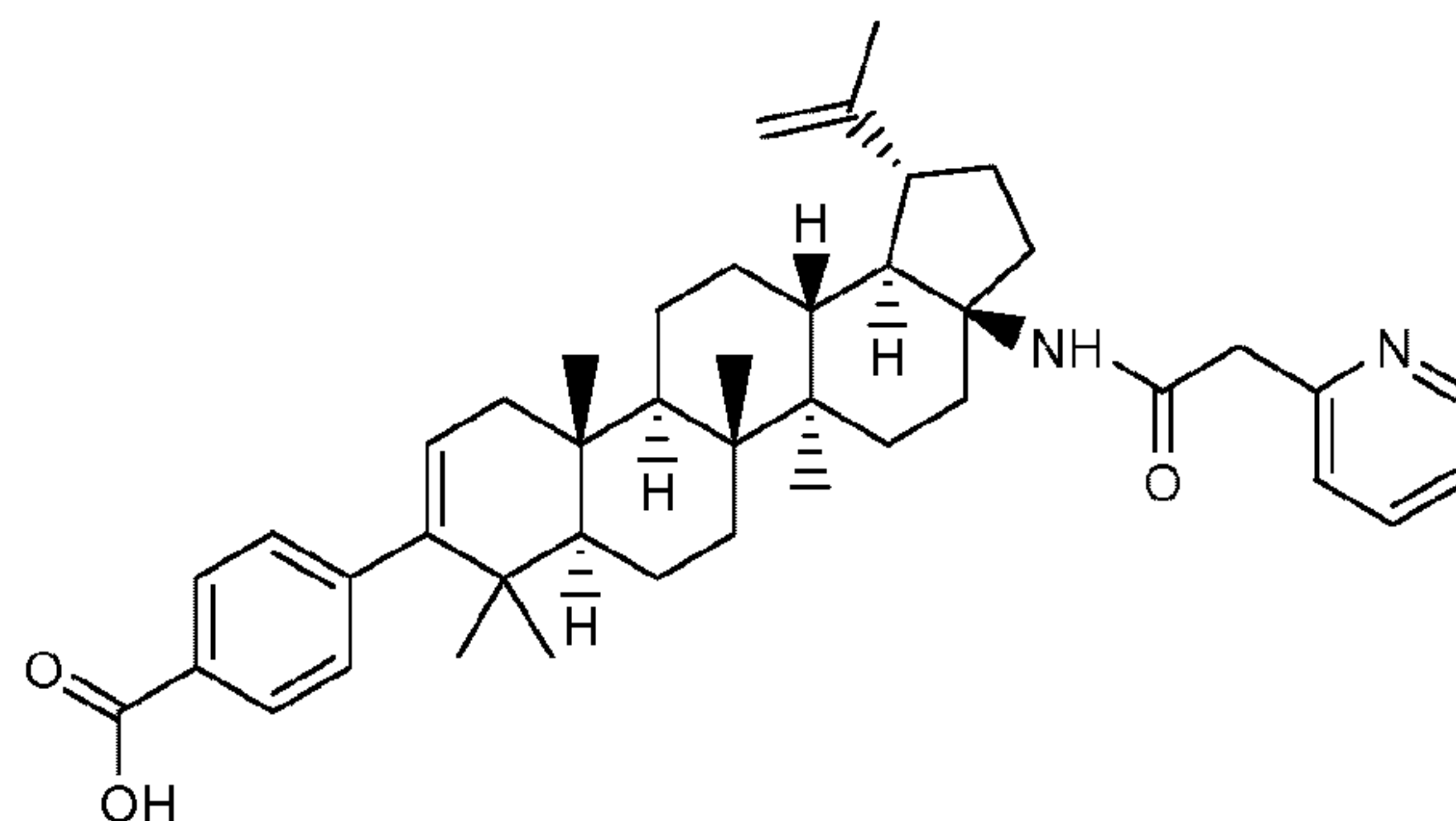


The title compound was prepared from methyl 4-  
 20 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-  
 1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

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)<sup>+</sup>, 5.57 min (method 3). <sup>1</sup>H NMR (599MHz, <DMSO-CDCl<sub>3</sub>>)  $\delta$  = 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

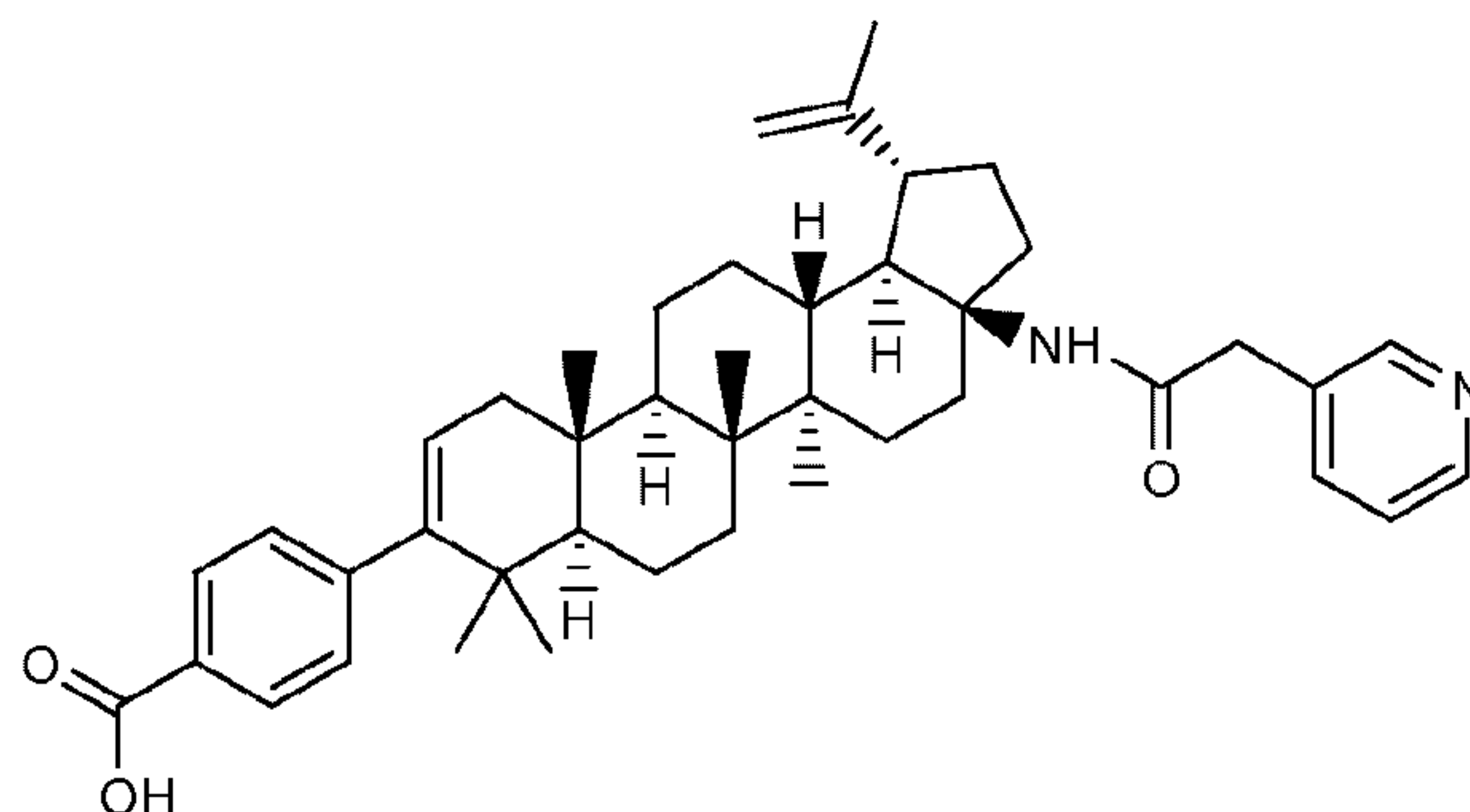
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-2-yl)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



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)<sup>+</sup>, 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.



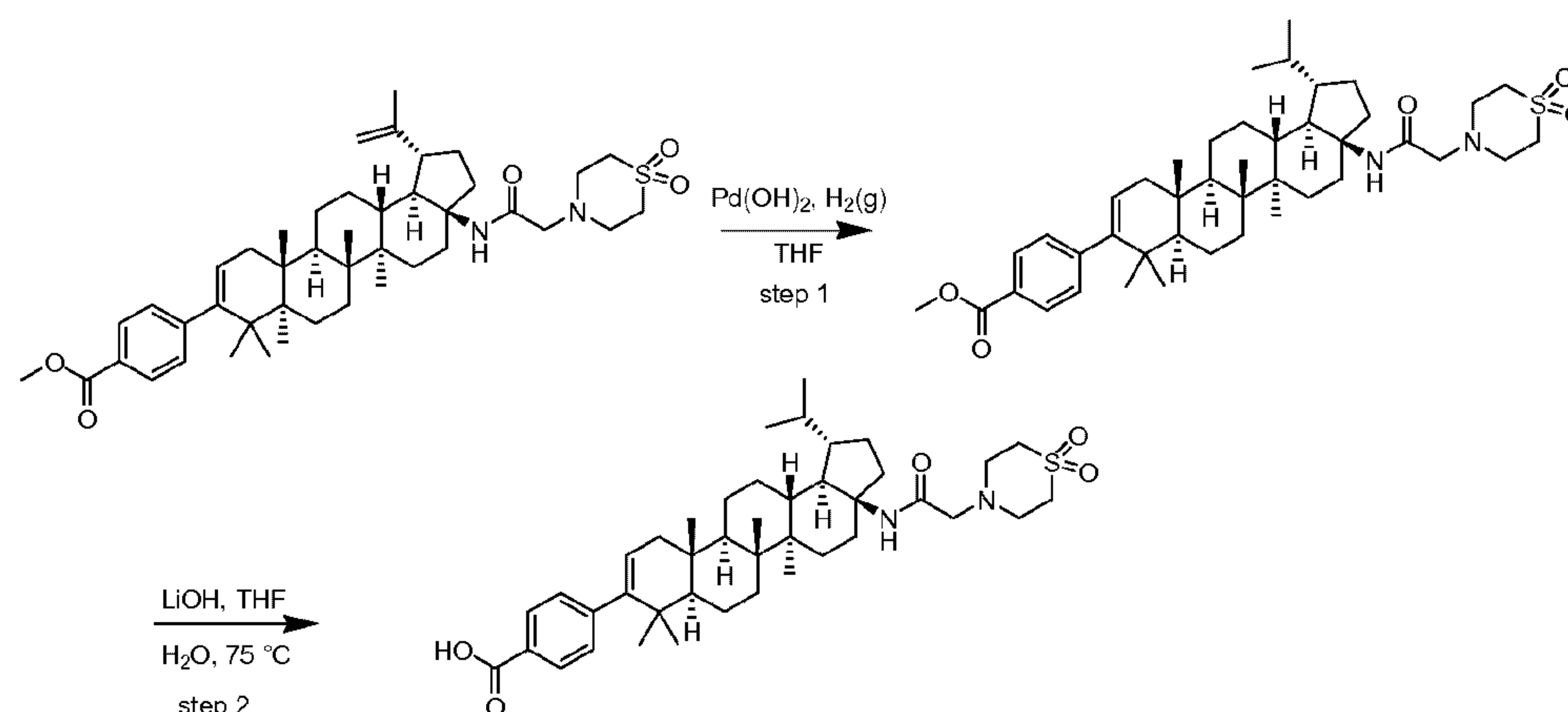
The title compound was prepared from methyl 4-  
 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the 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)<sup>+</sup>, 4.07 min (method 3). <sup>1</sup>H NMR (599MHz, <DMSO-CDCl<sub>3</sub>>) 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).  $^1\text{H}$  NMR (500MHz, *CHLOROFORM-d*)  $\delta$  = 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).

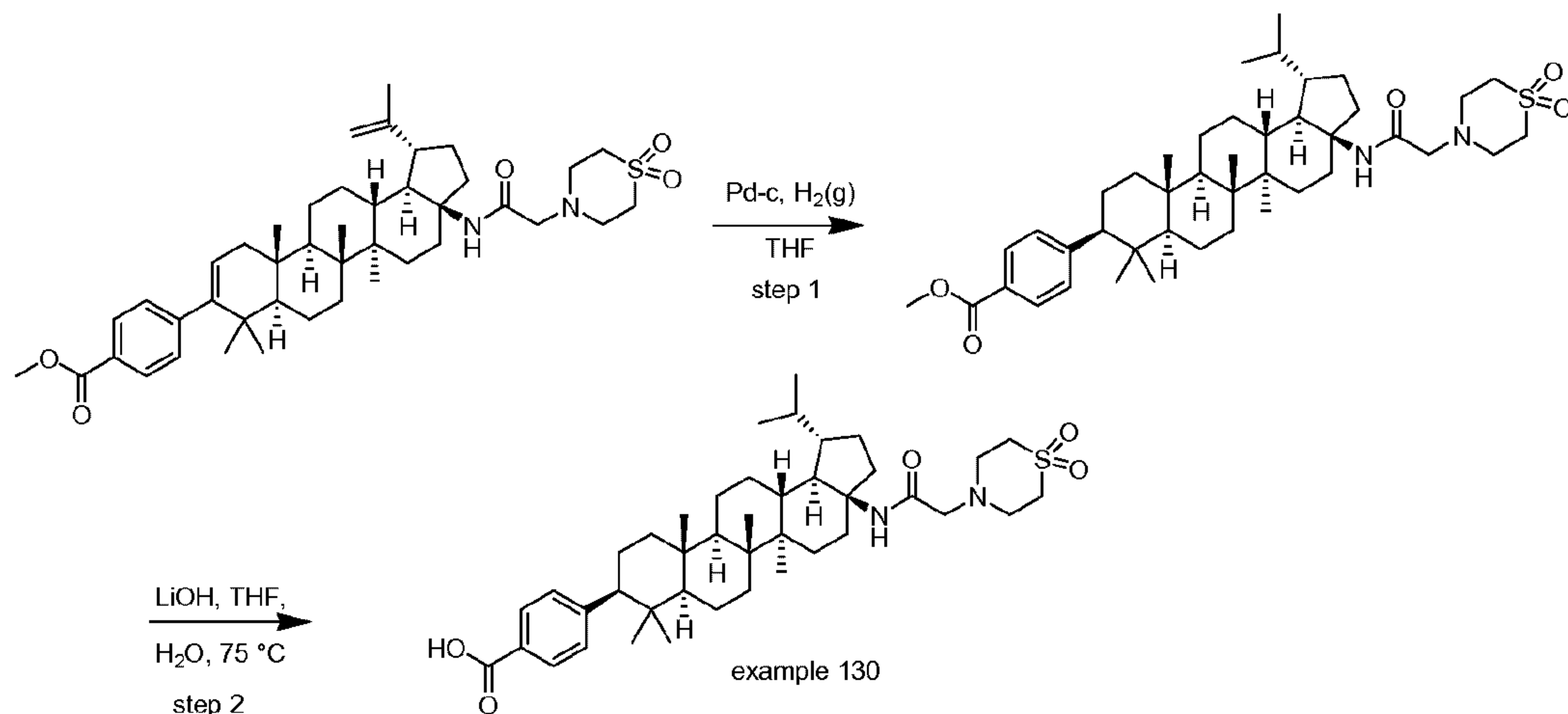
- 5 Step 2. Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

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 H<sub>2</sub>O. 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). <sup>1</sup>H NMR (500MHz, *METHANOL-d*<sub>4</sub>)  $\delta$  = 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).

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 H<sub>2</sub> (g) slowly into the mixture over 30 mins. and then the mixture was stirred under H<sub>2</sub> (g) atmosphere. After 24 h, the reaction mixture was purged with N<sub>2</sub> (g) and more catalyst (36 mg, 0.034 mmol) was added. The reaction mixture was stirred under H<sub>2</sub> (g) for an additional 24 h. The mixture was then purged with N<sub>2</sub> (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<sup>+</sup>),

retention time 2.648 min (method 6).  $^1\text{H}$  NMR (500MHz, *CHLOROFORM-d*)  $\delta$  = 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).  $^{13}\text{C}$  NMR (*CHLOROFORM-d*)  $\delta$  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.

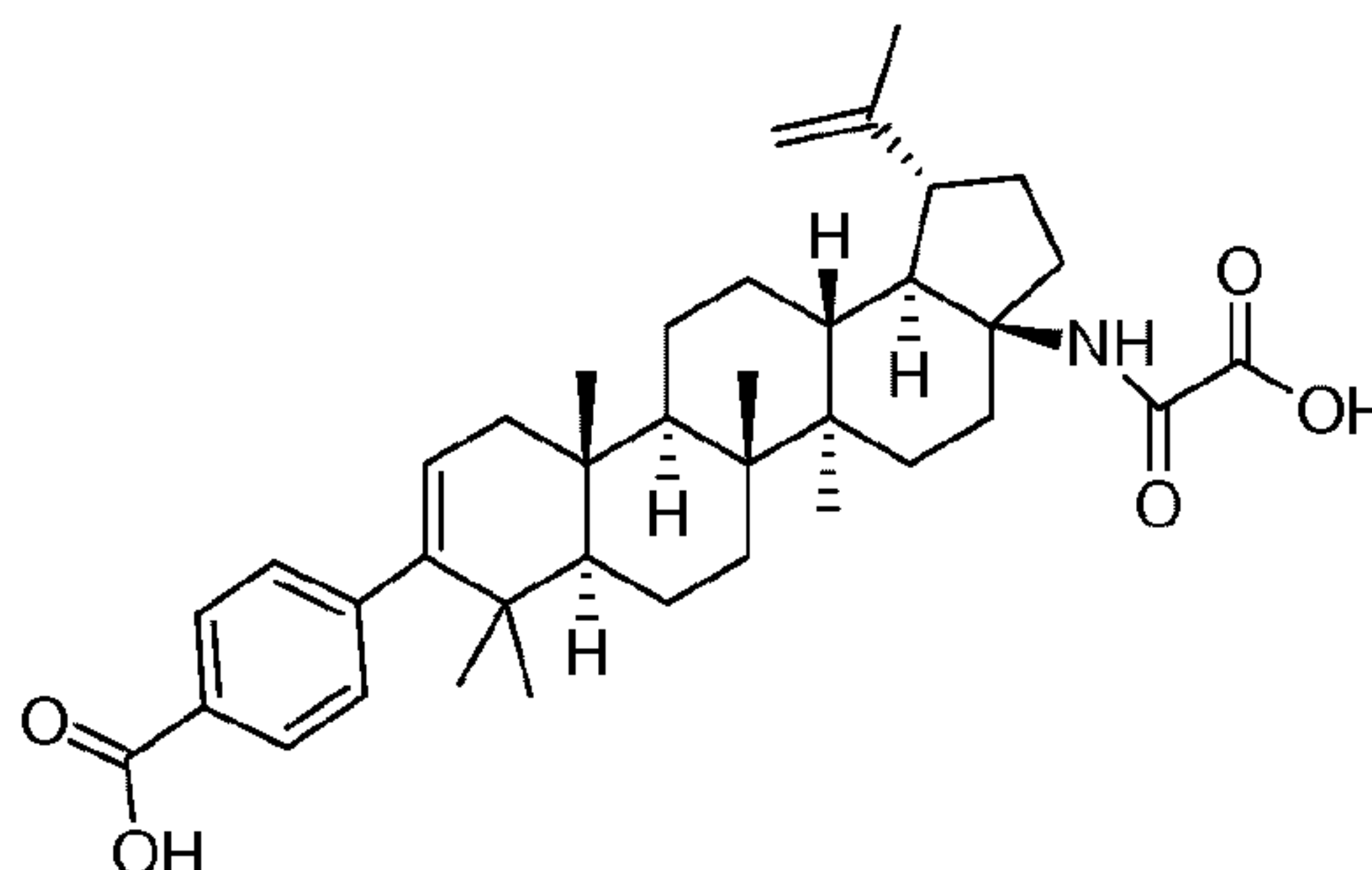
Step 2. Preparation 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

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).  $^1\text{H}$  NMR (500MHz, *METHANOL-d<sub>4</sub>*)  $\delta$  = 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)-

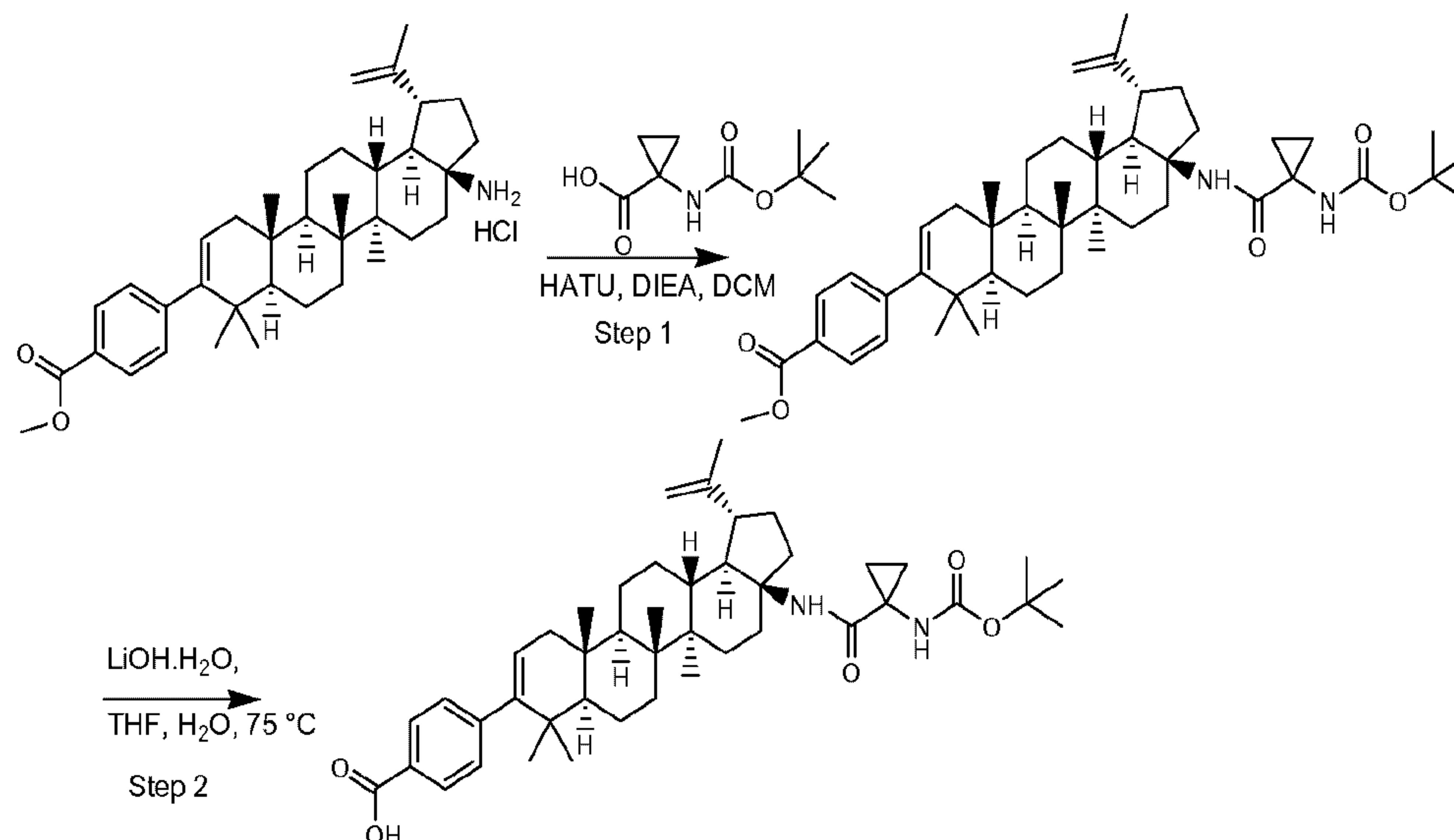
- 15 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. LCMS:  $m/e$  600.5 (M-H)<sup>-</sup>, 1.33 min (method 5). <sup>1</sup>H NMR (500MHz, CHLOROFORM-*d*)  $\delta$  = 8.02 (d,  $J = 8.2$  Hz, 2 H), 7.26 (d,  $J = 8.2$  Hz, 3 H), 5.33 (d,  $J = 4.9$  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).
- 20

### Example 130-2

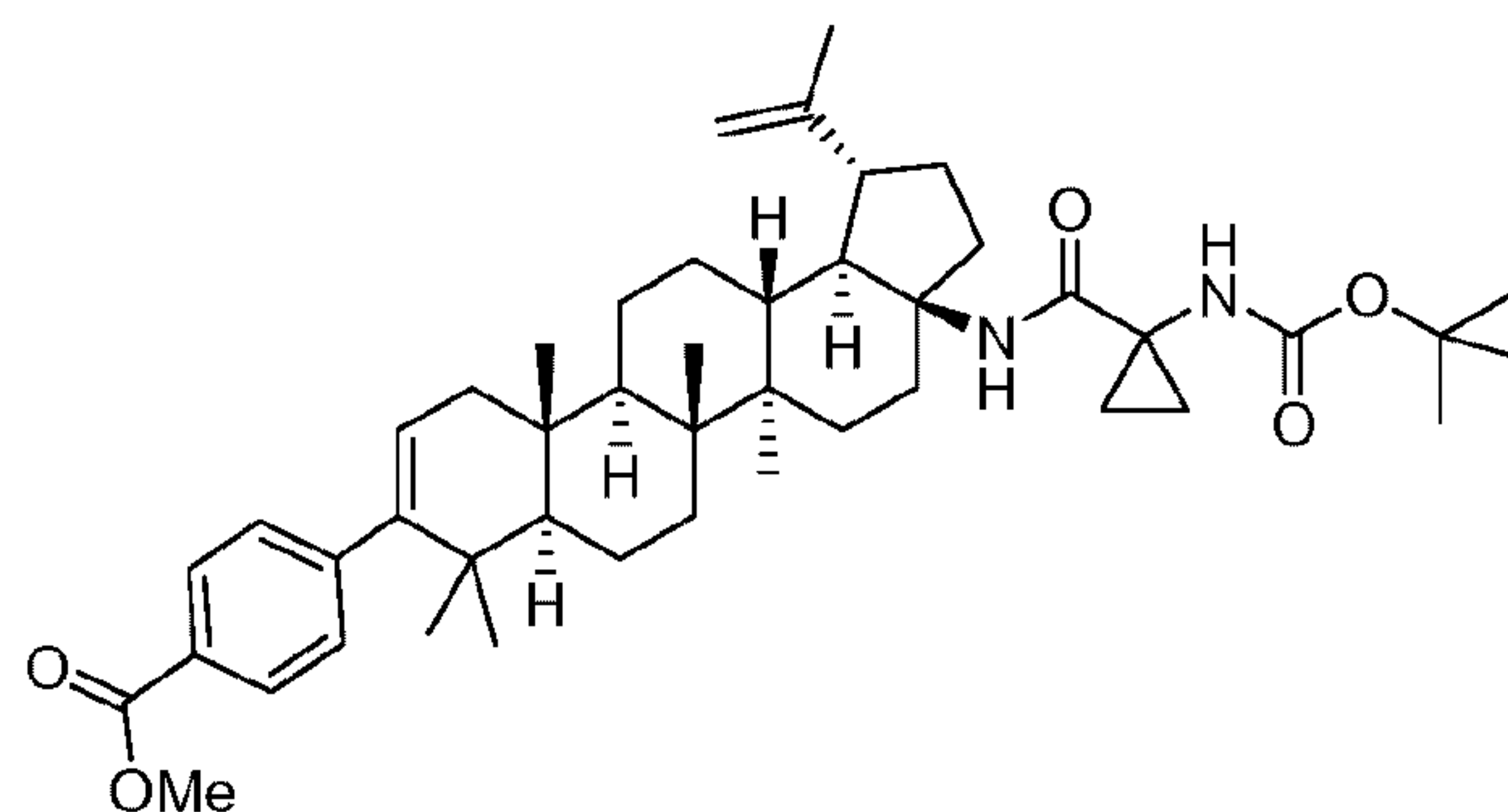
25

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.

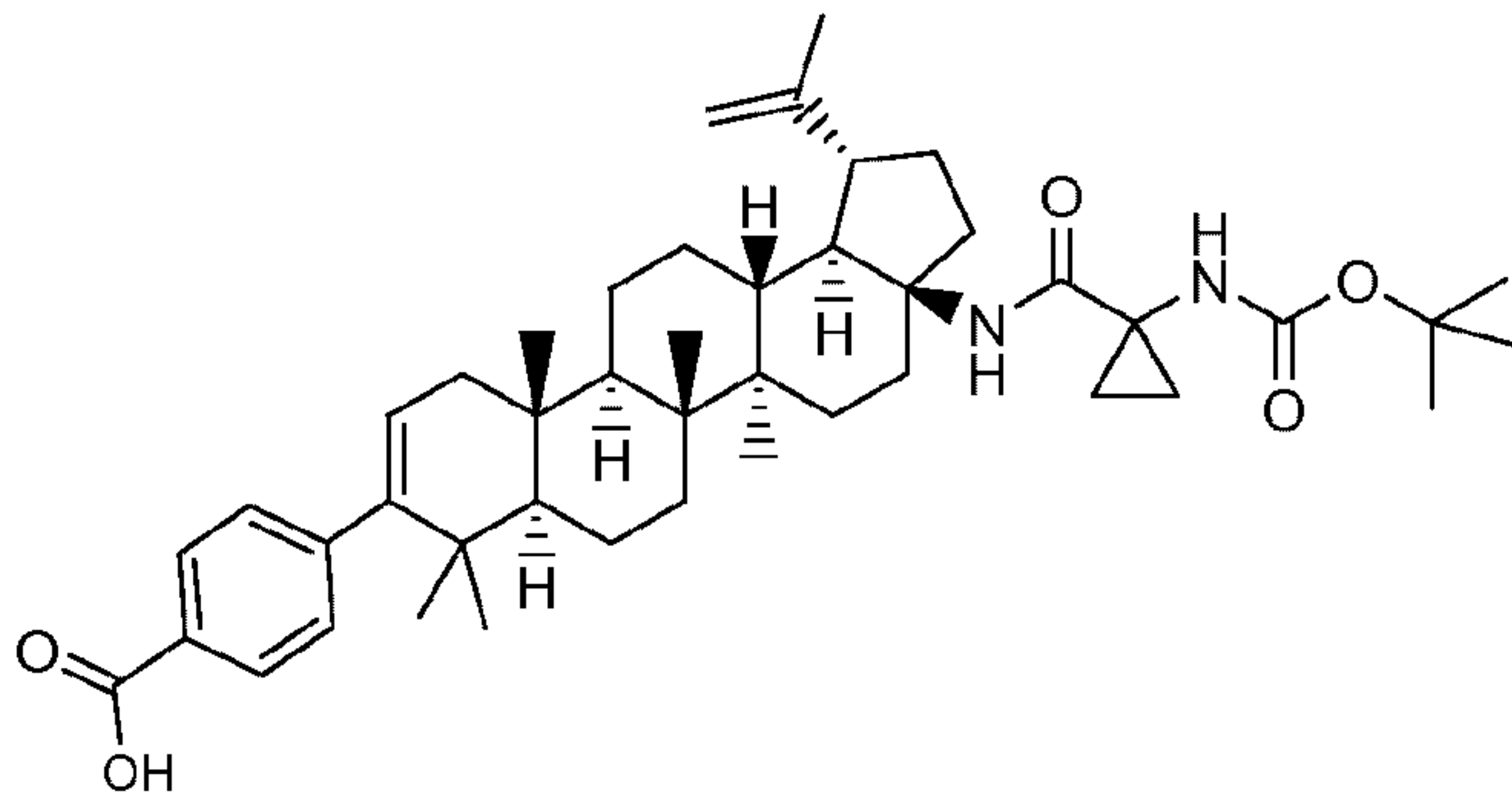


10

- 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-  
 5 ((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-  
 10 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)<sup>+</sup>, 5.17 min (method 2). <sup>1</sup>H NMR (500MHz, CHLOROFORM-*d*)  $\delta$  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),  
 15 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).

20 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-

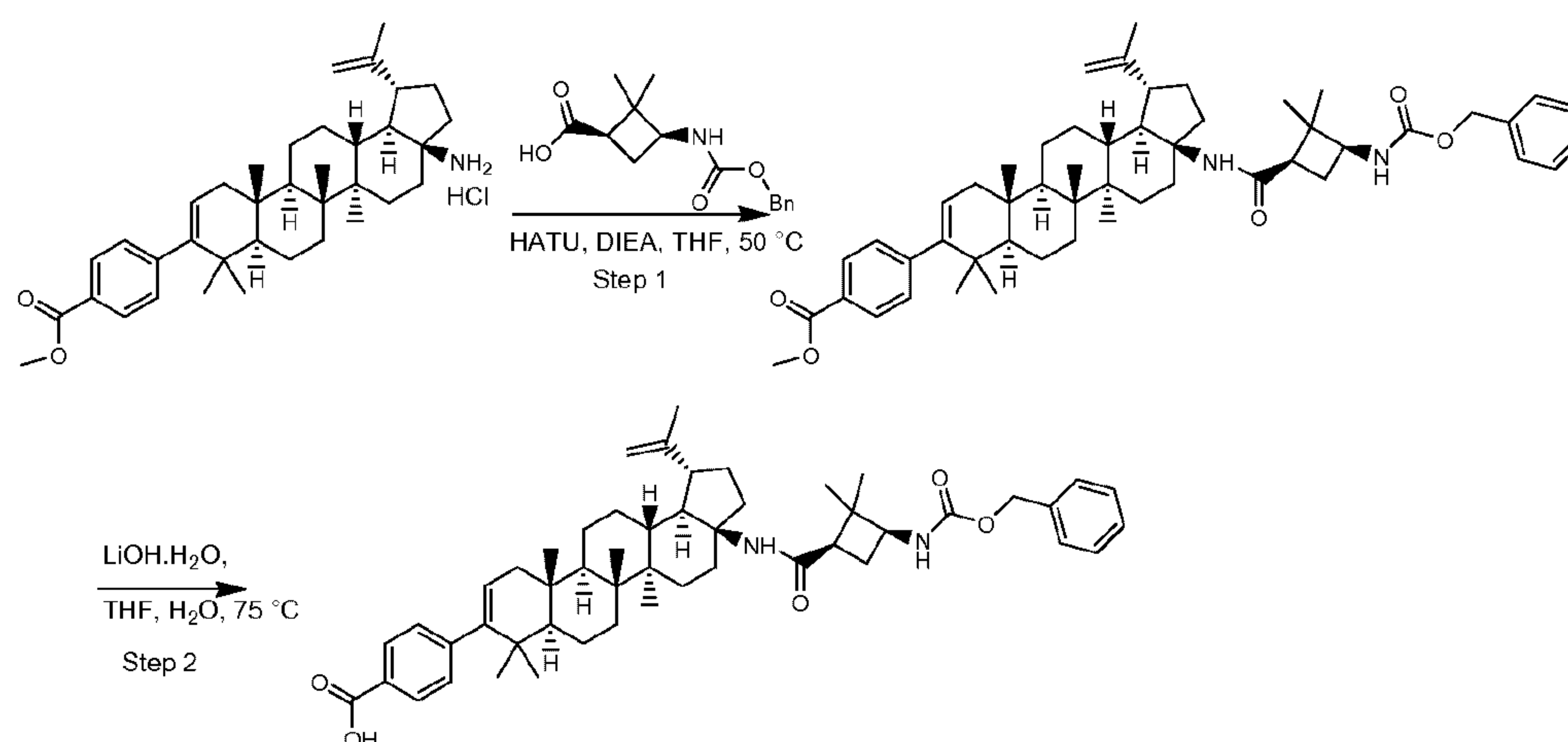
1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (101 mg, 0.139 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (17.49 mg, 0.417 mmol) in water (1.000 mL). The resulting mixture was stirred at 75°C. After 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)<sup>+</sup>, 2.32 min (method 1). <sup>1</sup>H NMR (500MHz, 1:1 CDCl<sub>3</sub>:METHANOL-d<sub>4</sub>) 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.**



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% NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, 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)<sup>+</sup>, 4.23 min (method 8). <sup>1</sup>H 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  
20 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  
25 (30.4 mg, 0.035 mmol, 21.09 % yield) as white solid. LCMS: m/e 789.4 (M+H)<sup>+</sup>, 3.14 min (method 8). <sup>1</sup>H 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 -  
30 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).

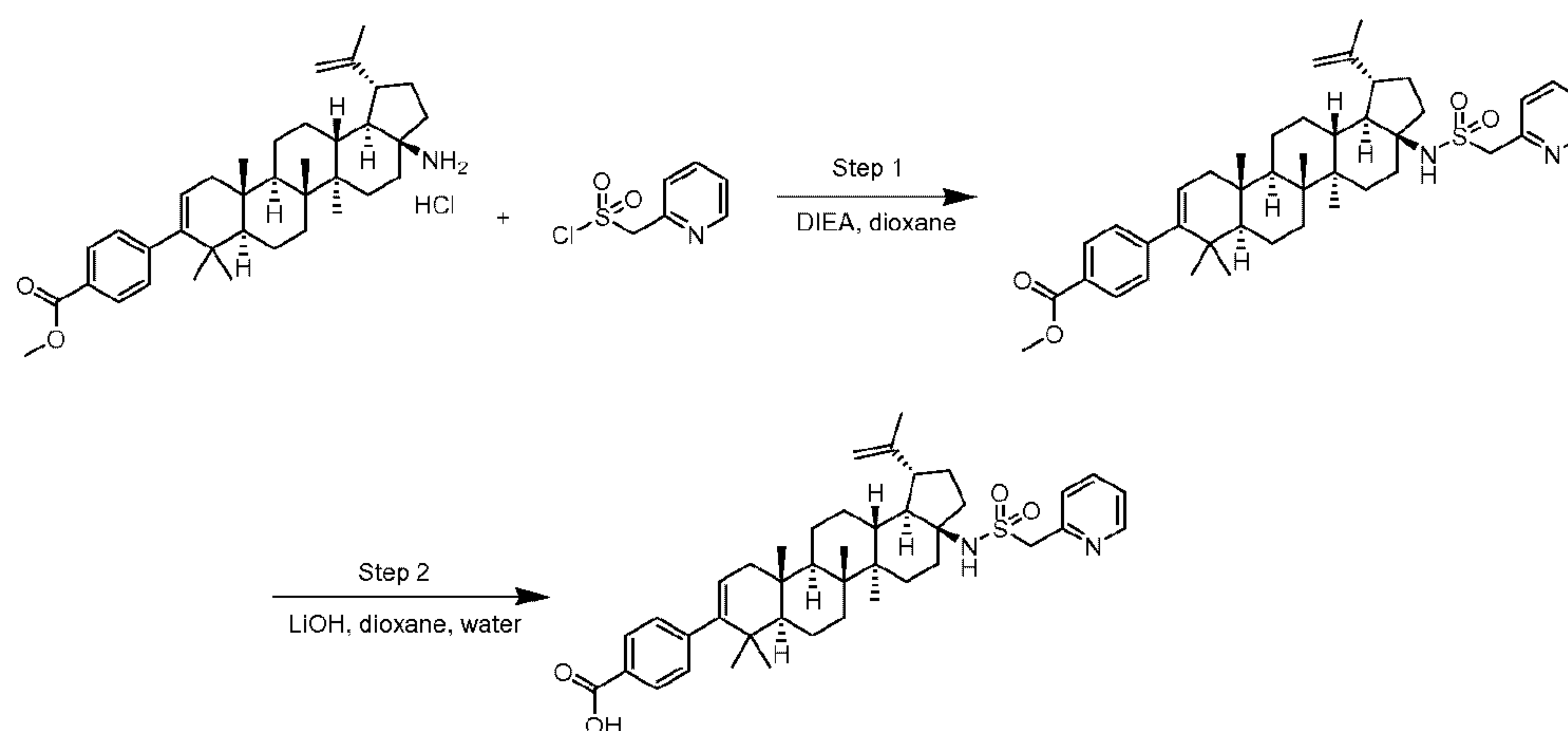
## Section 4. Sulfonyl amides

## Example 131

5

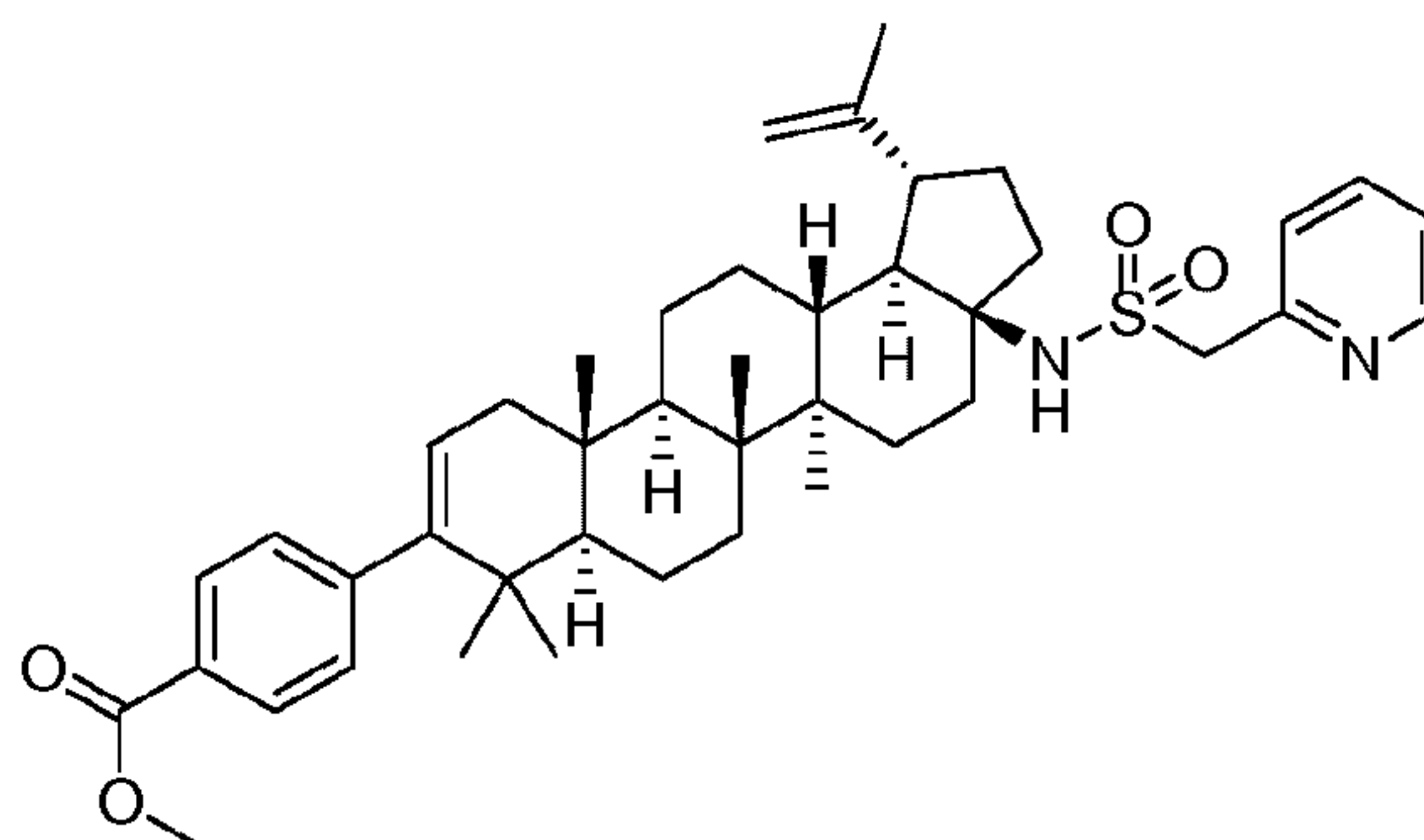
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

10



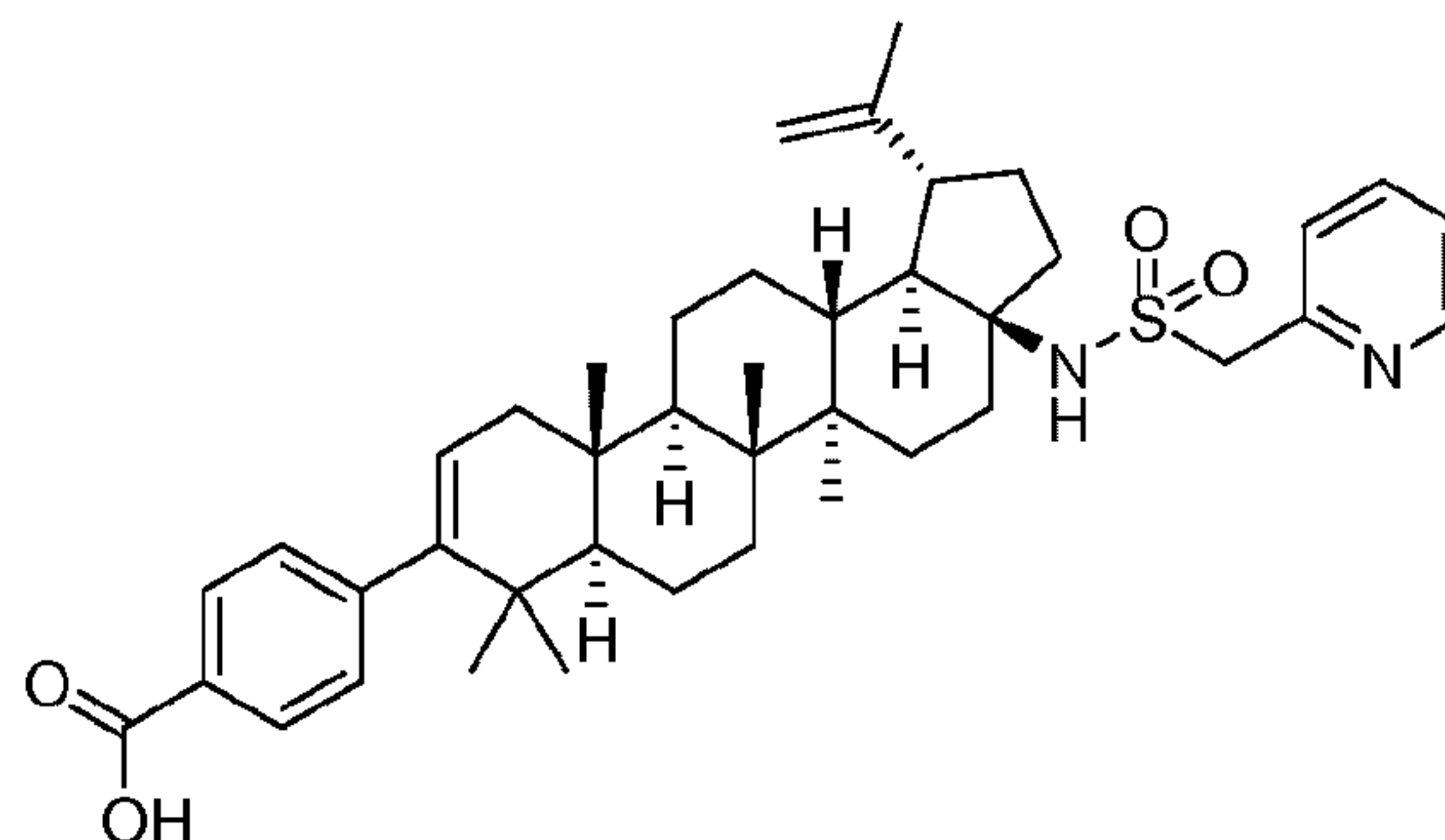
Step 1: Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

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)  $\delta$  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<sup>+</sup>), retention time 2.62 min (method 11). <sup>1</sup>H NMR (500 MHz, 1:1 mixture of CDCl<sub>3</sub> 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).

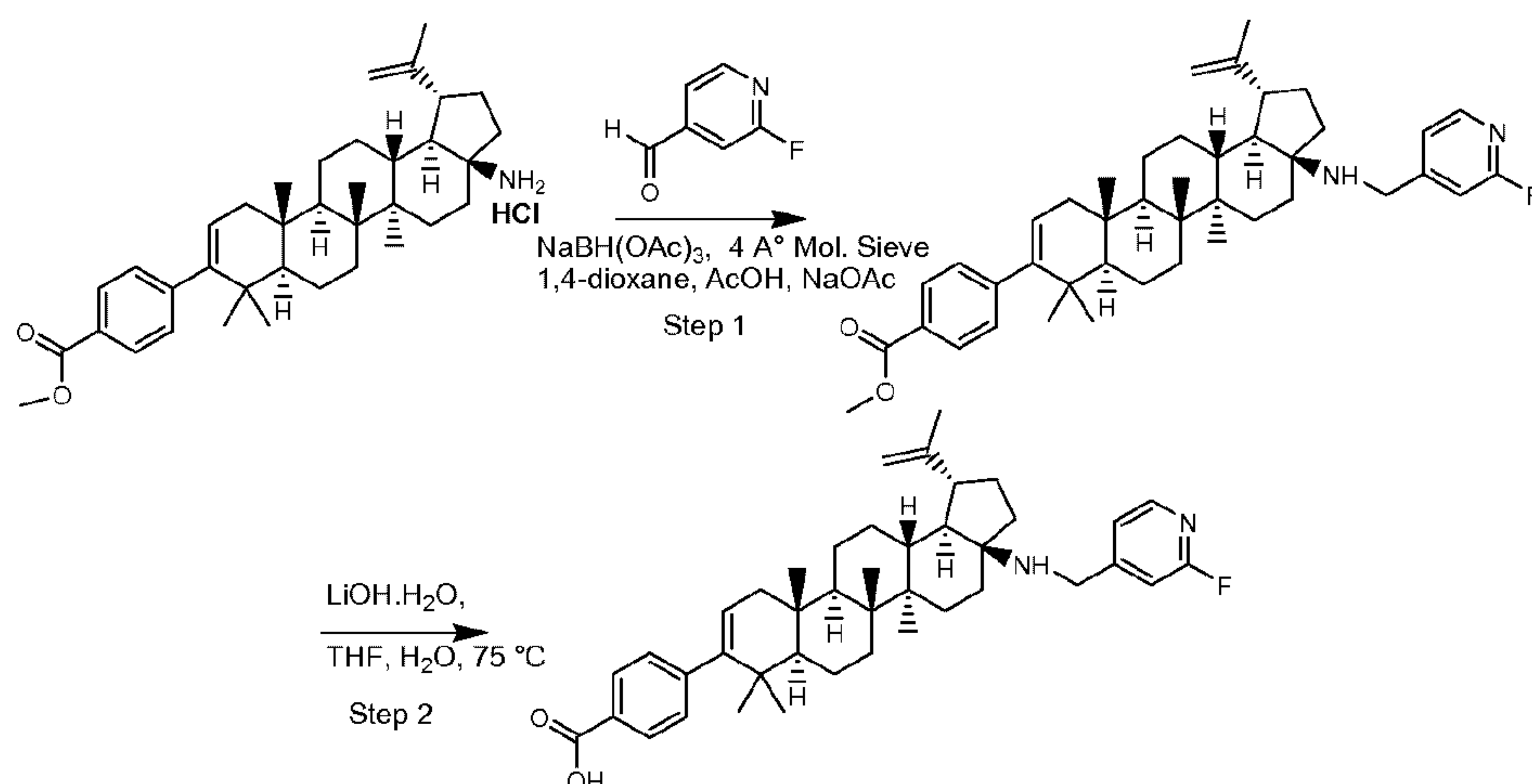
## Section 5. Amines

### Example 132

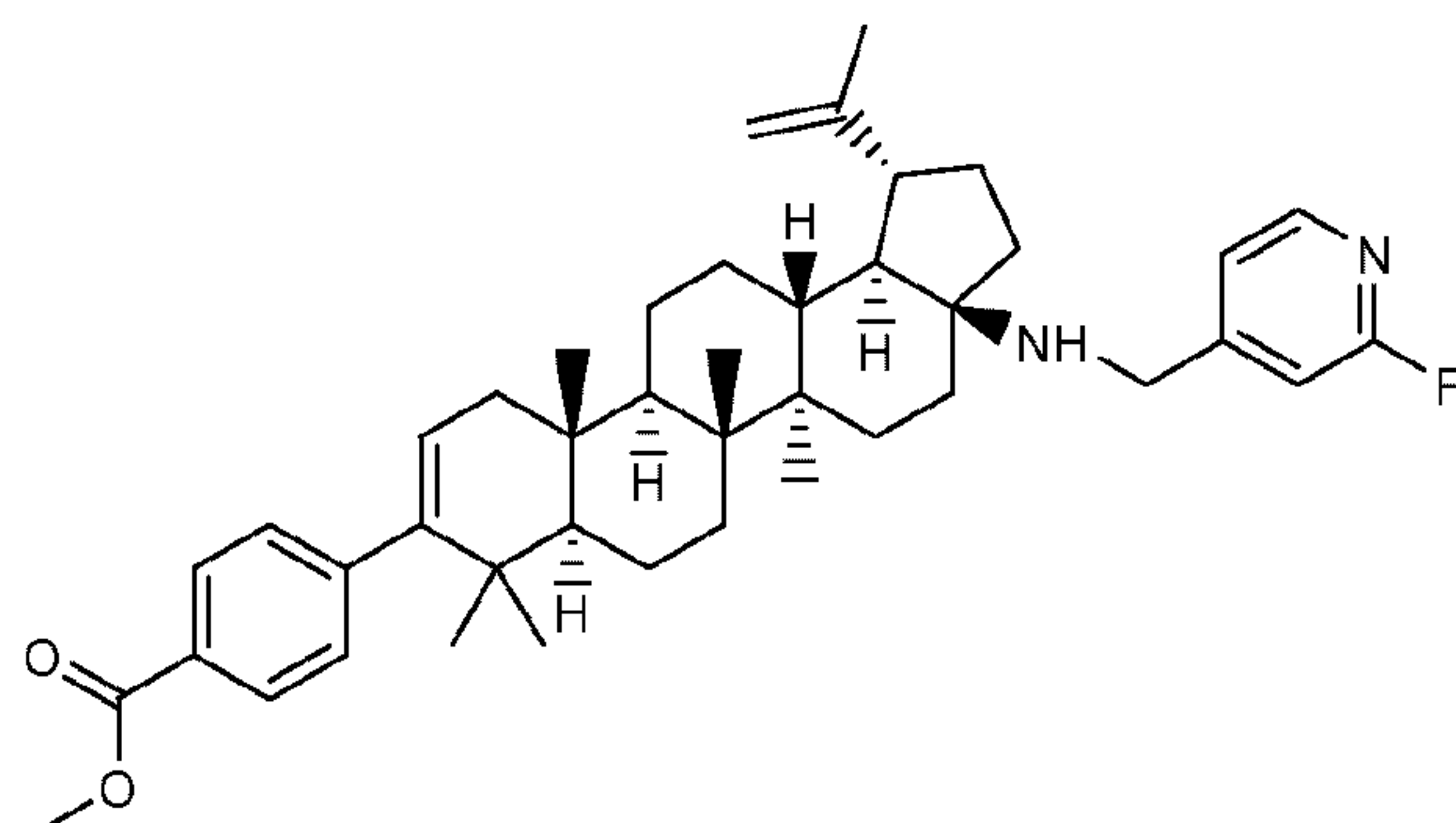
20

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)-  
 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.

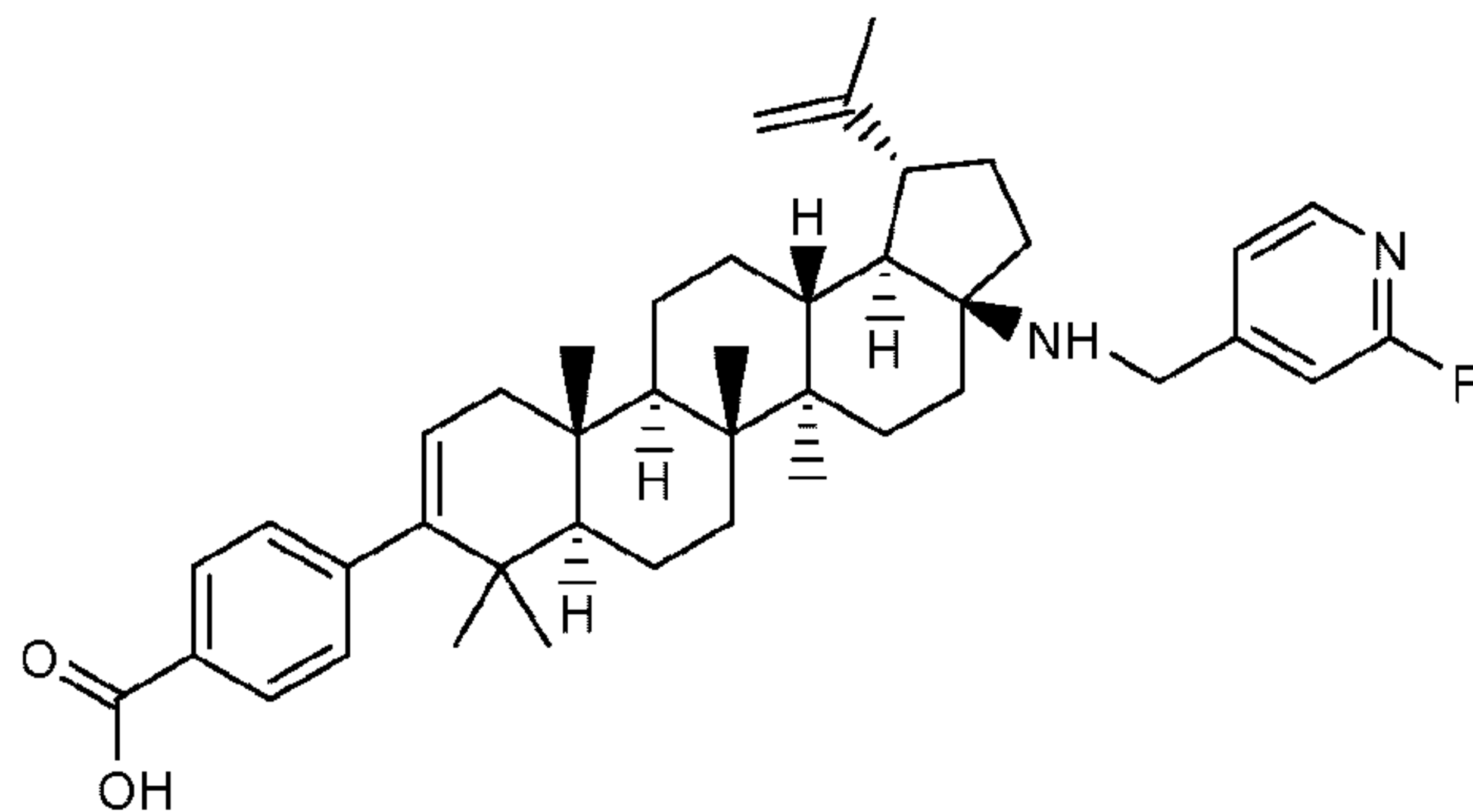


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-  
 10 amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-  
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-  
 cyclopenta[a]chrysen-9-yl)benzoate, HCl (318 mg, 0.548 mmol) in DCE (10 mL) was  
 added glacial 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  
 15 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<sub>3</sub> (20

mL). The aqueous layer was extracted with DCM (2 x 25 mL). The combined organic layer was dried over  $\text{MgSO}_4$ , 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 ( $\text{M}+\text{H}$ )<sup>+</sup>, 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  $\mu\text{L}$ ), 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-

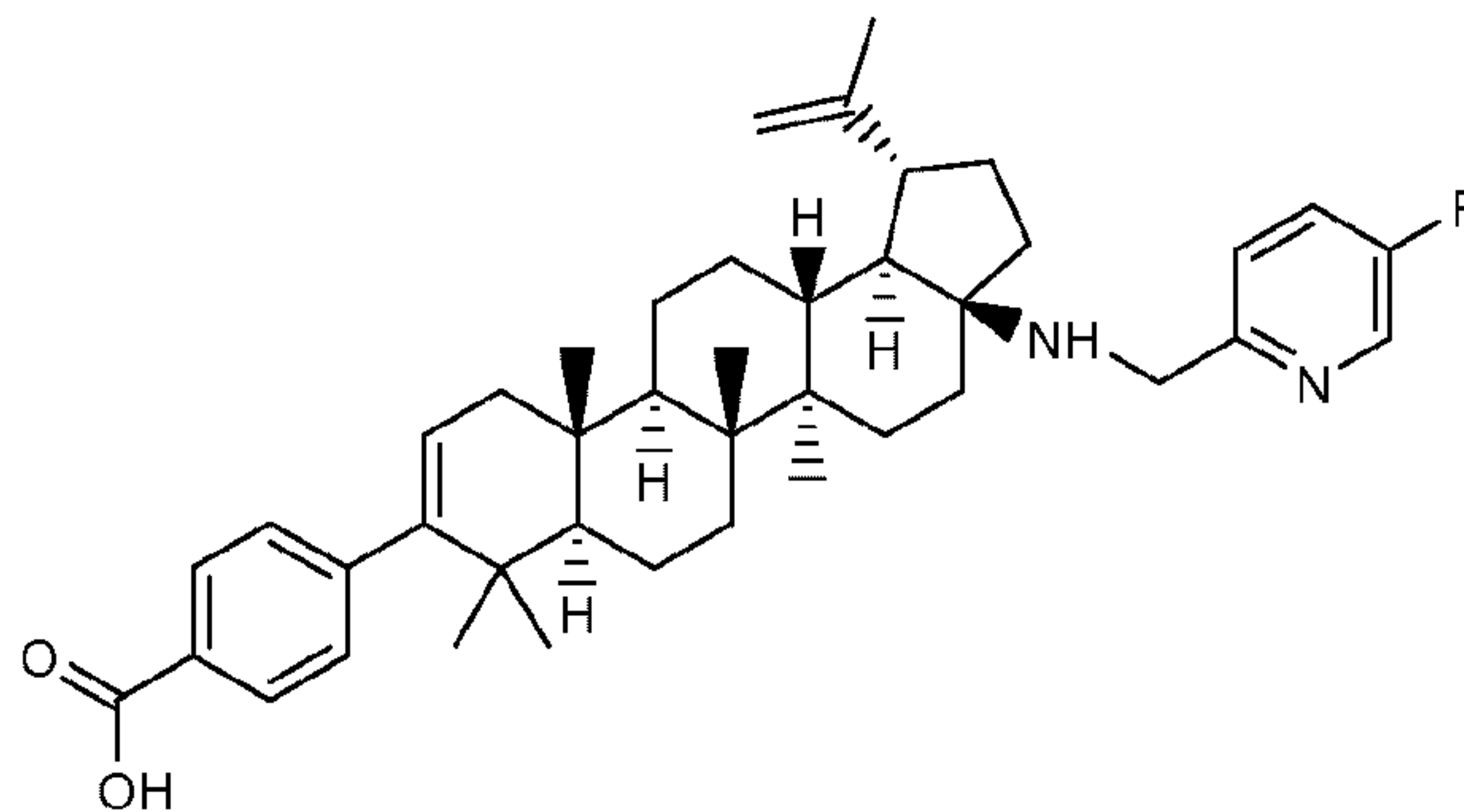
cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (30.6 mg, 0.037 mmol, 36.1% yield) as a white solid. LCMS:  $m/e$  637.7 (M-H)<sup>+</sup>, 3.12 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 CDCl<sub>3</sub>:MeOD)  $\delta$  = 8.24 (d,  $J$  = 5.2 Hz, 1 H), 7.92 (d,  $J$  = 8.2 Hz, 2 H), 7.43 (d,  $J$  = 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). <sup>13</sup>C NMR (1:1 CDCl<sub>3</sub>:MeOD)  $\delta$  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

15

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.

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25

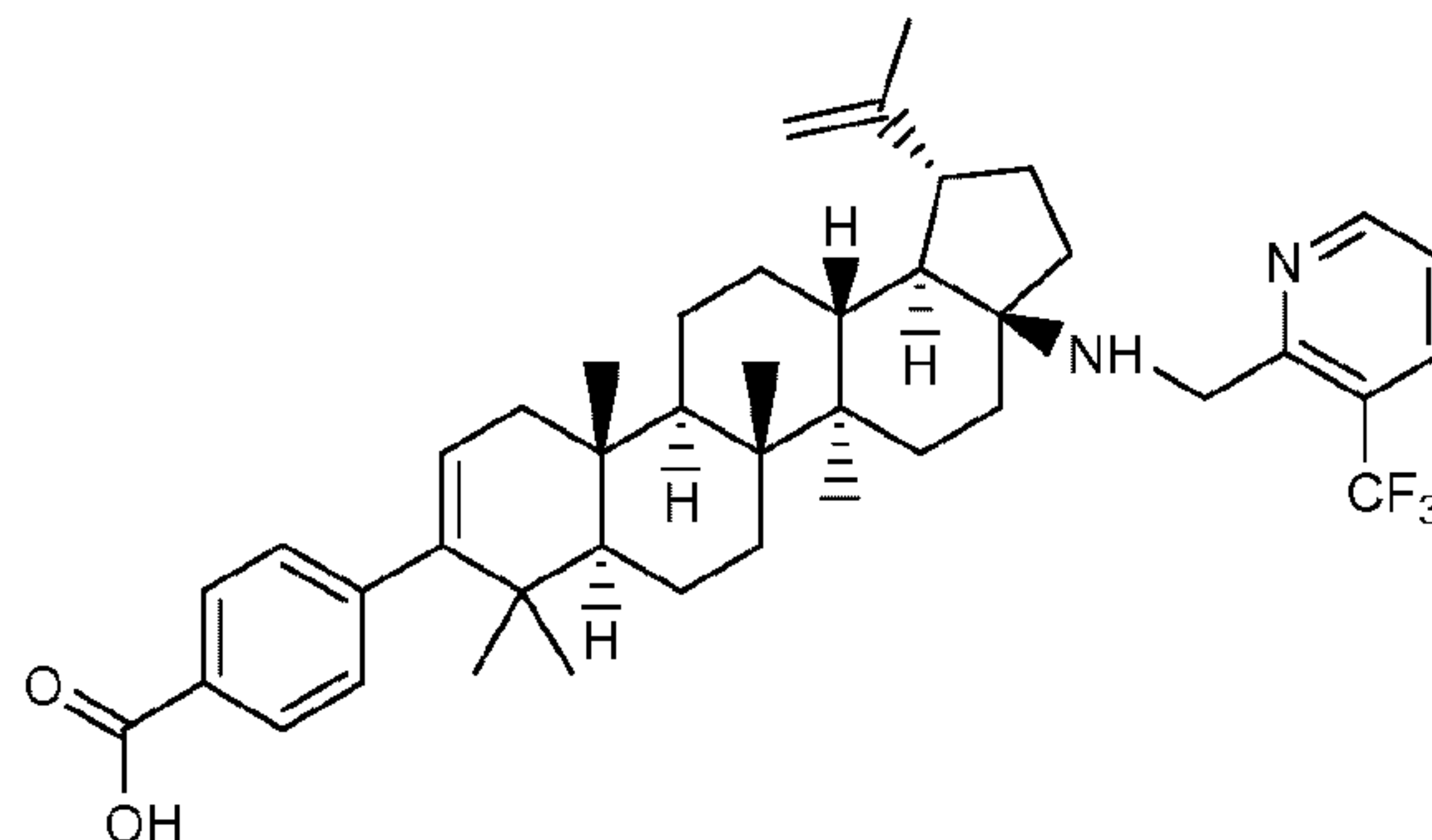
The title compound was prepared in 47% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for 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 ( $M+H$ )<sup>+</sup>, 3.33 min (method 6). <sup>1</sup>H NMR (500MHz, 1:1 *CDCl*<sub>3</sub>:*MeOD*)  $\delta$  = 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

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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-((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.



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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

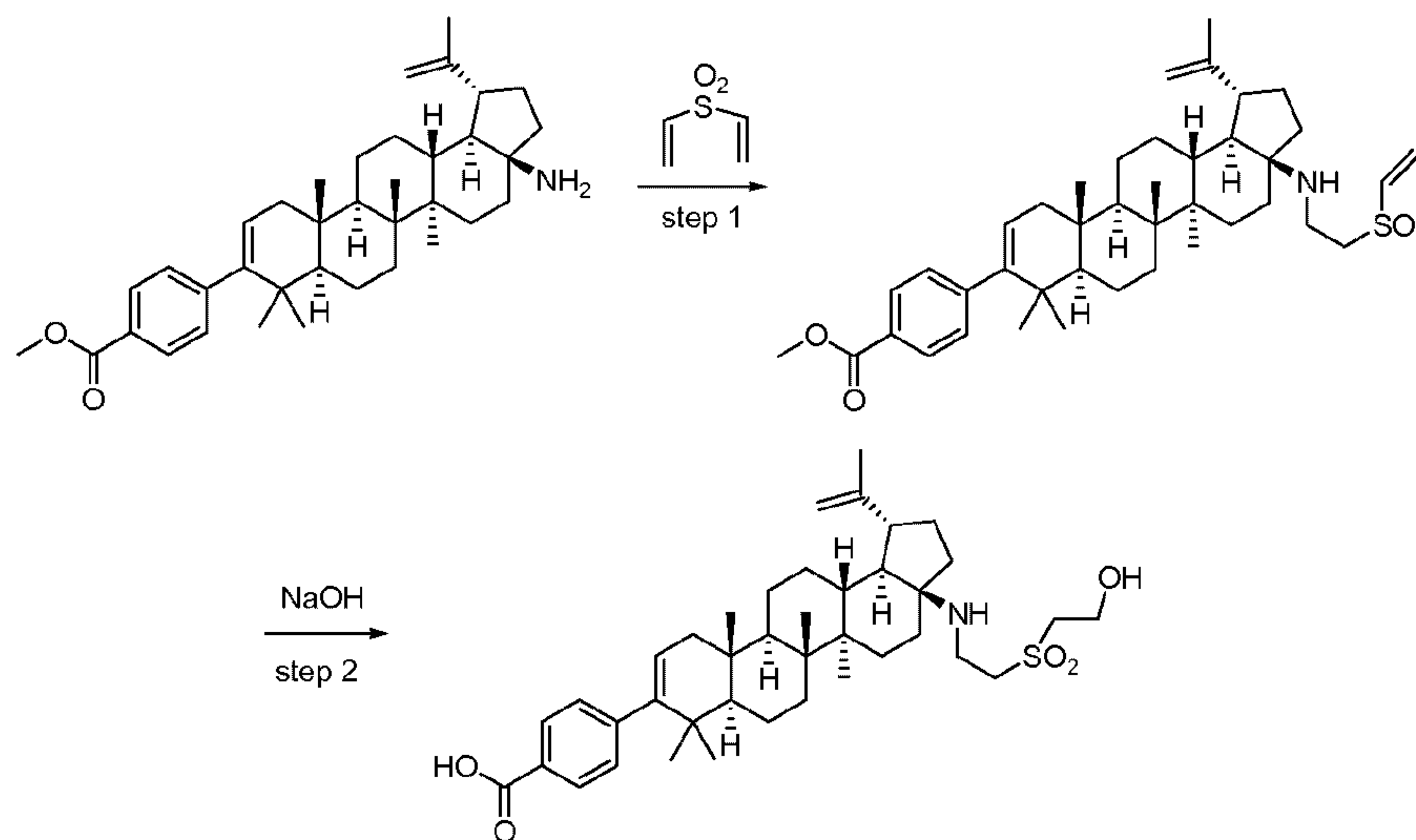
yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-trifluoromethylpyridine-2-carbaldehyde was used instead of 2-fluoropyridine-4-carboxaldehyde in Step 1.

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

- 5  $CDCl_3:MeOD$ )  $\delta$  = 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.



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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-(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 vinylsulfonylethene (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)<sup>+</sup>, 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.

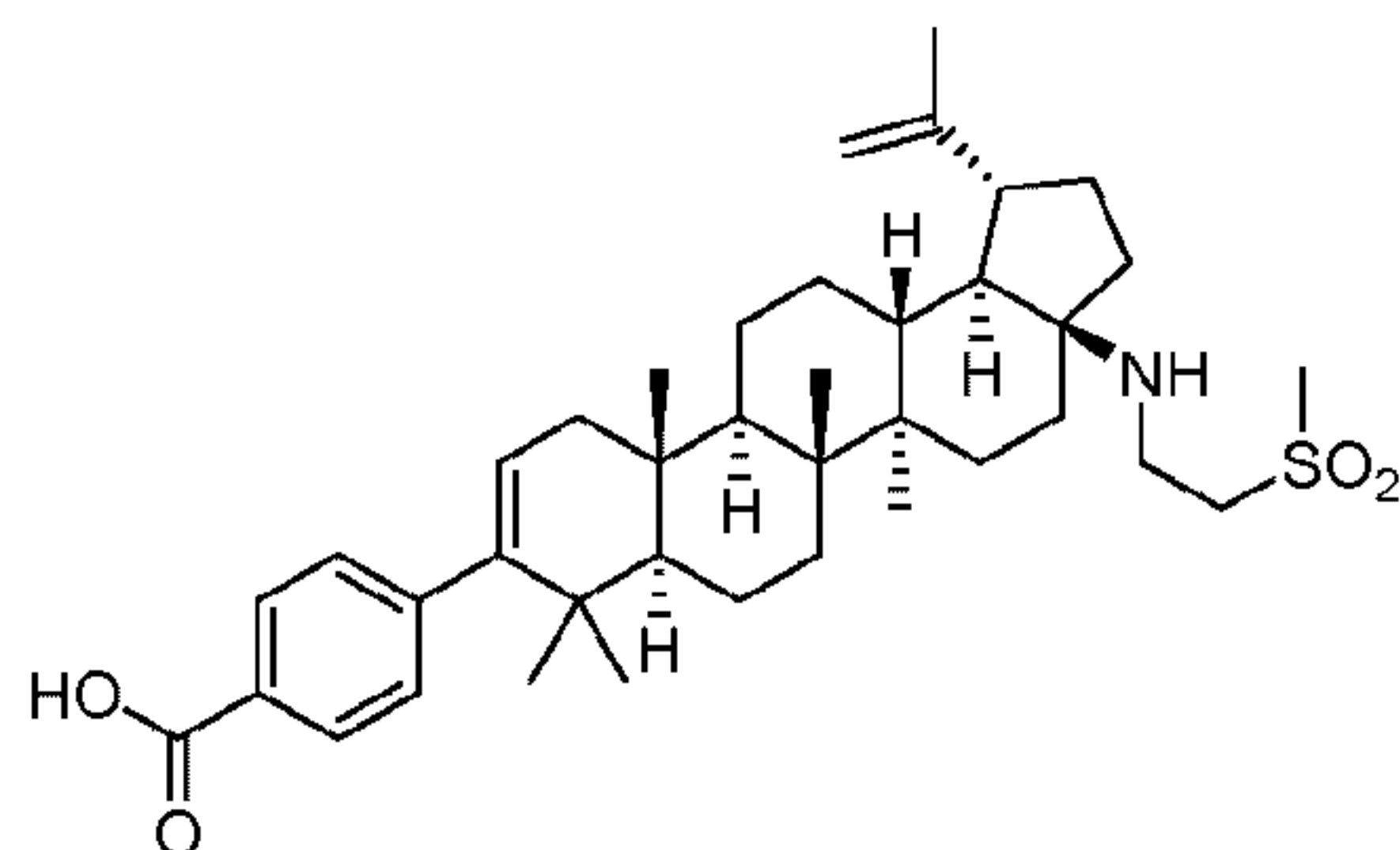
- A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(vinylsulfonyl)ethylamino)-  
20 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (25 mg, 0.038 mmol) and sodium hydroxide (0.189 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)<sup>+</sup>, 2.48 min (method 10). <sup>1</sup>H 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

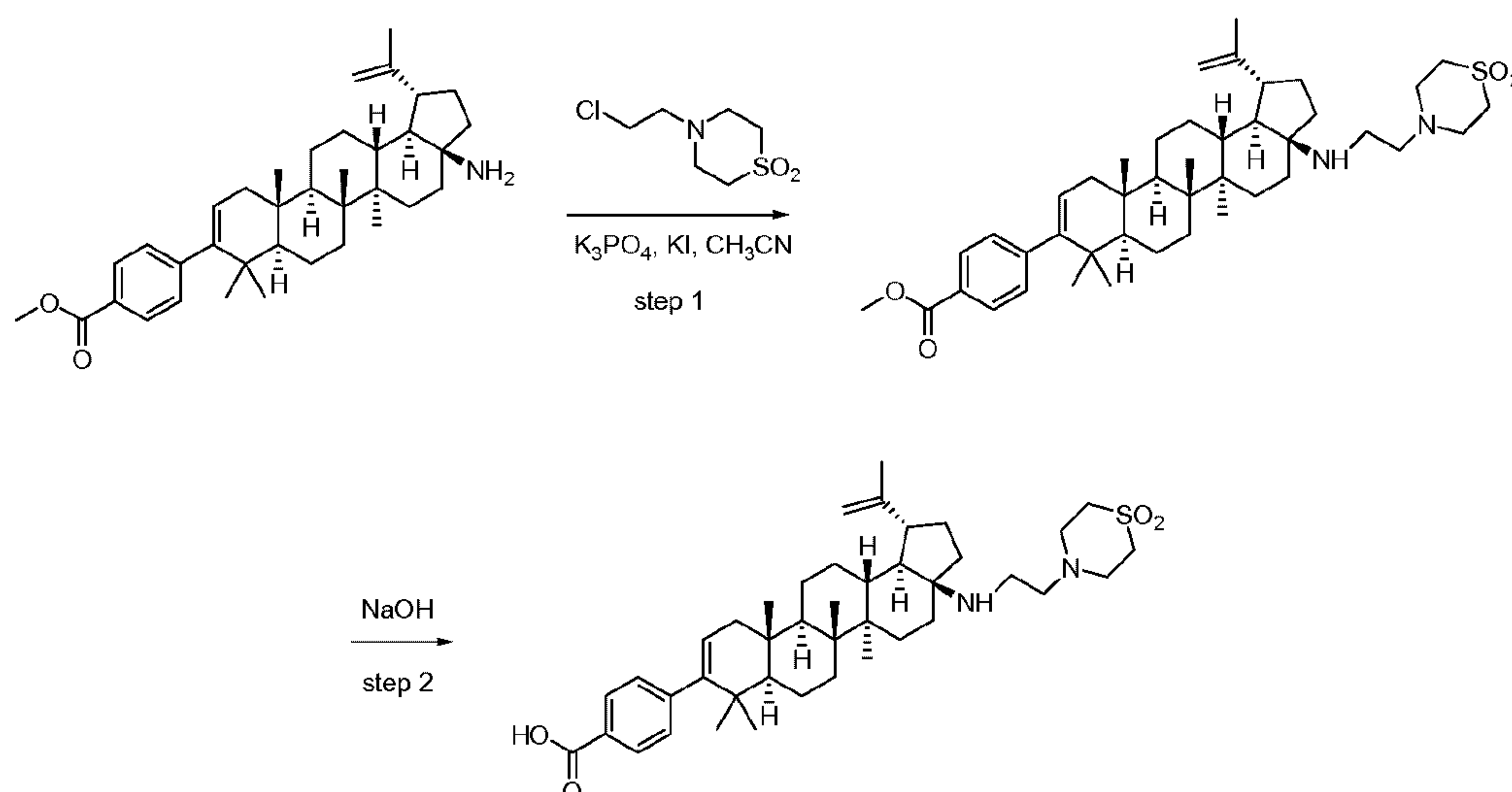
The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic 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 ( $M+H$ )<sup>+</sup>, 2.53 min (method 10). <sup>1</sup>H NMR (500 MHz, *Acetic acid* *d*4)  $\delta$  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

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.

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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)  $\delta$  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)<sup>+</sup>, 3.01 min (method 10).

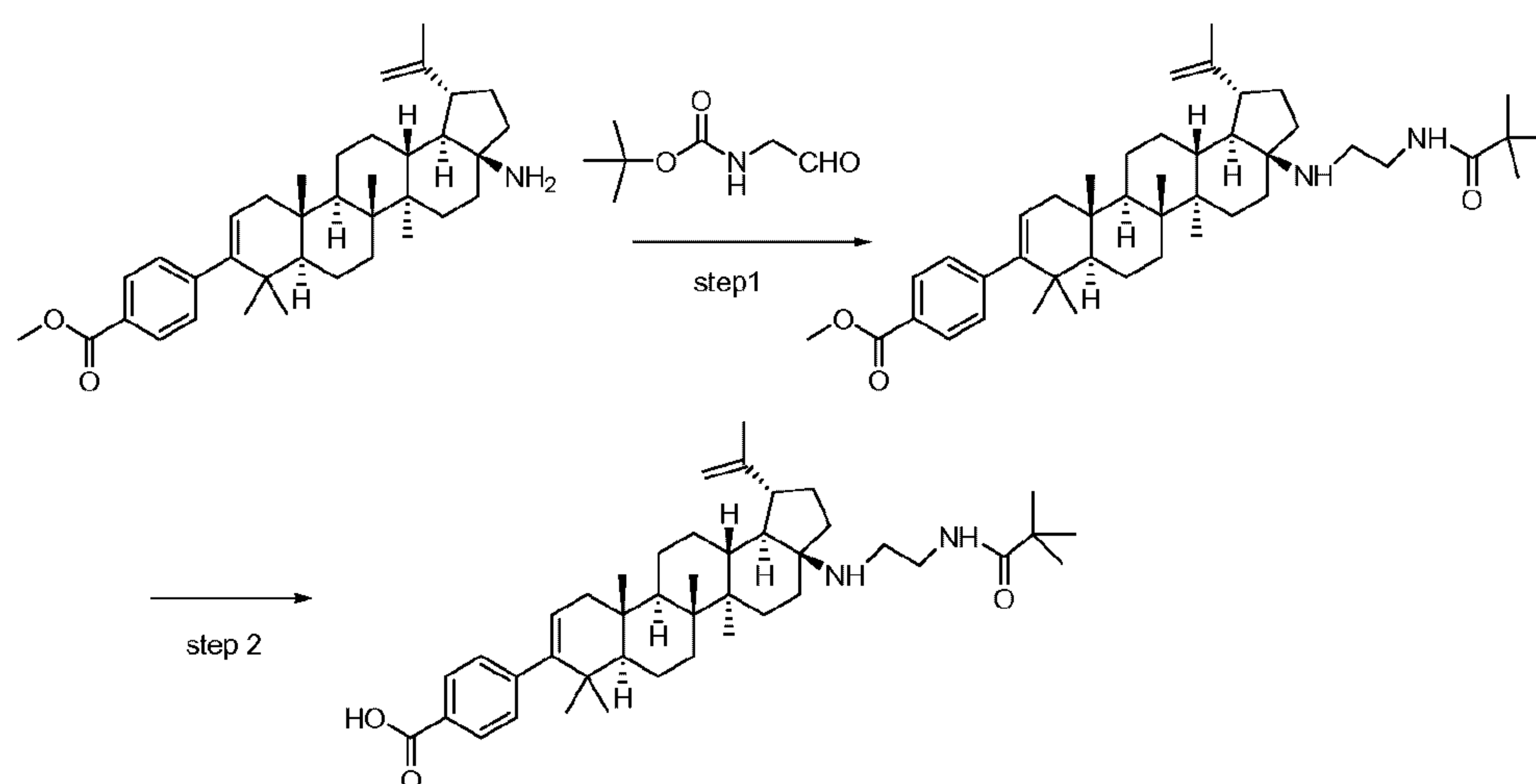
Step 2. Preparation of 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-  
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]- benzoic acid

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)<sup>+</sup>, 2.53 min (method 10). <sup>1</sup>H 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).

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### 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.

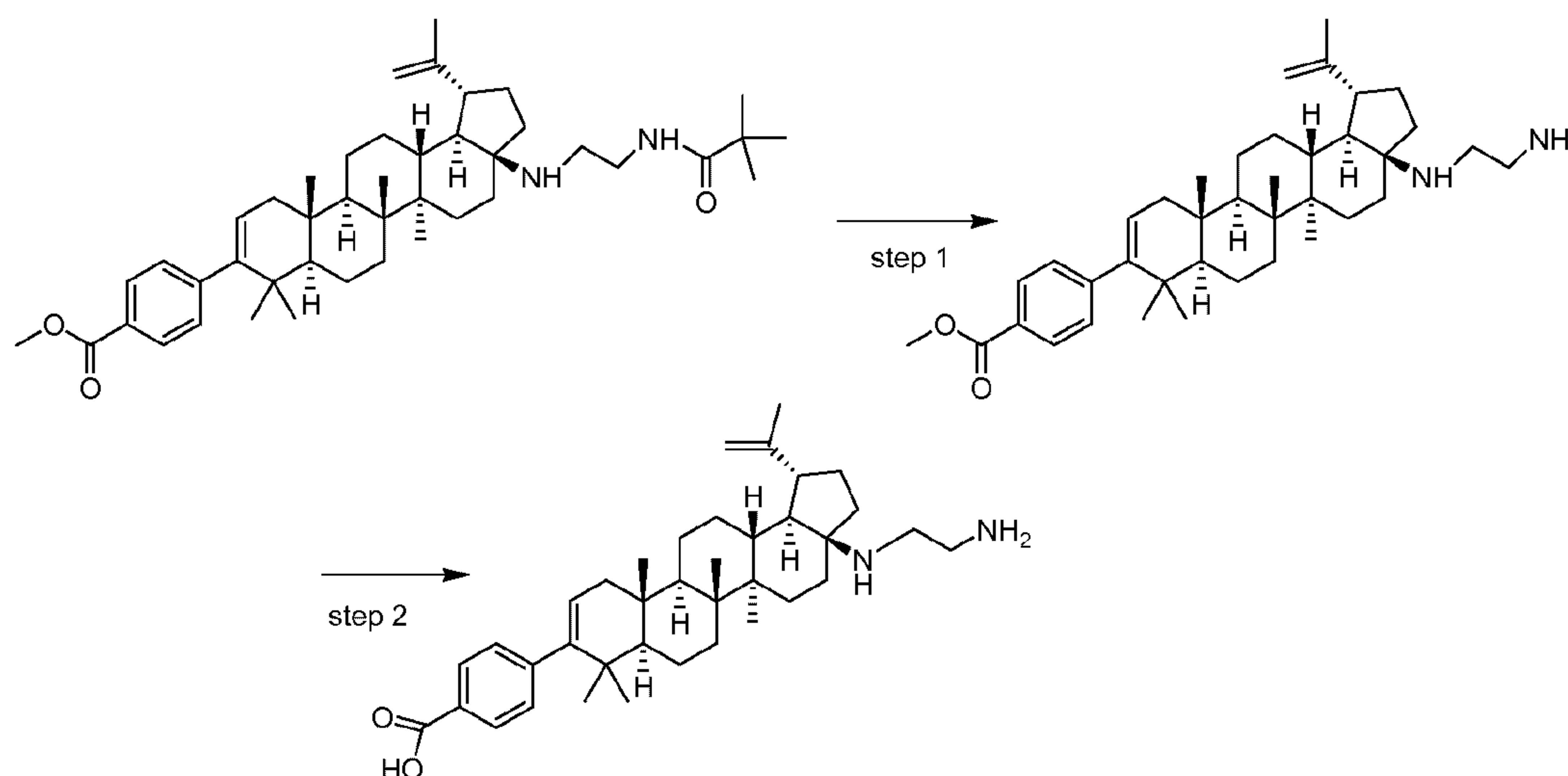
To methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (1.00 g, 1.84 mmol) in DCE (5 mL) was added *tert*-butyl 2-oxoethylcarbamate (1.17 g, 7.36 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 ( $M+H$ )<sup>+</sup>, 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 ( $M+H$ )<sup>+</sup>, 2.65 min (method 10). <sup>1</sup>H NMR (500 MHz, *Acetic acid d4*)  $\delta$  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.

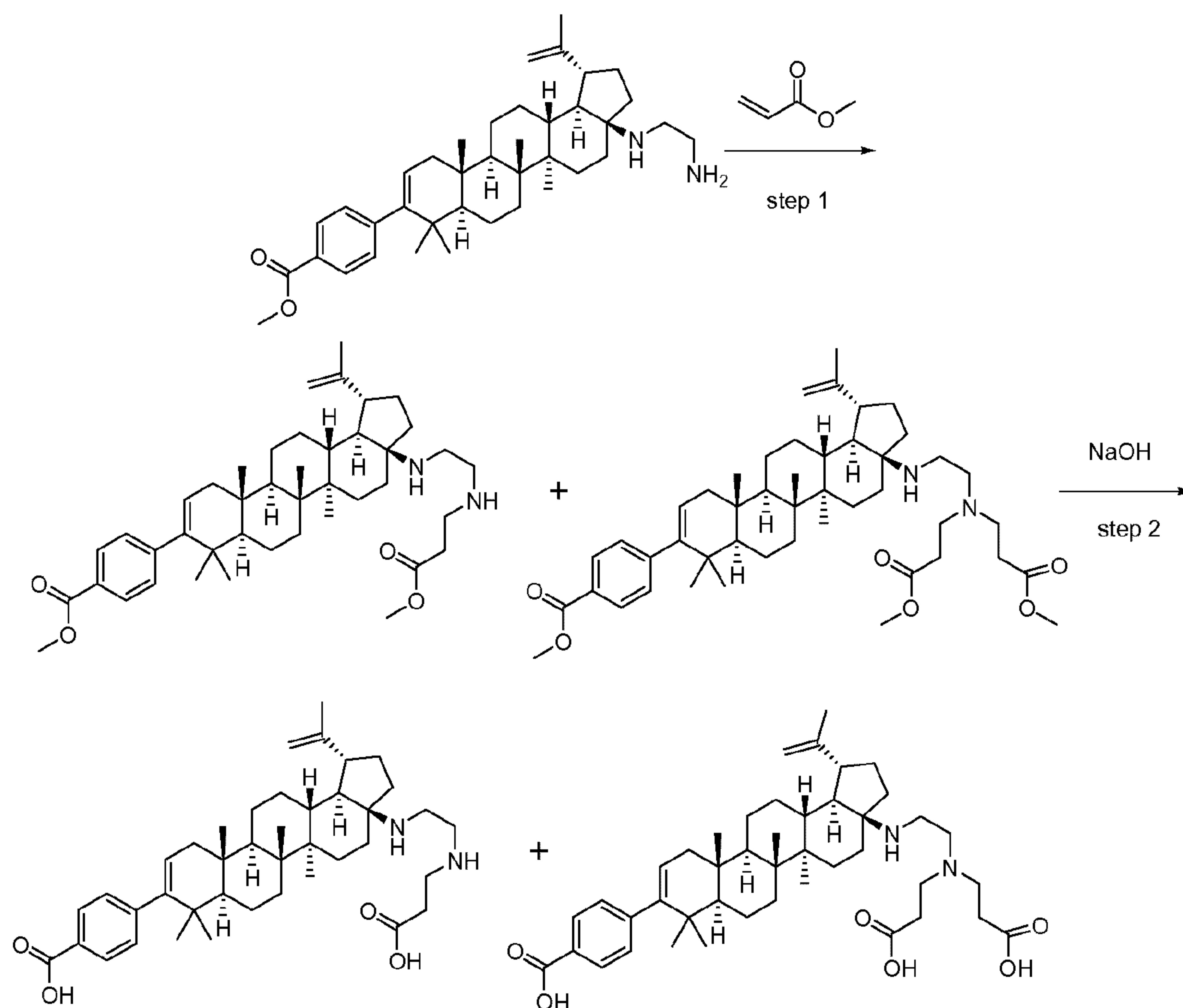
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(tert-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (900 mg, 1.310 mmol) in dioxane (1 mL) was 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)<sup>+</sup>, 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)<sup>+</sup>, 2.39 min (method 10). <sup>1</sup>H 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)ethylazanediyl)dipropionic 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-

# **DEMANDES OU BREVETS VOLUMINEUX**

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS  
COMPREND PLUS D'UN TOME.**

**CECI EST LE TOME \_\_1\_\_ DE \_\_2\_\_**

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

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# **JUMBO APPLICATIONS / PATENTS**

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
THAN ONE VOLUME.**

**THIS IS VOLUME \_\_1\_\_ OF \_\_2\_\_**

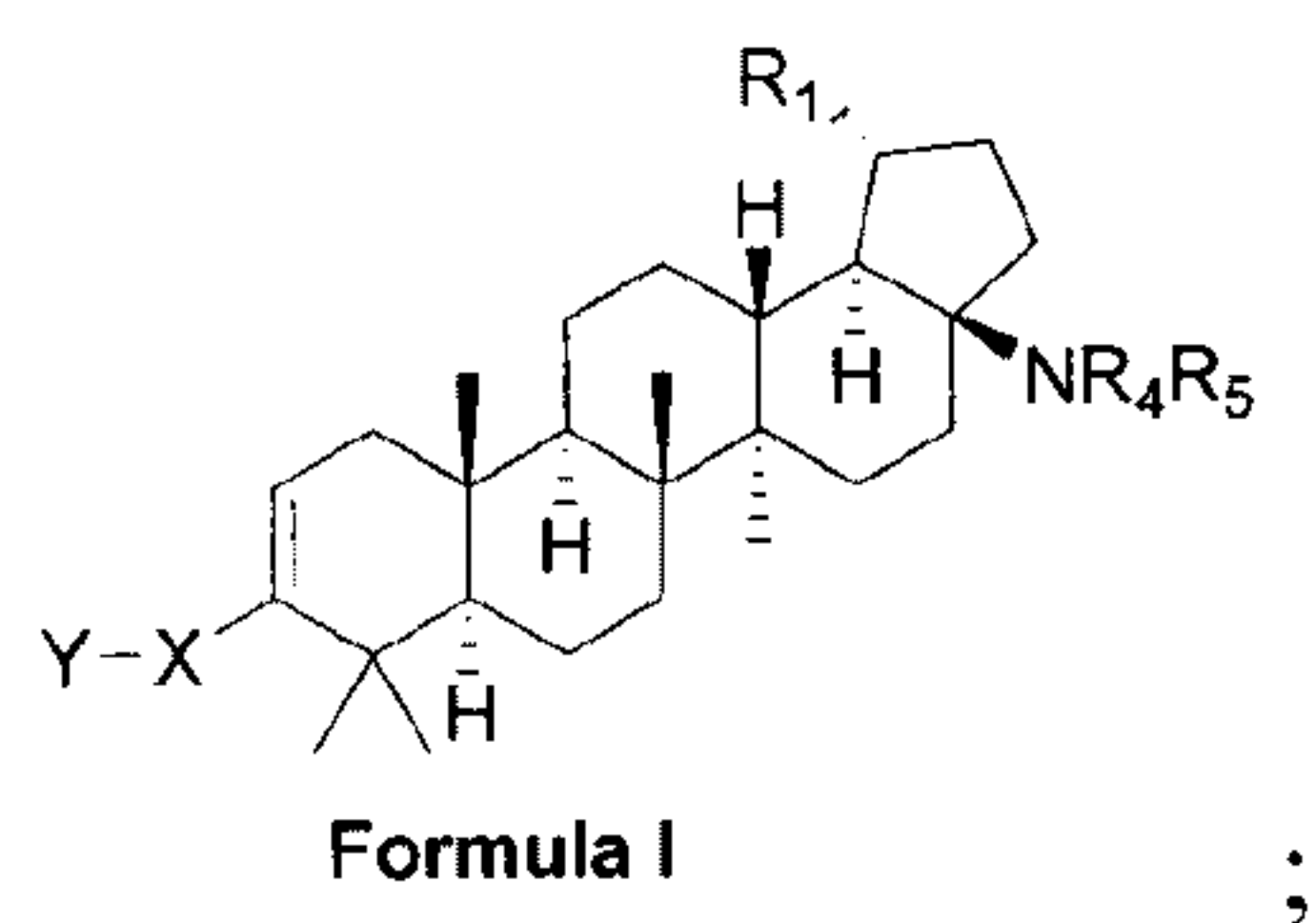
NOTE: For additional volumes please contact the Canadian Patent Office.

## CLAIMS

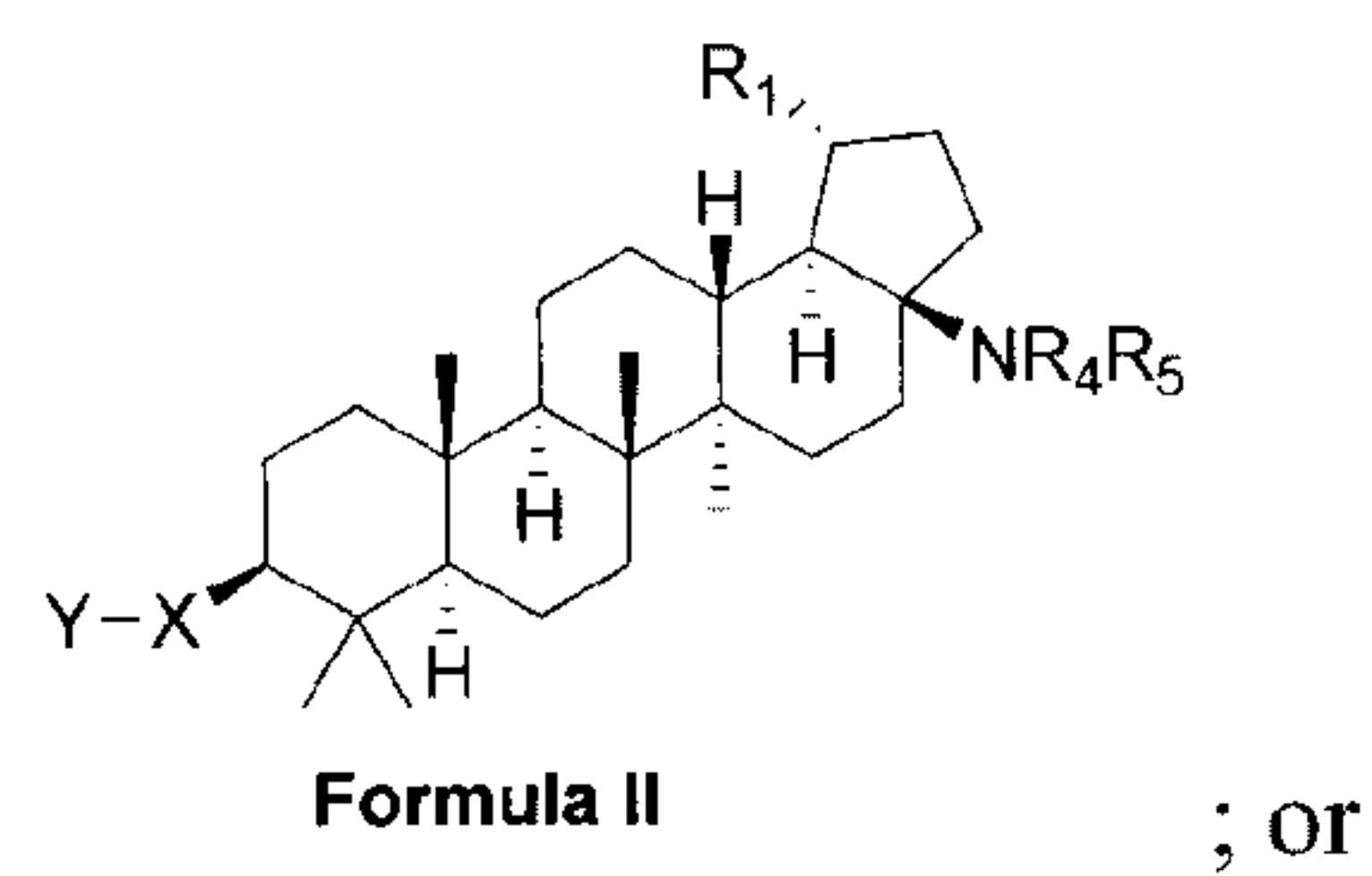
What is claimed is:

1. A compound or a pharmaceutically acceptable salt thereof, which is:

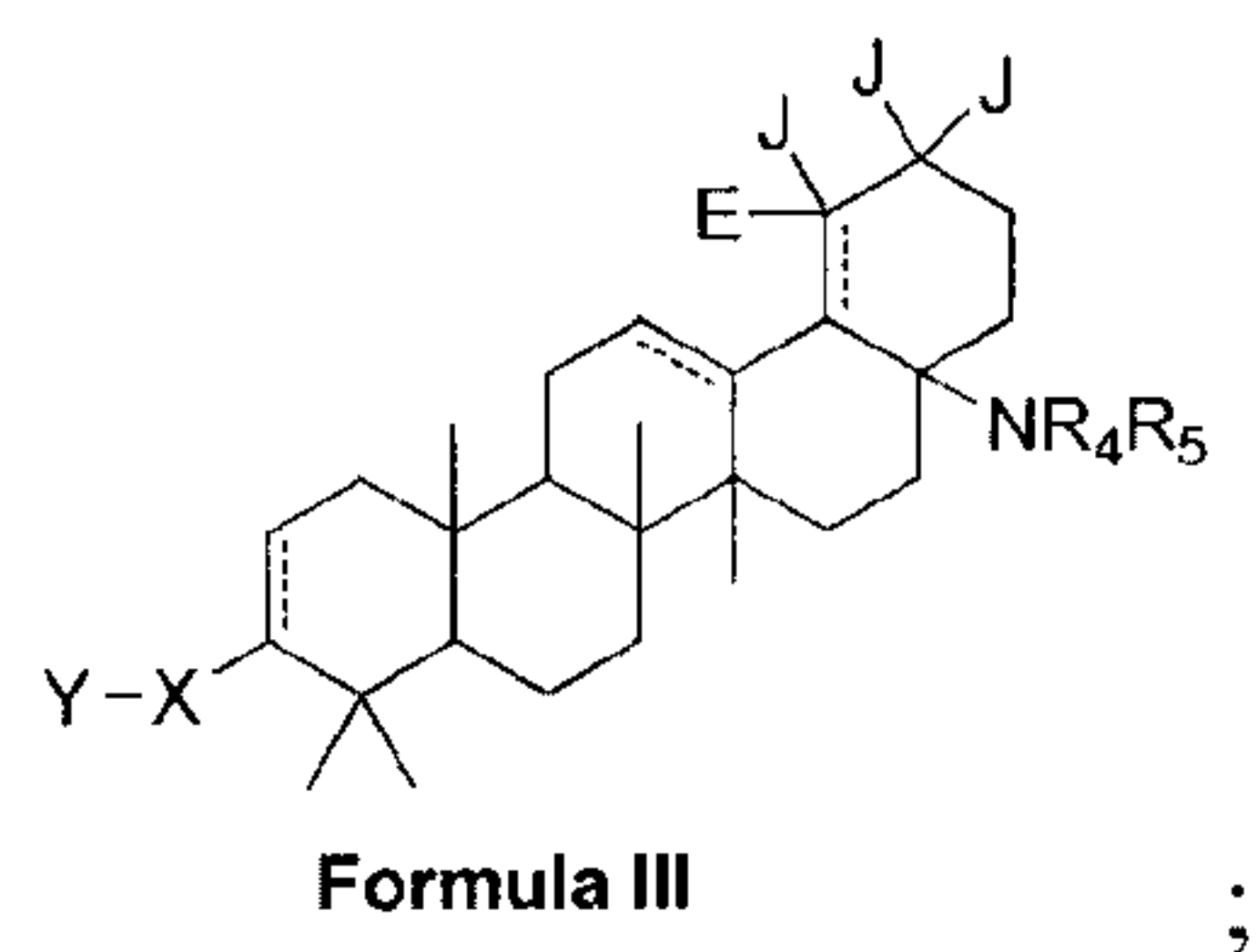
a compound of formula I



a compound of formula II



a compound of formula III



wherein R<sub>1</sub> is isopropenyl or isopropyl;

J and E are -H or -CH<sub>3</sub>, and E is absent when the double bond is present;

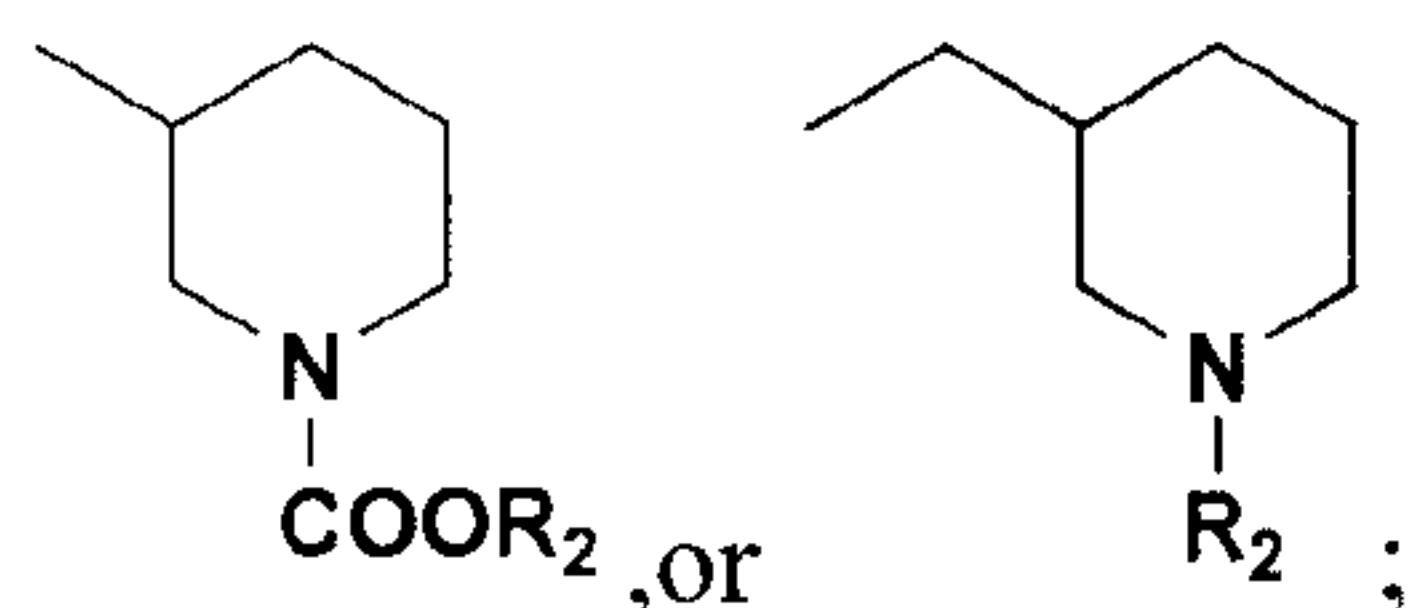
X is a phenyl or heteroaryl ring substituted with A, wherein A is at least one member which is -H, -halo, -hydroxyl, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkoxy, or -COOR<sub>2</sub>;

R<sub>2</sub> is -H, -C<sub>1-6</sub> alkyl, -alkylsubstituted C<sub>1-6</sub> alkyl or-arylsubstituted C<sub>1-6</sub> alkyl;

Y is -COOR<sub>2</sub>, -C(O)NR<sub>2</sub>SO<sub>2</sub>R<sub>3</sub>, -C(O)NHSO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>, -NR<sub>2</sub>SO<sub>2</sub>R<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>, -C<sub>3-6</sub> cycloalkyl-COOR<sub>2</sub>, -C<sub>2-6</sub> alkenyl-COOR<sub>2</sub>, -C<sub>2-6</sub> alkynyl-COOR<sub>2</sub>, -C<sub>1-6</sub> alkyl-COOR<sub>2</sub>, -NHC(O)(CH<sub>2</sub>)<sub>n</sub>-COOR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>C(O)R<sub>2</sub>, -tetrazole, or -CONHOH, wherein n=1-6;

R<sub>3</sub> is -C<sub>1-6</sub> alkyl or -alkylsubstituted C<sub>1-6</sub> alkyl;

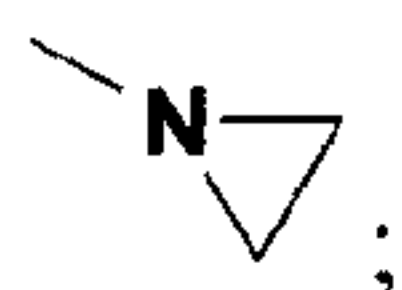
R<sub>4</sub> is -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkyl-C(OR<sub>3</sub>)<sub>2</sub>-C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>1-6</sub> alkyl-C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> alkyl-Q<sub>1</sub>, -C<sub>1-6</sub> alkyl-C<sub>3-6</sub> cycloalkyl-Q<sub>1</sub>, aryl, heteroaryl, substituted heteroaryl, -COR<sub>6</sub>, -COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub>, -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>,



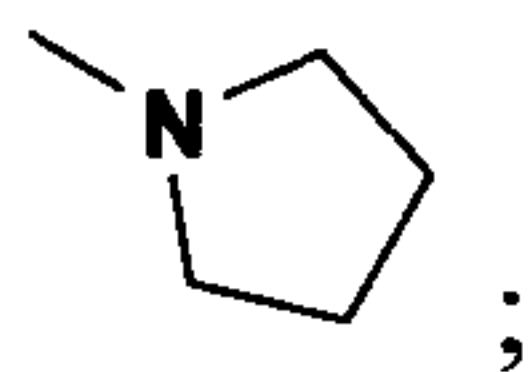
wherein Q<sub>1</sub> is heteroaryl, substituted heteroaryl, halogen, -CF<sub>3</sub>, -OR<sub>2</sub>, -COOR<sub>2</sub>, -NR<sub>8</sub>R<sub>9</sub>, -CONR<sub>10</sub>R<sub>11</sub> or -SO<sub>2</sub>R<sub>7</sub>;

R<sub>5</sub> is -H, -C<sub>1-6</sub> alkyl, -C<sub>3-6</sub> cycloalkyl, -C<sub>1-6</sub> alkylsubstituted alkyl, -C<sub>1-6</sub> alkyl-NR<sub>8</sub>R<sub>9</sub>, -COR<sub>10</sub>, -COR<sub>6</sub>, -COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub> or -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>;

with the proviso that only one of R<sub>4</sub> or R<sub>5</sub> can be -COR<sub>6</sub>, -COCOR<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub> or -SO<sub>2</sub>NR<sub>2</sub>R<sub>2</sub>; or R<sub>4</sub> and R<sub>5</sub> are taken together with the adjacent N to form

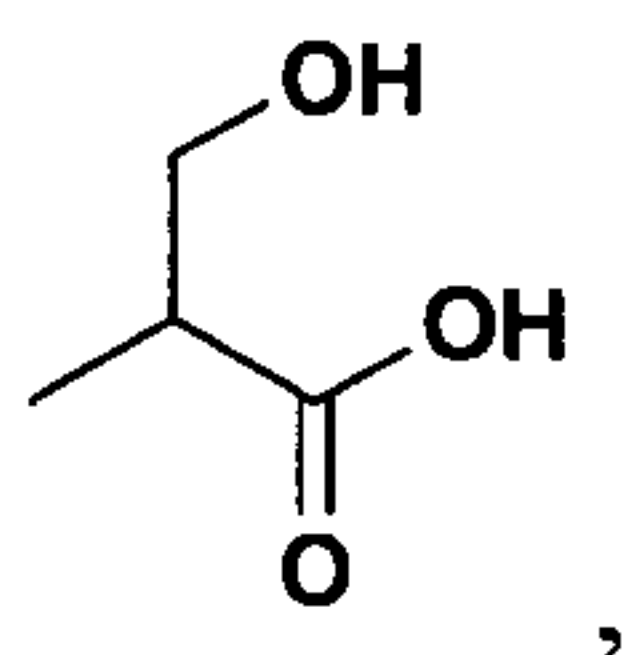




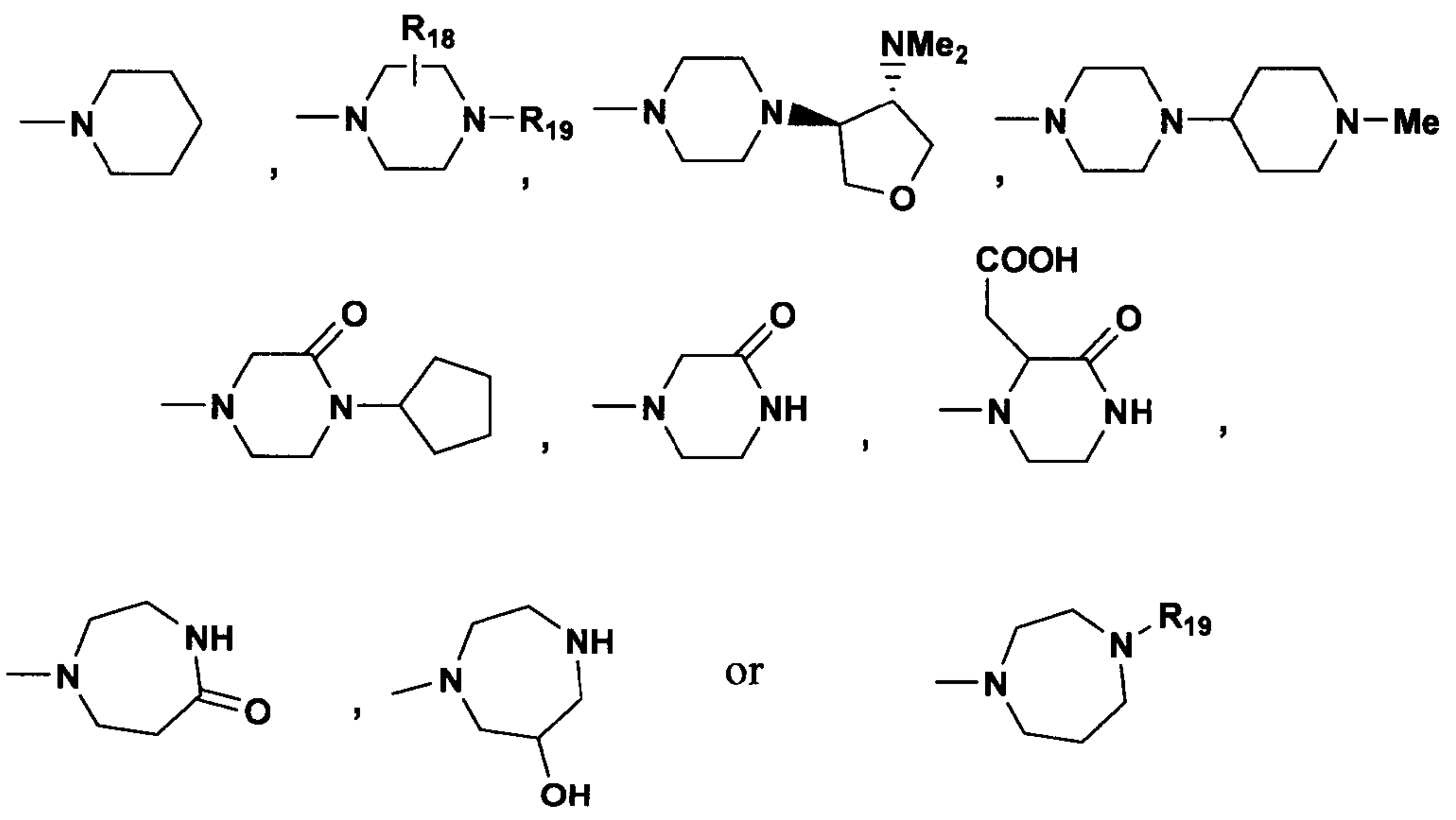


$R_{12}$  is  $-C_{1-6}$  alkyl,  $-NR_2R_2$ ,  $-C_{1-6}$  alkyl-OH,  $-C_{1-6}$  substituted alkyl,  $-C_{3-6}$  cycloalkyl,  $-COR_7$ ,  $-COONR_{22}R_{23}$ ,  $-SOR_7$ , or  $-SONR_{24}R_{25}$ ;

$R_{13}$  and  $R_{14}$  are independently  $-H$ ,  $-C_{1-6}$  alkyl,  $-C_{3-6}$  cycloalkyl,  $-C_{1-6}$  substituted alkyl,  $-C_{1-6}$  alkyl- $Q_3$ ,  $-C_{1-6}$  alkyl- $C_{3-6}$  cycloalkyl- $Q_3$ ,  $C_{1-6}$  substituted alkyl- $Q_3$  or



or  $R_{13}$  and  $R_{14}$  are taken together with the adjacent N to form a cycle which is:



$Q_3$  is heteroaryl, substituted heteroaryl,  $-NR_{20}R_{21}$ ,  $-CONR_2R_2$ ,  $-COOR_2$ ,  $-OR_2$ , or  $-SO_2R_3$ ;

$R_{15}$  is  $-C_{1-6}$  alkyl,  $-C_{3-6}$  cycloalkyl,  $-C_{1-6}$  substituted alkyl,  $-C_{1-6}$  alkyl- $Q_3$ ,  $-C_{1-6}$  alkyl- $C_{3-6}$  cycloalkyl- $Q_3$  or  $-C_{1-6}$  substituted alkyl- $Q_3$ ;

$R_{16}$  is  $-H$ ,  $-C_{1-6}$  alkyl,  $-NR_2R_2$ , or  $-COOR_3$ ;

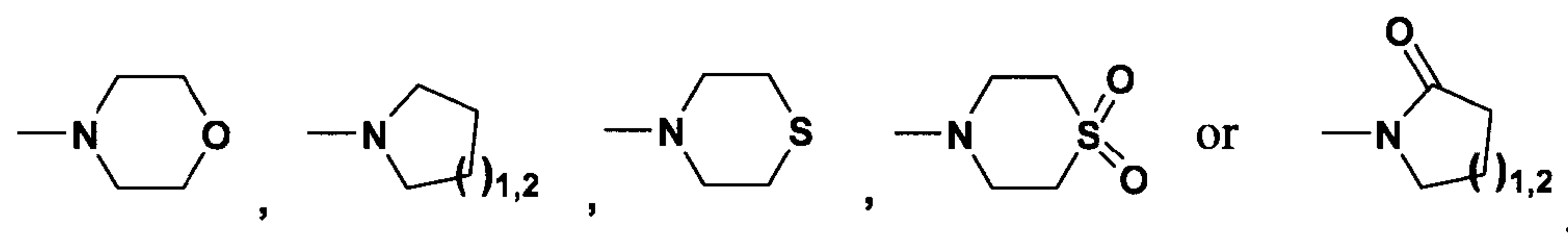
R<sub>17</sub> is -H, -C<sub>1-6</sub> alkyl, -COOR<sub>3</sub>, or aryl;

R<sub>18</sub> is -COOR<sub>2</sub> or -C<sub>1-6</sub> alkyl-COOR<sub>2</sub>;

R<sub>19</sub> is -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> alkyl-Q<sub>4</sub>, -COR<sub>3</sub>, or -COOR<sub>3</sub>,  
wherein Q<sub>4</sub> is -NR<sub>2</sub>R<sub>2</sub> or -OR<sub>2</sub>;

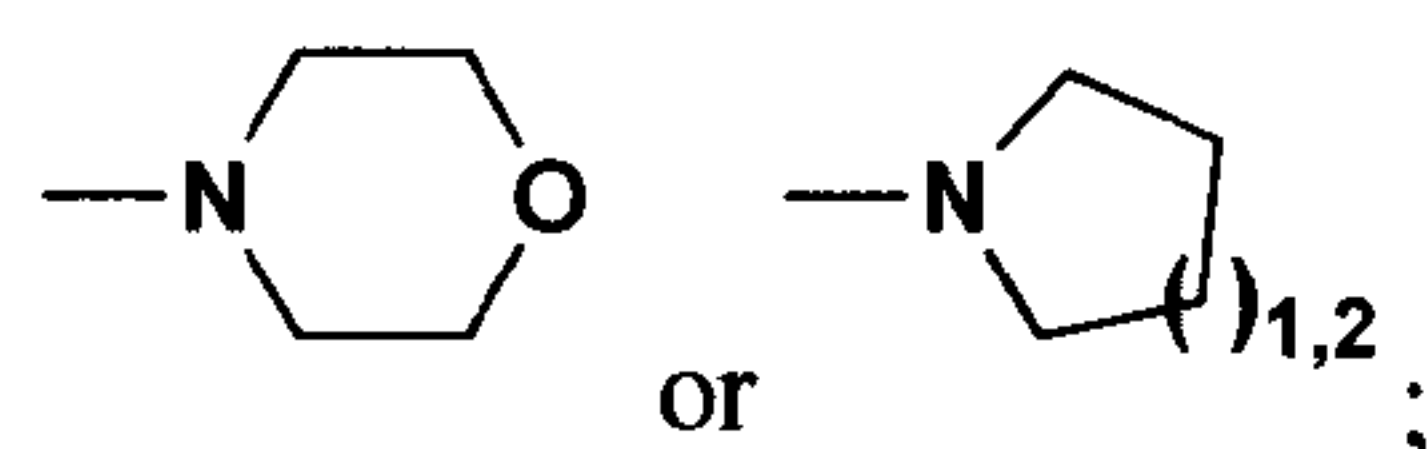
R<sub>20</sub> and R<sub>21</sub> are independently -H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>1-6</sub> substituted alkyl-OR<sub>2</sub>,  
or -COR<sub>3</sub>,

or R<sub>20</sub> and R<sub>21</sub> are taken together with the adjacent N to form a cycle which is



with the proviso that only one of R<sub>20</sub> or R<sub>21</sub> can be -COR<sub>3</sub>;

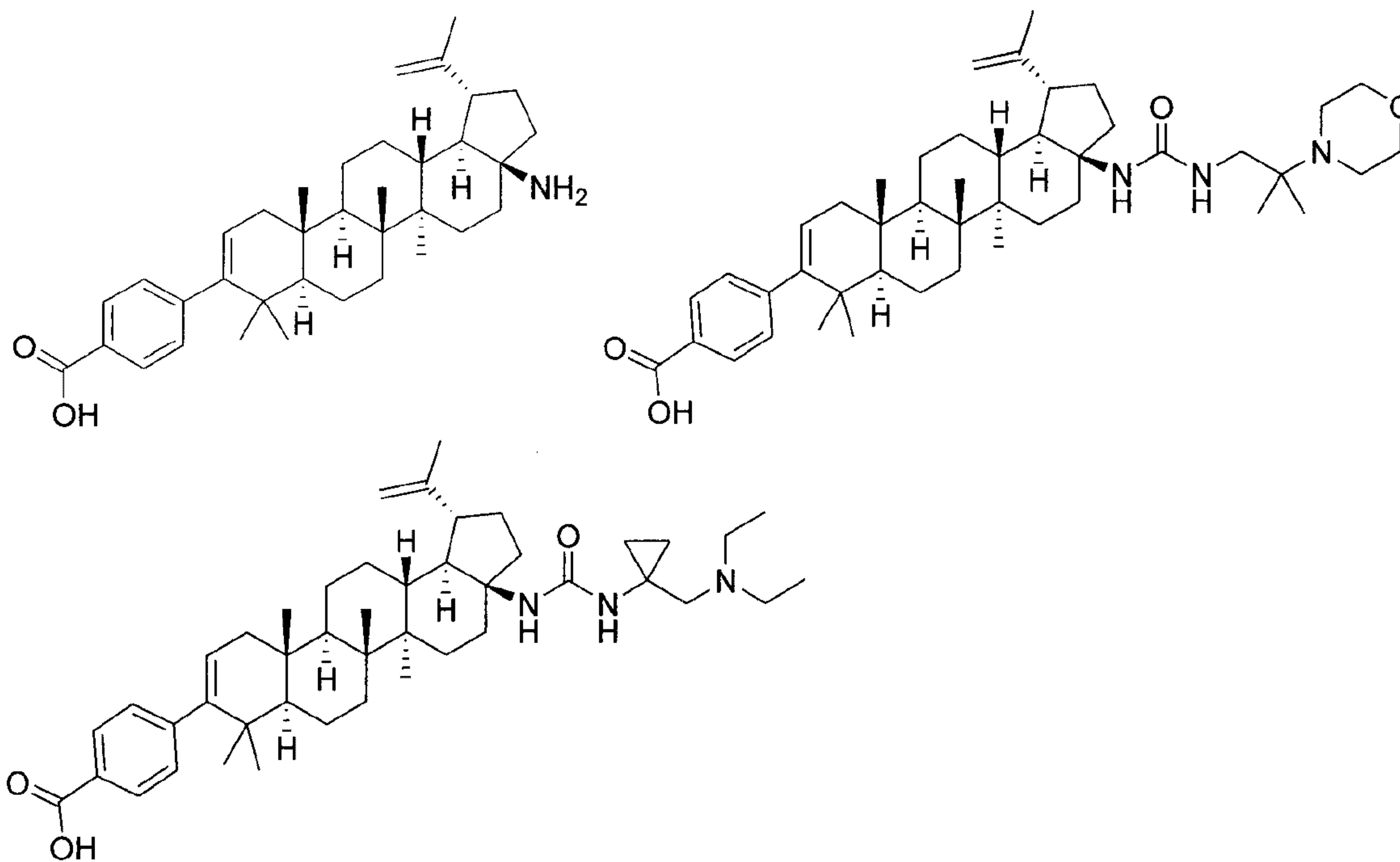
R<sub>22</sub> and R<sub>23</sub> are independently H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, or -C<sub>1-6</sub> cycloalkyl,  
or R<sub>22</sub> and R<sub>23</sub> are taken together with the adjacent N to form a cycle which is

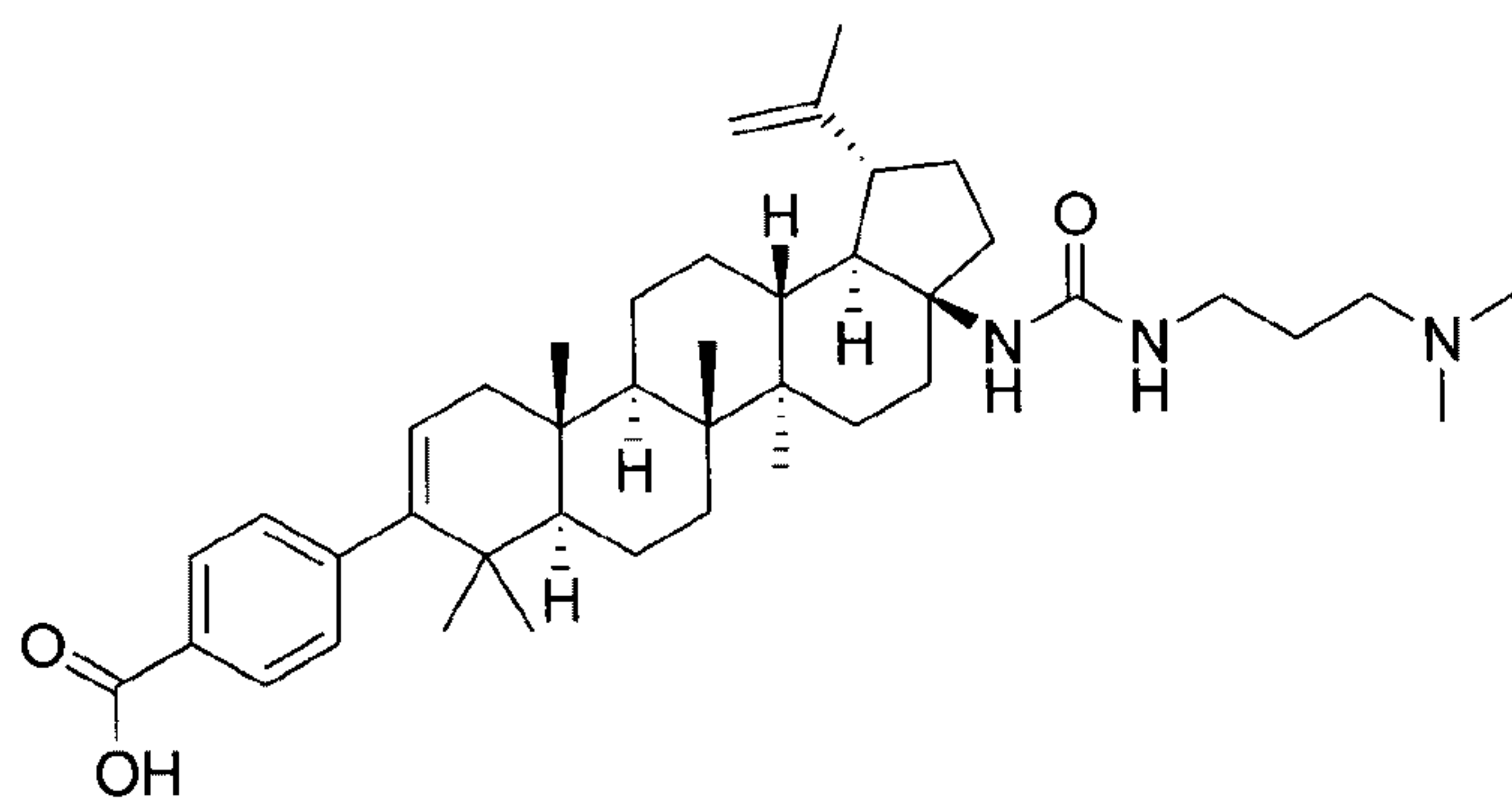


R<sub>24</sub> and R<sub>25</sub> are independently H, -C<sub>1-6</sub> alkyl, -C<sub>1-6</sub> substituted alkyl, -C<sub>1-6</sub> alkyl-Q<sub>5</sub>, -C<sub>1-6</sub>  
cycloalkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl,  
and Q<sub>5</sub> is halogen or SO<sub>2</sub>R<sub>3</sub>.

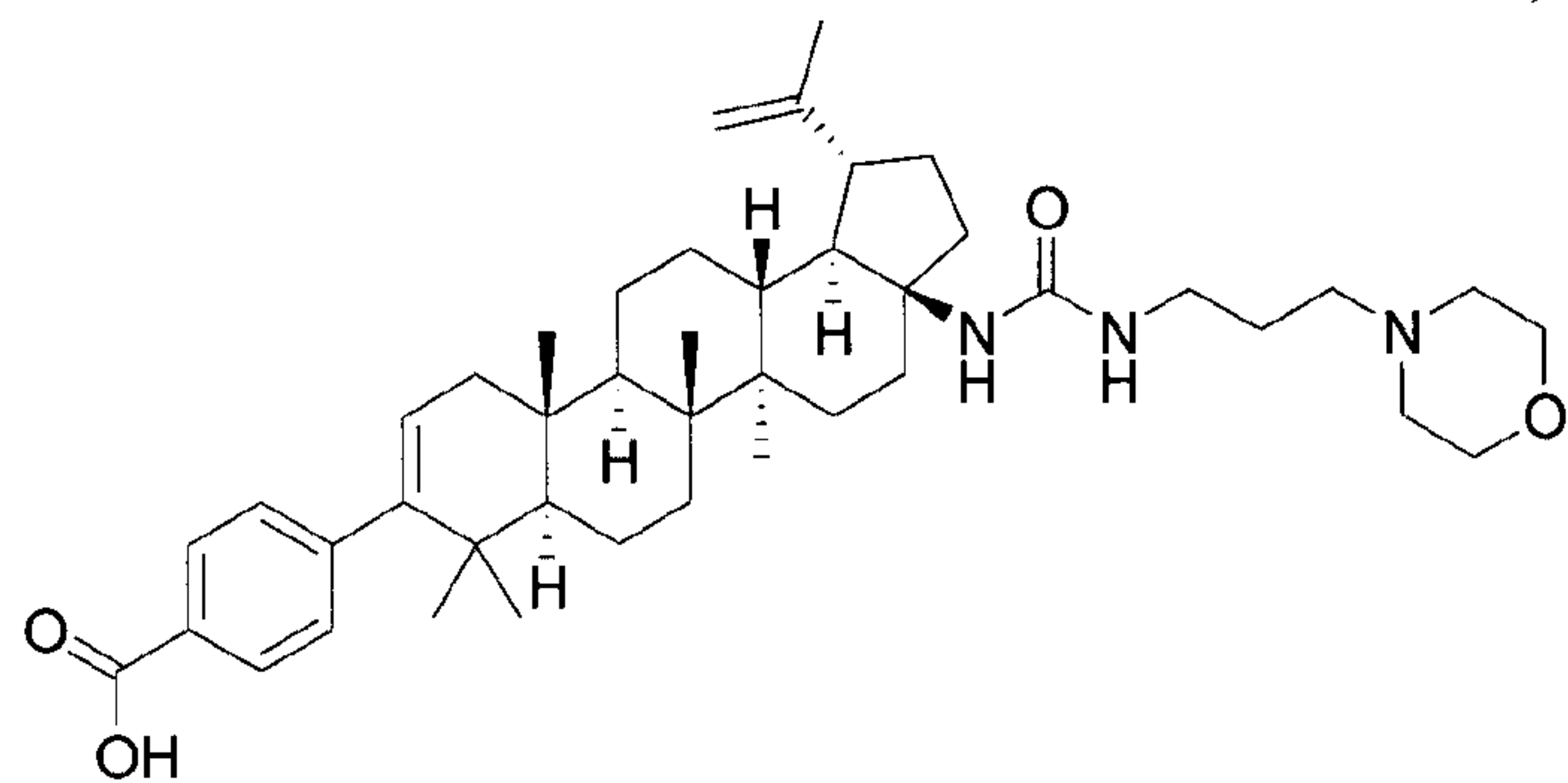
2. The compound as claimed in claim 1, wherein said compound has the Formula I.
3. The compound as claimed in claim 1, wherein said compound has the Formula II.
4. The compound as claimed in claim 1, wherein said compound has the Formula III.
5. The compound as claimed in claim 2, wherein R<sub>1</sub> is isopropenyl.
6. The compound as claimed in claim 5, wherein X is phenyl.

7. The compound as claimed in claim 6, wherein Y is  $-\text{COOR}_2$ .
8. The compound as claimed in claim 7, wherein Y is  $-\text{COOH}$ .
9. The compound as claimed in claim 6, wherein A is  $-\text{H}$ .
10. The compound as claimed in claim 6, wherein  $\text{R}_4$  is  $-\text{H}$ ,  $-\text{C}_{1-6}$  alkyl,  $-\text{C}_{1-6}$  alkyl- $\text{Q}_1$ , or  $-\text{COR}_6$ .
11. The compound as claimed in claim 10, wherein  $\text{R}_5$  is  $-\text{H}$ .
12. The compound as claimed in claim 10, wherein  $\text{R}_4$  is  $-\text{C}_{1-6}$  alkyl- $\text{Q}_1$ .
13. The compound as claimed in claim 12, wherein  $\text{Q}_1$  is  $-\text{NR}_8\text{R}_9$ .
14. The compound as claimed in claim 10, wherein  $\text{R}_4$  is  $-\text{COR}_6$ .
15. A compound or a pharmaceutically acceptable salt thereof, which is:

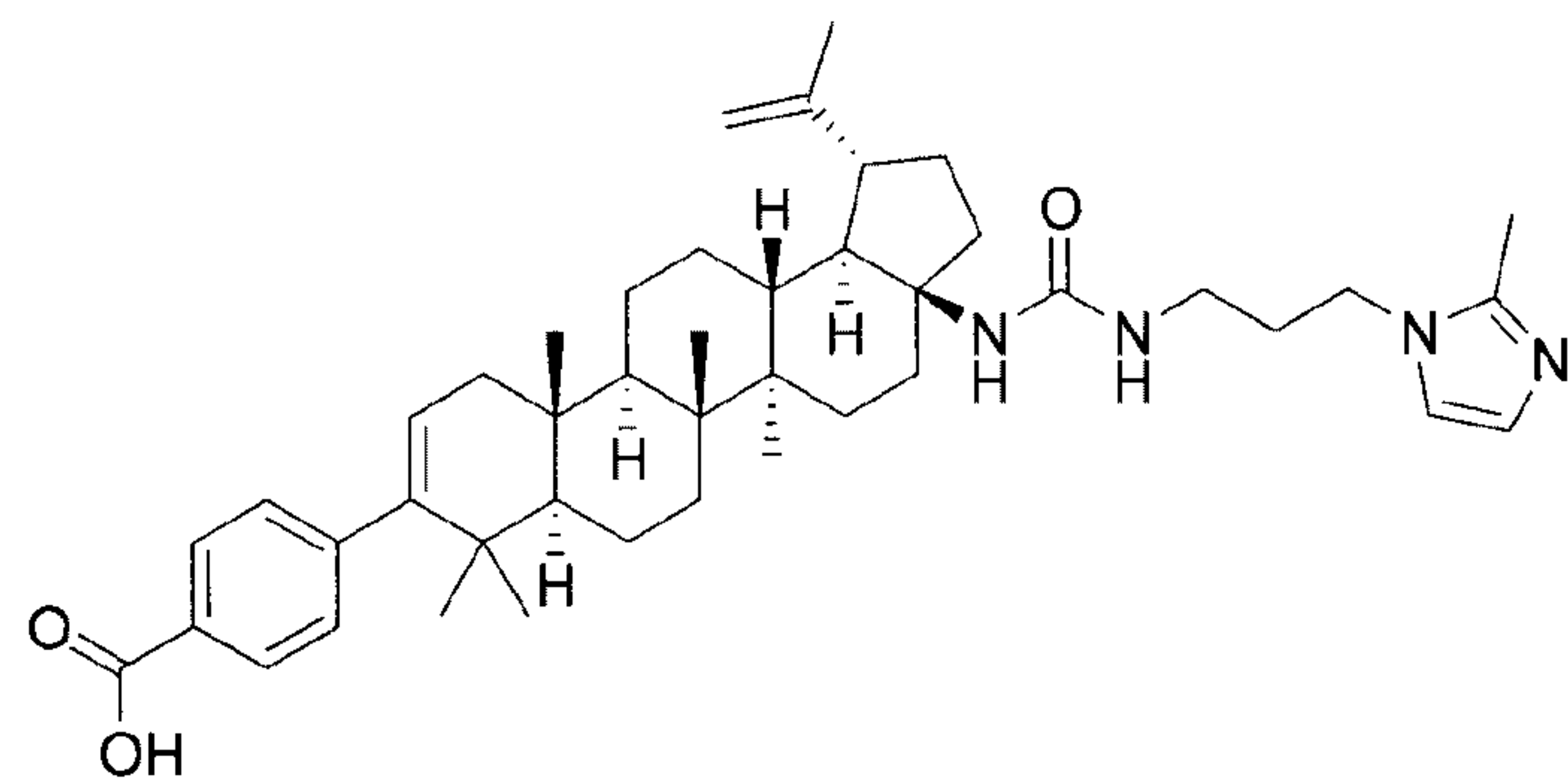




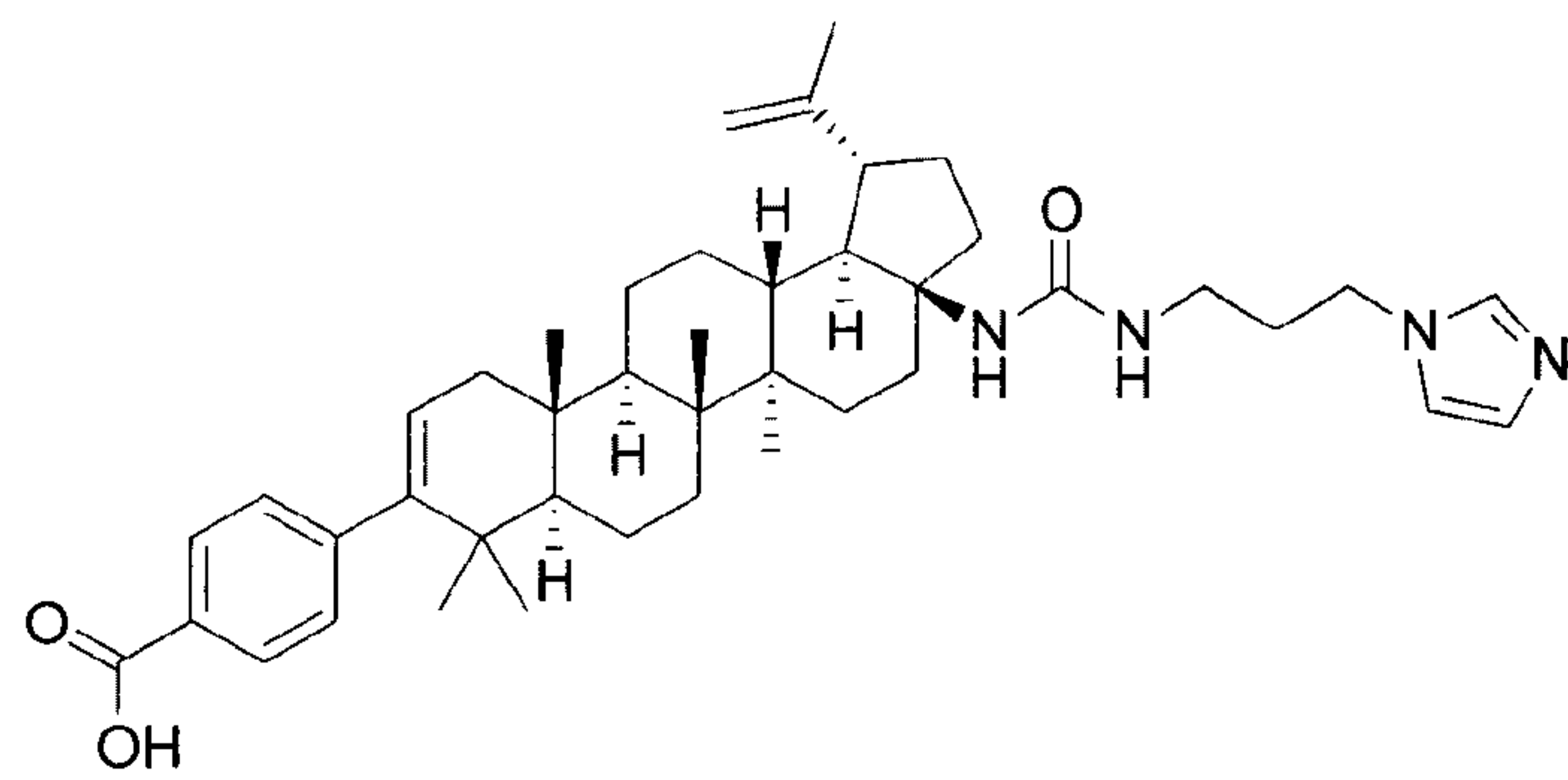
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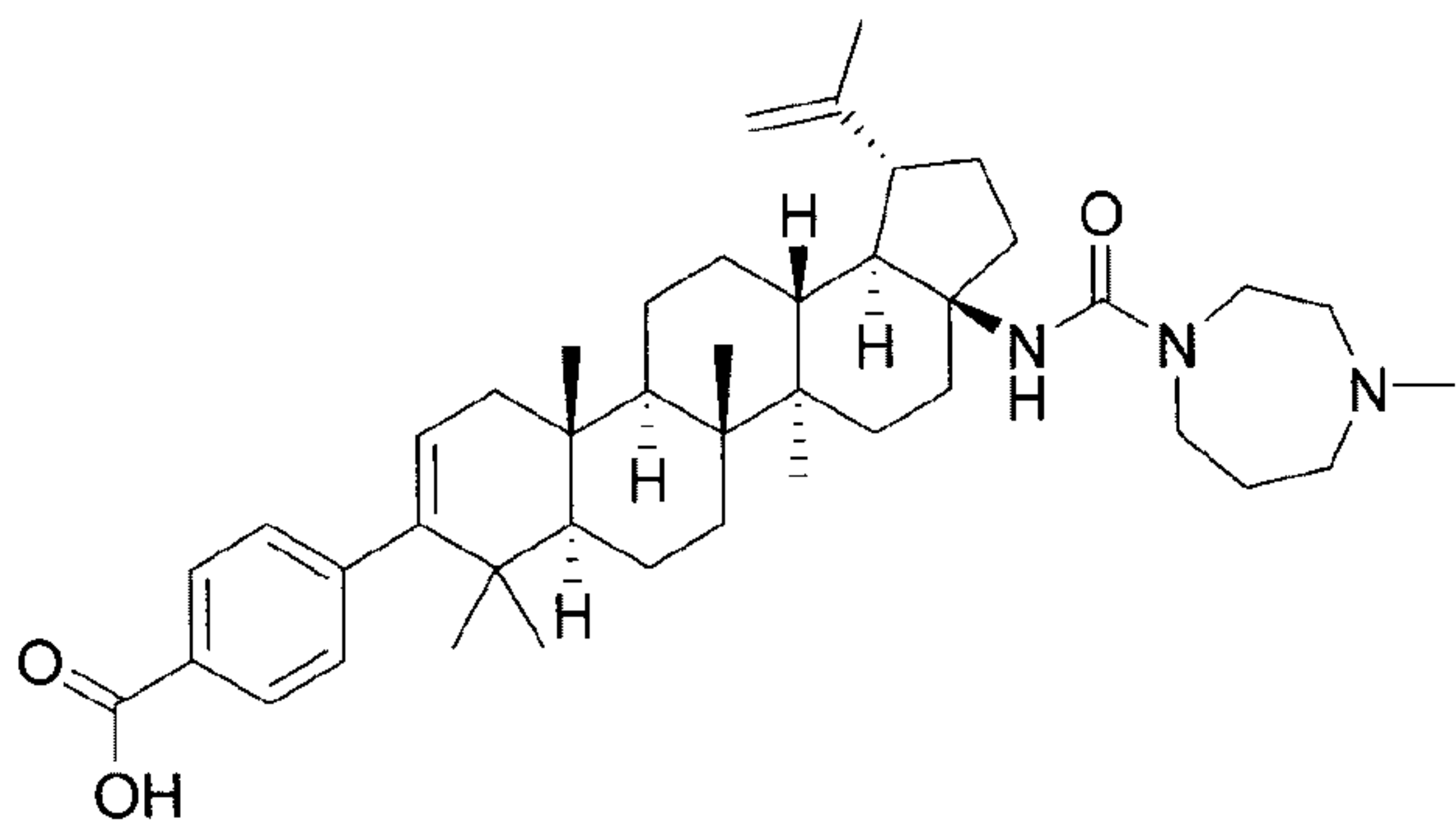
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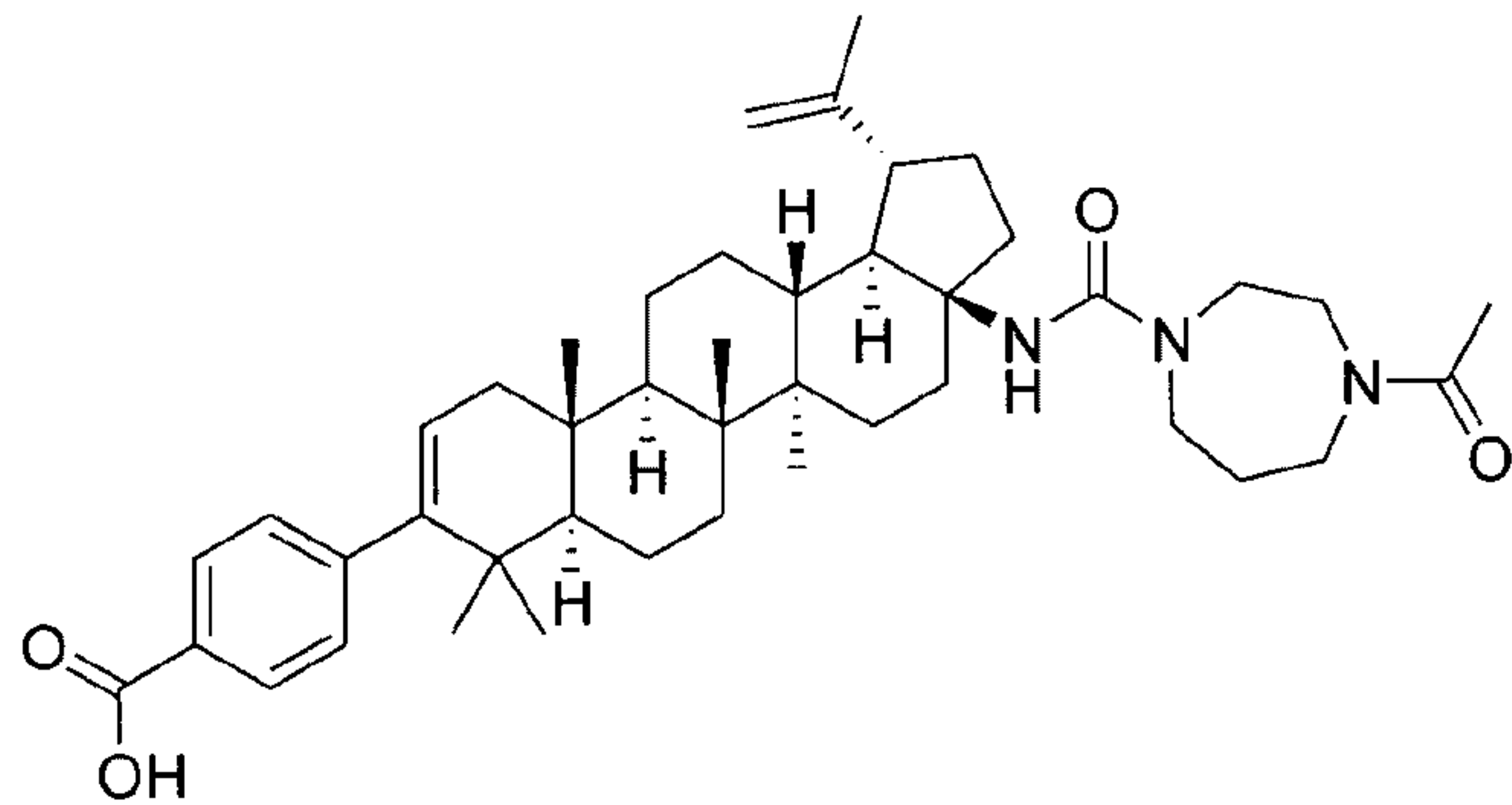
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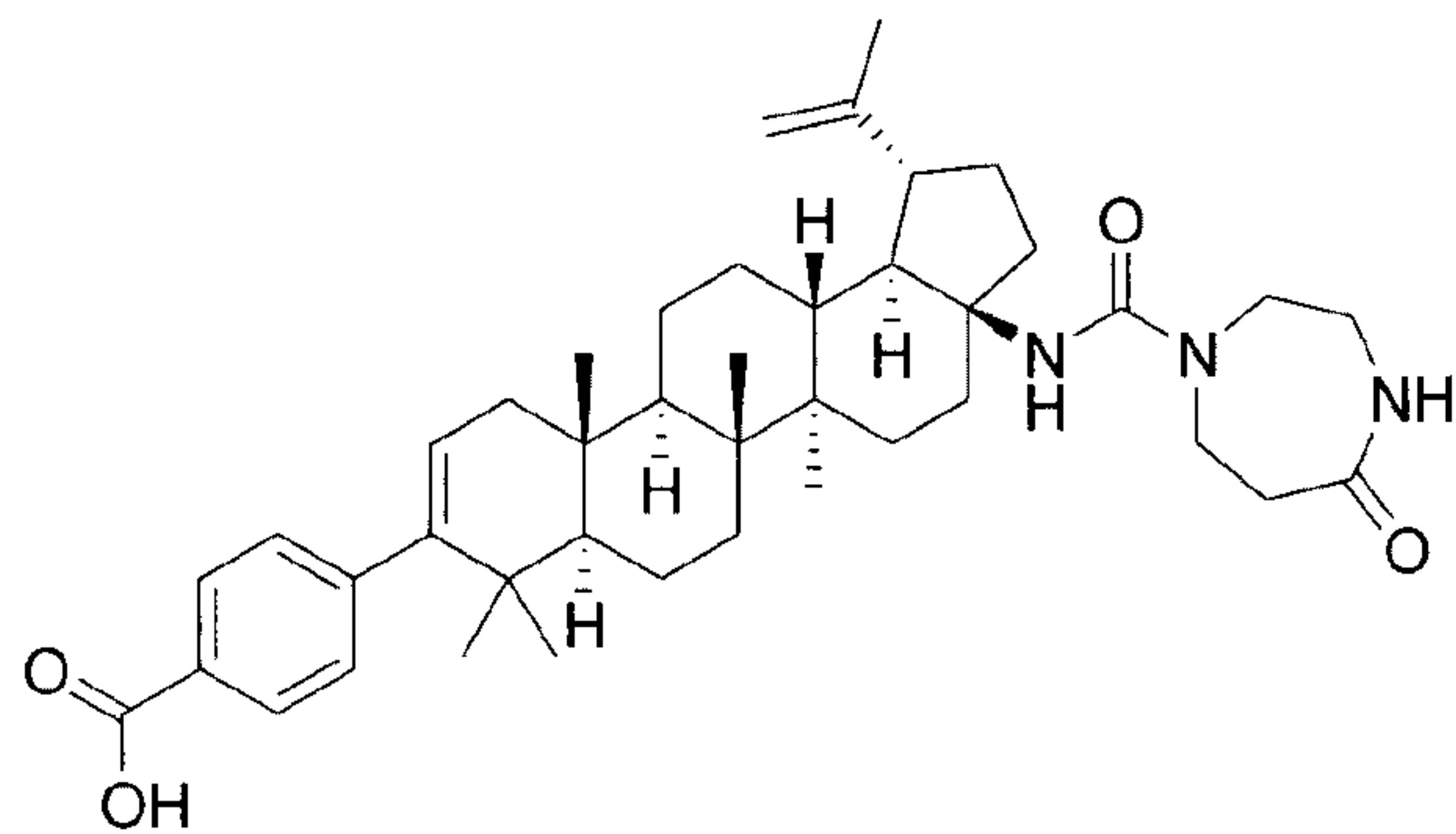
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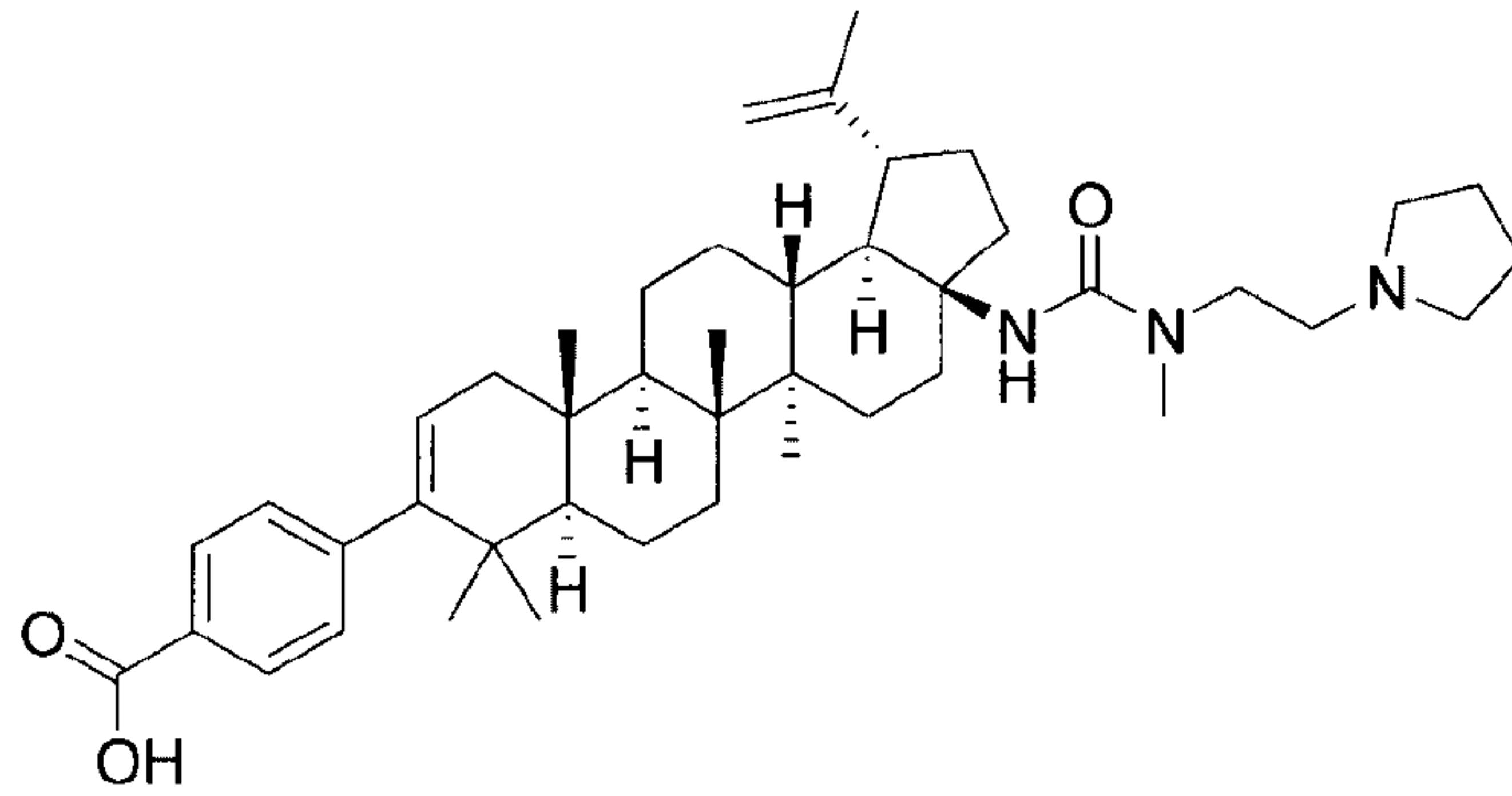
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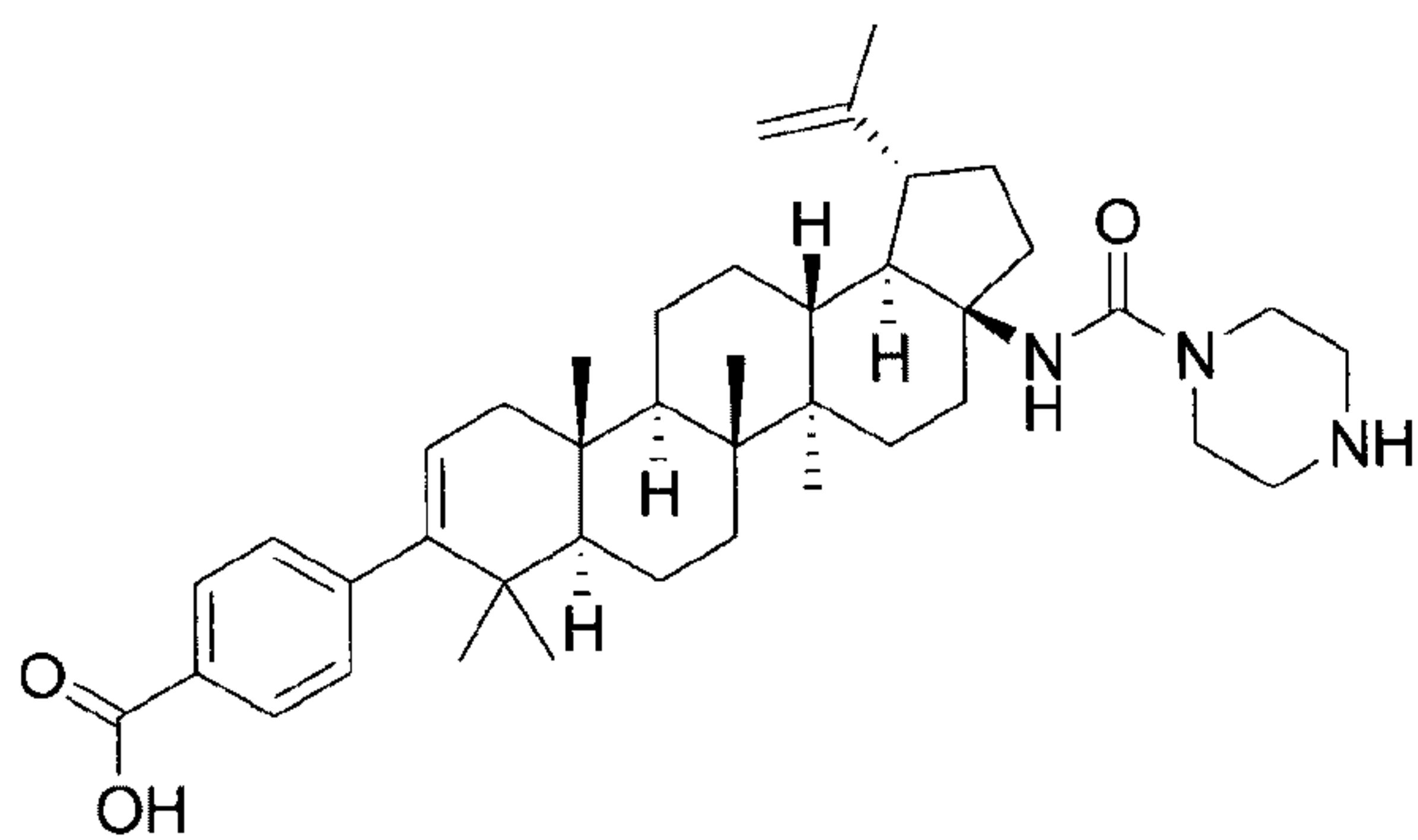
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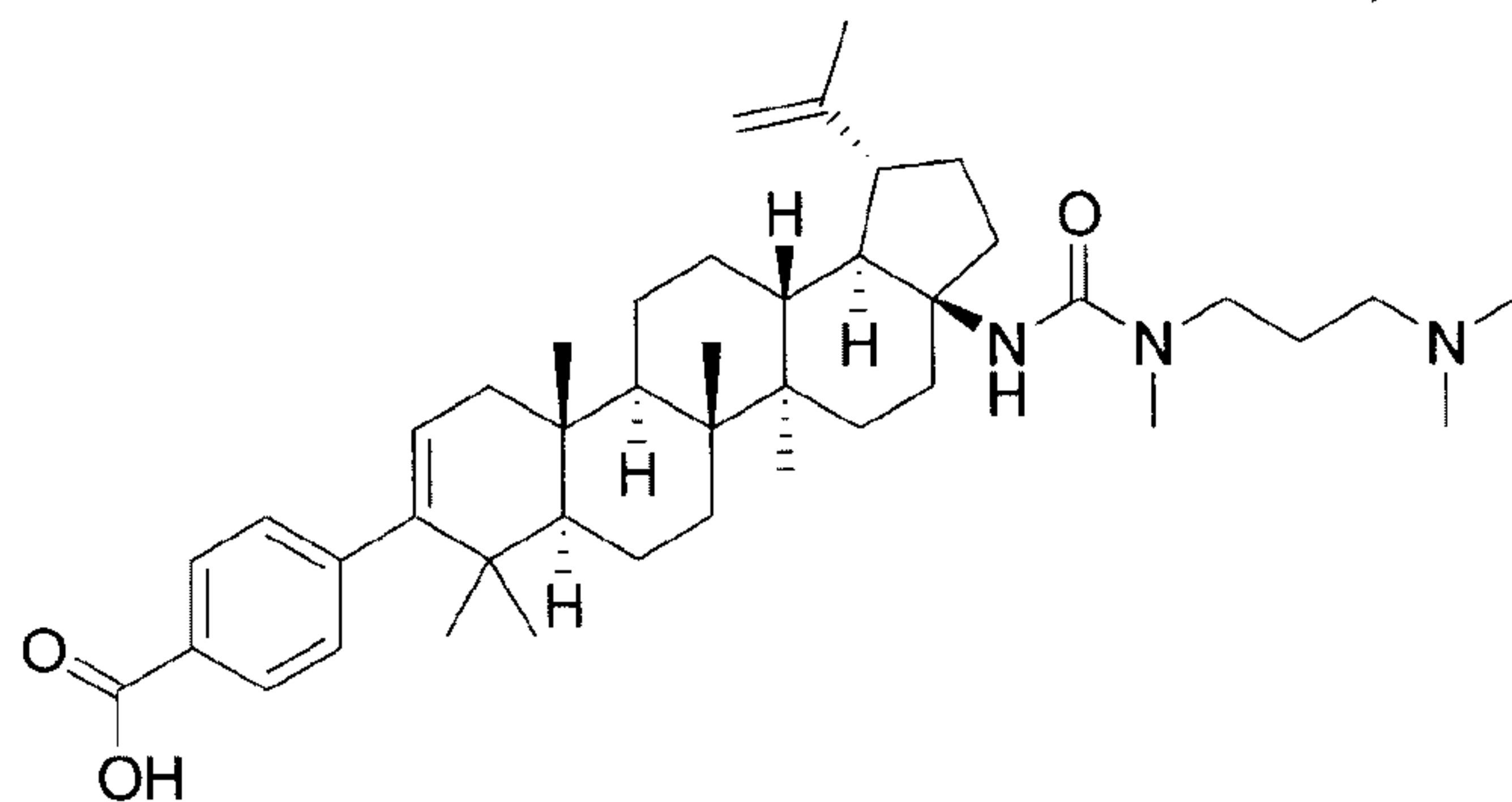
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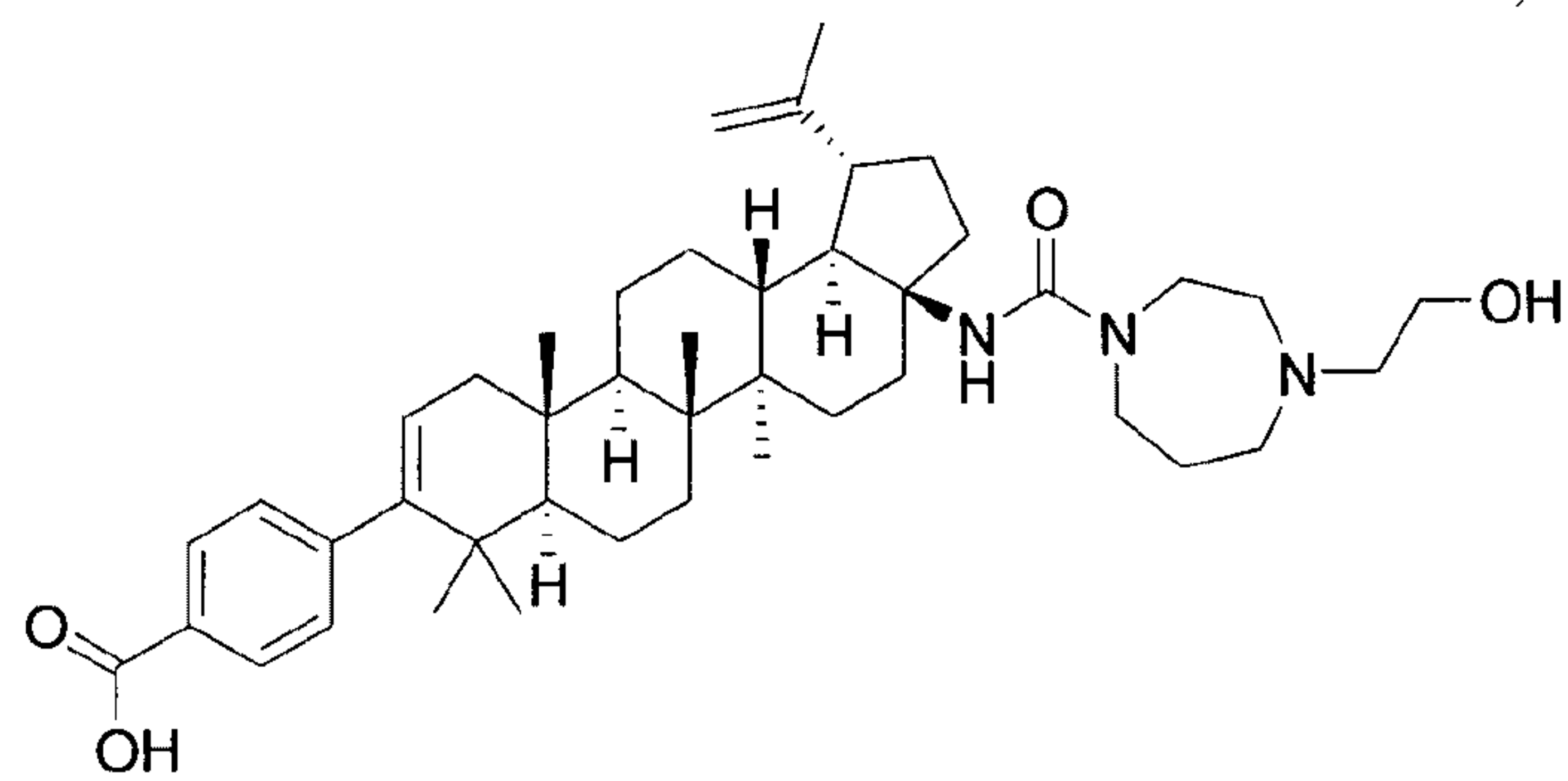
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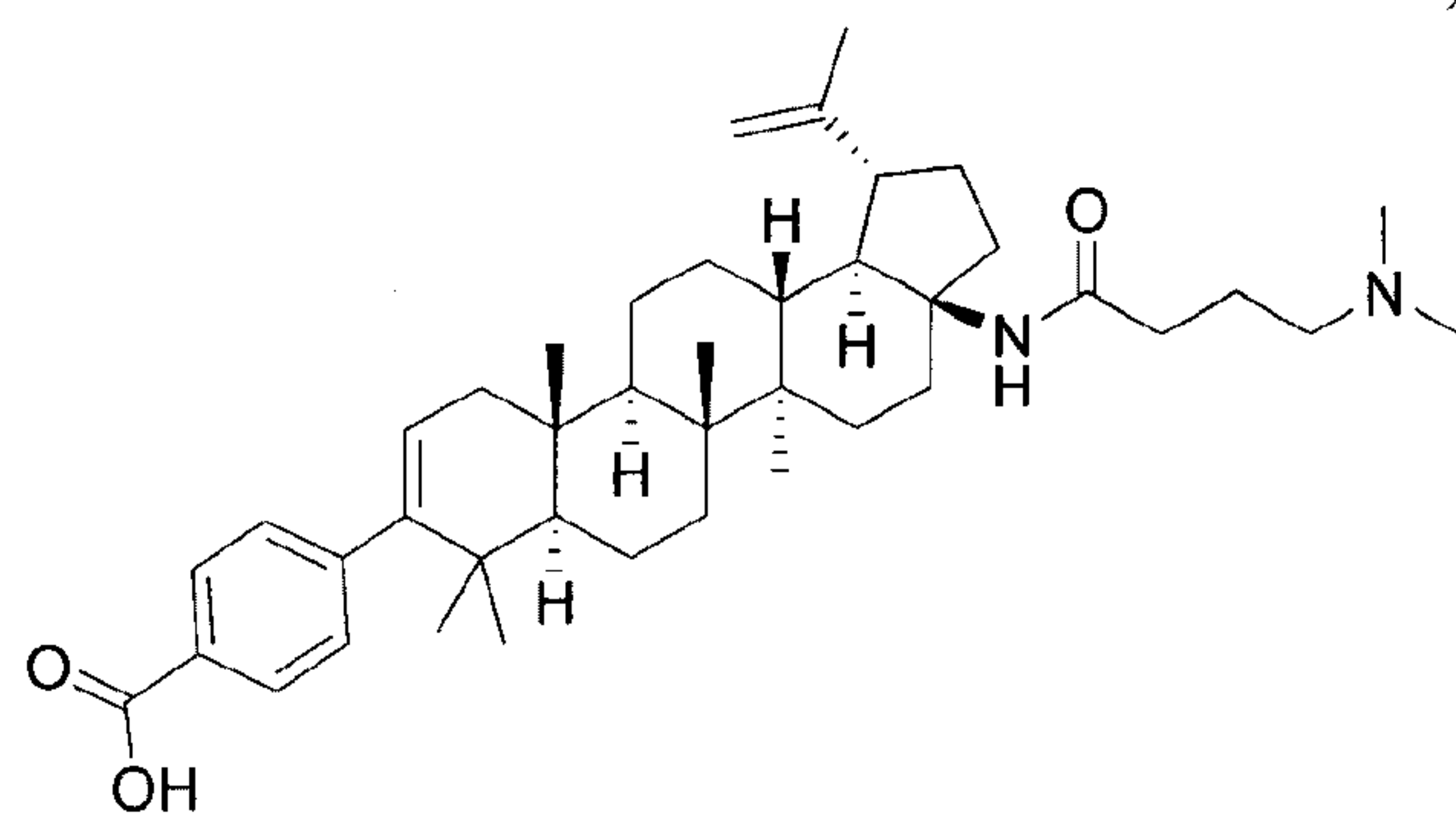
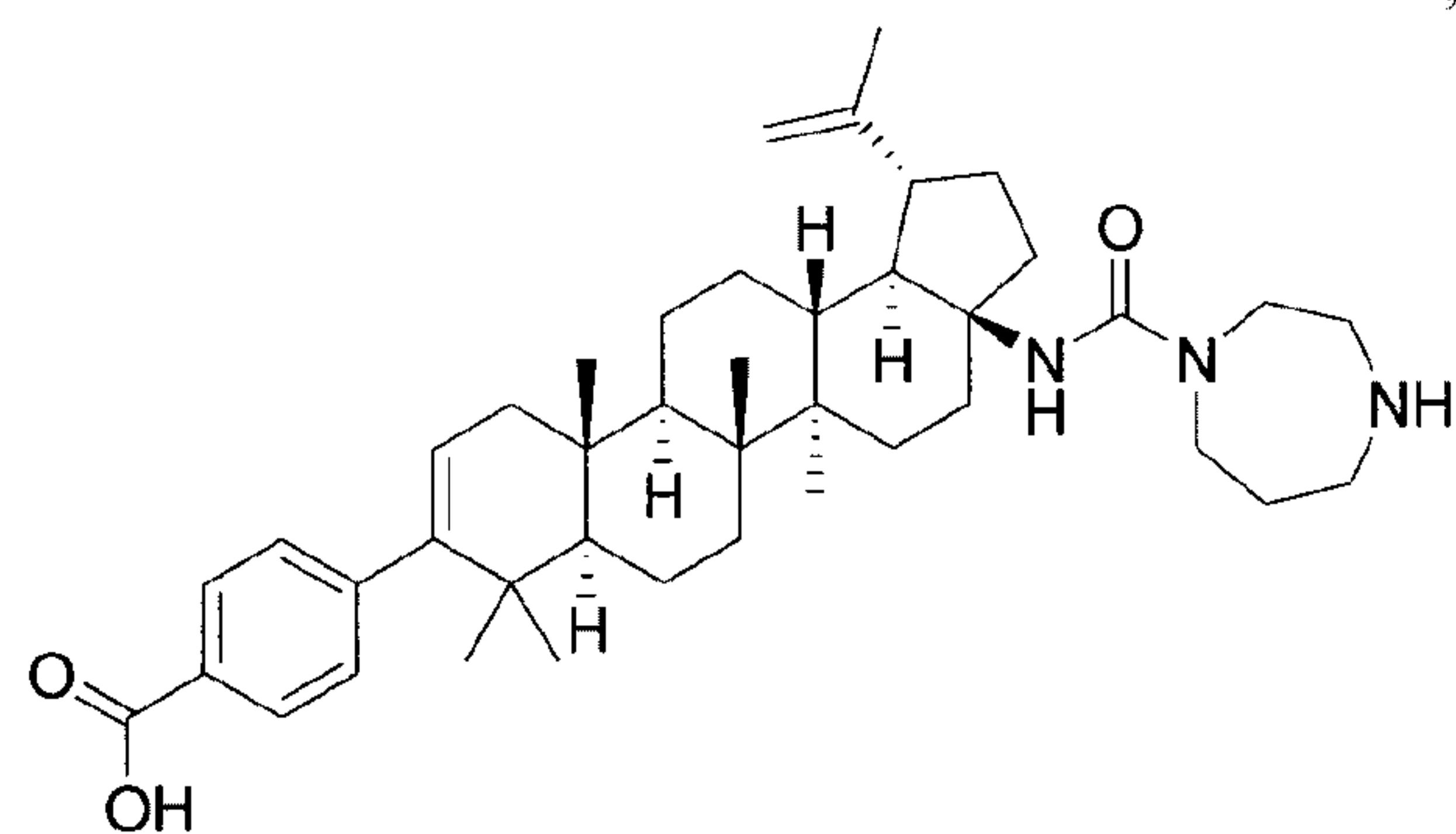
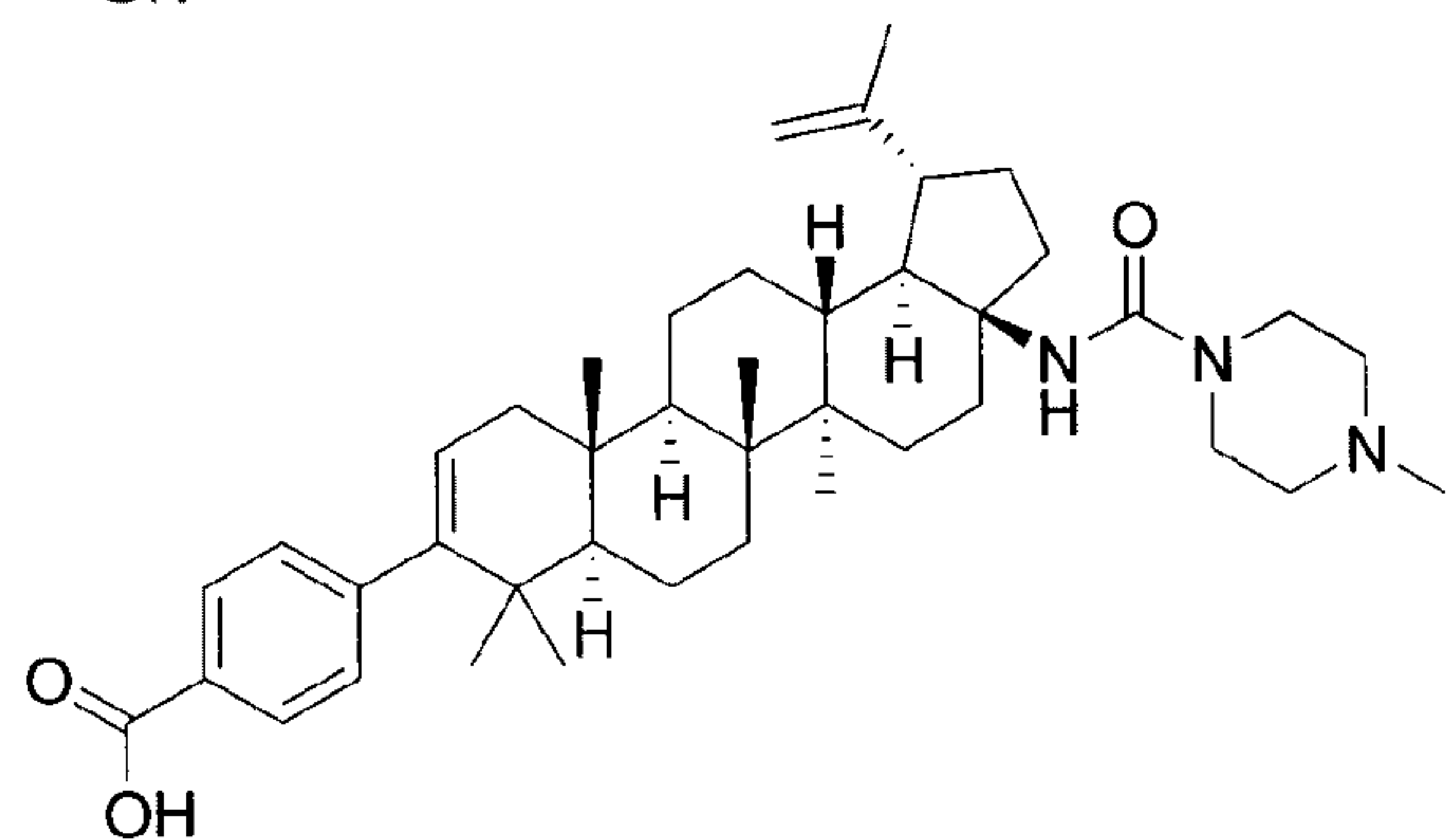
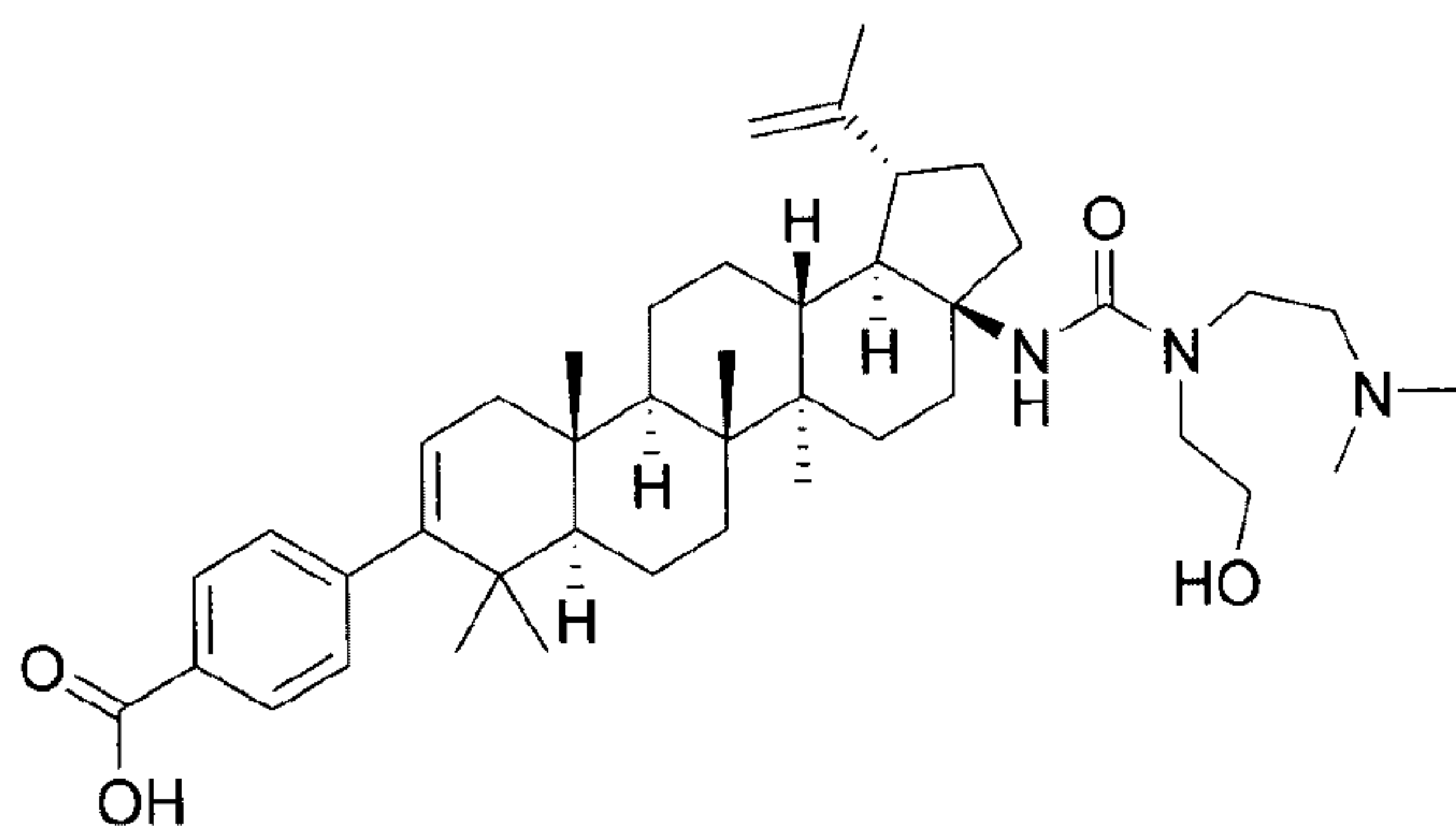
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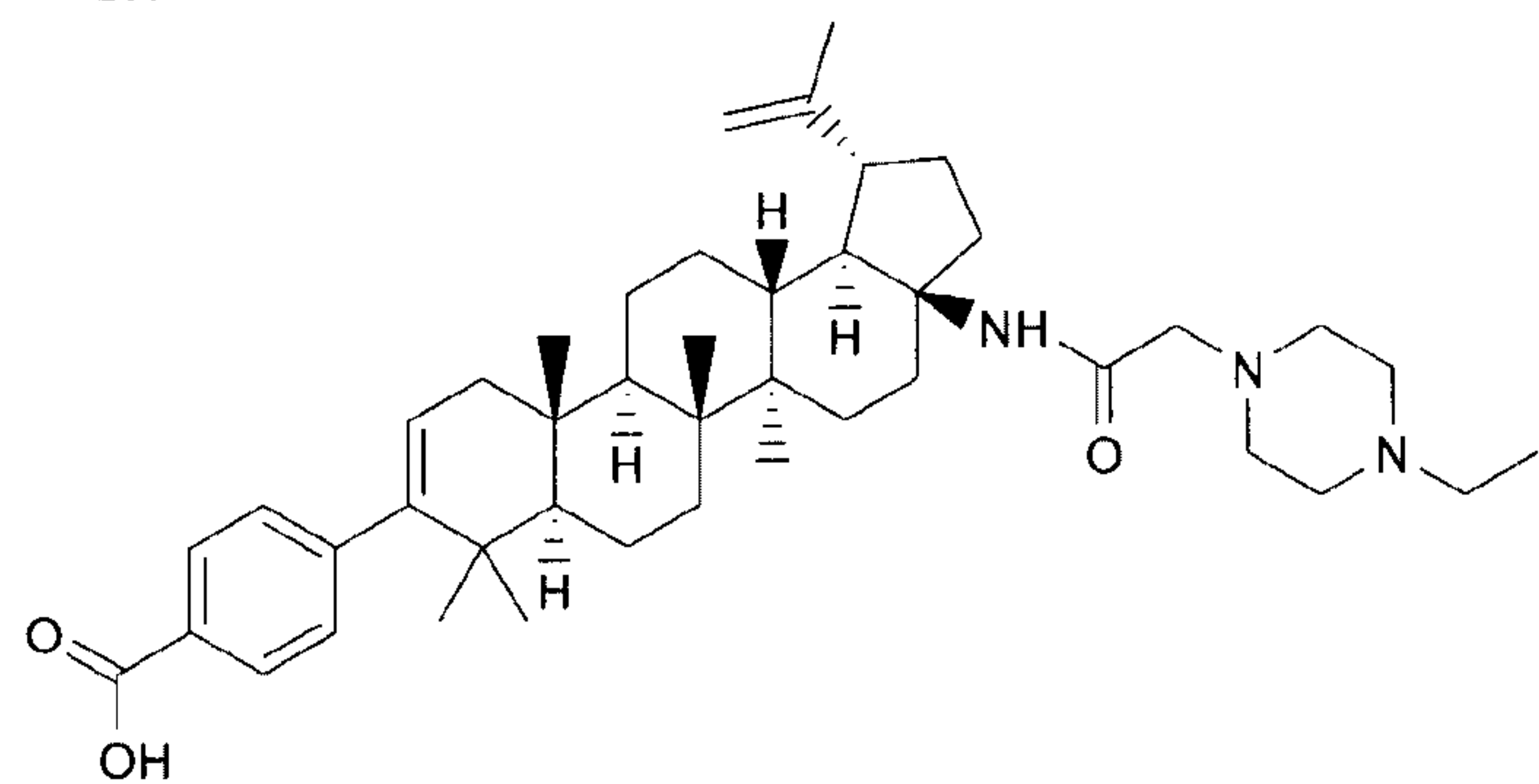
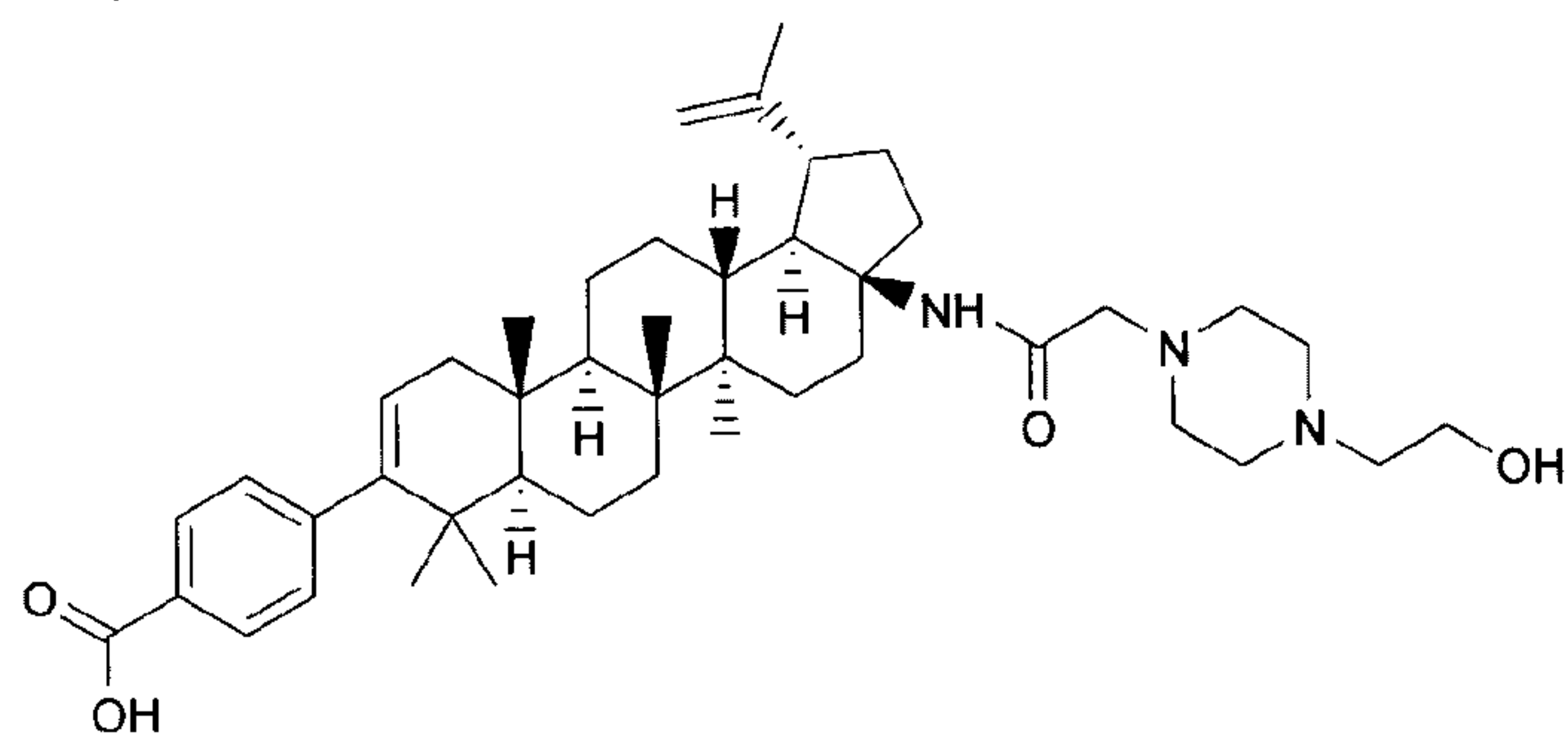
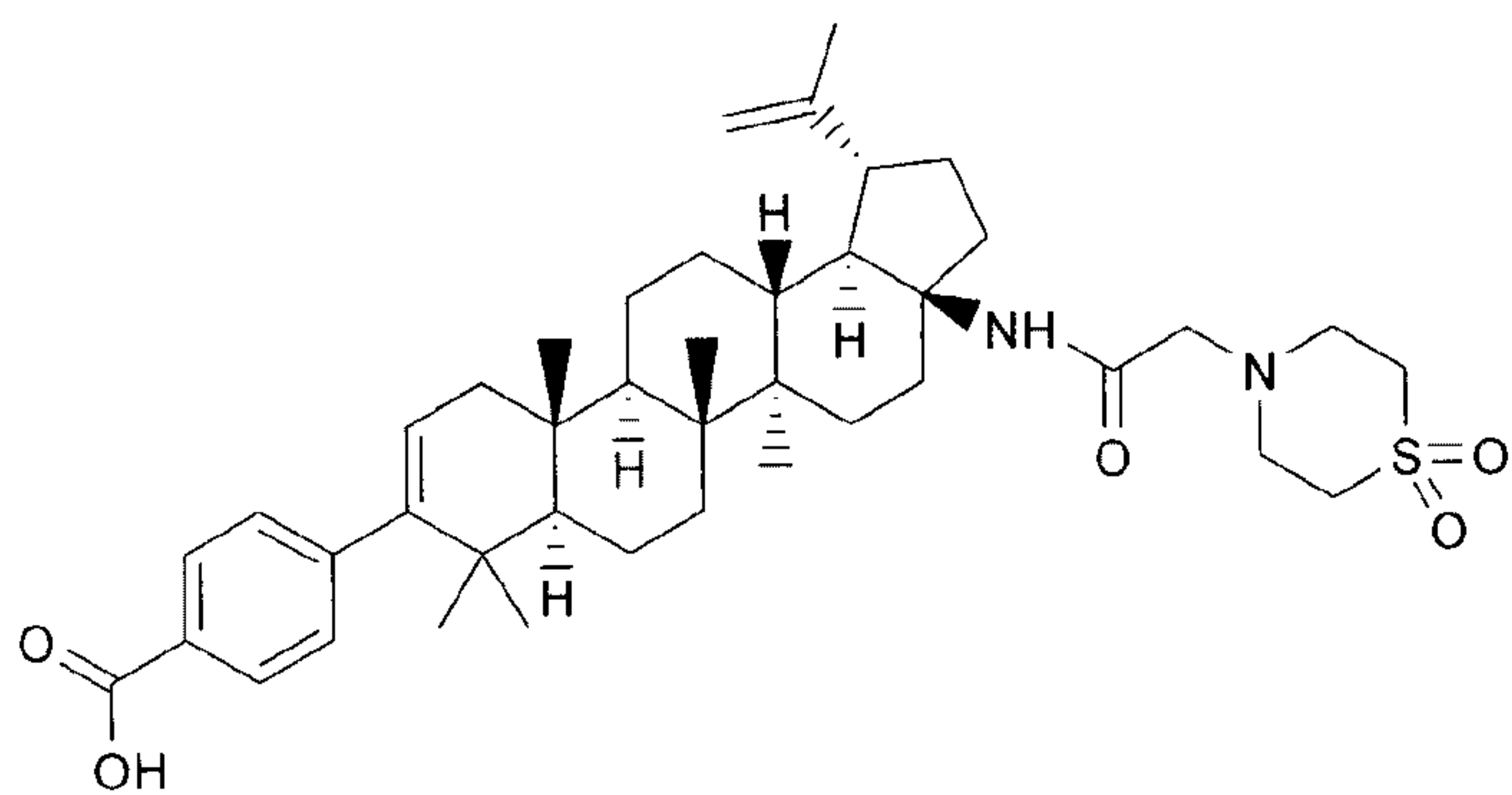


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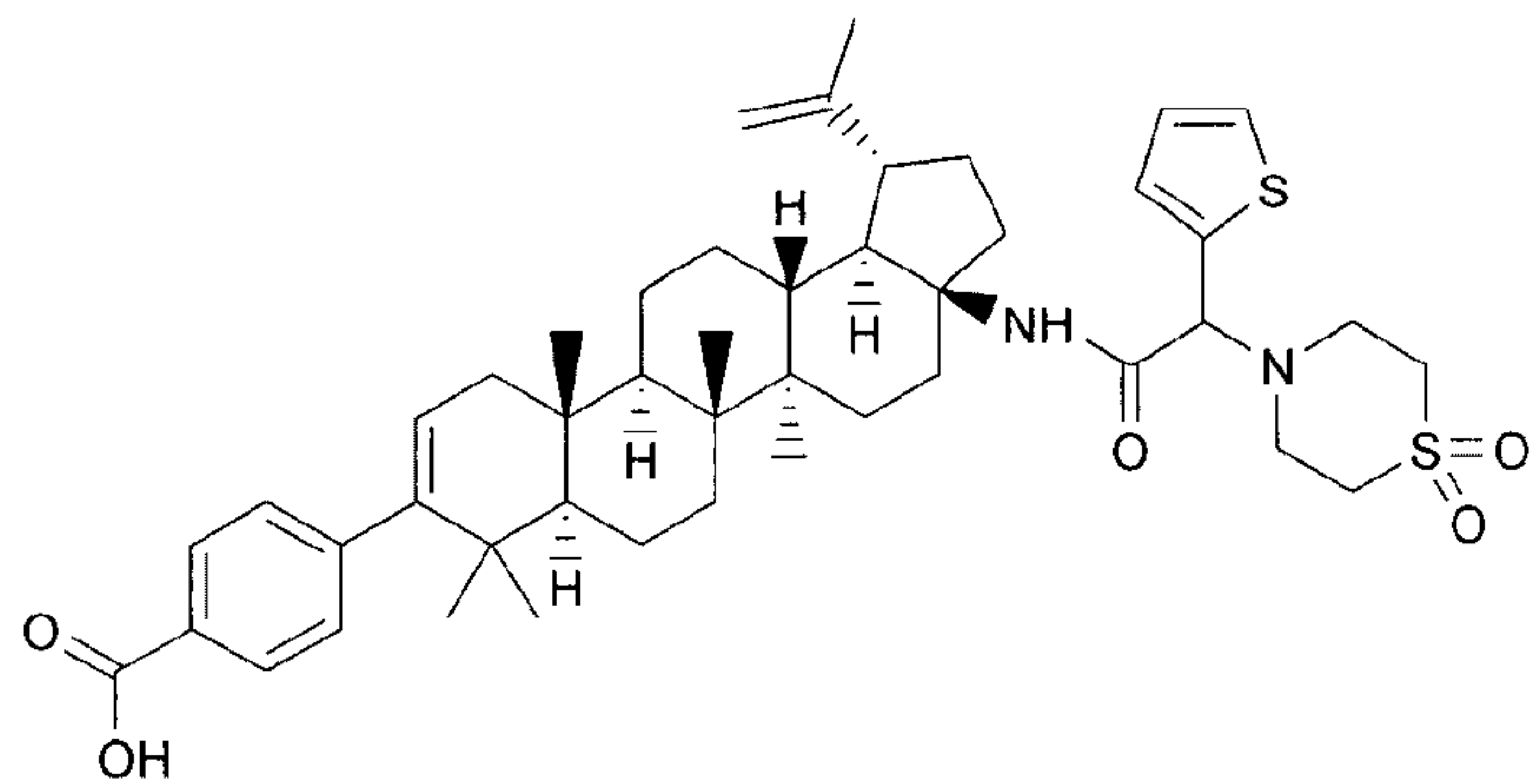
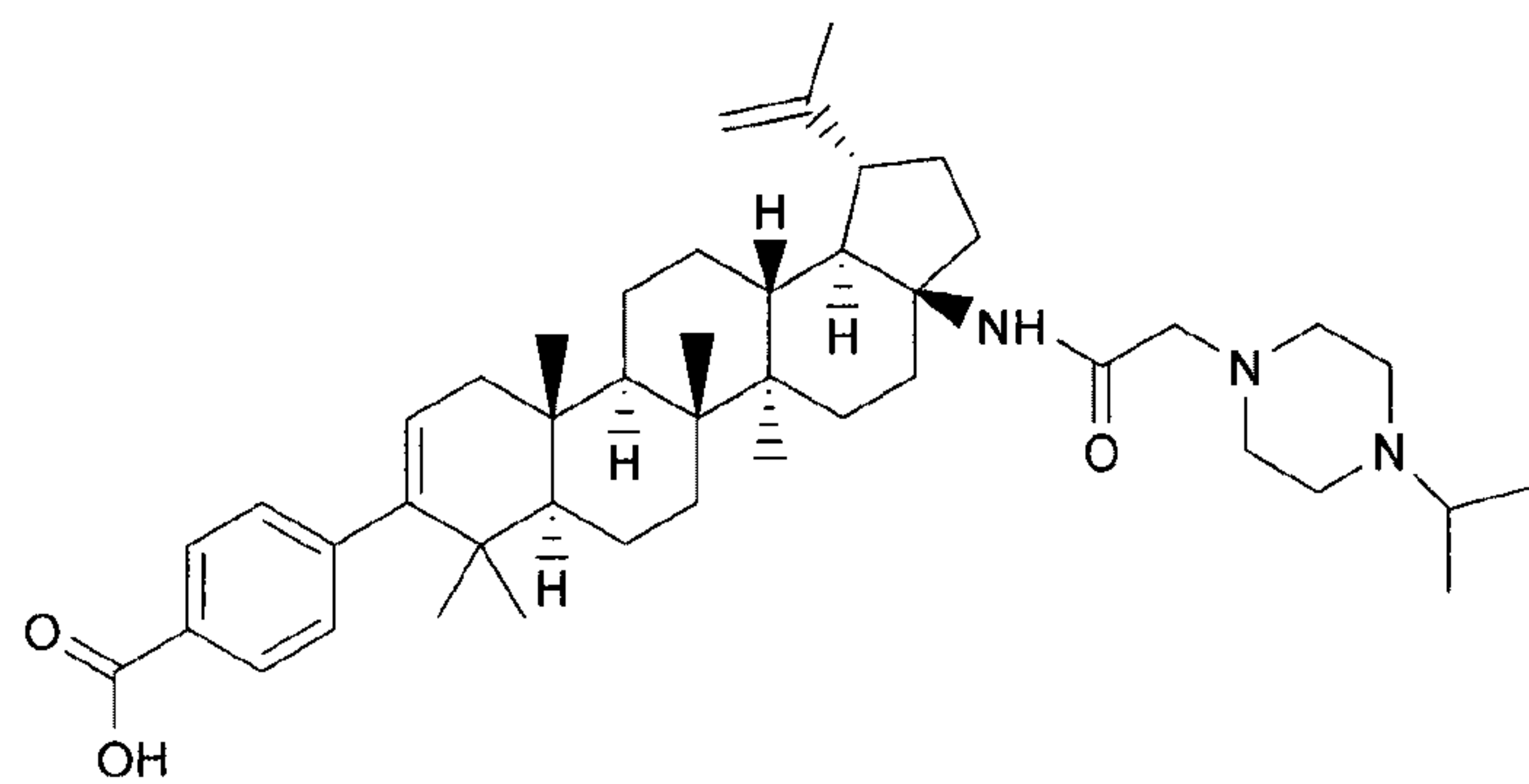
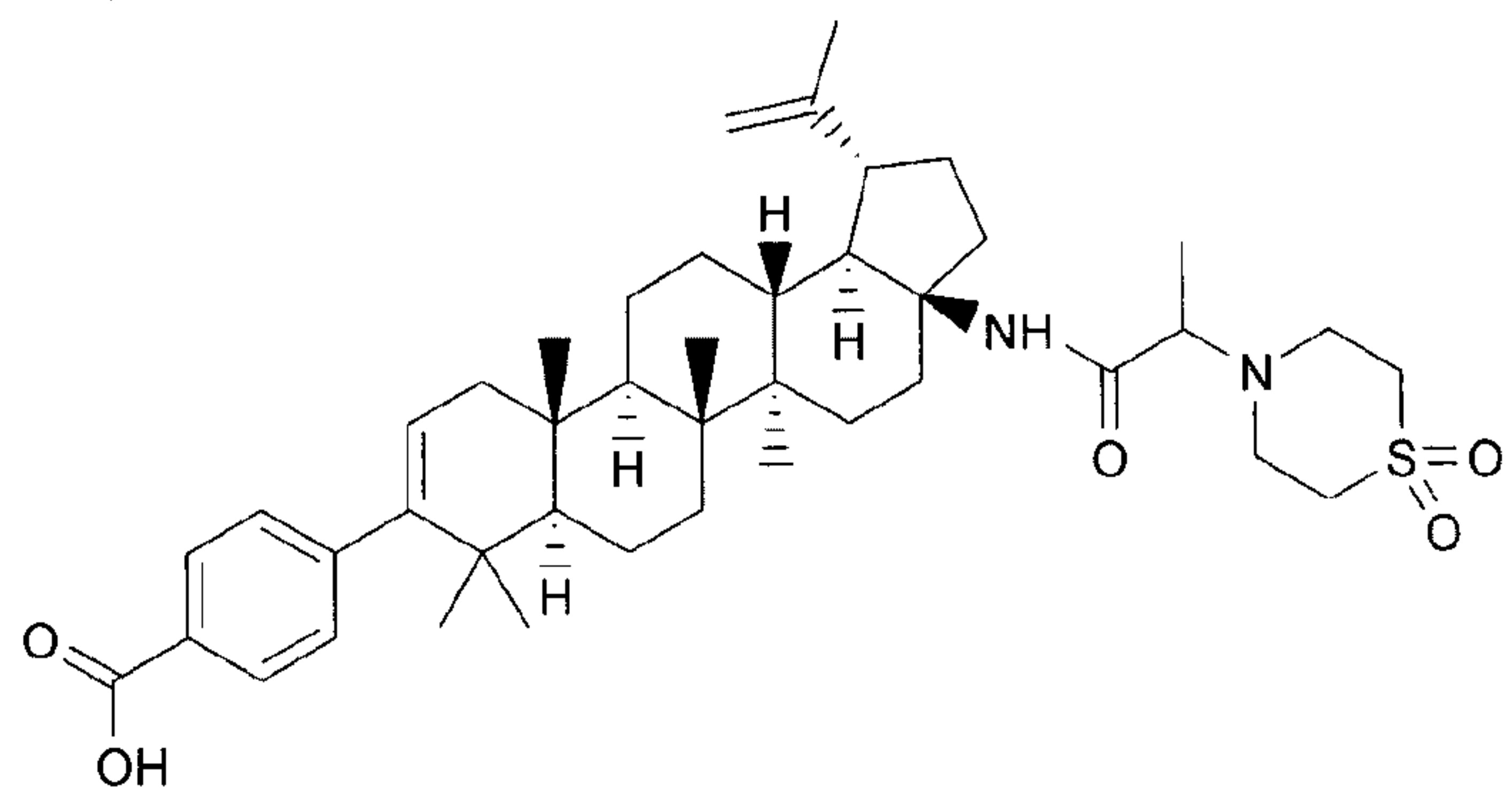
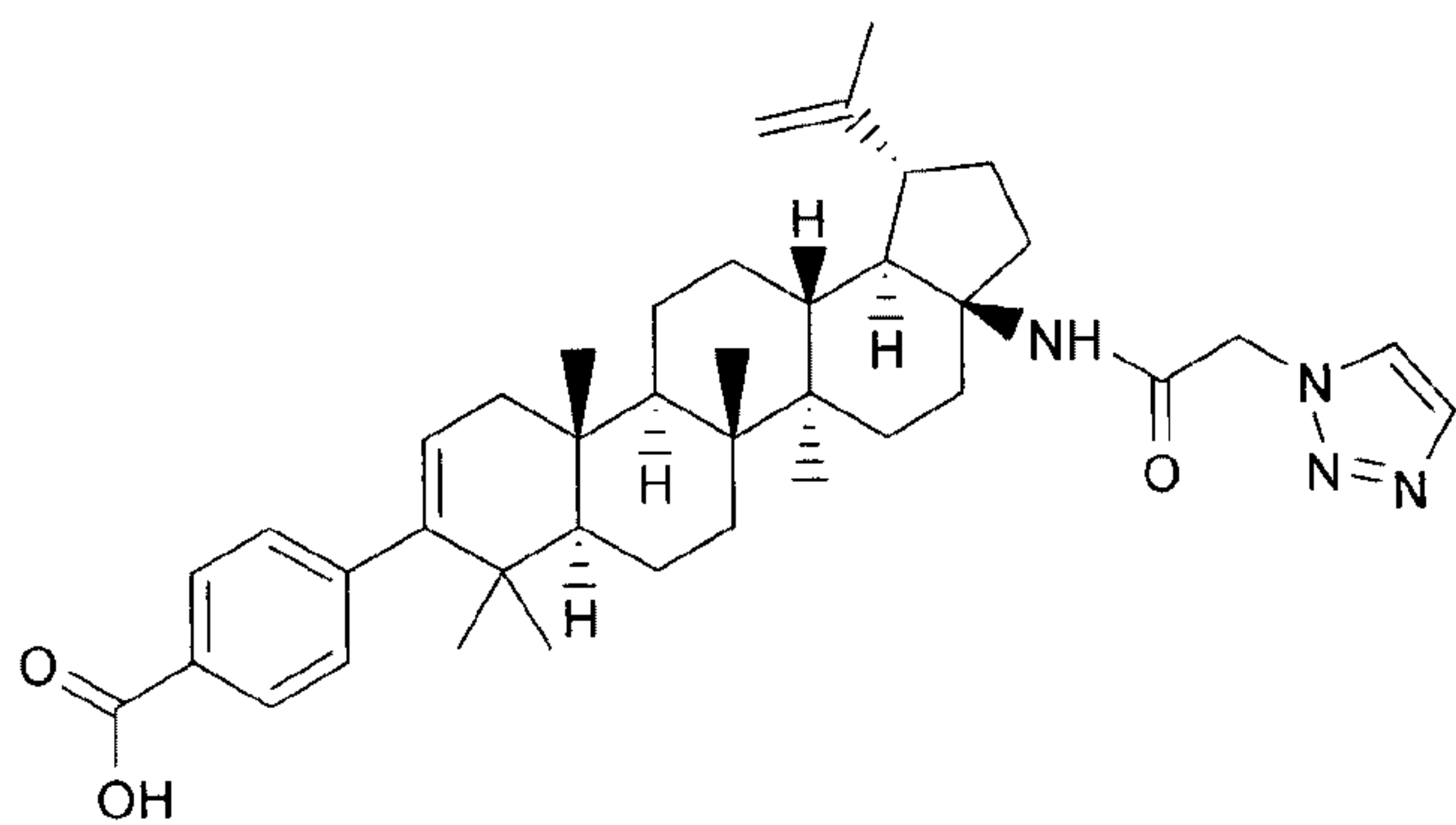


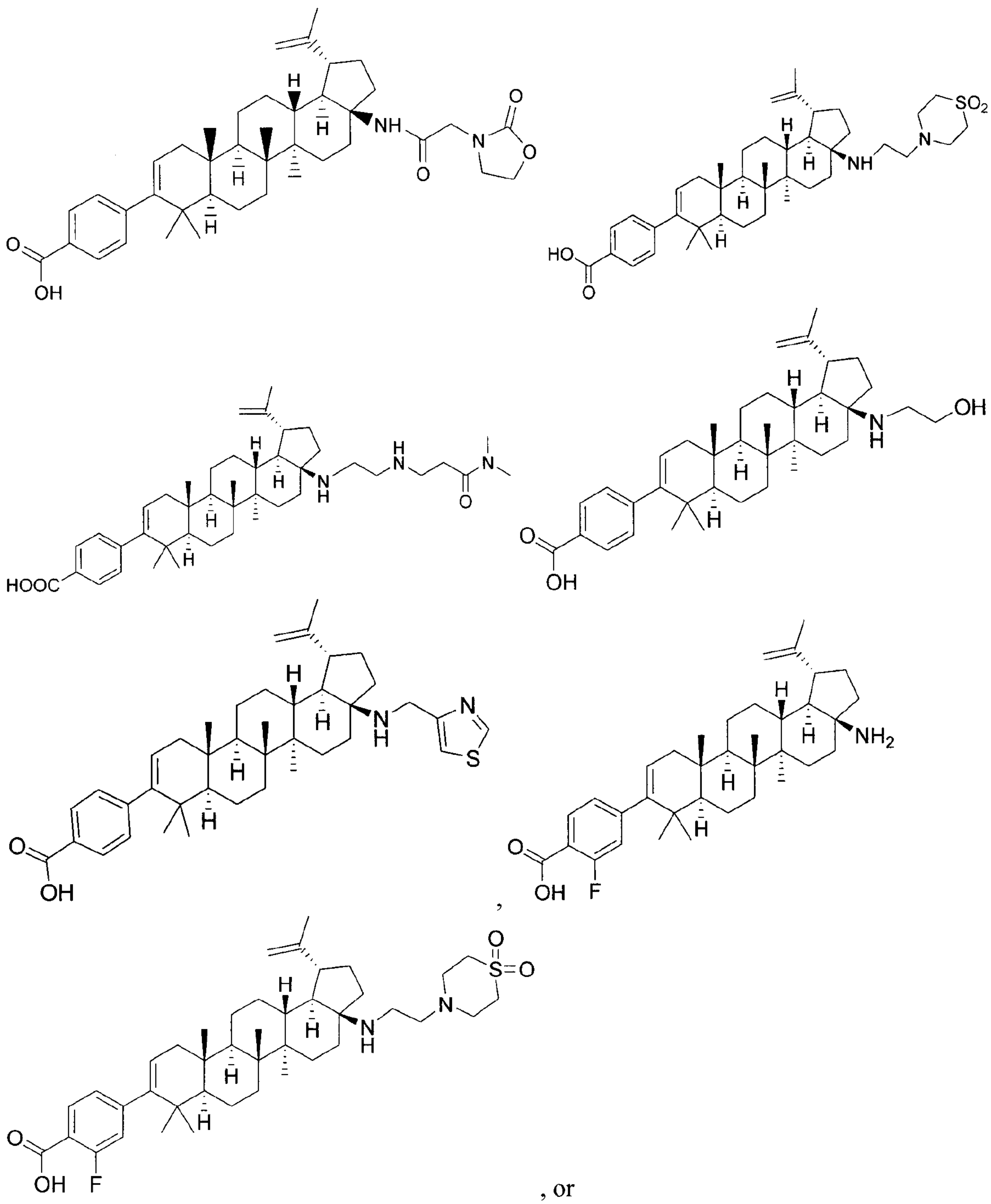
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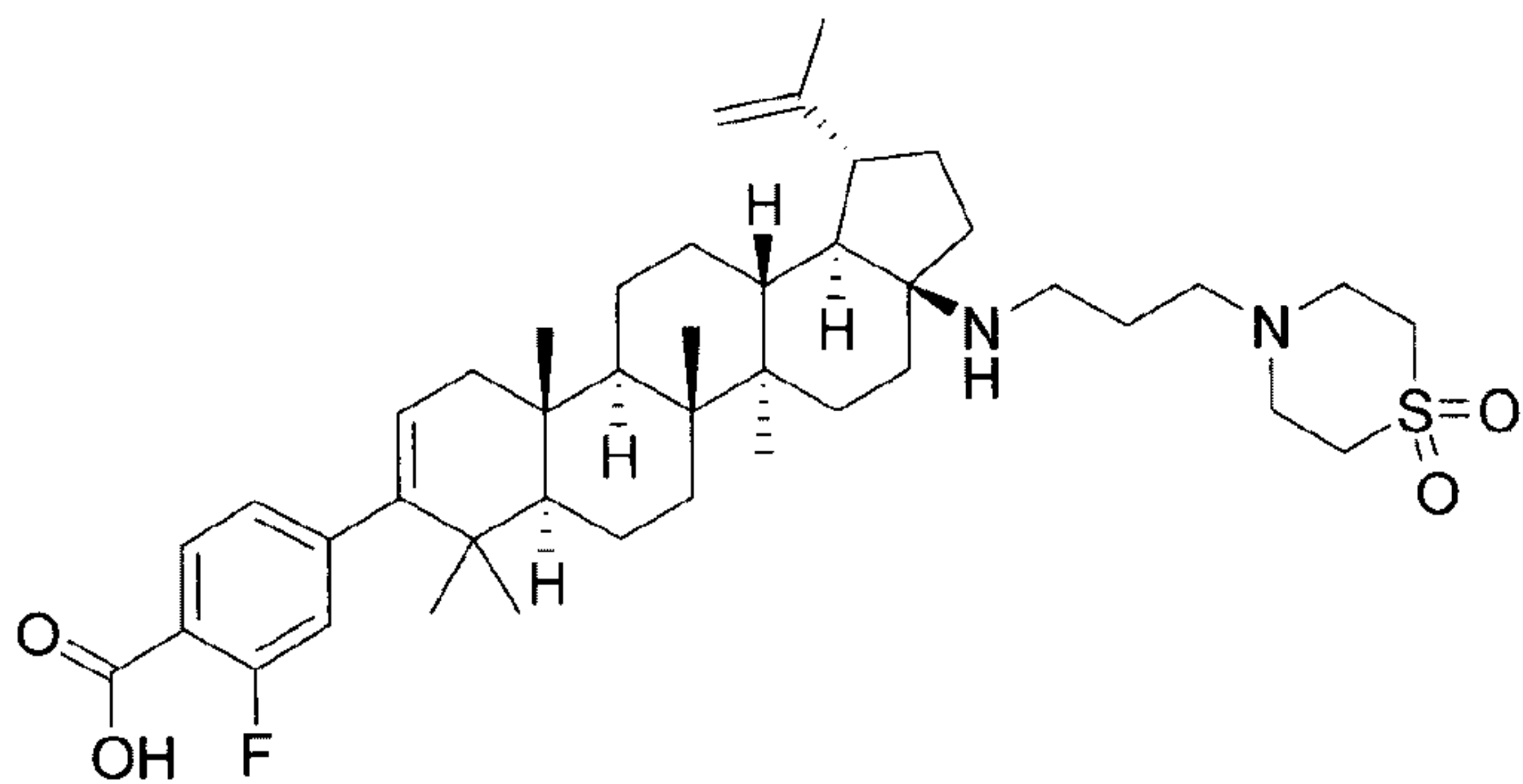




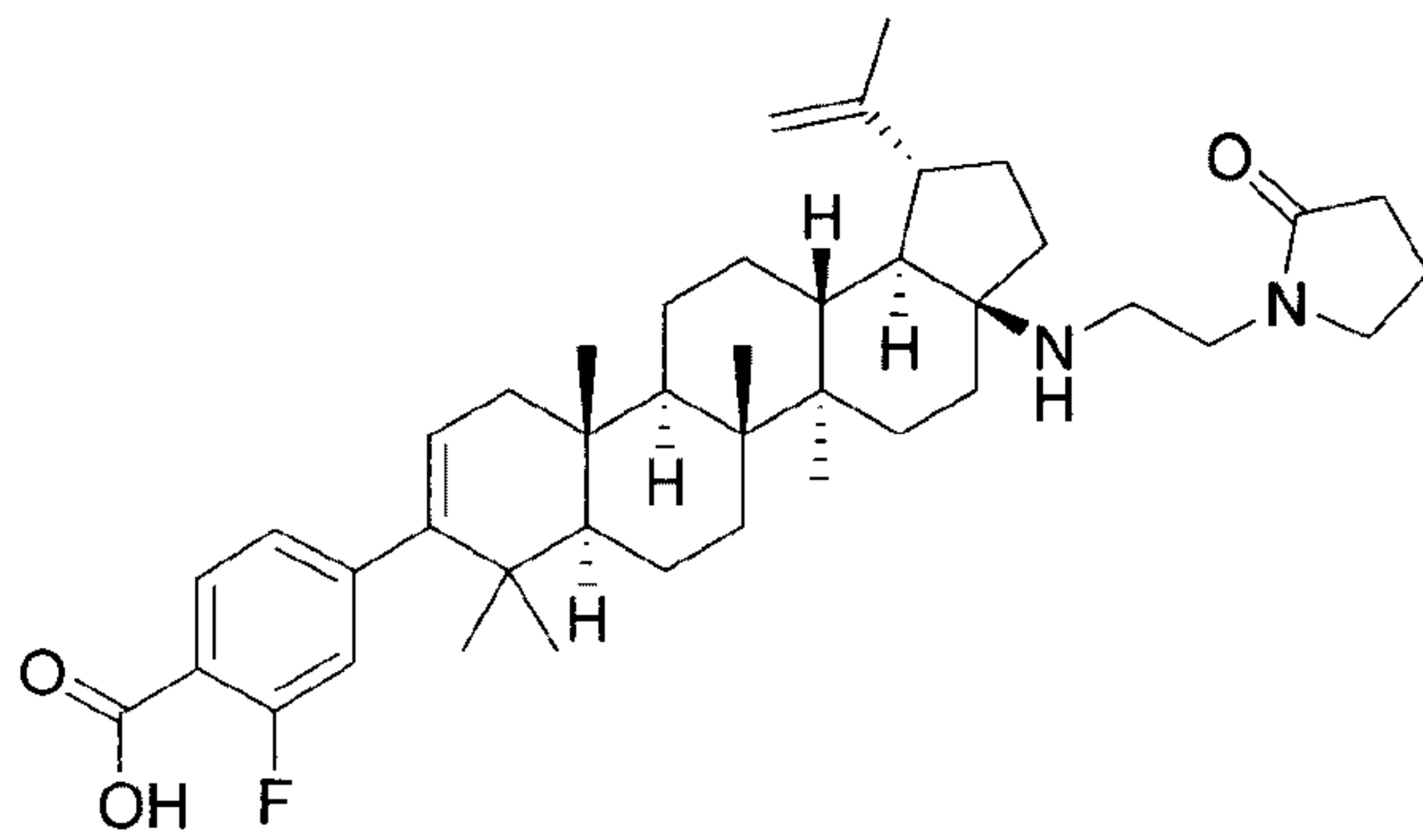
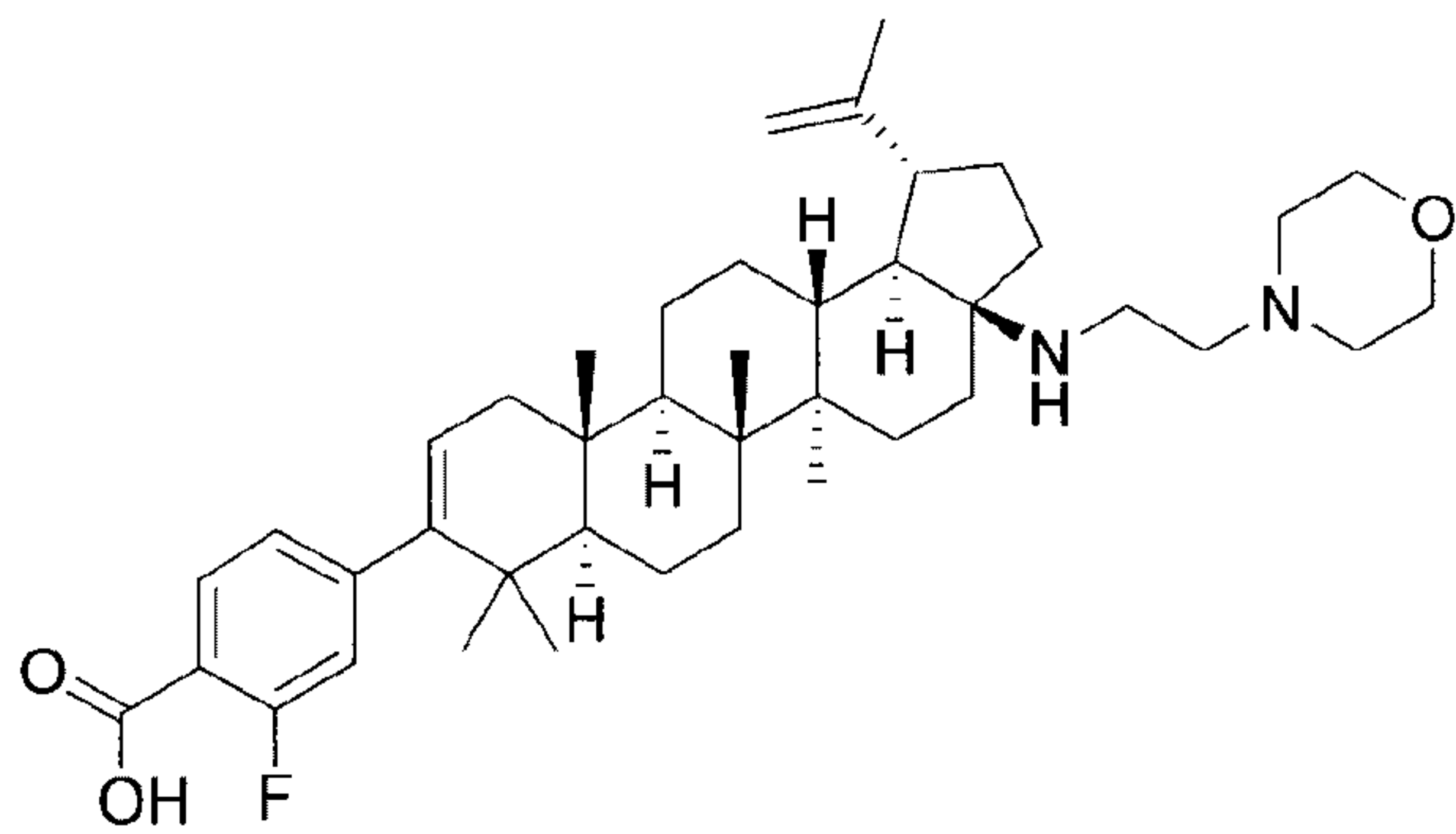
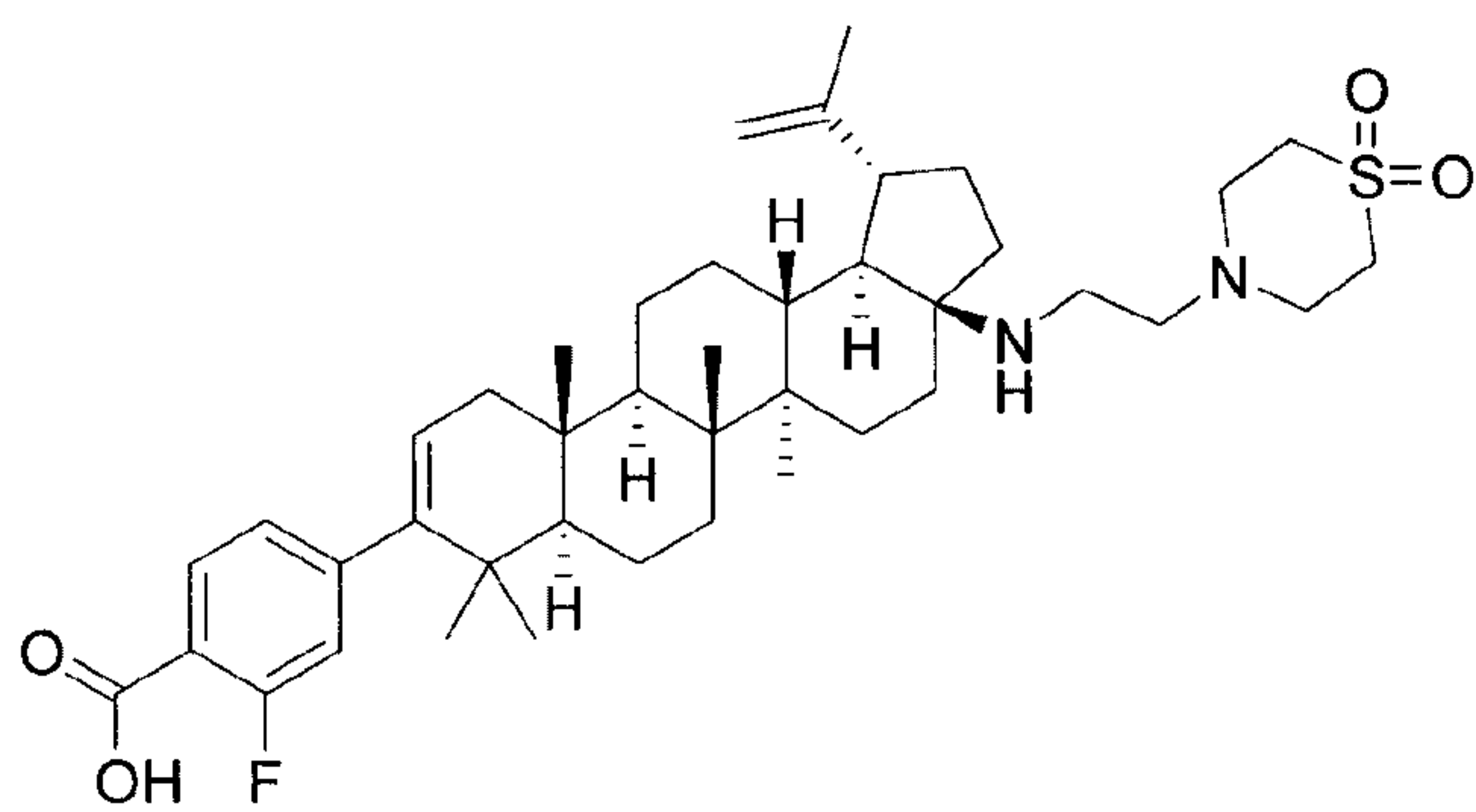
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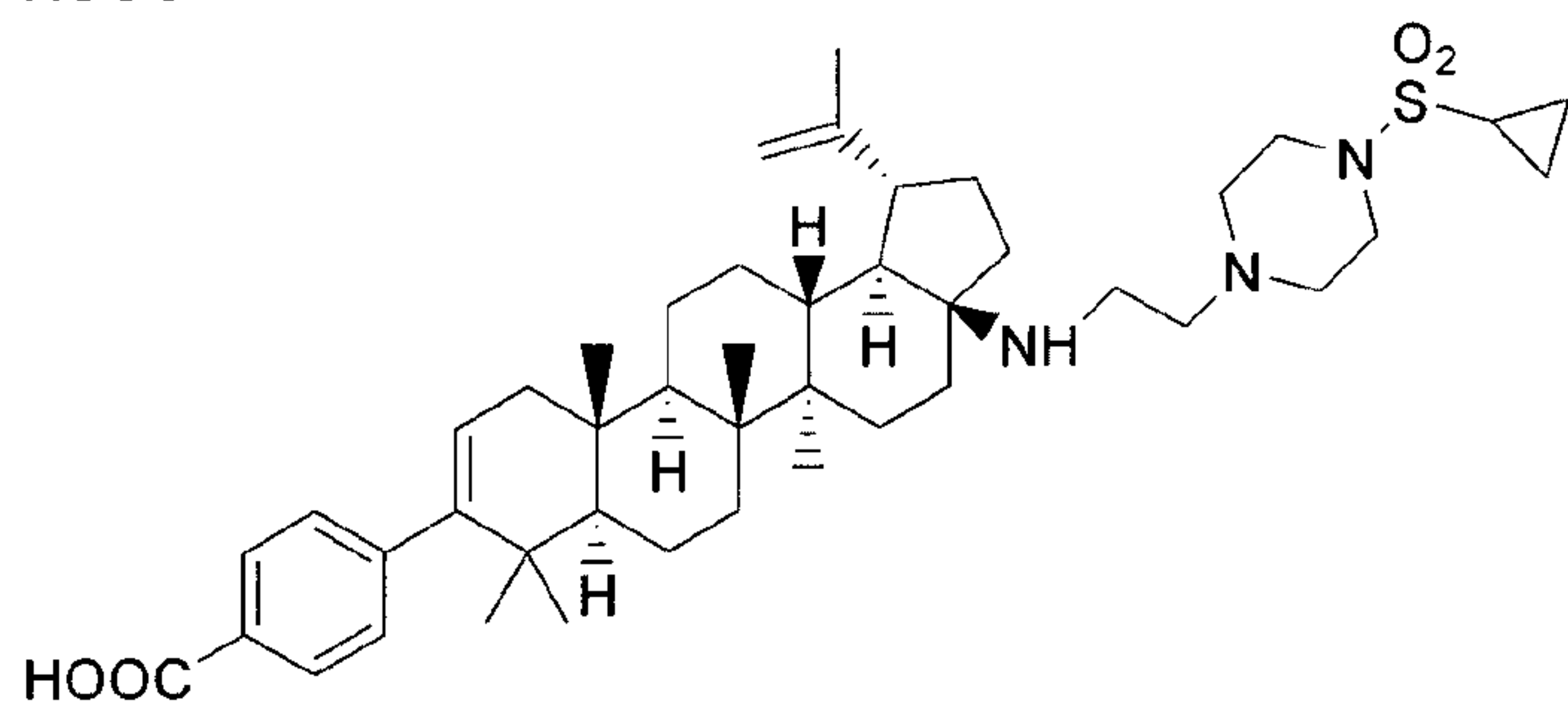
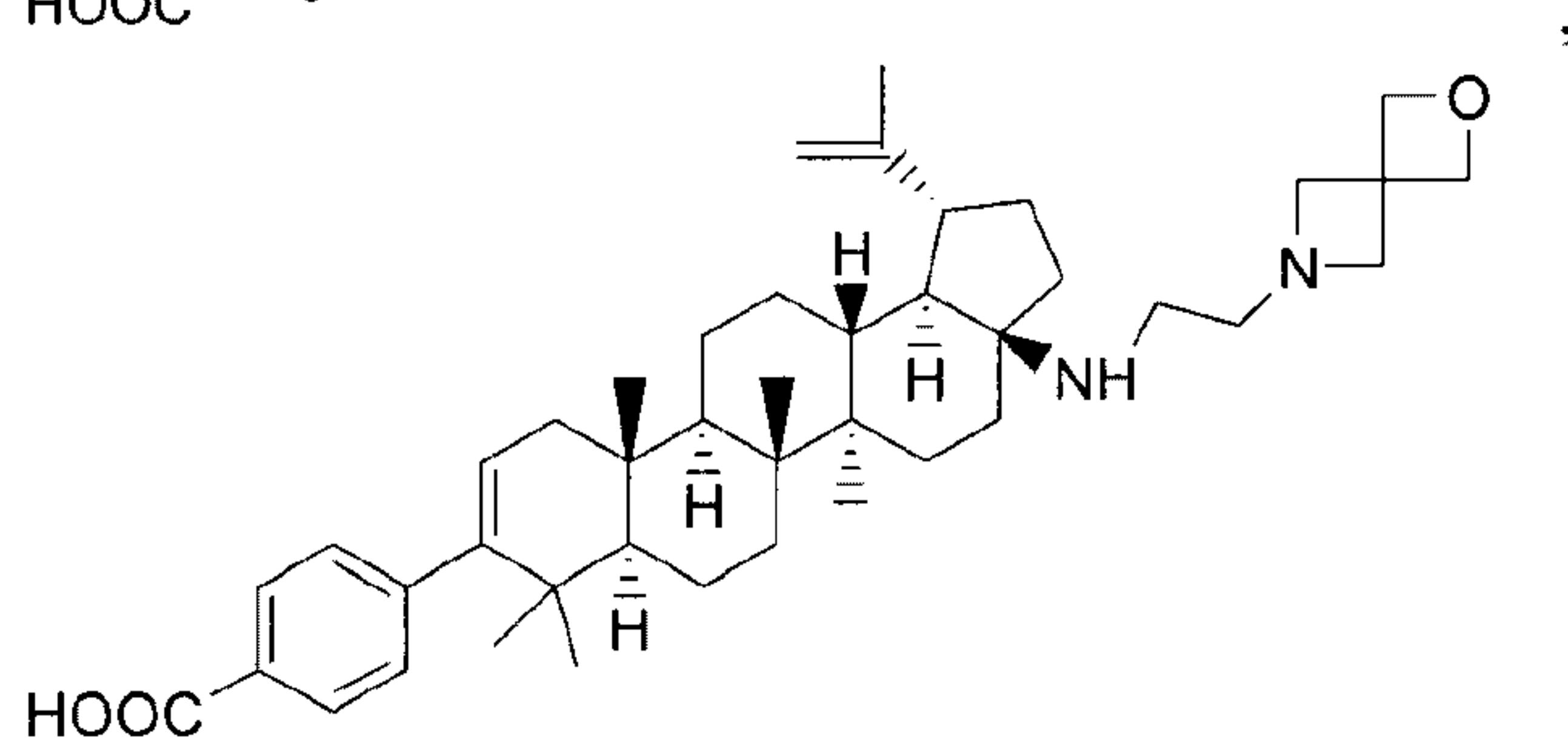
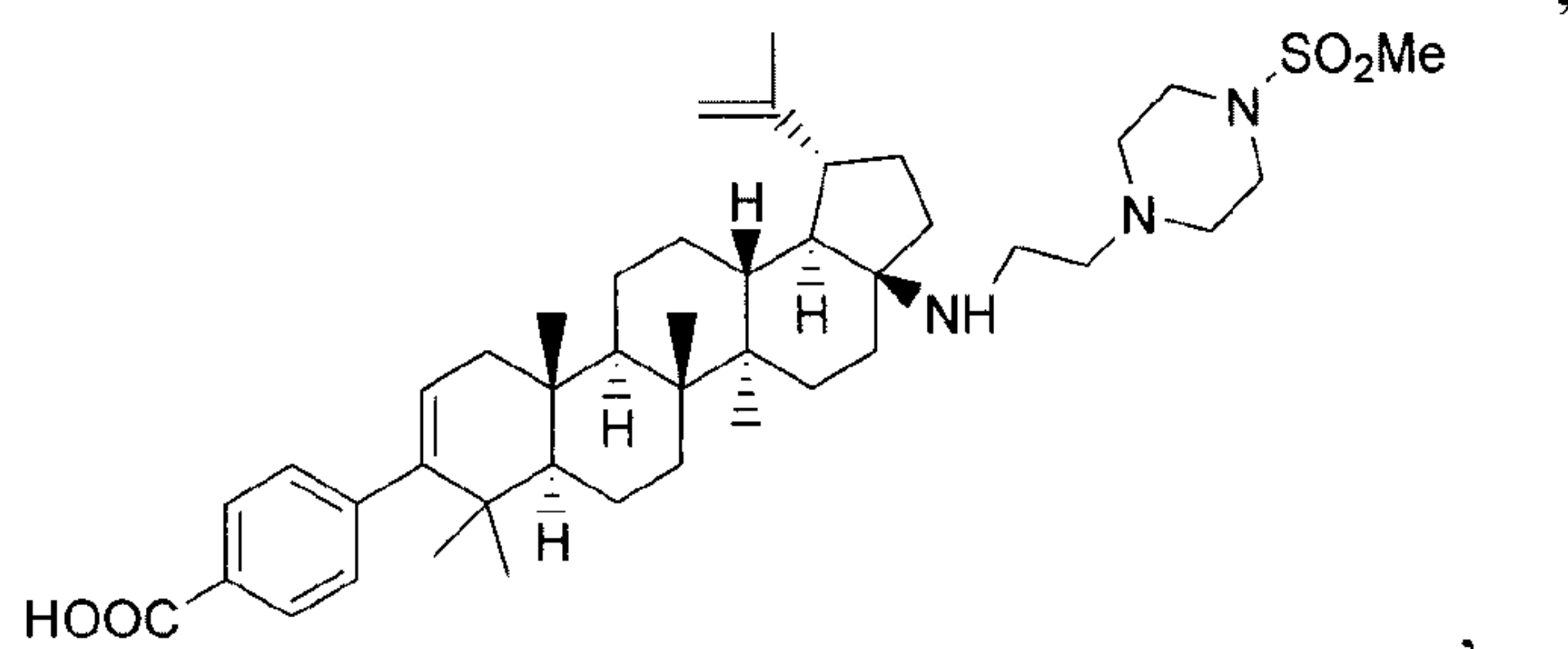
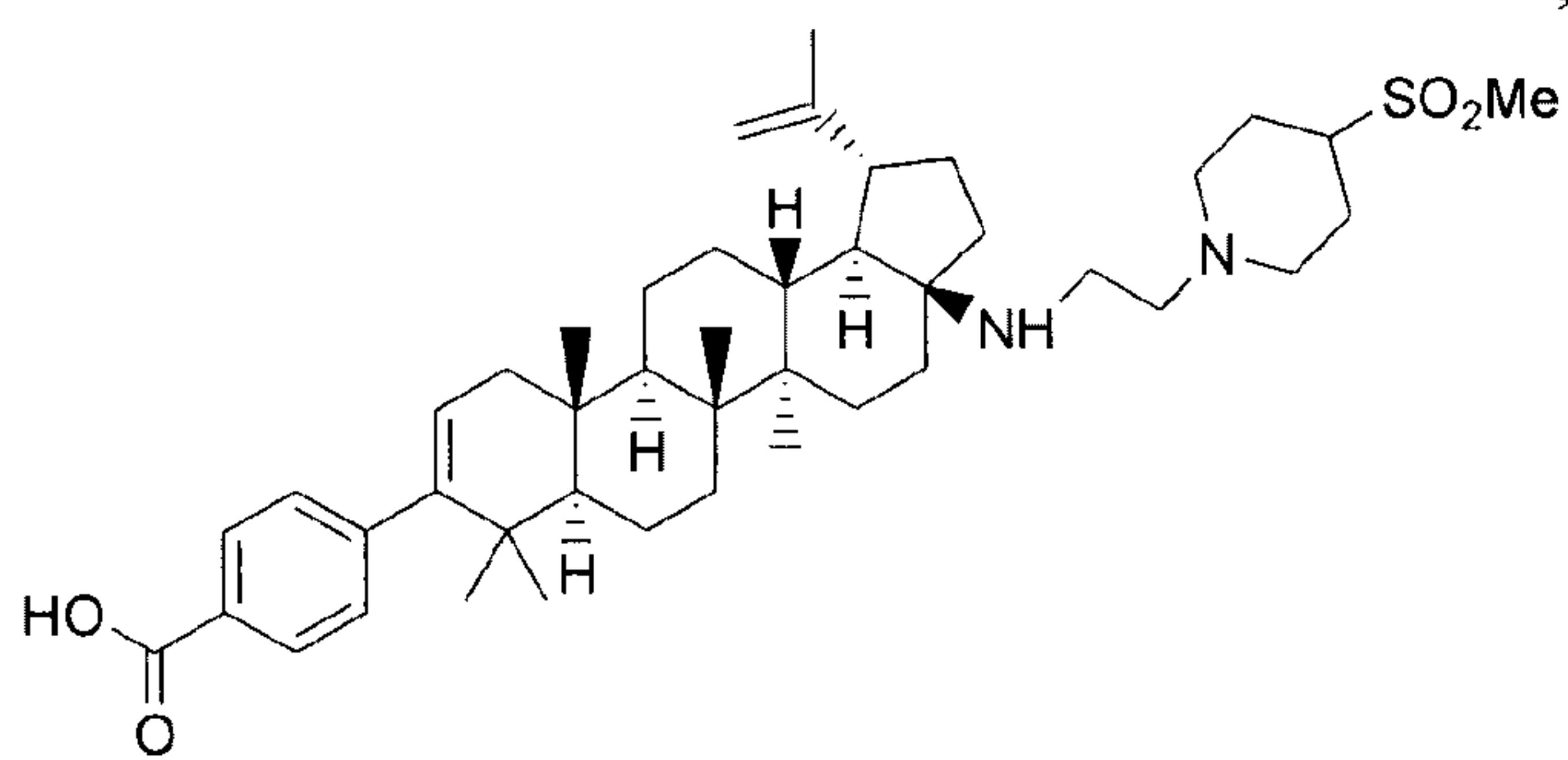
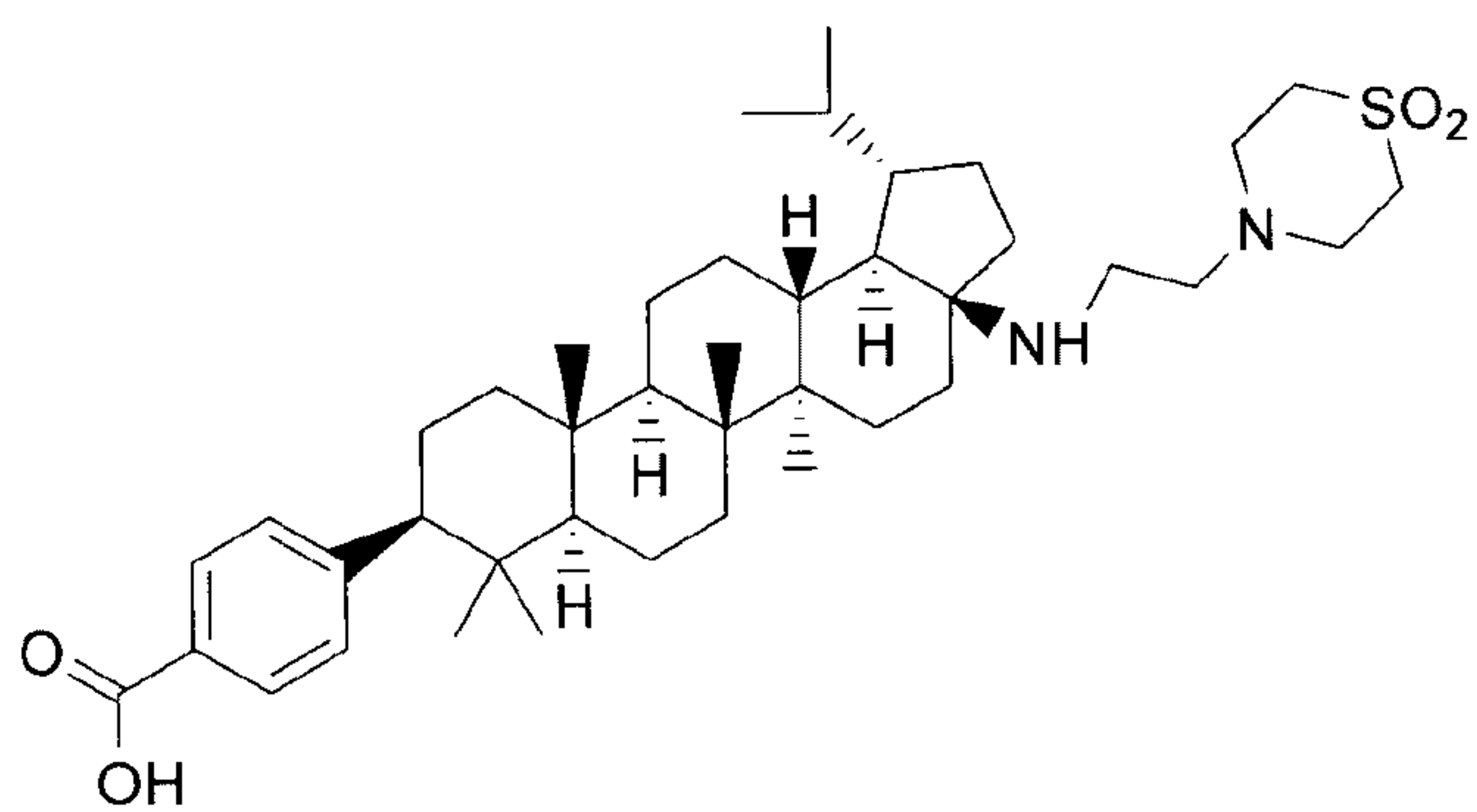


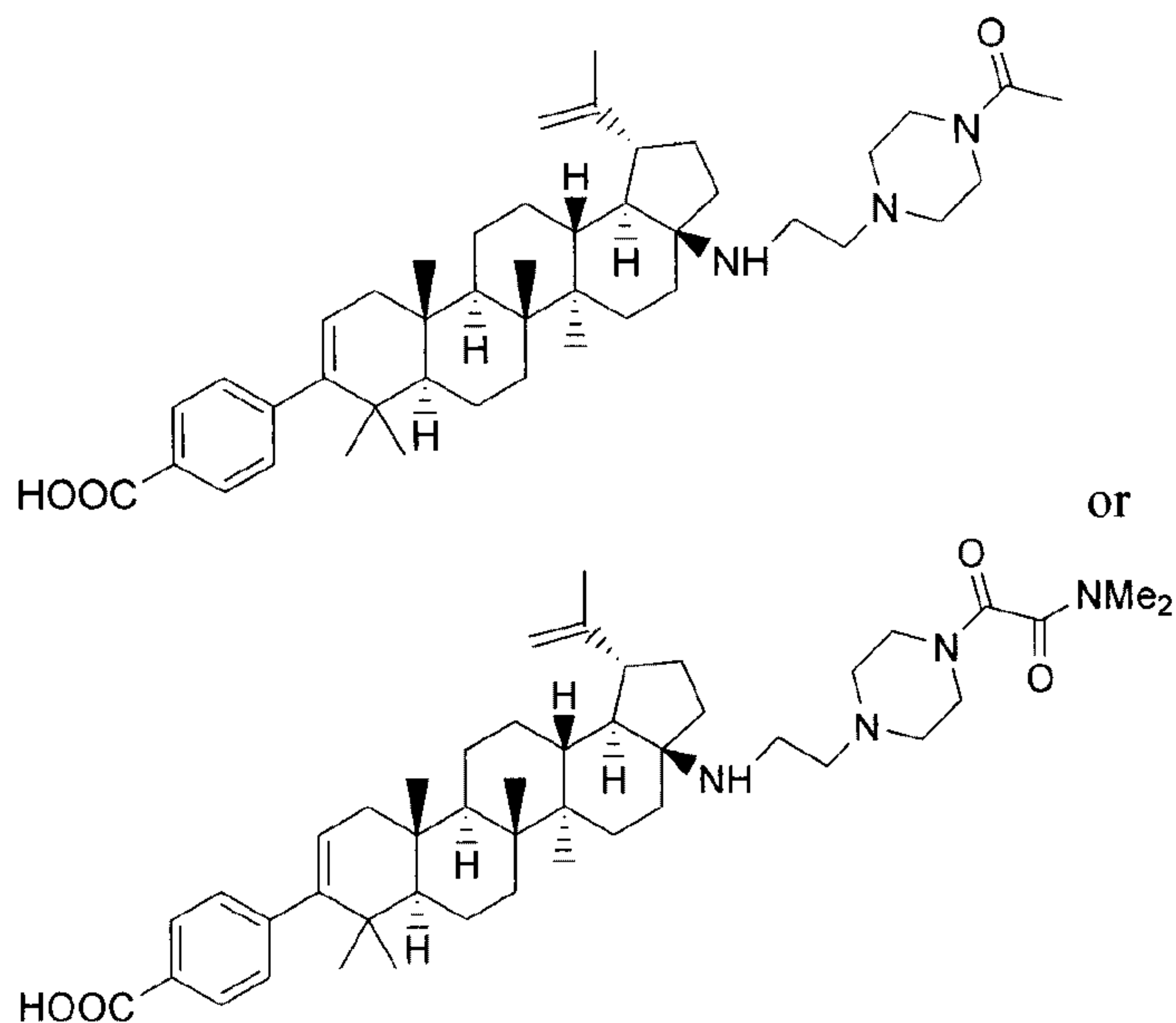




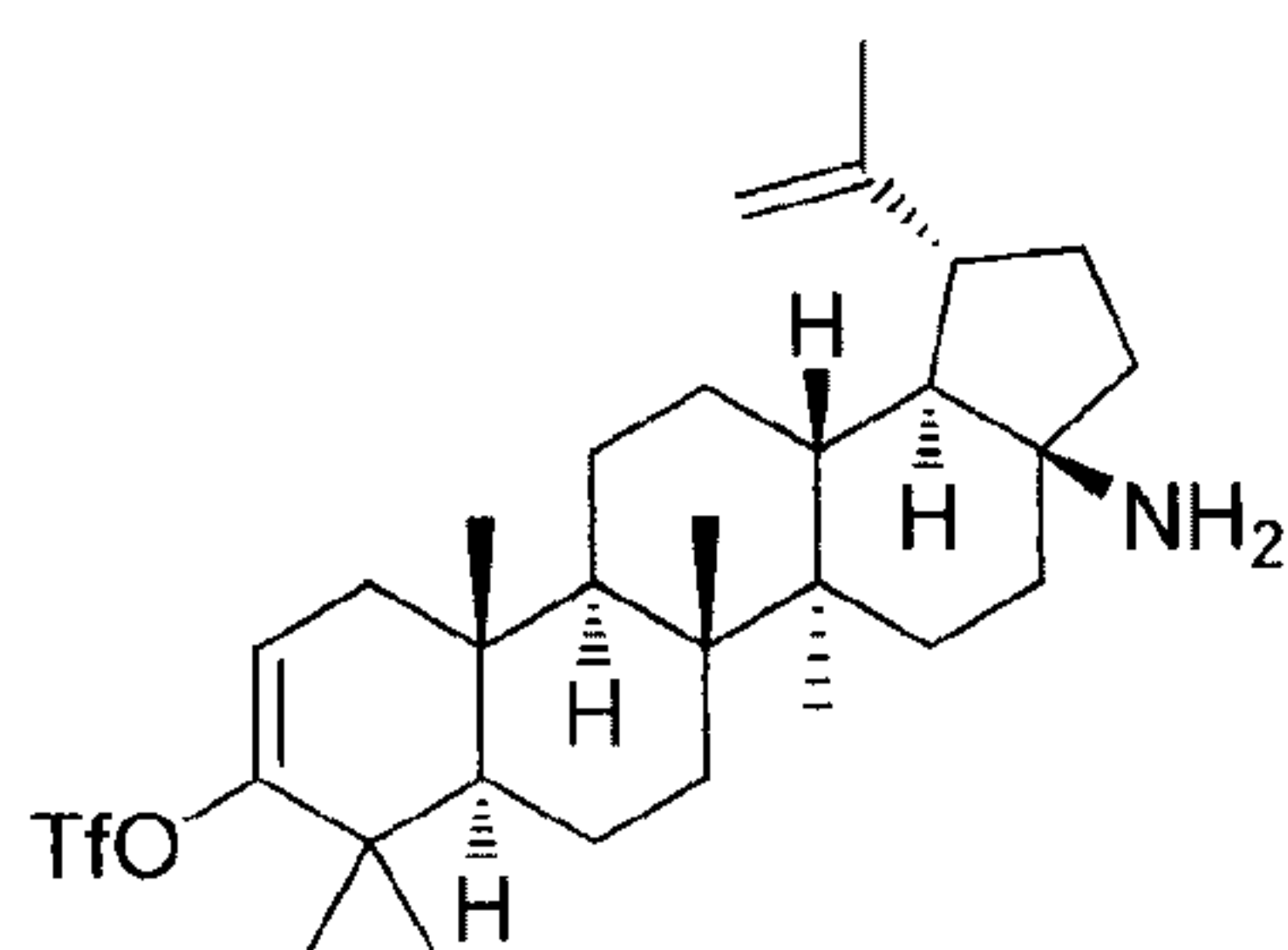
16. A compound or a pharmaceutically acceptable salt thereof, which is:

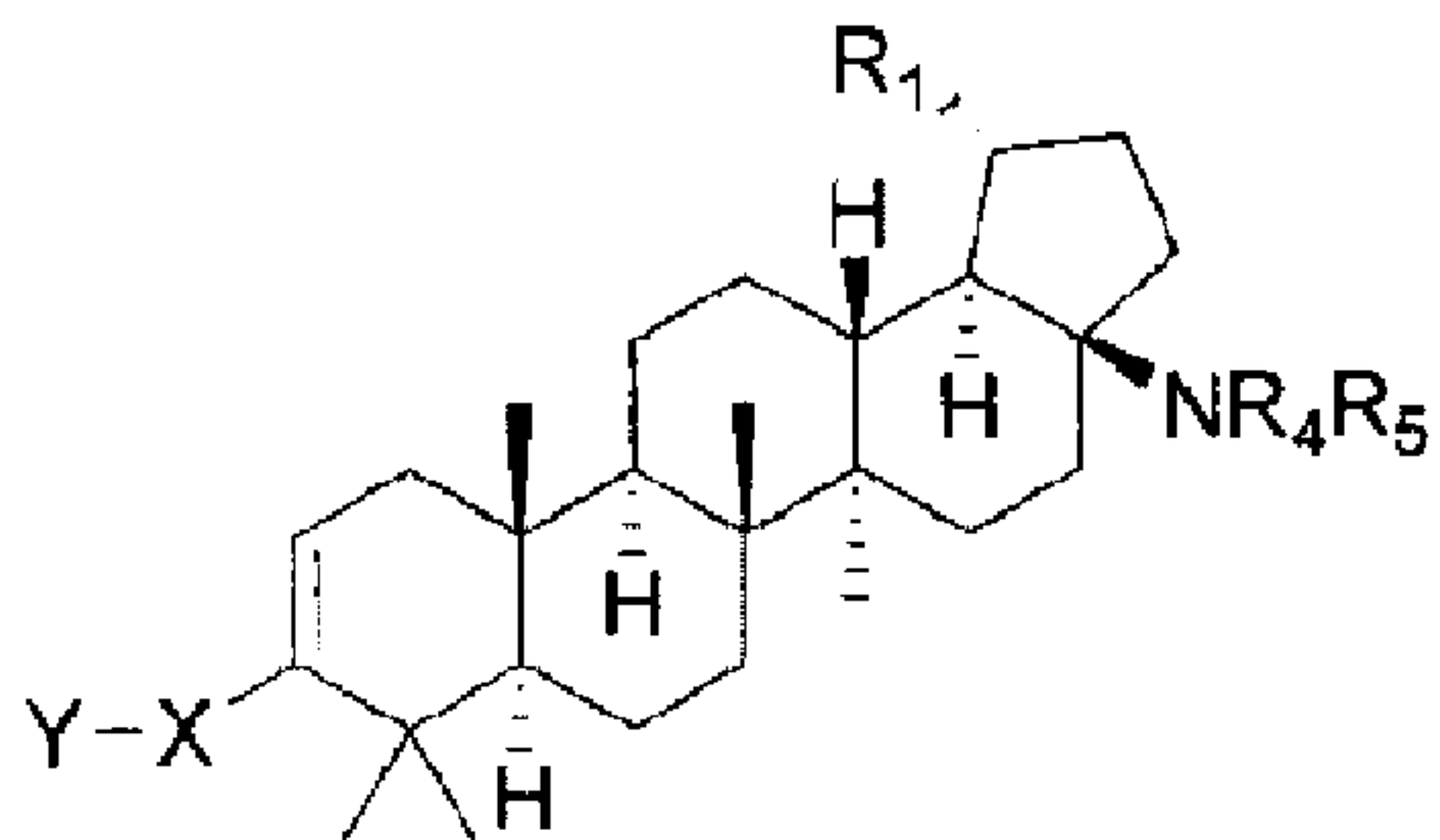




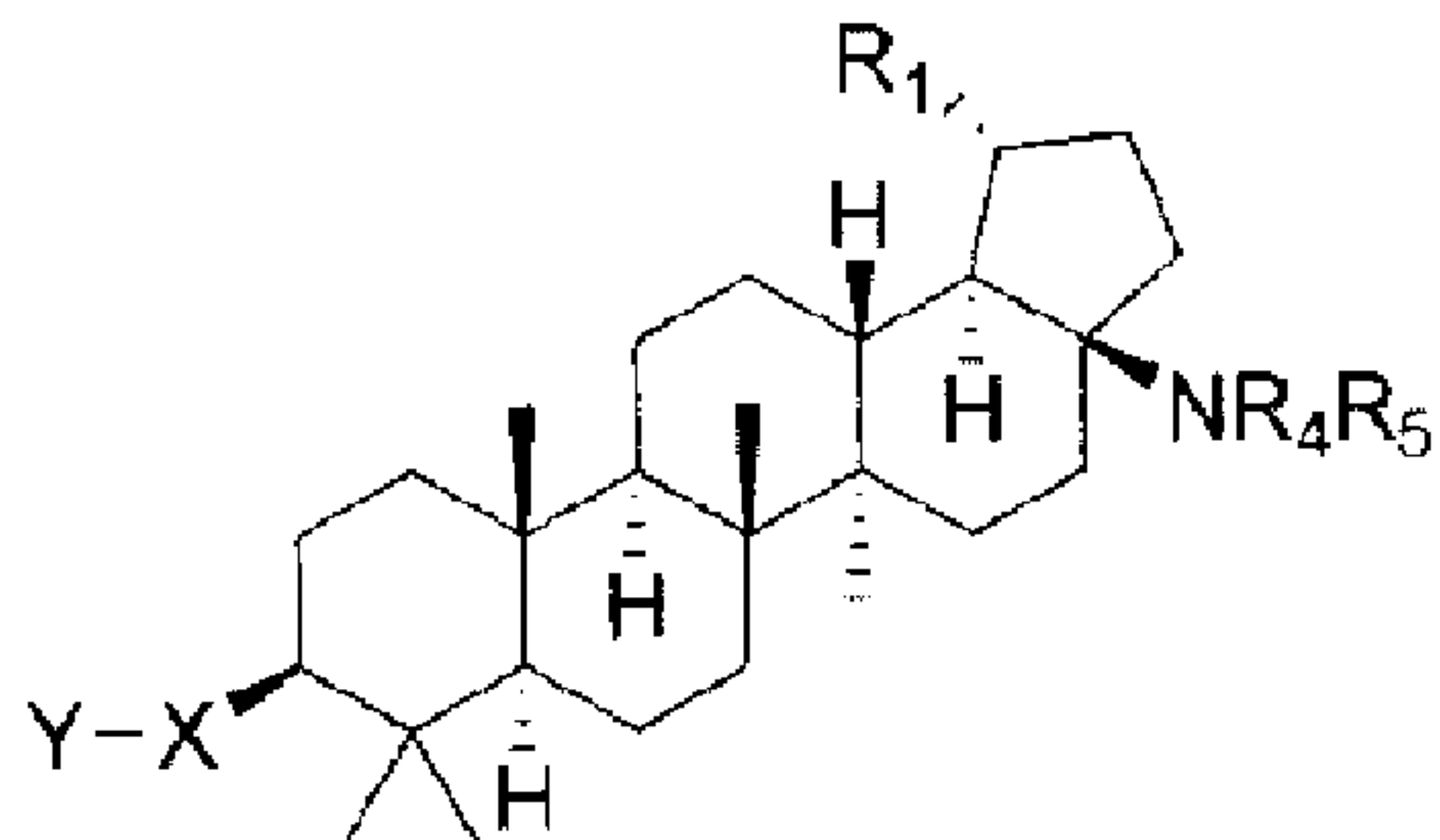


17. A pharmaceutical composition which comprises one or more of the compounds as claimed in any one of claims 1 to 16, together with one or more pharmaceutically acceptable carriers, excipients or diluents.
18. The pharmaceutical composition of claim 17, for use in treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent which is: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; or (d) another HIV entry inhibitor.
19. Use of a compound as claimed in any one of claims 1 to 16 for treating a mammal infected with an HIV virus.
20. Use of a compound as claimed in any one of claims 1 to 16 in the manufacture of a medicament for treating a mammal infected with an HIV virus.
21. An intermediate compound which is

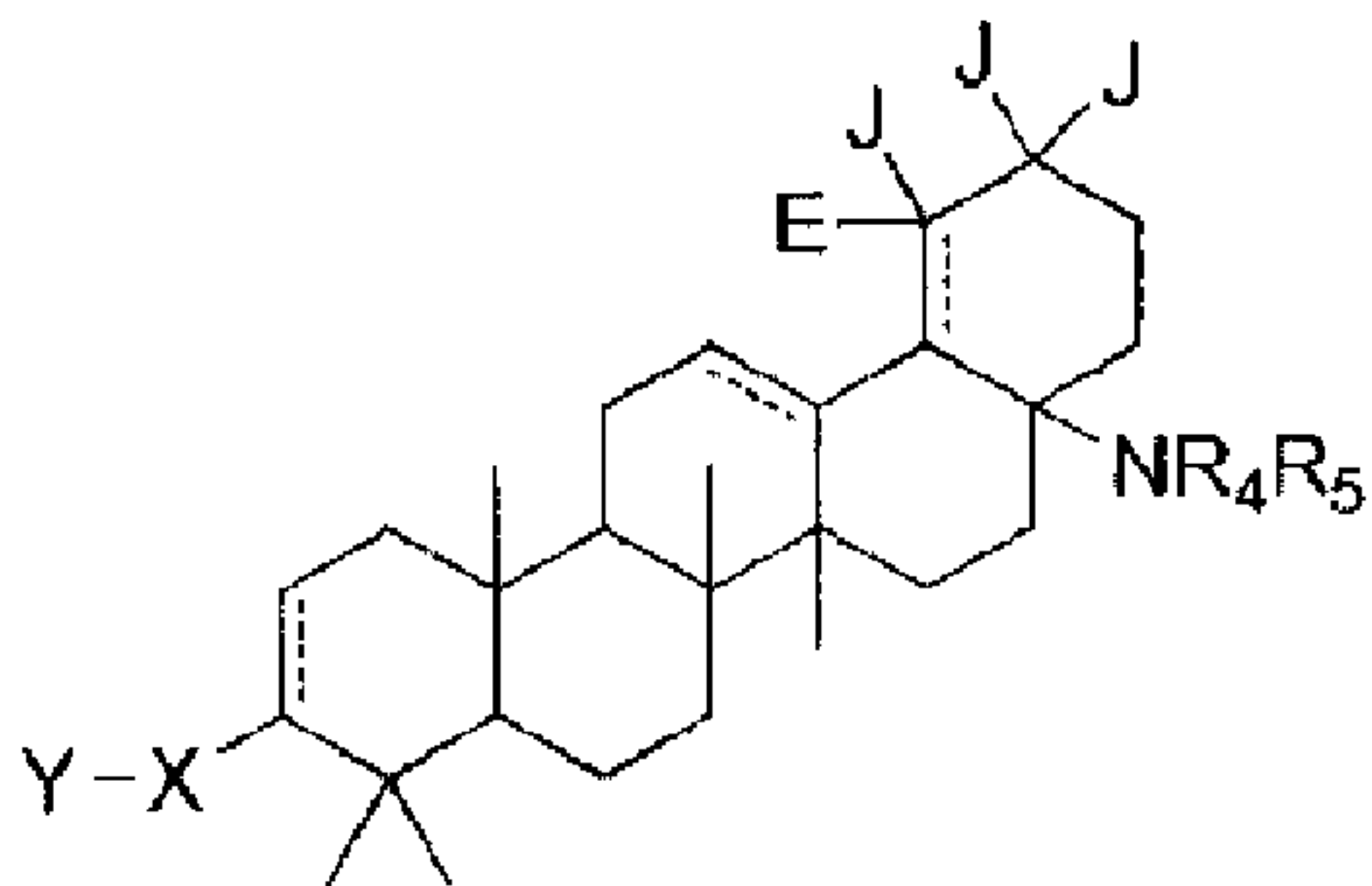




**Formula I**



**Formula II**



**Formula III**